Identifying and Prioritising Interventions to Reduce Emergency Hospital Admissions



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Green Templeton College

University of Oxford

A thesis submitted for the degree of

Doctor of Philosophy

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Abstract

The aim of this thesis was to identify and prioritise evidence-based interventions that reduce emergency hospital admissions and explore their implementation in clinical practice. To achieve its aim, this thesis first identified evidence-based interventions that reduce emergency admissions using a systematic review of systematic reviews. Second, it determined which of the evidence-based interventions had been recommended in national clinical guidelines, developed into quality of care indicators, and featured in national audits in England. Thirdly, it explored the extent to which evidence- and guideline-based interventions were being optimally utilised in primary care in the United Kingdom. Fourthly, it evaluated an innovative access to care initiative implemented in primary care to reduce hospital admissions. Fifthly, it explored the use of evidence by decision makers when designing and implementing local interventions as part of national campaigns to reduce admissions. Overall, the findings showed that there are a variety of evidence-based interventions that reduce emergency hospital admission rates. However, the thesis showed gaps in the promotion and use of these interventions in clinical practice in the United Kingdom. It also demonstrated that increasing access to primary care using innovative interventions may not be an effective or evidence-based approach to reducing hospitalisations. Stakeholders seeking to reduce admission rates may consider optimising use of the evidence- and guideline-based interventions prioritised in this thesis. This may be done using existing quality improvement infrastructure or by developing or expanding health care services that feature the interventions. Furthermore, efforts should be made to robustly evaluate novel interventions implemented in clinical practice to reduce hospital admissions. The results of such evaluations should be systematically disseminated to facilitate peer-peer learning, avoid duplicated efforts, and promote use of evidence-based interventions.

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Statement of Contributions

I certify that the work in this thesis is my own. Where others have contributed to the work, their initials are used. The contributions of others are summarised as follows:

Dr. Igho Onakpoya, Dr. Ben Fletcher, Dr. Dylan Collins, Alice Tompson, Dr. Joe Lee, Dr. Dave Nunan, Dr. Rebecca Fisher, Dr. Jack O'Sullivan, Dr. Oliver Van Hecke, Dr. Brian Nicholson, Dr. Sarah Stevens, and Dr. Jack Dunn acted as second reviewers in the systematic review in chapter three. They reviewed abstracts and full-length articles for inclusion, extracted data on the characteristics of the reviews, and assessed review quality in duplicate with the thesis author. Information on specific treatment comparisons in the reviews was extracted by the thesis author and verified by one of the second reviewers.

Dr. Joseph Lee reviewed the coding framework in the guideline analysis in chapter four. Dr. Dylan Collins acted as second reviewer and applied the coding framework in duplicate with the thesis author.

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List of Abbreviations

A&E: Accident and emergency
AMSTAR: Assessment of Multiple Systematic Reviews tool
AT: Alice Tompson
BF: Benjamin Fletcher
BN: Brian Nicholson
CCG: Clinical commissioning group
CH: Carl Heneghan
CI: Confidence Interval
DC: Dylan Collins
DJ: Dunn Jack
DN: David Nunan
EHA: Emergency Hospital Admission(s)
EM: Eduard Mathieu
GRADE: Grading of Recommendations Assessment, Development and Evaluation
GP: General Practitioner
IO: Igho Onakpoya
JA: Jeff Aronson JL: Joseph Lee
JO: Jack O'Sullivan
KK: Karen Kearley
KM: Kamal Mahtani
MS: Margaret Smith
NHS: National Health Service
NIHR: National Institute for Health Research
OECD: Organisation of Economic Co-Operation and Development
OH: Oliver Van Hecke
RCT: Randomised controlled trial
RF: Rebecca Fisher
RH: Richard Hobbs
SPCR: School for primary care research
SS: Sarah Stevens

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1.0 Chapter overview

This chapter provides a summary of the thesis aims and objectives, the key results of each chapter, key accomplishments, and skills developed.

1.1 Overview of thesis

1.1.1 Aim of thesis

The aim of this thesis was to identify and prioritise evidence-based interventions that reduce emergency hospital admissions and explore their implementation in clinical practice.

1.1.2 Objectives

A. Synthesise evidence from systematic reviews to identify, characterise, and prioritise evidence-based interventions that reduce EHA;
B. Determine which evidence-based interventions that reduce EHA have been formally recommended in national clinical guidelines, incorporated into national quality of care standards and indicators, and featured in national audits;
C. Determine the extent to which a set of evidence- and guideline-based interventions that reduce EHA are being optimally utilised in UK primary care;
D. Evaluate a real-world initiative implemented in primary care to reduce EHA;
E. Explore the use of evidence by decision makers when designing and implementing local interventions as part of a national initiative to reduce EHA.

1.2 Structure of thesis

Chapter 2: Background

Chapter 2 sets the foundation for the thesis by discussing the epidemiology and burden of rising emergency hospital admission rates in the UK, previous initiatives to alleviate the problem, and previous research on the topic. The chapter concludes by describing the rationale for the thesis projects, including the need to better utilise existing evidence with a wide-scoping systematic review, a content analysis of clinical guidelines, the need to determine whether evidence-based interventions that reduce EHA are being optimally utilised in clinical practice, the need to examine real-world initiatives implemented to reduce EHA; and the need to better understand the use of evidence by decision-makers when designing and implementing interventions to reduce EHA.

Chapter 3: Identifying and prioritising evidence-based interventions that reduce emergency hospital admissions: a systematic review of systematic reviews

Chapter 3 describes a systematic review of systematic reviews to identify and prioritise evidence-based interventions that reduce EHA. Overall, 306 systematic reviews were included, with an underlying evidence base of 1,667 unique randomised controlled trials that reported hospital admissions data for over 1,000,000 patients. There was moderate or high quality evidence for 30 medications; 22 health systems interventions; two diagnostic interventions; and two medical or surgical procedures. These 56 interventions were intended for use in 31 populations, representing a total of 73 unique intervention-clinical indication combinations. The main conclusion of this chapter was that there are evidence-based interventions that could be implemented or optimised in clinical practice in order to reduce emergency hospital admissions.

Chapter 4: Mapping national efforts to promote use of evidence-based interventions that reduce emergency hospital admissions: a content analysis of NICE resources in England

Chapter 3 produced a comprehensive list of interventions that reduce EHA however, it was unclear which had been promoted in clinical guidelines and used to inform quality measurement and improvement efforts. Therefore, a content analysis was conducted on NICE national guidelines, quality standards, quality indicators, and audits in England. The results showed that, of the 73 evidence-based intervention-clinical indications identified in the previous chapter, 43 were recommended in national guidelines. However, only 16 had been incorporated into quality standards or quality indicators and only 15 had been targeted by national audits. Of those interventions that have been audited, gaps in utilisation had been demonstrated. The main conclusion of this chapter was that there may be opportunities to further promote and utilise evidence-based interventions in England, which may lead to reductions in emergency hospital admissions.

Chapter 5: Prioritising research on the utilisation of interventions that reduce emergency hospital admissions

After having identified evidence- and guideline-based interventions that reduce EHA, the next step in research was to explore utilisation of the interventions in clinical practice. However, examining all of the interventions identified in chapters 3 and 4 would not have been feasible as part of this thesis. Therefore, chapter 5 describes a multi-step prioritisation process used to select a sub-set of interventions to explore in-depth. The process included engagement of the public, clinical experts, and methodological experts; scientific peer-review; and a literature review. Ultimately, five pharmacological interventions were prioritised, all medications indicated for heart failure patients.

Chapter 6: Utilisation of heart failure medication and associations with emergency hospital admissions: a national cohort study in UK primary care

Chapter 6 is a national cohort study that explores utilisation of five heart failure medications identified in previous chapters as high-value interventions for reducing EHA. The chapter used data on 8,274 patients and 383,369 prescriptions from the Clinical Practice Research Datalink. The chapter shows that the majority of heart failure patients experienced gaps in coverage from their primary care prescriptions and average doses were below recommended target doses. The chapter also shows that lower doses of first line-therapies were associated with an increased risk of EHA. The chapter concludes by suggesting that utilisation of heart failure medications in UK primary care may be sub-optimal and there may be opportunities to reduce rates of EHA through improved medication utilisation.3

Chapter 7: The association between 'real-world' primary care access interventions and emergency hospital admissions: a time-series analysis

Chapter 7 aimed to explore the feasibility of evaluating 'real-world' interventions for reducing hospital admissions and to build the evidence base for access to care interventions. A quasi-experimental design was used to evaluate Six interventions implemented in a health region in England as part of a national campaign to increase primary care access and reduce EHA. The results showed that evaluation is feasible however, use of strong study designs may be precluded by challenges in obtaining individual patient data for creating matched controls and time and financial pressures. Time series analysis shows that the interventions increased primary care access but were not associated with a significant change in admission rates for ambulatory care sensitive conditions and may have increased all-cause admission rates.

Chapter 8: The use of evidence when designing and implementing local interventions as part of a national campaign to reduce emergency hospital admissions: a qualitative study

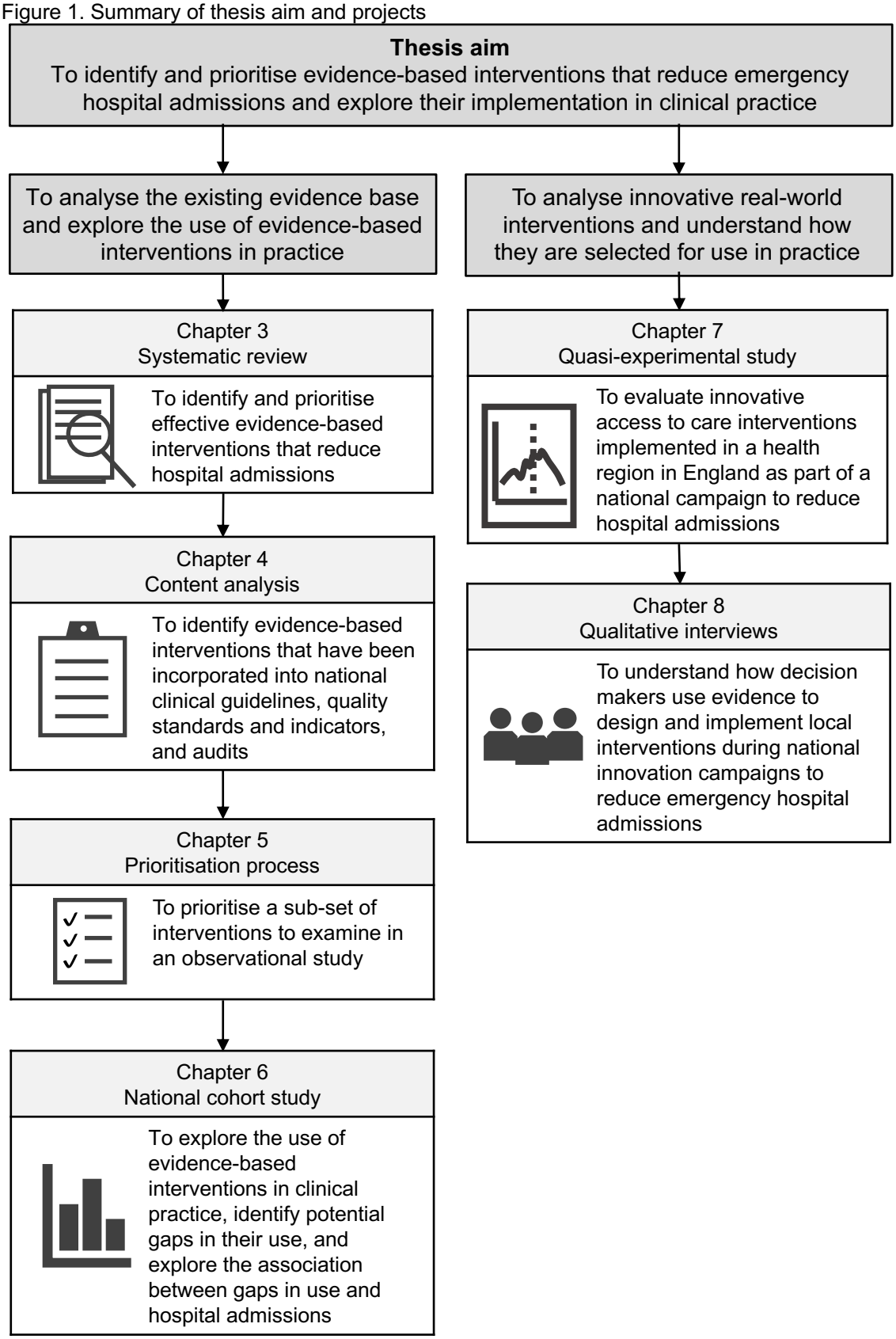
The Prime Minister's GP Access Challenge, evaluated in chapter 7, was a national initiative to increase primary care access and reduce hospital admissions with innovative interventions designed and implemented by local stakeholders. This type of arrangement was becoming more common in efforts to reduce hospital admissions in the UK. However, the process of local decision making in the context of these national campaigns was unclear, including how evidence was used. To better understand this process and derive lessons for future initiatives, interviews were conducted with seven decision makers involved in the Challenge. Thematic analysis showed that decision makers used expert opinion and service evaluations to inform the design and implementation of interventions. Although these types of evidence were considered weak, they were seen to offer crucial contextual and operational details needed for implementation. Decision makers also felt that the campaign's emphasis on innovation meant that robust evidence of effectiveness was not needed to inform action. No academic research evidence was used. Practical challenges to using evidence were identified including lack of skill, time pressures, and political constraints. Opportunities to increase the quantity and strength of evidence used in decision making were also identified. These were broadly categorised as generating evidence that better aligns with the needs of decision makers and helping decision makers to make better use of existing evidence.

Chapter 9: Discussion

Chapter 9 summarises the main findings of chapters 3 to 8 and discusses the overall implications for practice, policy, and research, the overall strengths and limitations, and the conclusions of the thesis.

1.3 Figure summarising thesis aim and projects

Figure 1. Summary of thesis aim and projects



1.4 Key accomplishments

1.4.1 Research collaborations

This thesis required research collaborations. Firstly, the thesis author developed collaborations with 14 students, academic clinical fellows, and clinical lecturers at three universities to verify extracted data for the systematic review in chapter 3. Secondly, the author was a member of the Prime Ministers Challenge Fund Evaluation Steering Committee and collaborated closely with the Oxfordshire clinical commissioning group (CCG) to complete the quasi-experimental study detailed in chapter 7. Coordination was required with CCG members and the Health Intelligence Senior Information Analyst at the National Health Service (NHS) South, Central and West Commissioning Support Unit to establish and verify data linkages. Thirdly, the author recruited a team of six, including general practitioners, a clinical pharmacologist, a heart failure expert, and a statistician, to help inform the design of the national database study in chapter 8.

1.4.2 Training and skills development

The author engaged in six major activities to develop skills. Firstly, he completed five courses through Oxford University, Johns Hopkins University, and the School for Primary Care Research: the Practice of Evidence-Based Health Care (Appendix 1.1); Teaching Evidence-Based Practice (Appendix 1.2); Excel- 3D formulae, charts and sharing data; the Data Scientist's Toolbox (Appendix 1.3); and a CPRD Training Day (Appendix 1.4). Secondly, the author completed informal training and self-taught by reading academic articles and textbooks, watching video tutorials, using free online resources, and consulting with colleagues. Specifically, the author learned to design overviews of systematic reviews, to assess the quality of systematic reviews using AMSTAR criteria, to assess the quality of randomised controlled trial evidence using GRADE criteria, to design and analyse data from a quasi-experimental study, to complete time-series analysis, to design pharmaco-epidemiological studies, and to analyse data using multi-variate Cox proportional hazards models. New skills were learned in the use of STATA, SPSS, Excel, and R statistical software packages. Thirdly, the author attended conferences, including the "Urgent Care: Reducing Avoidable Admissions Conference" in Manchester (September, 2015) and the "Urgent and Emergency Care Conference" hosted by

the King's Fund in London (September, 2016). Fourthly, the author shadowed a GP in an East Oxford surgery to better understand primary care pressures and the complexities of managing patients with chronic disease and multi-morbidity.

1.4.3 Teaching and knowledge translation

The goal of the thesis author is to become an academic clinician that practices medicine, teaches, and conducts research to improve human health and quality of life. To progress along this path, he invested time into teaching and knowledge translation during completion of this thesis. He developed and delivered plenary teaching sessions, workshops, and tutorials for Oxford Medical students and on three courses offered at Oxford University: Practice of Evidence-Based Medicine; Teaching Evidence-Based Practice; and Evidence into Action. The author taught the following topics: appraising randomized controlled trials and systematic review evidence; audit and service evaluation; developing clinical guidelines; measures of association and effect; and designing research to have value and impact. For this teaching, he received the Best Post-Graduate Teacher of the Year Award from the Oxford Students Union in 2017.

With respect to knowledge translation, the author has shared results of this thesis at three conferences: Evidence Live (June, 2016); Preventing Overdiagnosis (September, 2016); and the School for Primary Care Research Trainee Showcase (September, 2017). The author has published the methodology and results of the overviews of systematic reviews in chapter 3.[1,2] These publications have informed the design of published overviews conducted by other authors.[3] They have also garnered the attention of NHS decision-makers from four NHS CCGs (Grampian, Bristol, North Somerset, and South Gloucester), who contacted the thesis author to discuss urgent and emergency care policies.

1.4.4 Funding

To support completion of this DPhil thesis, the author was awarded a Clarendon scholarship, a Goodger and Schorstein Medical Sciences Research Scholarship, and funding from the National Institute for Health Research School for Primary Care Research (NIHR SPCR).

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Chapter 1. Appendix

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Appendix 1.1 Practice of evidence-based medicine course certificate



CEBM

UNIVERSITY OF OXFORD

The Practice
of
Evidence-Based Medicine

CERTIFICATE OF ATTENDANCE

Niklas Bobrovitz

Attended
The Practice of Evidence-Based Medicine
University of Oxford

Prof Carl Heneghan

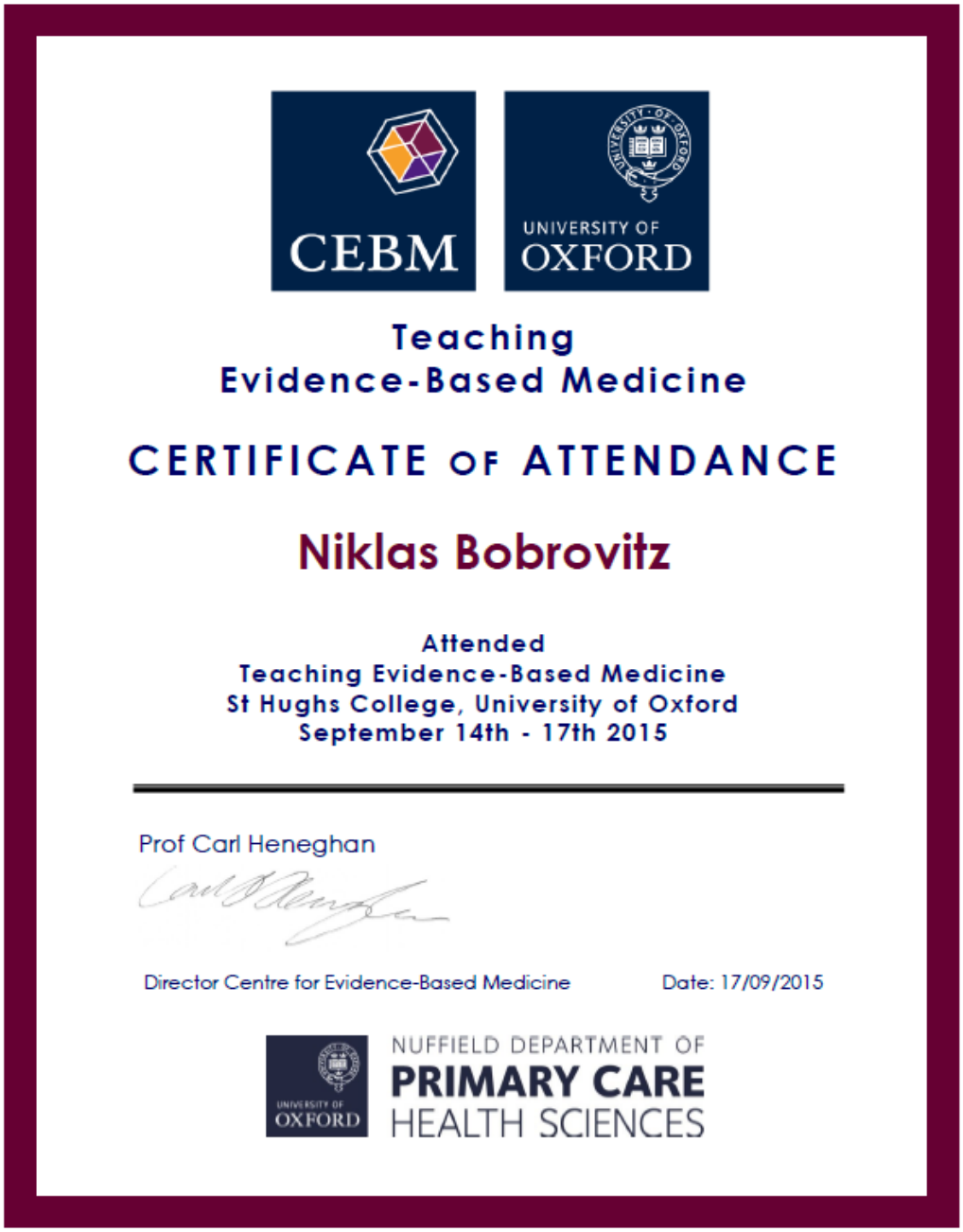
Director Centre for Evidence-Based Medicine

Date: 16/04/2014

UNIVERSITY OF OXFORD

NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

Appendix 1.2 Teaching of evidence-based medicine course certificate



CEBM

UNIVERSITY OF OXFORD

Teaching
Evidence-Based Medicine

CERTIFICATE OF ATTENDANCE

Niklas Bobrovitz

Attended
Teaching Evidence-Based Medicine
St Hughs College, University of Oxford
September 14th - 17th 2015

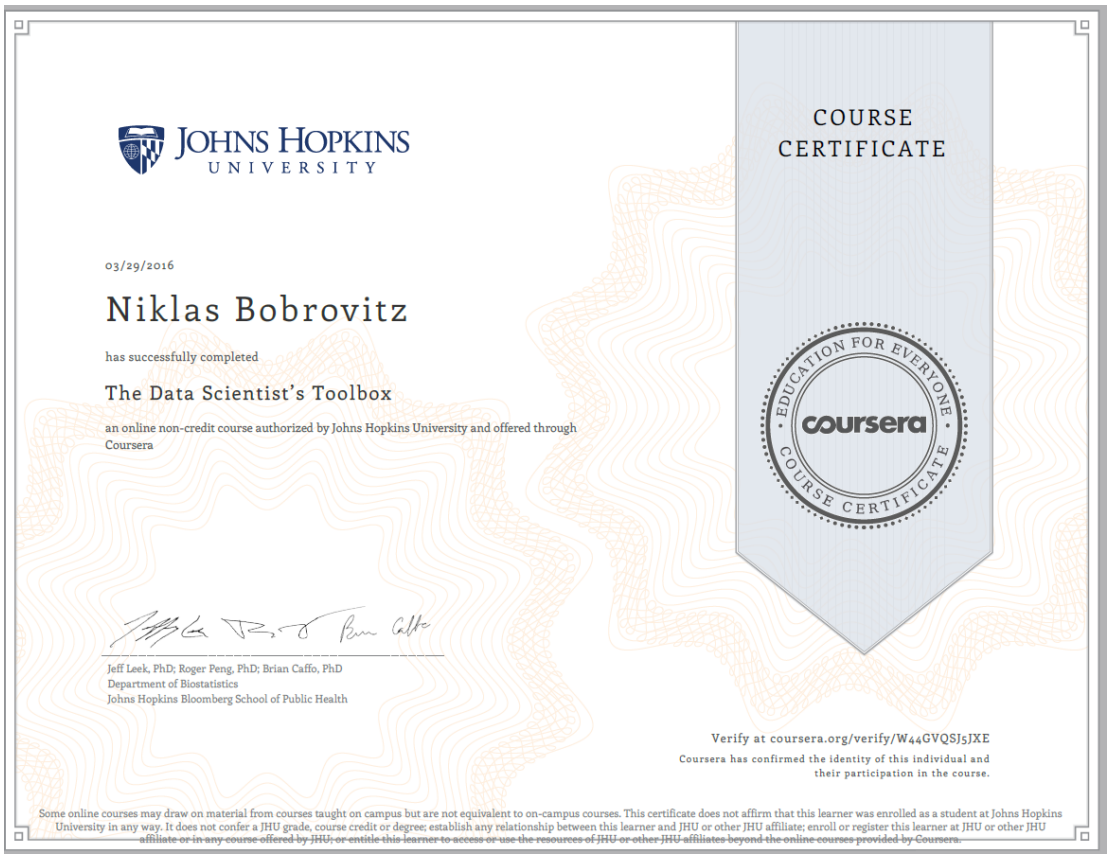
Prof Carl Heneghan

Director Centre for Evidence-Based Medicine Date: 17/09/2015

UNIVERSITY OF OXFORD

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PRIMARY CARE
HEALTH SCIENCES

Appendix 1.3 The data scientist's toolbox course certificate



JOHNS HOPKINS UNIVERSITY

COURSE CERTIFICATE

03/29/2016

Niklas Bobrovitz

has successfully completed

The Data Scientist's Toolbox

an online non-credit course authorized by Johns Hopkins University and offered through Coursera

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Jeff Leek, PhD; Roger Peng, PhD; Brian Caffo, PhD
Department of Biostatistics
Johns Hopkins Bloomberg School of Public Health

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Appendix 1.4 Clinical Practice Research Datalink training certificate



School for Primary Care Research

NHS National Institute for Health Research

CPRD Training Day

Certificate of Attendance

This certificate verifies that

Niklas Bobrovitz

attended the
School for Primary Care Research CPRD Training Day
on 12th December 2017
at St Luke's Chapel, University of Oxford

S. L. Stevens

Sarah Stevens,
on behalf of the School for Primary Care Research

School for Primary Care Research
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Chapter 2. Background

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2.0 Chapter overview

This chapter sets the foundation for the thesis by discussing the epidemiology and burden of rising emergency hospital admission rates in the UK, the potential for reducing admissions, previous initiatives to alleviate the problem, previous research on the topic, and the rationale for the thesis projects.

2.1 Chapter methods

This chapter was informed by structured literature searches of Pubmed, Google, and websites for national governments and health institutes in countries in the Organisation of Economic Co-Operation and Development (OECD), which have broadly similar health systems as the UK. The searches were originally conducted in July 2014 and were updated in February 2018. The following search terms were used: “emergency hospital admissions”, “unplanned hospital admissions”, “unscheduled hospital admissions”, “avoidable admissions”, and “preventable admissions”. For UK-based information, the websites of the National Audit Office, King’s Fund, Quality Watch, Nuffield Trust, and the Health Foundation were searched (Appendix 2.1).

2.2 Terminology

For the purpose of this thesis the following definition of emergency hospital admissions was used: “An unanticipated admission to hospital which occurs at short notice because of a perceived need for immediate health care. These admissions are acute, are not scheduled or planned in advance, and do not occur solely for the purpose of elective care”.[1] This definition was adapted from the National Health Service (NHS) data dictionary, which is used to classify and report emergency hospital admissions in the UK. Unlike the NHS definition, this definition does not include the term “unpredictable” because there are now tools, including the QAdmissions tool, that can prospectively identify patients at high risk of admission. Four other terms are commonly used in the academic literature to describe “emergency” admissions: non-elective; acute; unplanned; and unscheduled. These terms refer to the same phenomenon. The term “emergency” has been selected as it is used by the health service to report national UK data.[2]

Any admission that did not meet the above criteria was considered a non-emergency admission, including admissions solely for the purpose of receiving elective care, for the birthing of babies, and transfers from other hospitals under non-emergency conditions.

In this thesis, the phrase “emergency hospital admissions”, refers to both index admissions and readmissions after an index admission. Readmissions are identified when this distinction is relevant (i.e., when discussing interventions that target hospital readmissions).

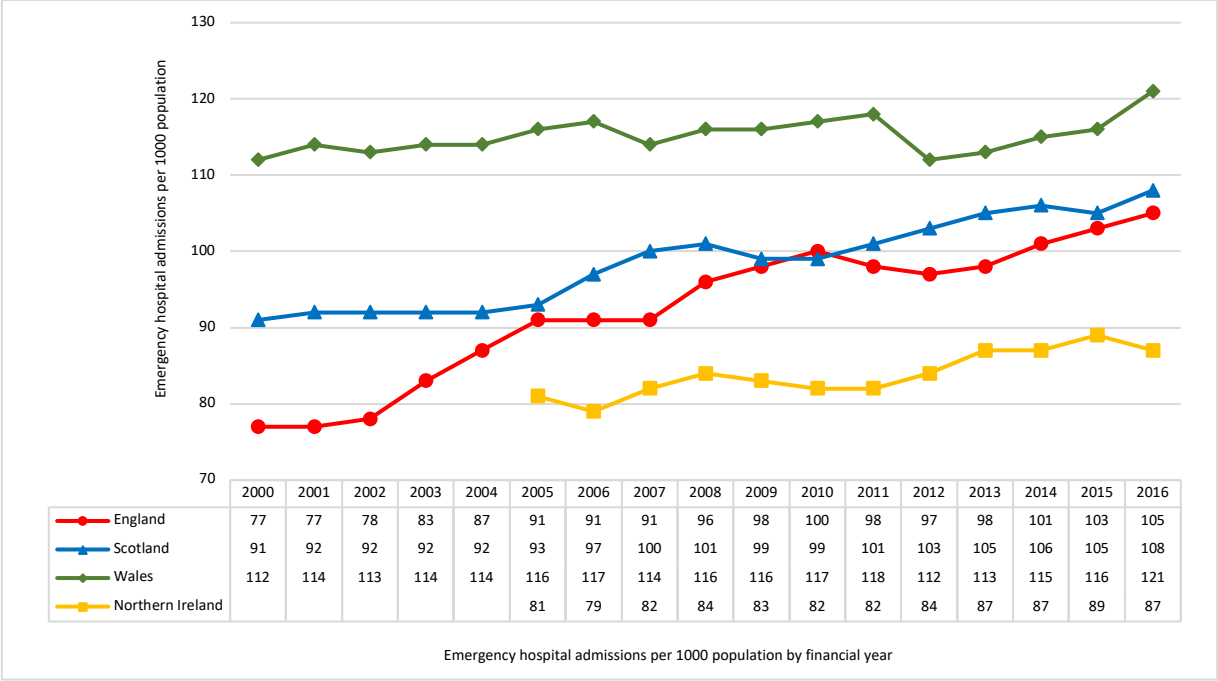
Although the above definition clarifies the meaning of ‘emergency’ it does not provide a strict definition of an ‘admission’ and, in fact, there is no consensus definition of an ‘admission to hospital’. Recent changes in hospital care, including the creation of ‘observation units’ and ‘acute assessment units’, have started to blur the concept and definition of a ‘hospital admission’. For the purpose of this thesis, the author accepted the definitions of ‘admission’ offered in the source data used in analysis (i.e., in the Hospital Episode Statistics database or in studies included in the systematic review).

2.3 The emergency care crisis in the UK

2.3.1 Increasing rates of EHA

Over the past 20 years, the UK has experienced substantial increases in annual rates of emergency hospital admissions (EHA). In 2013, the National Audit Office published a report showing increases in rates of EHA in every nation in the UK between 1998/99 to 2011/12. Since 2013, the National Health Service and Department of Health in each nation have published quarterly admissions data which show that the problem has persisted. In 2016/17, England, Scotland, Wales, and Northern Ireland reported their highest-ever rates of EHA - a combined 6.9 million admissions (Figure 1, Table 1).[3–6] EHA rates are growing approximately 2.5% per year across the UK, compared to 0.74% annual growth in population (Table 1).

Figure 1. Trends in emergency hospital admission rates in the UK from 2000/01 to 2016/17



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
England	77	77	78	83	87	91	91	91	96	98	100	98	97	98	101	103	105
Scotland	91	92	92	92	92	93	97	100	101	99	99	101	103	105	106	105	108
Wales	112	114	113	114	114	116	117	114	116	116	117	118	112	113	115	116	121
Northern Ireland						81	79	82	84	83	82	82	84	87	87	89	87

(1) Data from 2000/01 to 2011/12 sourced from National Audit Office report "Emergency admissions to hospital: managing the demand", which collated data from NHS England's Hospital Episode Statistics, NHS Wales' Patient Episode Database, Scotland's Information Services Division and Department of Health, and Northern Ireland's Social Services and Public Safety. (2) Data from 2011/12 to 2016/17 sourced from in-patient activity reports released directly by NHS England's Digital Hospital Episode Statistics, NHS Wales' Patient Episode Database, Scotland's Information Services Division, and Northern Ireland's Department of Health, Social Services, and Public Safety. Population estimates sourced from the UK Office for National Statistics. (3) Data for Northern Ireland is only available from 2005-06.

Table 1. Number of emergency hospital admissions and annual percent population growth in the UK from 2012/13 to 2016/17

	2012/13	2013/14	2014/15	2015/16	2016/17
UK	6,241,796	6,341,407	6,568,213	6,741,828	6,922,984
England	5,199,594	5,272,621	5,482,616	5,652,786	5,800,183
Scotland	546,258	561,369	569,412	565,344	585,512
Wales	342,949	349,114	356,511	359,804	375,861
Northern Ireland	152,995	158,303	159,674	163,894	161,428
UK percent increase in admissions from previous year	1.80%[1]	1.60%	3.57%	2.64%	2.69%
UK population growth from previous year	0.66%[1]	0.63%	0.77%	0.79%	0.83%

[1]2011/2012 data not shown but used to calculate the percent increase for 2012/13.

England has experienced the largest increases in EHA. The country's annual emergency admission volume has grown 61% over the last 20 years - four and a half times the growth in population (13.5%).[4,7] In 2016/17 there were 5.8 million emergency admissions, which represented 36% of all hospital admissions and 70% of all hospital bed days. The rate of 30-day emergency readmissions has also increased, rising 0.8% from 65 per 1,000 index admissions in 2006/07 to 73 per 1,000 index admissions in 2016/17. This corresponds to an increase of 22.8% in the total number of patients that were readmitted.[2] Overall, there were 457,880 emergency readmissions within 30-days of an index hospitalisation in 2016/17, which represents 8% of all emergency admissions.

In terms of routes into the hospital, the majority of the increases have been via accident and emergency (A&E) departments. Between 1998/99 and 2012/13 there was a 116% increase in admissions via the A&E, most of which were through major (type 1) A&E departments. During the same time period, admissions via GP referral decreased, likely because patients bypassed primary care to directly attend A&E departments. As of 2012/13, approximately 70% of EHA come via the A&E department, 16% come via GPs, and 13% come via other routes (i.e., referral after outpatient appointment).[7,8]

In terms of the nature of admissions, the greatest increases have been for patients that have short hospital stays. Between 1998/99 and 2016/17 there was a 152% increase in the number of admissions for patients who stayed less than two days, while patients that stayed more than two days (long stay) only increased 11%. Patients who did not stay overnight in hospital accounted for most of the increase between 2013/14 and 2016/17; 79% of the increase in admissions was for these types of very short stay admissions. Overall, in 2016/17, 32% of all emergency admissions were for people that were admitted to hospital and discharged on the same day.

2.3.2 A note on global rates of EHA and the focus of the thesis

The UK is experiencing the largest and longest upward trend in emergency admissions of any OECD country.[9,10] However, it is not the only nation with sustained increases in EHA. Other OECD countries are experiencing similar, albeit less severe, trends. For example, Australia experienced a 7% increase in the rate of EHA from 98 per 1,000 in 2011/12 to 105 per 1,000 in 2015/16[11,12], and the United States experienced a 13% rise in emergency admissions between 2000/01 and 2008/09.[13–15] However, this trend is not ubiquitous.[16]

This thesis focused on the UK context because, at the outset of the thesis, it was experiencing the most severe emergency care crisis of any OECD country. Furthermore, given the burden of EHA, it was thought that the clinical, policy, and research environment would be supportive of investigation into EHAs and receptive to recommendations for reform.[2,17–19]

2.3.3 Impact of increasing EHA rates

Emergency hospital care is intended to be utilised however, large increases in hospital admissions rates place strain on patients, health care practitioners and health care systems.[2] Although small increases in admissions may be accommodated by shifting resources and increasing capacity in the system, the rate and persistence of admission increases in UK hospitals are unsustainable. The impact of rising EHA rates on key stakeholders and organisations are summarised in the next three sections.

A. Patients

Rising EHA rates have direct consequences for patients. Increases in EHA rates can threaten quality of care and patient safety: they can disrupt the delivery of timely care by causing delays and cancellations of elective procedures; prolong A&E department wait times as patients requiring admission are forced to wait for available beds; and increase the risk of hospital-acquired infections.[20–26]

These problems are complex, and the pressures compound one another. For example, organisations that monitor quality of care in England have suggested that the rapidly rising readmission rates are a symptom of pre-mature, unsafe hospital discharges driven by the need to make hospital beds available for incoming patients.[6] This represents a vicious circle. The pressure to admit patients drives unsafe discharges, which adds subsequent pressure when pre-maturely discharged patients return to hospital in need of care.[27]

Furthermore, the rise in EHA may represent a trend that goes against patient preferences. Studies have shown that the location of services is one of the most important variables determining preferences for different models of care. Evidence from discrete choice experiments show that patients, including those with complex care needs, prefer home-based care to outpatient care, nursing home care, or hospital care, with hospital care being least preferred.[27]

B. Health practitioners

The emergency care workforce is also under enormous pressure as a result of increasing demands for acute care. An insufficient number of physicians are selecting to specialise in emergency medicine or acute general medicine, in part due to the growing workload, intensity of work, and working conditions.[28,29] These specialties are short of staff, which places pressure on existing doctors, some of whom report working more than their contracted hours to fill rotation gaps.[30]

C. The health system

In addition to negative impacts on patients and practitioners, increases in emergency admissions are financially crippling health systems. In 2015/16, emergency admissions cost £13.7 billion in England[2], 11% of the total Department

of Health budget. It is estimated that increases in admissions cost an additional £400 million per year.[2,7] If this trend continues, one-third of budget increases for the Department of Health (£1.1 billion per year) will be consumed by the cost of growing EHA rates, leaving little for the rest of the health system.[7,8,31–33]

Ongoing increases in EHA are unsustainable, yet rates of admissions continue to rise faster than population growth. The result of these increases is an unprecedented emergency care crisis which is affecting the entire health system and 65 million potential health care users in the UK.[7,34–36]

2.4 Factors associated with EHA rates

Given the significant impact of the UK emergency care crisis on patients, practitioners, and the health system, there has been much UK-based research on causes of emergency admissions. The UK government, the National Health Service, health researchers, and health charities such as The Health Foundation, Quality Watch, The King's Fund, and The Nuffield Trust have analysed variations in admissions rates and trends over time to identify factors associated with EHA rates. These stakeholders suggest that the causes of rising admission rates are complex, multi-factorial, and inter-related. Factors associated with EHA can be broadly categorised as patient factors and system/policy factors (Table 2). These factors are discussed in the sections below.

Table 2. Factors associated with emergency hospital admission rates

Patient factors	System/Policy factors
Demographics • *Aging population[2,8,37] • Sex[38] • Ethnicity[79] • Deprivation[39] • Urban/rural status[80] • Distance to hospital[39] • Social isolation and lack of social support[37,41]	**Primary and community care** • Decreasing continuity and access to primary care[37,40,42,43] • Quality of primary care[37,42] • Quality of prescribing[44]
Disease burden • *Increased rates of chronic disease and multi-morbidity[2,7,37,45–47]	**Accident and emergency departments** • Four hour wait target forcing admission near the four hour threshold[7,8] • Defensive medicine: concern about the consequences of not admitting due to lack of social or community care and medicolegal fear[41,48,49] • Lack of A&E senior doctor coverage[41,50–52] • Increasing attendance at A&E[39,53]
Perceptions and behaviours • *Increased expectations of health care[8,41] • *Uncertainty about appropriate resources and alternatives to hospital[54] • *Changing perceptions of primary care[55] • Prevalence of health behaviours such as smoking[39]	**In-patient secondary care** • Financial incentive structures: payment by result - fixed payment per admission rather than block payment[7,8] • Efficient discharge and shorter lengths of stay which increase availability of hospital beds and allow greater flow into hospitals (supply induced demand)[8,42] • Improved in-hospital survival increasing the population of frail and severely ill[56] • Increase in day-case elective procedures driving readmissions due to complications[2,7]

*There is evidence that these factors are contributing to the increasing trend in admission rates.

2.4.1 Patient factors

A. Demographics

Changes in the population age distribution are contributing to the increases in EHA rates. There has been a rise in the proportion of people over 65 in the UK[57] and this shift has been associated with an increase in EHA rates.[2,7,8,37,45–47] Aging is accompanied by a cluster of interrelated issues which put patients at higher risk of emergency hospital admission, including frailty, chronic disease. multi-morbidity, poly-pharmacy, social isolation, and limited social support.[47] In England, it is estimated that approximately 40% of the increase in EHA may be due to the effects of population aging.[8]

The impact of population ageing on hospital admission rates is expected to increase in coming years. In 2016/17, patients over 65 made up 18% of the population in

England but accounted for 43% of emergency admissions and 65% of emergency hospital bed-days. By 2027, the number of people age 65 and older is project to increase by 20%.[57]

Other demographic factors have also been associated with admission rates. Being an ethnic minority, being male, having low socioeconomic status, having high economic deprivation, living in urban areas, having no family support at home, and living closer to hospitals have been associated with increased rates of EHA. However, there is little evidence that the distribution of these demographic factors is changing and, therefore, it is unlikely they are driving increases in admission rates[37–41]

B. Disease burden

Changes in the burden of chronic disease in the UK may be contributing to rising EHA rates. The number of people with multiple long-term conditions increased 43% in England between 2007/08 and 20017/18 and 56% in Wales between 2004/05 and 2014/15 (after adjusting for population growth).[47,58,59] The number of people with one or more long-term conditions has also increased and this rise is projected to continue. By 2025, it is estimated that 18 million people in England will have one or more long term conditions, an increase from 15 million in 2017/18.[47] The prevalence of chronic disease increases with age and, therefore, this rise is partially tied to the aging of the population however, changes in lifestyle are also thought to be playing a role.[46,47]

These increases in the prevalence of chronic disease are likely driving some of the increases in EHA rates. Chronic disease patients have an elevated risk of EHA compared to patients with no disease, with multi-morbid patients at highest risk.[40,47,60–63] Chronic disease patients experience exacerbations of their conditions which often require immediate high-acuity care. They also have complex ongoing care needs that health care providers in the community are sometimes unable to manage, thereby necessitating assistance from secondary care.

Despite the importance of population aging and chronic disease prevalence, they do not account for all of the increases in admission rates. In fact, studies have

documented increases in admission rates across all age and disease groups, thereby suggesting that additional factors are contributing.[2,8,64]

C. Perceptions and behaviours

Increasing expectations of care, uncertainty about alternatives to hospital, and changing perceptions of primary care may be driving increases in A&E attendances and hospitals admissions. Although A&E physicians act as gatekeepers to hospital admissions, increased burden of A&E attendances combined with system/policy factors, such as wait-time targets, defensive medicine, and limited coverage by senior A&E consultants may be contributing to rising EHA rates.

The UK is experiencing unprecedented demand across all health care services. Given that self-reported health status has remained stable, this suggests that patient expectations of health care are increasing.[8] For example, in 2017/18 there were record breaking numbers of patients presenting to A&E departments in the UK, many of whom were self-referred. Expectations within A&E may also be changing. Physicians have reported that patient expectations seem to be getting “higher and higher” and that their decisions to not admit patients are often criticised by patients and their family.[49]

Uncertainty about alternatives to hospital has been documented. Studies have shown that patients presenting to the A&E department often do not know about other appropriate resources to access in the first instance.[51] Despite the availability of alternatives to hospital, such as walk-in centres, the fragmented nature of acute care services can make it difficult for patients to understands the options.[65] Therefore, patients may bypass primary care and hosptial alternatives knowing that they will likely be seen by a health care provider within four hours.

There have been national changes in the perceptions of primary care. This is relevant as patient perceptions of primary care access and satisfaction have been associated with A&E attendances and emergency hospital admissions.[37] Between 2012 and 2017 the national GP patient survey showed that a greater proportion of patients reported difficulties contacting their GPs by phone, reductions in how often they see their preferred GP, decreases in the ability to get an appointment when

they wanted one, increases in 'poor' experiences of making appointments, increases in the proportion 'waiting too long' for appointments, and decreased satisfaction with opening hours.[66] These reports provide some evidence of changes in the expectations and perceptions of primary care given that primary care activity actually increased between 2010/11 and 2014/15. There was a 15% increase in face-to-face and telephone consultations and a 10% increase in practice list size, both of which outpaced population growth (3%) during that period.[55,67] There was also an increase in the rate of consultations per registered patient per year from 4.29 in 2011 to 4.91 in 2015.

The prevalence of poor health behaviours in an area, such as smoking rates, has been associated with increased rates of EHA.[39] However, there is little evidence that changes in these factors are affecting rates of EHA.

2.4.2 System and policy factors

Many elements of the health system may be contributing to rising EHA rates, including factors in primary and community care, A&E departments, and in-patient secondary care.

A. Primary and community care

Evidence for the impact of quality of primary care on EHA rates has been mixed. There is evidence that better performance on condition-specific quality indicators for diabetes, angina, and asthma is associated with lower hospital admissions rates however, there are significant gaps in this research which are discussed in sections 2.8 and 2.9 of this chapter.

The relationship between EHA and changes in primary and community care policies have been investigated.[37,40,42,43,68,69] The introduction of policies in 2004 that allowed GPs to opt out of out-of-hours care have been associated with increases in admissions however, some researchers argue that this policy simply continued an established increasing trend at that point.[67,68,70] Overall, the evidence for the impact of access to care on admissions is mixed and may be context-specific.[37,42] Evidence from the United States and Canada has shown that better access to care is

associated with reductions in EHA however, there is no consistent data from the UK or Europe to support this.

There is evidence that the continuity of primary care is associated with emergency admissions and that continuity of care may be declining in the UK.[37,43] Between 2012 and 2016 there was a 7% reduction in the proportion of people in England who reported being able to see their preferred GP, although this may be a function of changing expectations of care.[66] This is a particularly relevant issue given the rising rates of elderly patients with complex chronic illnesses, many of whom prefer to see the same GP and for whom care coordination and personalised care support is important for successful management.[47,71]

B. Accident and emergency departments

Several factors in A&E departments may be driving admission rates up. The introduction of the four-hour A&E wait target in the UK (i.e., discharge decision within four hours of patient arrival) corresponded to accelerated increases in rates of short-stay admissions. Some physicians have even reported admitting patients close to the threshold to avoid financial penalisation.[7,8,41,48]

Fragmented support in the community, (i.e., home care, out of hours GP care, intermediate care and out-patient follow-up[2,8,41)], along with the rising threat of litigation[72] may also be driving admissions for less severe cases. Studies have shown that these factors may contribute to A&E physicians practicing defensive medicine; admitting patients out of concern for patient safety and the consequences of discharging from the A&E.[41,48,73] Data showing an increase in the proportion of A&E attendances that are admitted to hospital support this. Between 2003/04 and 2015/16 the proportion of attendances converted to admissions rose from 19% to 27%.[74]

Decreases in senior consultant coverage in the A&E may also be contributing to EHA increases.[52,73] Having senior emergency medicine clinicians available to review patients in the A&E has been shown to reduce emergency admissions by 12%, compared to review by junior staff.[51] Senior staff may be less likely to admit due to a mixture of experience and confidence, which enables them to accept more

risk in discharging a patient. Less experienced physicians have reported feeling more risk-averse compared to their senior colleagues and less confident in decision-making.[41,50–52]

All of these factors may be exacerbated by high A&E volumes. Evidence has shown that A&E departments with greater attendance rates have higher rates of emergency admissions.[39] In 2016/17 the UK reported its highest ever rates of A&E attendance.[36]

C. In-patient secondary care

At the hospital level, several policies and trends have likely affected rising EHA rates. Increased hospital bed availability has been correlated with higher rates of admissions in a phenomenon known as supply-induced demand; if services are available, they will be used.[8,42] In the UK, there is evidence that a complex type of supply-induced demand may be occurring due to more rapid turnover of patients in hospital. Although the overall number of available acute care beds has been decreasing (-6% between 2010/11 and 2016/17), the bed occupancy rate has increased (+3.7% between 2010/11 and 2016/17). Meanwhile, there has been a downward trend in average length of stay after an emergency admission, from 9.7 days in 1998/99 to 5.8 days in 2012/13.[7] The result has been greater use of the beds that are available; as short-stay patients are discharged, beds become available for other short-stay admissions. Although it is difficult to discern why lengths of stay have been decreasing, it has been suggested that advances in hospital care have accelerated in-patient care. It has also been suggested that patients with less severe illness are more commonly being admitted. The decreasing hospital case-fatality rate in England supports both of these possibilities.[77]

There is evidence that improved in-hospital survival after an emergency admission may be increasing admissions due to greater frailty and severe illness among surviving patients.[56] In England, it is estimated that improvements in hospital survival between 2000 and 2009 resulted in an additional four patients surviving per 100 emergency hospital admissions and, within one year, eight subsequent emergency admissions among these surviving patients.[56]

Changes in how elective hospital care is delivered may be having an impact on emergency admissions.[2,7] Many elective procedures that used to involve an overnight hospital stay are now delivered as day-case procedures in which patients return home on the same day of the intervention. Between 1997/98 and 2012/13 the number of day-case procedures increased from 3 million to 7.4 million. Although this is beneficial for many patients, complications that used to occur during elective in-patient care are now experienced in the community. About 3% of day-case procedures require emergency readmission for complications. It has been estimated that these complications account for approximately 10% of the total increase in emergency admissions.[7]

One important financial factor that likely affected admission rates has been phased out but is worth mentioning. The introduction of the financial reimbursement program "payment by result" may have unintentionally incentivised hospital admissions between 2003/04 and 2010/11.[7,8,68] Under the "payment by result" system, hospitals received a fixed payment per admission rather than a block payment to cover anticipated admissions activity. Staged introduction of this policy began in 2003 and was associated with rapid increases in short-stay admissions. However, a tariff on short-stay admissions was introduced in 2010/11 eliminated this incentive.

Many other potential drivers of hospital admissions have been investigated however, the elements described in the above sections are supported by evidence, have been consistently reported by different organisations, and feature in major national audits and investigations of trends in emergency admissions in the UK.

2.5 Potential for reducing EHA

There is no consensus on what rate of hospital admissions are appropriate or acceptable and there is debate about the extent to which emergency admission rates can be reduced. However, research suggests that reductions are possible both in the UK and other OECD countries. This research centres on two concepts which are described in the next sections: hospital admissions for ambulatory care sensitive conditions and variations in admission rates.

2.5.1 Admissions for ambulatory care sensitive conditions

Emergency hospital care is clinically necessary and appropriate for many health problems however, there are some health issues which can and should be managed outside of the hospital. These are known as ambulatory care sensitive conditions (ACSC).[76] ACSC are medical conditions for which hospital admission is considered unnecessary and avoidable because they can be managed by interventions in primary and community care. As such, admissions for ACSC are considered markers of access or quality in primary and community care.[77] Lists of ACSC conditions have been developed by consensus among clinical experts. A common feature among ACSC is that the evidence base for their prevention or treatment is well-established and can be delivered at the primary care level. Some conditions are widely considered to be 'ambulatory care sensitive' and admissions rates for these (e.g., asthma, diabetes, congestive heart failure) are used to compare health system performance between countries.[78] However, there is variation in the lists used by different organisations and countries.

Generally, these lists include: (1) preventable diseases (e.g., vaccine preventable); (2) acute diseases for which immediate management could prevent admission (e.g., dehydration and gastroenteritis) and; (3) chronic diseases for which effective management should prevent admissions for exacerbations or complications (e.g., heat failure, complications from diabetes).

A list of 36 ACSC identified in a systematic review are listed in Table 3. Nineteen of these are commonly used in the NHS.[79]

Table 3. Ambulatory care sensitive conditions (ACSC)

ACSCs in common use in the NHS (n=19)	ACSCs not in common use in the NHS (n=17)
Angina	Alcohol-related diseases
Asthma	Atrial fibrillation and flutter
Cellulitis	Constipation
Congestive heart failure	Deliberate self-harm
Convulsions and epilepsy	Failure to thrive
Chronic obstructive pulmonary disease	Fractured proximal femur
Dehydration and gastroenteritis	Dyspepsia/stomach function disorders
Dental conditions	Hypokalaemia
Diabetes complications	Low birth weight
Ear, nose, and throat infections	Migraine/acute headache
Gangrene	Neuroses
Hypertension	Peripheral vascular disease
Influenza and pneumonia	Ruptured appendix
Iron-deficiency anaemia	Tuberculosis
Nutritional deficiency	Schizophrenia
Other vaccine-preventable diseases	Senility/dementia
Pelvic inflammatory disease	Stroke
Perforated/bleeding ulcer	
Pyelonephritis	

2.5.2 The concept of variations in health service utilisation

Variations in health care utilisation and patient outcomes across geographic regions can be used to identify poor quality or inappropriate health care services and, therefore, opportunities to improve care. In a seminal 1982 paper John Wennberg and colleagues demonstrated that individual physician decision making was a major factor in the variation for common surgical procedures in the United States.[80,81] Since then, large systematic efforts to identify and reduce variations in health care have emerged, including the Dartmouth Atlas of Health Care[81] and NHS Atlas of Variation.[82] The primary purpose of these efforts is to ensure equal access to high-quality evidence-based services. There are warranted reasons for variation including differences in the burden of illness in different regions. However, some variations are unwarranted as they are caused by over- or under- provision of services, failure to implement evidence-based guidelines, or limited access due to distance from services, socioeconomic factors, or poor health literacy. If variations persist after risk-adjustment, the variations may be unwarranted.

2.5.3 Evidence of variation in EHA rates

Risk-adjusted geographic variations in EHA have been identified in the UK and other OECD countries, which suggests that reductions in admission rates may be possible. In 2017/18 the National Audit Office in England reported considerable geographic variation in emergency admissions at the level of clinical commissioning groups ranging from 73 to 155 per 1,000 GP registered population. This analysis adjusted for confounding factors including demographics, health needs, deprivation, and costs.[40]

Geographic variation has also been demonstrated in ACSC admissions. A 2015 systematic review showed that significant geographic variations in admissions for ACSC were common in six OECD countries: the UK, United States, Canada, Australia, New Zealand, and Spain.[46] In a follow-up investigation in the UK, researchers used national data to provide more robust, risk-adjusted evidence of variations in admissions for a broader range of ACSC.[69] The authors showed a 26% risk-adjusted difference between regions with the highest and lowest admission rates for ACSC (95%CI 23% to 30%). Mental health had the most extreme variation, with a 446% difference between regions with the highest and lowest admission rates (95%CI 337% to 596%). The researchers also showed a high level of variation for short-stay admissions (less than 2 days). The authors suggested that GPs and commissions should ensure they are offering best-practice care for the most variable clinical conditions and patient subgroups, including patients with chronic diseases and conditions causing short-stay admissions.[42,69,83] They estimated that 0.4 to 2.8 million bed days could be saved by reducing these variations.

2.6 UK policy and practice initiatives to reduce EHA

Reducing emergency hospital admissions has become vital for the National Health Services in the UK in order to alleviate pressure on acute care systems, ensure the sustainability and quality of health care, and minimise patient burden.[2,17–19] Therefore, many initiatives have been implemented. These have primarily targeted the organisation, delivery, or access to care. However, most initiatives have failed, and it has been suggested that the lack of effective evidence-based interventions to inform initiatives has been a key limitation.

2.6.1 National initiatives

Reports by the National Audit Office, NHS England, and health charities have described major policy and practice initiatives to reduce admissions.[2,7,84,85] These initiatives are described in Table 4. There have also been national initiatives whose secondary aims have been to reduce emergency admissions. Several of these initiatives were proposed in the Five Year Forward View Report in 2014, a landmark document laying out major reforms to transform the health system.[86] Those most relevant to reducing admissions are described in Table 5.

Despite these efforts, admission rates have continued to rise. The National Audit Office, NHS England, and other stakeholders have identified a key limitation in these efforts to reduce admissions: the lack of evidence-based interventions to inform the design and selection of initiatives.[2,7,69,87,88]

Many initiatives to reduce admissions had been implemented despite poor evidence underpinning their efficacy or evidence demonstrating no effect.[89–91] For example, the NHS implemented a £157 million direct enhanced service contract in 2014 for GPs to identify and case-manage patients at highest-risk of hospital admission.[92] The service was renewed in 2015 by NHS despite research evidence showing no effect.[93–95] It failed to produce benefit in practice and was eliminated from GP contracts in 2017.[87]

These failed efforts demonstrate the risk of widely implementing interventions which are not supported by evidence in the first instance and may represent an inefficient use of resources. In landmark reports in 2013 and 2018 the National Audit Office emphasised the need for robust evidence on what works in reducing emergency admissions in order to target efforts on useful action.[2,7]

In addition to uncertainty about what might work to reduce admissions, The Department of Health, NHS England, and NHS Improve have indicated that they do not know what elements of the health service are responsible for the significant geographic variation in admission rates. Efforts to explore risk-adjusted variations have been inconclusive.[2] This may be due to uncertainty about which clinical activities or interventions significantly impact on hospital admissions.[42,69,83]

Table 4. National initiatives with a primary aim to reduce emergency hospital admissions

Initiative	Description
Collaborative partnerships[97]	**Goal**: To bring together health and social care stakeholders (i.e., clinical commissioning groups, NHS England, and local health care providers) to learn from one another and to identify best practices for local service delivery. **Key examples** • Urgent Care Working Groups
Urgent and emergency care service audits and investigations[29]	**Goal**: To better understand capacity, demand, and performance of systems and to identify the needs of service providers and challenges in reducing admissions
Broad financial incentives[7]	**Goal**: To incentivise reductions in the rates emergency hospital admissions without specifying the method of doing so **Key examples** • Reduced hospital reimbursement for emergency admissions rates above a certain level • No hospital reimbursement for readmissions • Premiums for clinical commissioning groups to reduce admission rates for ACSC • Reimbursement for reviewing admission levels, comparing admissions rates between practices, and proposing service design improvements
Targeted financial incentives[92]	**Goal**: To incentive use of specific new services for reducing hospital admissions **Key examples** • Avoiding unplanned admissions directed enhanced service which payed GPs to identify and case manage patients at highest risk of emergency admission

Performance measurement and reporting[98]	**Goal**: To measure and report on hospital admissions in order to track progress over time and inform policy- and decision-making
	Key examples
	• Clinical Commissioning Group Outcomes Indicator set, which included indicators on:
	  ○ emergency admissions for chronic and ACSC in patients of all ages
	  ○ emergency admissions for asthma, diabetes, epilepsy, and lower respiratory tract infections in children and young people under the age of 19
	  ○ emergency admissions due to alcoholic liver disease for adults aged 19 and over

NHS Right Care	**Goal**: An NHS supported programme that helps local health teams understand and reduce variation in the quality of health care

Table 5. National initiatives with a secondary aim to reduce emergency hospital admissions

Initiative	Description
Redesign urgent and emergency care services	**Goal:** To integrate A&E departments, GP out-of-hours services, urgent care centres, NHS 111, and ambulance services
Multi-speciality community providers	**Goal:** To bring together multiple types of community health care providers into GP practices and shift ambulatory care out of hospitals
Integrate systems	**Goal:** To integrate primary and secondary acute care systems and offer GP, hospital, mental health, and community services in primary care
Enhance care homes	**Goal:** To enhance care homes by developing new shared care models and support

2.6.2 Local initiatives

There have been many localised efforts to reduce admissions for example, support workers providing personal nursing and social care, integrated health and social care teams, out-of-hours response services, volunteer-run assessment and sign-posting services, and intermediate and urgent care centres.[47,99,100]

In general, the results of local initiatives have been varied and the reporting of results fragmented. In addition, it has been suggested that the design and impact of local initiatives is likely to be context dependent, with limited generalisability for scaling-up to reduce admissions nationally.[99,101,102] However, despite potential limitations in generalisability, national health care stakeholders have encouraged innovation and evaluation at the local level in order to build the evidence base for interventions that reduce admissions.

2.7 Research on reducing EHA and gaps in the literature

Research on reducing EHA has focused on assessing the effectiveness of interventions and explaining variations in admission rates however, there are significant gaps in the literature.

2.7.1 Research on interventions and gaps in the literature

There have been systematic efforts to identify interventions that reduce emergency hospital admissions.[7,102–104] However, these reviews have been limited in scope. Most reviews have focused on organisation, delivery, and access to care interventions, in an attempt to identify interventions that apply to general patient populations.[88,105] This is valuable as admissions are increasing across all patient groups however, few effective interventions have been identified. This research suggests that the evidence base for organisation, delivery, and access to care interventions needs to be built with primary studies.

A major limitation of previous reviews is the exclusion of a vast literature on diagnostic interventions, medications, and medical and surgical procedures, which have the potential to reduce use of emergency health care services. For example, a systematic review of randomised controlled trials (RCTs) has shown that

aldosterone receptor antagonists reduce emergency admissions in heart failure patients by 21% over 20 months.[106,107] There have been no efforts to compare and contrast this broad range of evidence-based interventions between patient groups to identify and prioritise those which are most effective in reducing admissions.

Given that hospital admissions are increasing across all ages and conditions, it is likely that a variety of interventions targeting different elements of health care are needed. Therefore, systematically assessing a broad range of interventions across all patient groups represents a valuable step towards prioritising efforts for reducing admissions. Although some types of interventions, such as medications or diagnostic interventions, may not be utilised for the sole purpose of reducing hospital admissions, they may represent high-value activities in the overall care of patients. Therefore, comparing and contrasting evidence for these types of interventions could inform efforts to optimise clinical care and reduce emergency hospital admissions. This may include monitoring and optimising use of beneficial interventions that are already part of routine practice.

There are existing mechanisms for quality measurement and improvement in the UK and other health systems. Therefore, tracking and improving utilisation of clinical interventions that have proven efficacy in reducing hospital admissions may represent a feasible and efficient strategy to alleviate rising admission rates. Furthermore, this represents an evidence-based strategy, which may be more likely to succeed than previous initiatives which have implemented novel interventions with little supporting evidence.[102,108–110]

2.7.2 Research on variations in admissions and gaps in the literature

There have been investigations into causes of geographic variations in admission rates in the UK. Studies have attempted to identify factors within the control of the health system that are associated with variations, such as quality of care and use of evidence-based practices. It is thought that identifying these modifiable factors may help to focus efforts on improving care in areas with high admission rates.

Most studies have focused on the association between admission rates and achievement of clinical activities measured in the Quality and Outcomes Framework. The results of these studies have been mixed, with many showing that QOF achievement has little association with hospital admission rates. This would suggest that variations in quality of care and use of evidence-based clinical interventions may not impact on real-world hospital admission rates.[37,44,111–113] However, the interventions measured as part of QOF represent only a minority of evidence-based interventions and they may not represent the best interventions for reducing admissions. For example, a systematic review of RCTs has shown that aldosterone receptor antagonists reduce emergency admissions among heart failure patients by 21% over 20 months. [106,107] However, aldosterone receptor antagonists are not a component of the QOF.

Therefore, existing studies examining the association between evidence-based clinical activities and admission rates may be incomplete. This gap in research may be addressed by identifying evidence-based interventions that reduce EHA, then determining whether variations in use of those interventions in clinical practice is associated with emergency admissions.[42,69,83] This type of investigation would help to determine whether better use of evidence-based interventions, which is a factor within the control of the health system, may help to alleviate the emergency care crisis.

2.8 Rationale for thesis projects

This thesis was designed to address the gaps in the literature identified in this chapter. The aim of the thesis and the thesis projects are summarised in Figure 2.

The overarching aim of this thesis was: to identify and prioritise evidence-based interventions that reduce emergency hospital admissions and explore their implementation in clinical practice.

The specific gaps in knowledge addressed by this thesis and the rationale for the thesis projects are as follows:

1) **There was a need to better utilise existing evidence to identify and prioritise interventions that reduce emergency hospital admissions.** National health care stakeholders had identified the lack of evidence-based interventions as a key challenge in designing and prioritising programs to reduce admissions. Systematic reviews on interventions that reduce admissions had limited their scope to specific types of interventions or patients. This gap was addressed by conducting a wide-scoping systematic review of systematic reviews and prioritising effective interventions based on the quality of evidence (chapter 3).

2) **It was unclear whether evidence-based interventions that reduce hospital admissions were being promoted in clinical practice.** Chapter 3 produced a list of evidence-based interventions that reduce hospital admissions. However, it was unclear whether there had been efforts to promote use of the interventions in practice. Therefore, to map efforts promoting use of the interventions a content analysis was conducted which targeted national clinical guidelines, quality standards, quality indicators, and audits in England (chapter 4).

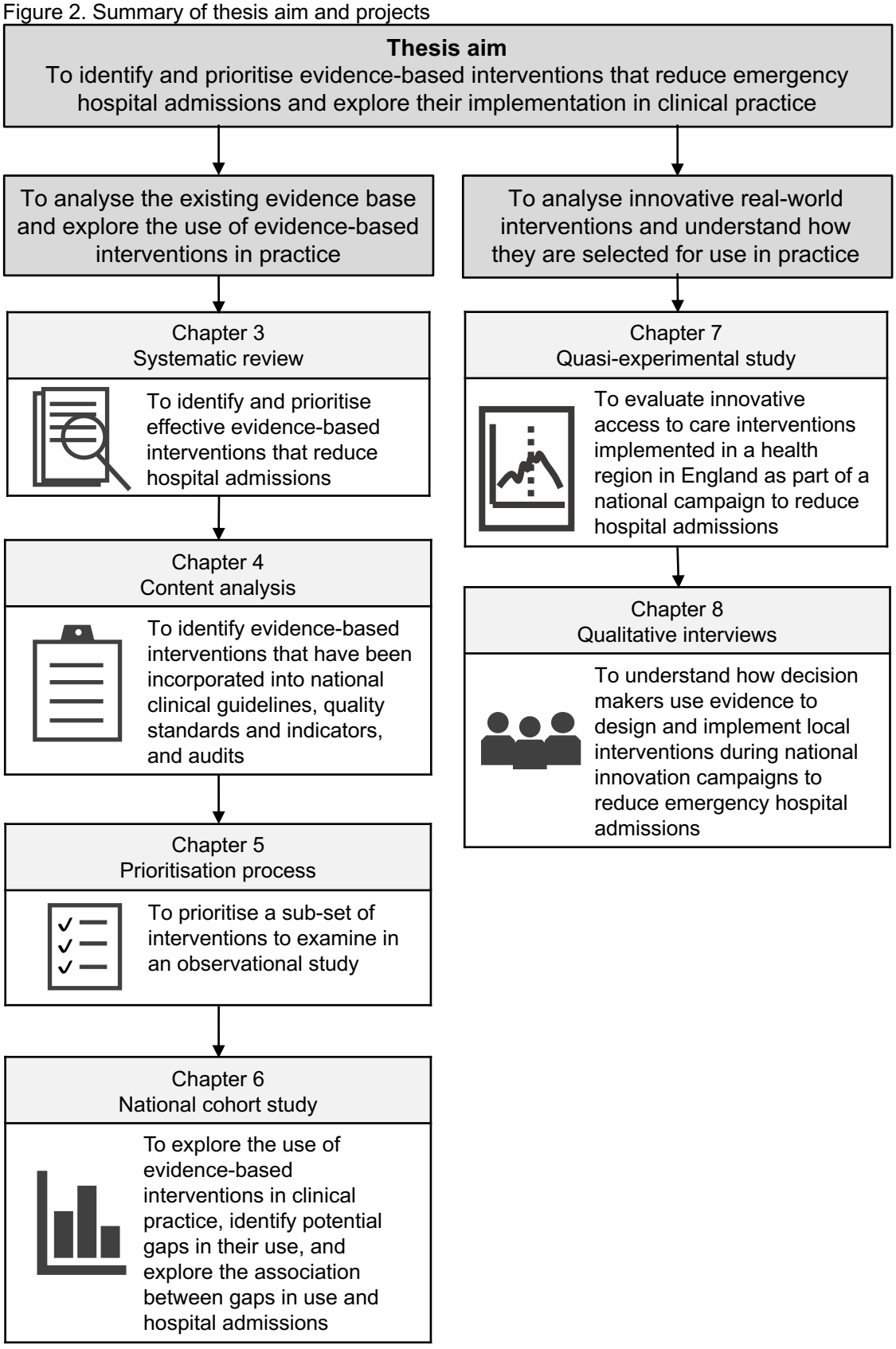
3) **It was unclear whether evidence- and guideline-based interventions that reduce emergency hospital admissions were being optimally utilised in clinical practice.** Chapter 3 and chapter 4 produced a list of evidence- and guideline-based interventions that reduce EHA. However, it was unclear whether these interventions were being optimally utilised in practice. Therefore,

utilisation of the interventions in clinical practice was explored. This required two steps. Firstly, a prioritisation process was conducted to select a set of interventions to investigate in-depth (chapter 5). Secondly, a national database study was conducted to describe utilisation of the prioritised interventions in UK primary care and to explore associations between utilisation of the interventions and emergency hospital admissions (chapter 6).

4) **There was a need to assess real-world interventions designed to reduce EHA and to build the evidence base for access to care interventions.** Although previous systematic reviews had been limited in scope, they did identify a lack of evidence for access to care interventions. This gap was echoed nationally in reports that called on researchers to build the evidence base by evaluating novel interventions. Therefore, a quasi-experimental study was conducted to evaluate an access to care initiative implemented in a health region in England (chapter 7). The initiative was implemented as part of the Prime Minister's GP Access Challenge, a national campaign to increase access to primary care and reduce EHA.

5) **The use of evidence by local decision makers during national campaigns to reduce EHA was unclear.** The Prime Minister's GP Access Challenge, evaluated in chapter 7, was a national innovation campaign to increase access to primary care and reduce hospital admissions with interventions designed and implemented by local stakeholders. These types of innovation challenges were becoming more common in UK however, it was unclear how local decision makers used evidence to design and implement interventions and whether they felt had sufficient evidence to inform action. Therefore, interviews were conducted with decision makers involved in the Challenge to better understand this process and to derive lessons for future initiatives.

Figure 2. Summary of thesis aim and projects



2.9 Chapter summary

- The UK has experienced large increases in EHA over the past 20 years
- Reducing EHA rates is a national health priority for the UK, as well as in other health systems, primarily due to the high cost of acute hospital care
- There is geographic variation in admission rates and a large burden of admissions for ambulatory care sensitive conditions, both of which suggest potential for reducing admission rates
- Policy and practice initiatives to reduce admissions have not been successful; have been limited by a lack of robust evidence for effective interventions; and have focused primarily on health care organisation, access, and delivery
- The existing evidence-base has not been adequately reviewed; previous research on interventions to reduce admissions have focused on a narrow array of interventions and patients, resulting in uncertainty about which interventions should be priorities for implementation or quality improvement
- It is unclear which 'best-practice' clinical activities could be optimised to reduce admission rates
- There is a need evaluate and better understand real-world interventions being implemented to reduce EHA

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Chapter 2. Appendix

Appendix 2.1 Literature search terms 56

Appendix 2.1 Literature search terms

Table 1. Structured search terms used in literature search

#1	“emergency hospital admissions” OR “unplanned hospital admissions” OR “unscheduled hospital admissions” OR “avoidable admissions” OR “preventable admissions”
#2	Australia OR Austria OR Belgium OR Canada OR Chile OR Czech Republic OR Denmark OR Estonia OR Finland OR France OR Germany OR Greece OR Hungary OR Iceland OR Ireland OR Israel OR Italy OR Japan OR Korea OR Latvia OR Luxembourg OR Mexico OR Netherlands OR New Zealand OR Norway OR Poland OR Portugal OR Slovak OR Republic Slovenia OR Spain OR Sweden OR Switzerland OR Turkey OR United Kingdom OR United States
#3	1 AND 2 AND 3

Chapter 3. Identifying and prioritising evidence-based interventions that reduce emergency hospital admissions: a systematic review of systematic reviews

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3.0 Chapter overview

This chapter reports a systematic review of systematic reviews to identify and prioritise interventions that reduce emergency hospital admissions. Overall, 306 systematic reviews were included, with an underlying evidence base of 1,667 unique randomised controlled trials that reported hospital admissions data for 1,031,163 patients. The quality of the evidence was assessed using GRADE criteria and used to prioritise interventions. There was moderate or high quality evidence for 30 medications; 22 health systems interventions; two diagnostic interventions; and two medical and surgical procedures. Most of the effective interventions were for ongoing community-based management of patients with major chronic diseases (e.g., heart failure), while a minority targeted non-disease specific populations (e.g., frequent health care users). Implications for practice, policy, and research are discussed.

3.1 Publication statement

The protocol for this study was published in BMJ Open.[1] Results for the medication interventions are published in BMC Medicine[2] and on the websites of the School for Primary Care Research[3,4], Oxford University Medical Sciences Division[5], Nuffield Department of Primary Care Health Sciences[6], and Oxford Centre for Evidence-Based Medicine.[7]

3.2 Introduction

3.2.1 The need to identify evidence-based interventions

Reducing emergency hospital admissions has become vital for health systems around the word in order to alleviate pressure on emergency care services, ensure the sustainability and quality of health care, and minimise patient burden.[8–11] In the UK, many national and local initiatives have been implemented to address rising admission rates.[12–14] However, most initiatives have failed. As described in chapter 2, the lack of effective evidence-based interventions to inform initiatives has been a key limitation of efforts to reduce admissions.[15–22]

Given that admission rates are increasing across all types of patients, there is a need to identify evidence-based interventions that are effective across patient groups. There is also a need to compare and contrast interventions designed for specific types of patients (e.g., diabetes patients) so that decision-makers can allocate scarce resources to those that are most effective.

3.2.2 Gaps in previous systematic review research

There have been attempts to review the evidence base to identify interventions that reduce hospital admissions. However, these reviews have been limited in scope.

Firstly, previous reviews have excluded relevant interventions. For example. Purdy et al. conducted a systematic review of interventions to reduce unplanned hospital admissions but excluded medications, surgery, and medical procedures.[17]
Although these types of interventions may not be utilised for the sole purpose of reducing hospital admissions, they may represent high-value activities in the overall care of patients that should be promoted in clinical practice. Therefore, systematically reviewing evidence for these types of interventions could inform efforts to optimise clinical care and reduce admissions.

Secondly, previous reviews have excluded patients with mental health issues.[23,24] This is problematic given the high burden of mental illness among users of emergency care. In 2013/14 in England, patient with mental health issues had 4.9 times more emergency admissions than people without mental health issues and 3.6 times more potentially avoidable emergency admissions. Although only one-fifth

of emergency admissions among these patients are directly for mental health issues, evidence of unwarranted variation in EHA rates suggests that many of these could be avoided.[25] These data highlight the importance of better understanding approaches to reducing admissions among people with mental illness and, therefore, a need to review the evidence for this group.

Thirdly, previous reviews have not robustly assessed the quality of evidence, which introduces uncertainty in any effects that are identified. Reviews have used the Cochrane risk of bias tool or JADAD scale to assess randomised controlled trials and the New Castle Ottawa Scale to assess observational studies.[23,26] While these assessments are valuable, additional relevant criteria should be considered in the effort to prioritise interventions for implementation or optimisation in practice, including the precision and consistency of estimates, presence of publication bias, and adequacy of the sample size and power. These criteria are recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) group and have been adopted by the Cochrane Collaboration.[27,28]

3.2.3 The need for a systematic review of systematic reviews

To address gaps in the literature a broad systematic review was needed without restriction by type of intervention or patient.

Given the prominence of hospital admissions as an end-point in health research, it was anticipated there would be a large evidence base to consider including many systematic reviews with meta-analysis of RCTs, which are considered the highest quality evidence for questions about intervention effectiveness.[29] Therefore, to balance feasibility, comprehensiveness, and robustness, a systematic review of systematic reviews was conducted.

Systematic reviews of systematic reviews, also known as umbrella reviews or overviews of reviews, are considered an ideal approach to map large evidence bases; to compare the estimates of effectiveness of different interventions in different populations for the same outcome; and to identify limitations in the methodology and quality of existing systematic reviews to inform future research.[30,31]

3.3 Aim and objectives

3.3.1 Aim

The aim of this chapter was to identify and prioritise evidence-based interventions that reduce emergency hospital admissions in adults.

3.3.2 Objectives

To achieve the aim, the objectives of this chapter were to:

A. Identify systematic reviews of randomised controlled trials that report emergency hospital admission outcomes
B. Describe the patient populations and interventions
C. Assess the quality of the evidence
D. Prioritise effective interventions based on the strength of their evidence

3.4 Methods

3.4.1 Protocol, registration, reporting

The methods for this systematic review were based on the Cochrane Handbook of Systematic Reviews of Interventions.[32] The protocol was registered (PROSPERO: CRD42014014779)[33] and published (Appendix 3.1).[1] The study was reported in accordance with PRISMA guidance.[34]

3.4.2 Key definitions

Emergency hospital admissions were defined as "an unanticipated admission to hospital as an in-patient which occurs at short notice because of a perceived need for immediate health care. These admissions are acute, are not scheduled or planned in advance, and do not occur solely for the purpose of elective care".[35] This included emergency readmissions to hospital after an index admission. Admission to an emergency department or an observational unit were not considered to be a hospital admission.

A systematic review was defined as "an attempt to identify, appraise, and synthesise all the empirical evidence that met clearly specified eligibility criteria to answer a given research question."[36]

An health intervention was defined as “an act performed for, with or on behalf of a person or a population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions.”[37]

3.4.3 Study inclusion criteria

Study inclusion criteria are described in Table 1.

Table 1. Study inclusion criteria

Characteristics of the study	Criteria for inclusion[a]
Population	• Adults (16 years of age or older)
Intervention	• Any intervention meeting the definition in section 3.4.2
Comparator	• Any
Outcome	• Reviews reporting emergency hospital admissions as an outcome defined in section 3.4.2 • Reviews reporting at least one meta-analysed effect estimate for emergency hospital admissions that was not part of a composite outcome • Outcomes for adults were reported separately from paediatric patients or the mean age of patients in the study was over 16 • Outcomes from RCTs were reported separately from observational studies
Study design	• The study was a systematic review of randomised controlled trials as defined in section 3.4.2 • The review searched two or more electronic databases[b] • The review assessed and reported the quality of included studies[b]
Other	• The review was published in English

[a] Studies had to meet all the criteria to be included. [b]Criteria derived from the AMSTAR tool.

Two elements of the Assessment of Multiple Systematic Reviews tool (AMSTAR) were used as inclusion criteria to ensure that reviews were ‘systematic’ and met a minimum level of methodological rigour: (1) the review searched two or more electronic database and (2) the quality of included studies was assessed and reported. Authors of other umbrella reviews have used similar quality criteria.[38,39]

Reviews were only included if they reported results from pooled analysis of emergency hospital admissions from two or more RCTs. This criterion was used to target interventions that had a fairly robust evidence base, having been assessed in multiple RCTs similar enough to warrant meta-analysis, and to protect against spurious findings (type 1 error) and bias in single RCTs.[40]

3.4.4 Study exclusion criteria

Study exclusion criteria are described in Table 2.

Table 2. Study exclusion criteria

Characteristics of the study	Criteria for exclusion
Population	• Children (less than 16 years of age)
Intervention	• Any intervention not meeting the definition in section 3.4.2
Comparator	• N/A
Outcome	• Studies reporting only scheduled or elective hospital admissions as defined in section 3.4.2 • Reviews reporting emergency admission outcomes from a single RCT • Outcomes for adults and paediatrics patients were combined and could not be separated or the mean age of patients was less than 16 years of age • Outcomes for RCTs and other study types were combined and could not be separated
Study design	• The study did not meet the definition for a systematic review of randomised controlled trials as defined in section 3.4.2 • The review searched only one electronic database • The review did not assess or report the quality of its included studies
Other	• Superseded (i.e., outdated) Cochrane reviews • Superseded (i.e., outdated) non-Cochrane reviews, defined as reviews whose RCT data was reported in a more recent review • Reviews not published in English

Reviews reporting single RCTs were excluded as these may be more prone to spurious findings (type 1 error), bias, and there is no chance the results could have been replicated or refuted, all of which decrease confidence in the results.[40]

Reviews were excluded if all the RCT data on hospital admissions were included in a more recent review of the same intervention and patients. When two reviews reported identical clinical trials data, the review with the higher AMSTAR score was selected as this score broadly indicates more robust review methods and detailed reporting of information.

3.4.5 Search strategy

MEDLINE (OvidSP); PubMed; the Cochrane Database of Systematic Reviews & Database of Abstracts of Reviews of Effects; Google Scholar; and the websites of ten major funding agencies and health charities were searched using broad search criteria from inception to February 2016. In preparing peer-reviewed manuscripts for submission to academic journals, the results of this review were split into medication and non-medication interventions (described below). The manuscript on non-medication interventions was submitted more recently and, therefore, the searches needed to be updated to May 2017. These updated results are included in this chapter. Experts in emergency admissions were contacted and references lists of included reviews were examined to identify additional studies. Details of the search can be found in Appendix 3.2.

3.4.6 Study selection

Two authors (the thesis author and one of IO or BF) independently and in-duplicate screened eligible studies in two rounds. Firstly, titles and abstracts were screened for inclusion in full text review. Secondly, full-text articles were obtained and screened for final inclusion. Discrepancies in article inclusion in both rounds were resolved by discussion.

3.4.7 Data extraction

Two authors independently and in-duplicate extracted information on salient characteristics of the reviews (the thesis author and one of IO, BF, DC, AT, JL, RF, DN, BS, JO, OH, BN, SS). Information on specific treatment comparisons in the reviews was extracted by the thesis author and verified by a second (IO, BF, DC, AT, JL, RF, DN, BS, JO, OH, BN, or SS). Discrepancies in extracted information or quality assessment scores were resolved by discussion. All reviews and each extracted treatment comparison were assigned a unique identifying number (e.g. review: #1; comparisons: 1a, 1b, 1c).

3.4.8 Mapping of underlying RCT evidence and exclusion of duplicate data

In order to limit the effect of duplicated trial evidence reported by multiple reviews, the thesis author extracted information about the underlying randomised controlled trials reported by the reviews. This data was verified by a second reviewer (IO, BF, DC, AT, JL, RF, DN, BS, JO, OH, BN, or SS). The extracted information included: the RCT publication reference; name or acronym for the RCT; RCT first author name; publication year; sample size; and whether data on hospital admissions were reported. Reviews reporting the same trial evidence were flagged. This trial database was used to de-duplicate overlapping systematic reviews and obtain a count of unique trials.

3.4.9 Classification of patients

In the included reviews, populations were reported using heterogeneous terminology. Therefore, to facilitate analysis, reporting, and interpretation, published frameworks were used to classify patients. Patient populations were categorised using the World Health Organization's International Statistical Classification of Diseases and Related Health Problems 10th Revision (WHO ICD 10).[41] Categorisations were completed by one author (NB) and verified by a second (IO, BF, DC, AT, JL, RF, DN, BS, JO, OH, BN, or SS).

Multi-morbid and co-morbid populations were defined as those with two or more codes at the ICD-10 summary chapter level (i.e., patients with coronary heart disease and depression coded as "Diseases of the circulatory system and Mental and behavioural disorders") or two or more codes within a disease group at the three-character block level (i.e., patients with heart failure and previous myocardial infarction coded as "Other forms of heart failure and Ischaemic heart diseases").

Mixed populations were defined as those with no defined disease group (i.e. elderly people) and those where two or more broad disease groups were included, as defined by the ICD-10 summary chapter level (i.e., heart failure or diabetes patients coded as "Disease of the Circulatory System or Endocrine, nutritional and metabolic diseases").

Chronic diseases were identified using the definition provided by the NHS data dictionary “a health problem that requires ongoing management over a period of years or decades, that cannot currently be cured, but that can be controlled with the use of medication and/or other therapies.”[42] Admissions for ambulatory care sensitive conditions were identified using the list of ACSC used in the NHS (Appendix 3.3).[26]

The disease definitions and thresholds provided in the reviews were used for example, the cut-off for reduced ejection fraction in heart failure (e.g., 45%).

3.4.10 Classification of interventions

To facilitate analysis, reporting, and interpretation, published frameworks were used to classify interventions. However, given the broad scope of interventions in this review, categorising the interventions with a single framework proved difficult. Therefore, three frameworks were used, all of which coded the “action” or “active ingredient” of interventions:

A. Health systems interventions were classified using the Cochrane Effective Practice and Organisation of Care (EPOC) taxonomy of health systems interventions.[45] The EPOC taxonomy was well-suited to this study as it has been used in previous overviews of systematic reviews and to categorise evidence in electronic databases.[46–50] Several minor revisions were made to the EPOC taxonomy for the purpose of this review. Three sub-categories were added based on their likeness to existing sub-categories within the taxonomy. These revisions were undertaken by one reviewer (NB) and verified by a second (JL). The taxonomy is provided Appendix 3.4 with annotations detailing the revisions.

B. Medications were classified using the World Health Organisation International Anatomical Therapeutic Chemical (WHO ATC) classification system.[51] Interventions that met the following definition of a medication were coded using this framework: "a substance or combination of substances that was administered in or on a patient to treat, prevent or

diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action."[52]

C. Diagnostic, medical, and surgical interventions were classified using the "Action" Axis of the World Health Organisation International Classification of Health Interventions (WHO ICHI).[37] This framework was originally developed to categorise diagnostic, medical, and surgical interventions and, therefore, was well-suited for this purpose. Although the WHO ICHI has been expanded in an attempt to cover all interventions, it does not classify individual medications or medication classes. Furthermore, it provides limited granularity when classifying health systems interventions, in particular, for changing the delivery arrangements of a service. Therefore, it was not used to categorise those interventions.

3.4.11 Quality assessment of included reviews

The quality of systematic reviews was assessed using the Assessing Methodological Quality of Systematic Reviews (AMSTAR) tool.[53] One minor revision to the AMSTAR tool was made: for item two (was there duplicate study selection and data extraction?) reviews only scored 'yes' if data selection or extraction was done in duplicate. Assessments were completed by two authors independently and in-duplicate (NB and one of IO, BF, DC, AT, JL, RF, DN, BS, JO, OH, BN, SS).

3.4.12 Quality assessments of meta-analysed effect estimates using GRADE and prioritisation of interventions

Given the vastness of the evidence base, a key objective of this study was to identify a prioritised list of interventions that could be considered for implementation or optimisation in practice to alleviate the admissions crisis.

Interventions that significantly reduced hospital admissions and were supported by high or moderate quality GRADE ratings were added to the prioritised list. These GRADE levels were chosen as high or moderate quality effect estimates are unlikely to change if additional studies are conducted.[54,55]

To identify this list, Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group criteria were used to assess the quality of meta-analysed effect estimates showing statistically significant reductions in emergency hospital admissions.[54] Effect estimates showing significant increases in admissions were also assessed. It was thought this information could be used to guide de-adoption of harmful interventions in practice. Quality assessments were completed by the thesis author and verified by a second author (DN, DC, or DJ).

It was anticipated that assessing the quality of all sub-group analysis would not be feasible. Therefore, pre-specified criteria were developed to select sub-group estimates for quality assessment. Criteria were informed by guidance from the Cochrane Collaboration[36] and methods in other published overviews to prioritise effect estimates.[24,56–58]

The quality of sub-group effect estimates was assessed if the sub-group analysis was pre-specified by the review authors and met one or more of the following criteria:

A. the sub-group estimate was calculated to explain the presence of substantial heterogeneity in the summary estimate ($I^2 \geq 50\%$ or chi-square $P<0.1$)[36];
B. the sub-group estimate was calculated from a subset of trials at low risk of bias (as assessed by the original review authors);
C. the sub-group estimate showed a significant reduction or increase in hospital admissions, while the summary estimate found no effect.

To complete the GRADE assessments and to provide contextual and clinically relevant information to users of this review, additional data on the RCTs included in meta-analysis were collected from the reviews. The data extracted included: detailed descriptions of the intervention and comparator; countries in which the RCTs were conducted; length of follow-up; age of participants; and control group hospitalisation event rate.

Countries within the OECD have broadly similar health systems as the UK. Therefore, quality ratings for the “Directness of Evidence” domain were downgraded if the majority of trial evidence was produced in an non-OECD country.[59]

The control group hospitalisation event rate was used to assess optimal information size as part of the “Imprecision” domain.

A minimal important threshold in effect had to be defined in order to utilise the GRADE method, specifically, the imprecision domain.[54] At the time of analysis, there was no consensus on what defined a minimal important threshold for hospital admissions. The goal of this study was to manage rising rates of emergency hospital admissions, therefore, a threshold that would achieve this goal was selected; a 3% relative risk reduction. This threshold was equivalent to the population-adjusted average year-on-year increase in admissions in the UK from 2011 to 2016.[60,61] The UK is facing the worst emergency care crisis of any OECD country. If this study were able to identify interventions for every patient group that reduced admission rates by 3%, then implementation of these interventions would stop admissions increases in the UK. In countries where annual increases are less than 3%, which is most other OECD countries facing emergency care pressures, these interventions would operate to reduce the annual rate of admissions.

3.4.13 Consideration of outcomes other than hospital admissions

The primary purpose of this review was to identify interventions that significantly reduce hospital admissions and, therefore, could be considered for implementation or optimisation in practice to alleviate the admissions crisis. However, outcomes other than hospital admissions may be relevant when determining if use of an intervention is warranted. In particular, there may be harms associated with an intervention that may outweigh the benefits. Therefore, to provide users of this review with additional relevant information for decision-making, a summary of the overall balance of benefit to harm was offered for interventions that reduced hospital admissions.

Given the anticipated volume of included evidence, a feasible and efficient method was needed to summarise study results. Previously published umbrella reviews have use the conclusions section of included studies for this purpose.[24] Therefore, a similar method was used in this chapter.

The conclusions of included reviews were assessed and categorised using the framework presented in Table 3. The categorisations served to summarise of the overall balance of benefits to harms for interventions that reduced admissions. Categorisations were completed independently by two reviewers (NB and DJ) with discrepancies resolved by consensus and arbitration by a third author (JL) when needed.

Table 3. Framework used to categorise the overall balance of benefit to harm

Symbol to summarise categorisation	Criteria for categorising review conclusions
+ Positive	The authors recommend use of intervention or the review conclusions indicated that the overall potential benefits of the intervention outweighed the potential harms.
- Negative	The authors recommended against use or the intervention or the review conclusions indicated that the overall potential benefits of the intervention did not outweigh the potential harms.
? Unclear	The authors did not comment on the overall balance of potential benefit to harm, the authors indicated that more research was required before a recommendation regarding use of the intervention could be made, or the review conclusions indicated that the overall balance of potential benefit to harm was unclear.

3.4.14 Identifying conflicting evidence for prioritised interventions

As described in section 3.4.8, all RCT data on hospital admissions were mapped to help minimise the impact of duplicate evidence between reviews. As a result, each review contributed a unique set of RCT data. However, in a few instances, there were multiple effect estimates for the same interventions, controls, and patients from different reviews that were informed by slightly different sets of RCTs.

To increase confidence in the effect estimates for prioritised interventions (i.e. effect estimates showing significant reductions in admissions and rated as high or moderate quality evidence), all treatment comparisons were searched to identify conflicting effect estimates. Estimates for the same interventions, controls, and patients were compared. Estimates were deemed conflicting if they were based on unique sets of RCT data and the significance or direction of effect for hospital admissions varied (i.e., significant effect vs. no significant effect, significant decrease vs. significant increase).

3.4.15 Quantitative data analysis

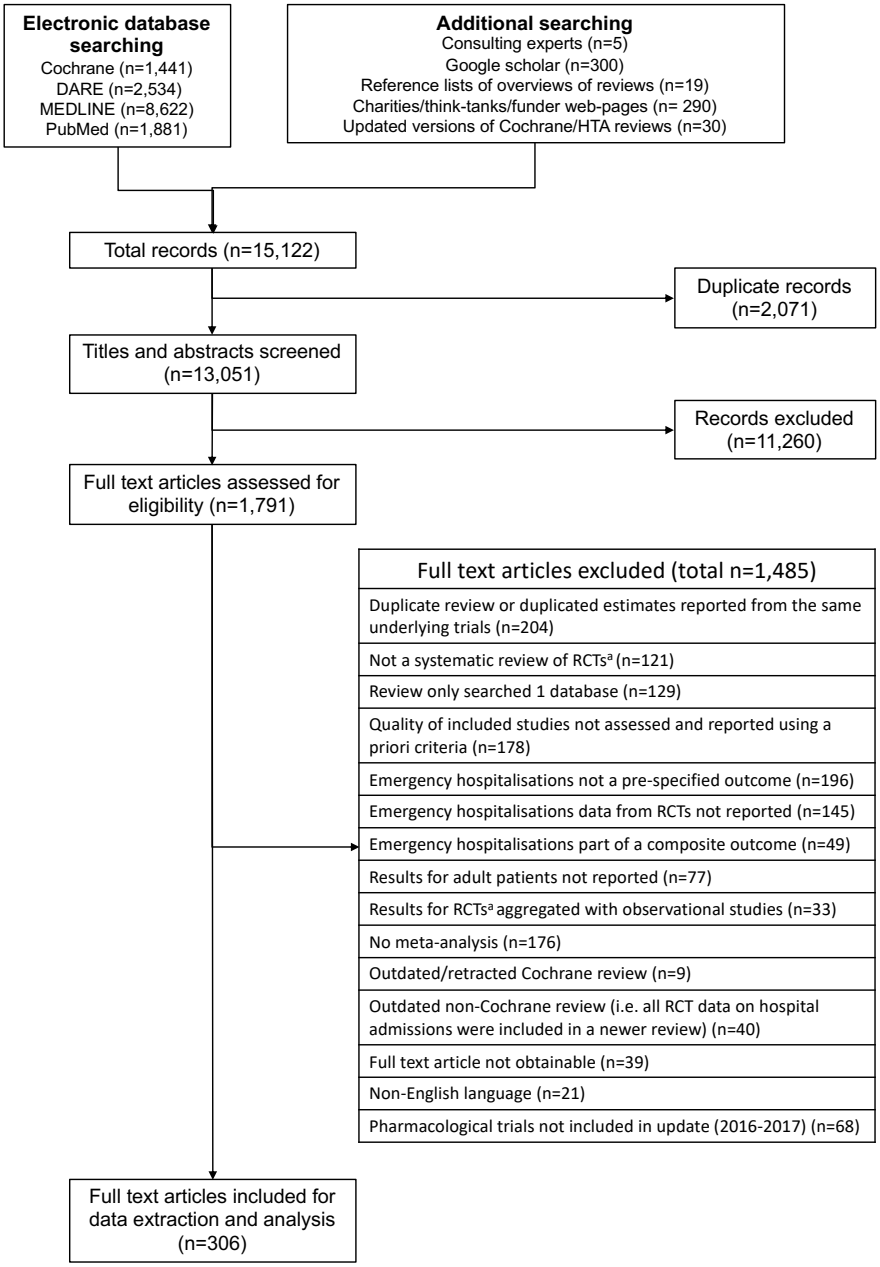
To facilitate interpretation and reporting, the number needed to be treated to avoid one hospitalisation and the number needed to treat to cause one hospitalisation were calculated from risk ratios, odds ratios, and hazard ratios. Calculations are provided in Appendix 3.5.[62–65] For each estimate, the median control group event rate was calculated from the RCTs in the meta-analysis.[1,63–66] When data on event rates were unclear or not reported by the review authors, the original RCTs were accessed to obtain this information. Follow-up times were standardised into months. One month was classified as 30.4 days. STATA 14[67] and R software packages[68] were used for quantitative data analysis.

3.5 Results

3.5.1 Results of study screening and selection

Overall, 13,051 titles and abstracts and 1,791 full text articles were screened (Figure 1). After screening, 306 systematic reviews met the inclusion criteria. The references for included reviews are reported in Appendix 3.6.

Figure 1. PRISMA flow diagram of study selection



[a]Randomised controlled trial. [b]Individual RCTs were defined "adult" if they had inclusion criteria of 16 years of age or older for participants. We considered results from meta-analysis as "adult" if the included participants' mean age was 18 years of age or older across all included trials.

3.5.2 Characteristics of included reviews

Table 4 summarises the characteristics of the 306 included reviews. The characteristics of individual reviews are presented in Appendix 3.7. Detailed definitions of populations, interventions, and comparators for each review are available in an online database that can be accessed by contacting the thesis author. This information will be hosted on a publicly accessible website after all academic manuscripts from this study are published.

Size of the evidence base

The 306 reviews included an underlying evidence base of 3,831 unique RCTs (1,576,423 patients), of which 1,667 RCTs reported hospital admission outcomes for 1,031,163 patients.

Summary of interventions reported in reviews

Overall, the reviews reported treatment comparisons for 188 unique interventions: 105 medications; 63 health systems intervention; 20 diagnostic, medical, and surgical interventions. The majority of reviews reported medications interventions (143 reviews, 47%) or health systems interventions (121 reviews, 40%) while a minority reported on diagnostic, medical, and surgical interventions (42 reviews, 14%). The distribution of review evidence by type of intervention is described in Appendix 3.8.

Summary of patient populations reported in reviews

The reviews examined interventions for 93 unique patient populations. Interventions for patients with chronic diseases were examined in 225 reviews (74%). Much of the evidence was for patients with circulatory diseases (90 reviews, 29%), respiratory diseases (85 reviews, 28%), patients in-contact with health services for example, patients being discharged from hospital (53 reviews, 17%), mental and behavioural disorders (29 reviews, 9%). The five most common conditions were heart failure (59 reviews, 19%), chronic obstructive pulmonary disease (37 reviews, 12%), chronic asthma (22 reviews, 7%), acute exacerbations of asthma (20 reviews, 7%), and schizophrenia and other types of schizophrenia-like psychoses (16 reviews, 5%). The distribution of review evidence by patient population is described in Appendix 3.8.

Table 4. Characteristics of included systematic reviews and the randomised controlled trial data captured within reviews

Characteristic	Reviews n (%)
Review level information (n = 306)	
Unique interventions investigated within reviews[a]	188
Types of interventions	
Reviews reporting medication interventions	143 (47%)
Reviews reporting health systems interventions	121 (40%)
Reviews reporting diagnostic, medical, and surgical interventions	42 (14%)
Unique patient populations investigated within reviews[b]	93
Reviews including patients with chronic diseases	225 (74%)
Patient populations[c]	
Diseases of the circulatory system	90 (29%)
Diseases of the respiratory system	85 (28%)
Factors influencing health status and contact with health services[d]	53 (17%)
Mental and behavioural disorders	29 (9%)
Mixed patient populations	16 (5%)
Multi-morbidity	11 (4%)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	6 (2%)
Diseases of the digestive system	5 (2%)
Diseases of the genitourinary system	5 (2%)
Pregnancy, childbirth and the puerperium	5 (2%)
Endocrine, nutritional and metabolic diseases	5 (2%)
Other[e]	6 (2%)
Hospital admission was a primary outcome	122 (40%)
Reviews reporting hospital admissions for ambulatory care sensitive conditions	101 (33%)
Reviews reporting pooled effect estimates showing significant reductions in hospital admissions	151 (49%)
AMSTAR[f] score for review quality, mean (SD)[g]	8 (2)
Review year of publication	
2010-2017	215 (70%)
2000-2009	85 (28%)
1991-1999	6 (2%)
Cochrane reviews	107 (35%)
Randomised controlled trial (RCT) information	
Number of unique RCTs	3,831
Number of unique patients	1,576,423
Number of unique RCTs reporting admissions data	1,667
Number of unique patients with admissions data	1,031,163
Number of patients per RCT reporting hospital admission outcomes, median (IQR)	158 (74 to 410)
Number of treatment comparisons reporting hospital admission outcomes	1,431

[a]Unique at the level of chemical sub-group in the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification system and the third level sub-category in the Cochrane Effective Practice and Organisation of Care (EPOC) Health Systems Taxonomy. When the WHO International Classification of Health Interventions was used, uniqueness of intervention was determined by comparing intervention descriptions provided by the review authors. [b]Unique at the four-character sub-category level using the WHO 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10). [c]These specific classifications represent the summary chapter level of coding in the ICD 10. The numbers do not add up to 306 because some reviews reported treatment comparisons for multiple, distinct populations. [d]For example, patients receiving day surgery. [e]Neoplasms (n=2, <1%); Diseases of the nervous system (n=2, <1%); Infectious and parasitic diseases (n=1, <1%); and Diseases of the musculoskeletal system and connective tissue (n=1, <1%) [f]Measurement Tool to Assess Systematic Reviews. [g]Standard deviation.

Summary of hospital admissions data reported in reviews

Hospital admissions were a primary outcome in 122 of the reviews (40%); 151 reviews (49%) reported significantly fewer hospital admissions in intervention arms compared with control arms, while a small minority (14 reviews, 5%) reported significant increases as a result of the intervention. Hospital admissions for ambulatory care sensitive conditions were reported in 101 reviews (33%).

Quality of included reviews

The mean AMSTAR score for review quality was 8 (SD=2) (Table 4). Review quality was most often downgraded because the review authors did not state their potential conflicts of interest (AMSTAR criterion 11). Full results of AMSTAR quality assessments for each review are included in Appendix 3.9.

3.5.3 Description of treatment comparisons extracted from reviews

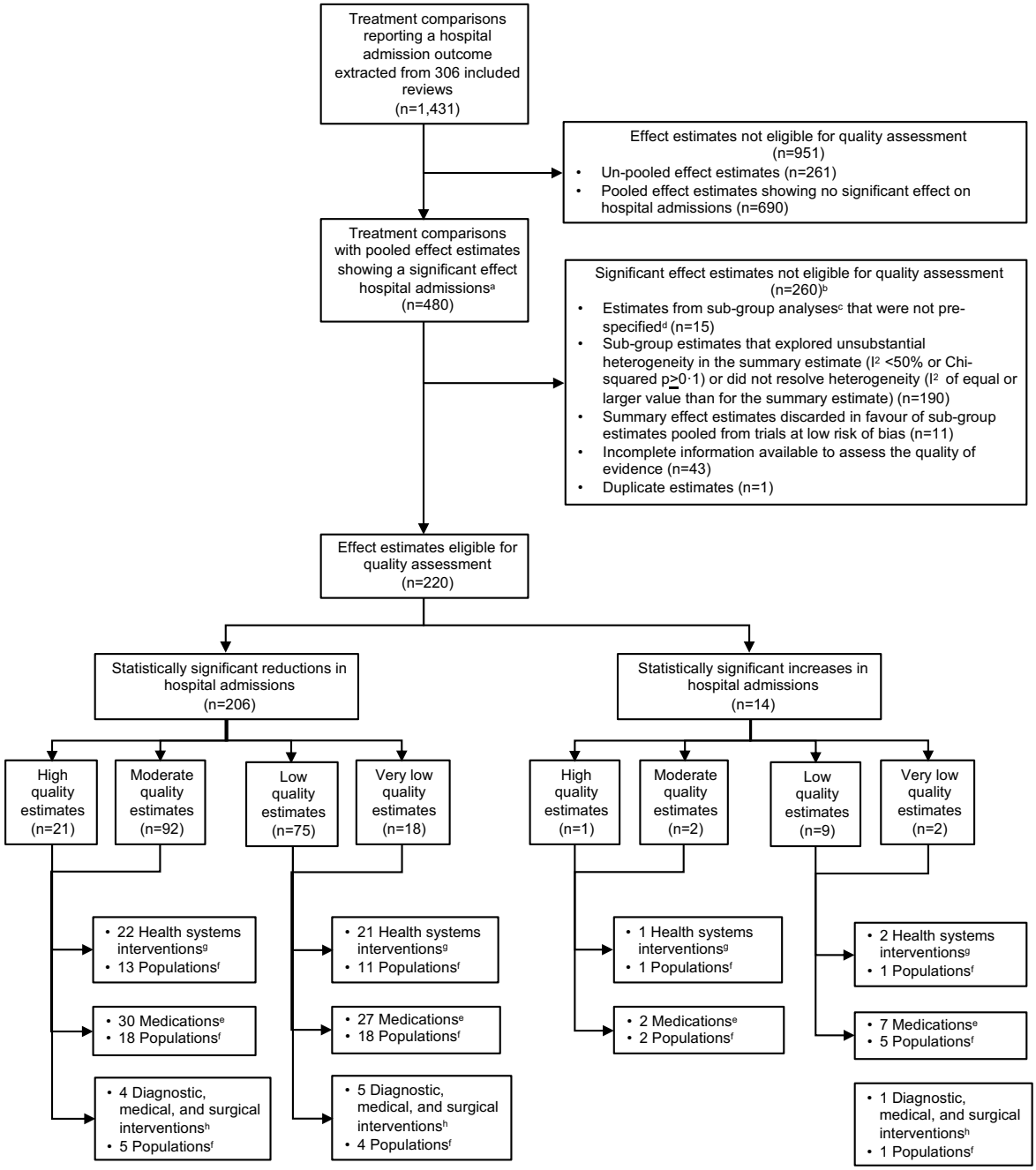
Overall, 1,431 treatment comparisons that reported hospital admission outcomes were extracted (Figure 2). A summary of the characteristics of the treatment comparisons are reported in Table 5. All 1,431 individual treatment comparisons are available in an online database that readers can access by contacting the thesis author. This information will be hosted on a publicly accessible website once all academic manuscripts from this study are published.

Table 5. Characteristics of treatment comparisons reporting hospital admission outcomes

Characteristic	Treatment Comparisons n=1,431 (%)
Effect estimates pooled from two or more RCTs[a]	1,170 (82%)
Significant reduction in hospital admissions	450 (32%)
Significant increase in hospital admissions	30 (2%)
No significant effect on hospital admissions	690 (48%)
Type of hospital admission outcomes reported	
Cause-specific hospital admission	473 (33%)
All-cause hospital admission or cause not specified	958 (67%)
Admissions for ambulatory care sensitive conditions	412 (29%)
Type of comparison	
Inactive control (placebo, standard care, no treatment)	1,060 (74%)
Active control	286 (20%)
Inactive control or active control	85 (6%)
Type of effect estimate reported	
Risk ratio or odds ratio	1,237 (86%)
Other	194 (14%)
Comparison was a sub-group or sensitivity analyses	819 (57%)
Median number of RCTs per comparison (range)	3 (1 to 184)
Median number of patients per comparison (range)	949 (333 to 88,367)

[a]Statistically significant defined as $p<0.05$ or a confidence interval that did not cross the null value. We also accepted review authors narrative description of statistically significant if thresholds were not described.

Figure 2. Flow diagram of the process to identify interventions supported by high or moderate quality evidence



[a]Statistically significant at the p<0.05 level. [b]Estimates were for sub-group estimates that did not meet our criteria for quality assessment. [c]Sub-group or sensitivity analysis as defined by authors. [d]Pre-specified in the methods section of the review article. [e]Unique at the level of chemical sub-group in the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification system. [f]Unique at the 3-character coding level using the World Health Organisation's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10). [g]Unique at the third level sub-category in the Cochrane Effective Practice and Organisation of Care (EPOC) Health Systems Taxonomy. [h]When the World Health Organisation International Classification of Health Interventions was used, uniqueness of intervention was determined by comparing intervention descriptions provided by the review authors.

3.5.4 Meta-analysed effect estimates and GRADE quality assessments

Of the 1,431 treatment comparisons, 480 had pooled effect estimates showing a statistically significant effect (decrease or increase) on hospital admissions. Of these, 220 estimates were eligible for assessment using GRADE criteria (Figure 2).

Summaries of the evidence for GRADED effect estimates showing a statistically significant reduction in emergency hospital admissions are presented in Appendix 3.10 (medications), Appendix 3.11 (health systems interventions), and Appendix 3.12 (diagnostic, medical, and surgical interventions).

The tables in Appendices 3.10 to 3.12 are organised alphabetically by ICD-10 disease codes. The evidence includes summaries of the interventions and comparators; median event rates for the intervention group and control group; mean ages of patients; mean follow-up durations; the numbers needed to treat; GRADE ratings; conclusions from the review; assessments of the overall balance of benefit to harm; and descriptions of contradictory evidence from other reviews in the study.

Summaries of the GRADE quality assessments for each estimate are presented in Appendix 3.14. Detailed descriptions of downgrading decisions for each estimate are located in Appendices 3.15 to 3.19. Information on the RCTs underpinning the effect estimates is available in an online database that readers can access by contacting the thesis author. This information will be hosted on a publicly accessible website once all academic manuscripts from this study are published.

3.5.5 Prioritised interventions that reduce emergency hospital admissions

High or moderate quality evidence was identified in 108 treatment comparisons. These comparisons contained 56 unique interventions that significantly reduced hospital admissions in 31 patient populations. These prioritised interventions for reducing emergency hospital admissions are listed in Table 6 (medications), Table 8 (health systems interventions), and Table 10 (diagnostic, medical, and surgical interventions). Summaries of the effect estimates and evidence underpinning these interventions are provided in Table 7 (medications), Table 9 (health systems interventions) and Table 11 (diagnostic, medical, and surgical interventions).

Detailed information on the effect estimates and evidence is presented in Appendix 3.10 (medications), Appendix 3.11 (health systems interventions), and Appendix 3.12 (diagnostic, medical, and surgical interventions).

Results for these prioritised interventions are presented in the next three sections.

Prioritised medications that reduce emergency hospital admissions

High or moderate evidence was identified for unique 30 medications that significantly reduced hospital admissions in 18 patient populations (Table 6, Table 7). The majority of medications (n=22/30) reduced admissions from out-patient, day procedure, or community settings for patients with chronic respiratory diseases (i.e., COPD) and circulatory diseases (i.e., heart failure, chronic ischaemic heart disease). However, there were also four medications utilised in the emergency department that reduced admissions for patients with acute asthma and four medications used in hospital or after discharge to prevent readmissions in patients with heart failure, schizophrenia, or malnourishment. A positive overall balance of benefit to harm was reported for 21 of the 30 interventions. Review authors reported against the use of only one intervention: dual use of angiotensin-converting enzyme inhibitors and angiotensin-ll receptor blockers in patients with heart failure.

There was one instance of conflicting effect estimates from multiple reviews:

- There was contradictory evidence for oral nutritional supplements in patients discharged from hospital with malnourishment suggesting that the intervention is not effective in elderly patients.

Table 6. Summary list of medications with high or moderate quality evidence that significantly reduce emergency hospital admissions

Population[a]	Medications
Reduces hospital admissions from the emergency department	
Asthma (acute exacerbation)	• Beta-2-agonists and anticholinergics • Early use of inhaled corticosteroids in the ED • Magnesium sulfate
Reduces hospital admissions from out-patient, day procedure, or community settings	
Chronic obstructive pulmonary disease	• Aclidinium bromide • Long-acting beta-2 agonists • Mucolytics • Tiotropium
Chronic ischaemic heart disease	• Angiotensin-converting enzyme inhibitors • Intensive statin therapy
Chronic ischaemic heart disease or Heart failure	• Aldosterone antagonists
Crohn's disease or ulcerative colitis	• Infliximab
Heart failure with reduced left ejection fraction or left ventricular dysfunction	• Aldosterone antagonists • ACE-inhibitors, ARB, combined therapy • Beta-blocker • Digoxin • Intravenous iron • Lipophilic statins
Heart failure and iron deficiency	• Erythropoiesis stimulating agent • Intravenous iron
Hepatic encephalopathy	• Probiotics
Human immunodeficiency virus	• Cotrimoxazole
High risk of cardiovascular events	• Angiotensin-converting enzyme inhibitors
Long term hemodialysis	• Topical prophylactic antibiotics
Multiple sclerosis	• Glatiramer acetate
Normal or high-risk pregnancy	• Magnesium supplementation
Prostate biopsy	• Antibiotics
Schizophrenia	• Second generation antipsychotics
Ulcerative colitis	• Tumor necrosis factor antagonists
Reduces readmissions after an index hospital admission	
Discharged from the hospital malnourished	• Oral nutritional supplements
Heart failure	• Hypertonic saline and furosemide
Schizophrenia	• Antipsychotic maintenance therapy • Second generation antipsychotics

[a]Based on the 3-character coding level using the World Health Organisation's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10). Abbreviations: ED= Emergency Department; ACE= Angiotensin converting enzyme inhibitors; ARB= Angiotensin-II receptor blockers.

Table 7. Medications with high or moderate quality evidence that reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces hospital admissions from the emergency department										
Rodrigo, 2005, 6568a	Asthma (acute exacerbation)	Beta-2-agonists and anticholinergics (19 per 100)	Beta-2-agonists (27 per 100)	1,556 (9)	Range 18 to 55	Admission (ED visit duration)	RR: 0.68 (0.53 to 0.86) NNT: 11 (8 to 26) I^2: 14%	Moderate	No	+
Edmonds, 2012, 2159		Early use of inhaled corticosteroids in the ED (11 per 100)	Placebo (26 per 100)	377 (5)	38 ±8	Admission (Unclear)	OR: 0.35 (0.20 to 0.60) NNT: 7 (5 to 12) I^2: 0%	Moderate	No	?
Kew, 2014, 4002h		Intravenous magnesium sulfate (27 per 100)	Placebo (34 per 100)	1,437 (8)	Unclear	Admission (3 ±1 hours)	OR: 0.72 (0.57 to 0.91) NNT: 14 (9 to 48) I^2: 35%	High	No	+
Shan, 2013, 7029b		Nebulized magnesium sulfate (12 per 100)	Control (18 per 100)	383 (6)	Range 18 to 65	Admission for asthma (ED visit duration)	RR: 0.63 (0.43 to 0.92) NNT: 15 (10 to 68) I^2: 0%	Moderate	No	+
Reduces hospital admissions from out-patient, day procedure, or community settings										
Danchin, 2006, 1752a	Chronic ischaemic heart disease	ACE inhibitor (2 per 100)	Placebo (3 per 100)	31,750 (5)	62 ±3	Admission for heart failure (50 ±15 months)	OR: 0.76 (0.66 to 0.88) NNT: 146 (103 to 294) I^2: Unclear	Moderate	No	+
Saha , 2007, 6746b		Tissue ACE inhibitor (2.5 per 100)	Placebo (3.2 per 100)	29,805 (4)	63 ±3	Admission for heart failure (12 months)	RR: 0.78 (0.67 to 0.9) NNT: 140 (93 to 308) I^2: Unclear	High	No	+
Afilalo, 2007, 100c		Intensive statin therapy (2 per 100)	Moderate statin therapy (3 per 100)	27,547 (4)	61 ±2	Admission for heart failure (41 ±20 months)	OR: 0.72 (0.62 to 0.83) NNT: 115 (84 to 189) I^2: 4%	Moderate	No	+
Costa, 2013, 1629a	Crohn disease or ulcerative colitis	Infliximab (19 per 100)	Placebo (31 per 100)	1,736 (2)	38 ±2	Admission (17 ±13 months)	OR: 0.51 (0.4 to 0.65) NNT: 8 (6 to 12) I^2: 0%	Moderate	No	+
Ziff, 2015, 8931a	Heart failure, any ejection fraction	Digoxin (63 per 100)	Placebo (67 per 100)	7,788 (2)	65 ±2	Admission (37 months)	RR: 0.94 (0.9 to 0.99) NNT: 25 (15 to 150) I^2: Unclear	Moderate	No	+
Le, 2016, 8817a	Heart failure with prior MI	Aldosterone antagonists (20 per 100)	Placebo (21 per 100)	15,786 (13)	63 ±6	Admission (15 ±10 months)	RR: 0.93 (0.88 to 0.98) NNT: 67 (39 to 233) I^2: 35%	Moderate	No	+

Table 7 continued. Medications with high or moderate quality evidence that reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces hospital admissions from out-patient, day procedure, or community settings										
Jank-owska, 2016, 8790a	Heart failure with reduced left ventricular ejection fraction and iron deficiency or anemia	Intravenous iron (6 per 100)	Placebo (20 per 100)	835 (4)	69 ±5	Admission for heart failure (7 ±5 months)	OR: 0.28 (0.16 to 0.5) NNT: 8 (6 to 11) I^2: 0%	Moderate	No	+
Ngo, 2010, 5606		Erythropoiesis stimulating agent (16 per 100)	Placebo or no treatment (25 per 100)	734 (9)	72 ±3	Admission for heart failure (7 ±5 months)	RR: 0.62 (0.44 to 0.87) NNT: 11 (7 to 31) I^2: 0%	Moderate	No	+
Xie, 2016, 8916a	Heart failure with reduced ejection fraction or left ventricular dysfunction	ACE inhibitor (13 per 100)	Placebo (18 per 100)	12,763 (5)	62 ±4	Admission for heart failure (32 ±12 months)	OR: 0.67 (0.61 to 0.74) NNT: 19 (16 to 25) I^2: 0%	Moderate	No	+
Xie, 2016, 8916b		Angiotensin II receptor blocker (18 per 100)	Placebo (23 per 100)	9,878 (4)	65 ±2	Admission for heart failure (26 ±15 months)	OR: 0.72 (0.64 to 0.82) NNT: 19 (14 to 30) I^2: 30%	Moderate	No	+
Xie, 2016, 8916c		Aldosterone antagonists (11 per 100)	Placebo (15 per 100)	11,477 (4)	65 ±3	Admission for heart failure (18 ±5 months)	OR: 0.67 (0.53 to 0.86) NNT: 22 (15 to 54) I^2: 74%	Moderate	No	+
Liu, 2014, 4629a		Beta-blocker (20 per 100)	No beta-blockers (28 per 100)	888 (2)	74 ±3	Admission (30 ±12 months)	RR: 0.71 (0.55 to 0.93) NNT: 12 (8 to 51) I^2: 7%	Moderate	No	?
Makani, 2013, 4838b		Angiotensin II receptor blocker and ACE inhibitor (37 per 100)	ACE inhibitor (48 per 100)	7,890 (3)	63 ±1	Admission for heart failure (36 ±10 months)	RR: 0.77 (0.68 to 0.88) NNT: 9 (7 to 18) I^2: 66%	Moderate	No	-
Jong, 2002, 3781d		Angiotensin II receptor blocker and ACE inhibitor (4.8 per 100)	ACE inhibitor (6.4 per 100)	5,560 (3)	Unclear	Admission for heart failure (12 ±10 months)	OR: 0.74 (0.64 to 0.86) NNT: 63 (45 to 118) I^2: p>0.1 heterogeneity	Moderate	No	-
Hood, 2014, 3415		Digoxin[f] (9 per 100)	Placebo (12 per 100)	7,262 (4)	61 ±3	Admission (12 ±17 months)	OR: 0.68 (0.61 to 0.75) NNT: 28 (23 to 37) I^2: 29%	High	No	?

Table 7 continued. Medications with high or moderate quality evidence that reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I²%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces hospital admissions from out-patient, day procedure, or community settings										
Bonsu, 2016, 8729a	Heart failure with reduced ejection fraction or left ventricular dysfunction	Lipophilic statin (13 per 100)	Placebo (24 per 100)	1,165 (9)	57 ±9	Admission for heart failure (13 ±12 months)	OR: 0.49 (0.36 to 0.67) NNT: 9 (7 to 15) I²: 38%	High	No	+
Liu, 2014, 8826a		Lipophilic statin (6 per 100)	Placebo or no statin (10 per 100)	1,087 (9)	58 ±10	Admission for heart failure (13 ±12 months)	RR: 0.60 (0.45 to 0.80) NNT: 25 (18 to 50) I²: 11%	Moderate	No	?
Brophy, 2001, 1021		Beta-blocker (7 per 100)	Placebo (12 per 100)	10,076 (22)	57 ±6	Admission for heart failure (9 ±6 months)	OR: 0.64 (0.53 to 0.79) NNT: 24 (18 to 43) I²: Unclear	Moderate	No	+
Saab, 2015, 8884a	Hepatic encephalopathy	Probiotics (18 per 100)	No treatment, placebo, or lactulose (30 per 100)	276 (4)	Range 16 or older	Admission (7 ±4 months)	OR: 0.53 (0.33 to 0.86) NNT: 9 (6 to 33) I²: 0%	Moderate	No	+
Grim-wade, 2009, 2933a	Human Immunodeficieny Virus	Cotrimoxazole (11 per 100)	Placebo (17 per 100)	764 (3)	34 ±2	Admission (Unclear)	RR: 0.66 (0.48 to 0.92) NNT: 17 (11 to 74) I²: 91%	Moderate	No	?
James, 2008, 3657	Long term hemodialysis	Topical prophylactic antibiotics (1 per 100)	No antibiotic therapy (22 per 100)	305 (2)	57 ±13	Admission for infection (3 ±3 months)	rR: 0.06 (0.03 to 0.12) NNT: 6 (5 to 8) I²: Unclear	Moderate	No	+
La Mantia, 2010, 4260	Multiple sclerosis	Glatiramer acetate (12 per 100)	Placebo (21 per 100)	489 (2)	34 ±0.3	Admission (23 ±19 months)	RR: 0.60 (0.40 to 0.91) NNT: 12 (8 to 54) I²: 0%	Moderate	No	?
Makrides, 2014, 4844	Normal or high-risk pregnancy	Magnesium supplementation (8 per 100)	Placebo (12 per 100)	1,158 (3)	Unclear	Admission (Unclear)	RR: 0.65 (0.48 to 0.86) NNT: 24 (16 to 60) I²: 0%	Moderate	No	?
Yang, 2015, 8918a	Prostate biopsy	Antibiotics (2 per 100)	Placebo or no treatment (13 per 100)	650 (3)	Unclear	Admission (Unclear)	RR: 0.13 (0.03 to 0.55) NNT: 9 (8 to 17) I²: 0%	Moderate	No	+
Kishimoto, 2013, 4065a	Schizophrenia	Second generation antipsychotics (15 per 100)	First generation antipsychotics (21 per 100)	2,869 (12)	33 ±6	Admission (13 ±4 months)	RR: 0.72 (0.58 to 0.9) NNT: 17 (11 to 48) I²: 18%	Moderate	No	+

Table 7 continued. Medications with high or moderate quality evidence that reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I²%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces hospital admissions from out-patient, day procedure, or community settings										
Kew, 2013, 4003a	Stable moderate to severe COPD	Long-acting beta2-agonists (4 per 100)	Placebo (5 per 100)	3,804 (7)	62 ±2	Admission for COPD (9 ±3 months)	OR: 0.73 (0.56 to 0.95) NNT: 77 (47 to 420) I²: 10%	Moderate	No	+
Ni, 2014, 8850a		Aclidinium bromide (2 per 100)	Placebo (3 per 100)	5,624 (10)	64 ±3	Admission for COPD (14 ±8 months)	OR: 0.64 (0.46 to 0.88) NNT: 106 (70 to 321) I²: 0%	High	No	+
Zou, 2016, 8933a		Aclidinium Bromide (2 per 100)	Placebo (3 per 100)	4,788 (5)	63 ±1	Admission for COPD (7 ±4 months)	OR: 0.64 (0.47 to 0.89) NNT: 103 (7 to 339) I²: 17%	Moderate	No	+
Poole, 2015, 8867		Mucolytic (19 per 100)	Placebo (25 per 100)	1,788 (4)	66 ±12	Admission (17 ±13 months)	OR: 0.68 (0.52 to 0.89) NNT: 15 (10 to 47) I²: 58%	Moderate	No	+
Cheyne, 2015, 8744d		Tiotropium (1 per 100)	Ipratropium bromide (2 per 100)	1,073 (2)	64 ±0.2	Admission for COPD (6 ±5 months)	OR: 0.56 (0.31 to 0.99) NNT: 102 (65 to 4551) I²: 0%	Moderate	No	+
Chong, 2012, 1438a		Tiotropium (3.8 per 100)	Long acting beta-2-agonist (4.8 per 100)	9,267 (4)	63 ±1	Admission for COPD (7 ±4 months)	OR: 0.87 (0.77 to 0.99) NNT: 183 (103 to 2390) I²: 0%	Moderate	No	?
Karner, 2014, 8692e		Tiotropium with soft mist inhaler (6 per 100)	Placebo (7 per 100)	6,522 (3)	65 ±1	Admission for COPD (9 ±5 months)	OR: 0.82 (0.68 to 0.99) NNT: 87 (49 to 1590) I²: 0%	Moderate	No	+
Lopez, 2015, 8829a	Ulcerative colitis	Tumour necrosis factor antagonists (anti-TNF) (12 per 100)	Placebo (17 per 100)	1,691 (2)	Unclear	Admission for ulcerative colitis (Unclear)	RR: 0.71 (0.56 to 0.9) NNT: 20 (13 to 58) I²: 0%	Moderate	No	+

Table 7 continued. Medications with high or moderate quality evidence that reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I²%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces readmissions after an index hospital admission										
Stratton, 2013, 7484a	Discharged from hospital malnourished	Oral nutritional supplements (21 per 100)	Usual care or dietary counselling (31 per 100)	852 (6)	Range 51 to 92	Readmission (13 ±4 months)	OR: 0.59 (0.43 to 0.8) NNT: 10 (7 to 22) I²: Unclear	Moderate	Yes[g]	+
Gandhi, 2014, 2599a	Heart failure (acute decompensation)	Hypertonic saline solution plus intravenous furosemide (19 per 100)	IV furosemide (37 per 100)	2,032 (4)	74 ±0.4	Readmission for heart failure (30 ±28 months)	RR: 0.50 (0.33 to 0.76) NNT: 5 (4 to 11) I²: 61%	Moderate	No	?
Kuenzli, 2010, 4206a	Heart failure with left ventricular dysfunction	Angiotensin II receptor blocker and ACE inhibitor (19 per 100)	ACE inhibitor (24 per 100)	17,895 (6)	64 ±2	Readmission for heart failure (23 ±12 months)	RR: 0.81 (0.72 to 0.91) NNT: 22 (15 to 47) I²: 57%	Moderate	No	-
Kuenzli, 2010, 4206c		Angiotensin II receptor blocker and ACE inhibitor (19 per 100)	ACE inhibitor (23 per 100)	8,049 (4)	64 ±2	Readmission for heart failure (22 ±14 months)	RR: 0.81 (0.72 to 0.91) NNT: 23 (15 to 48) I²: 23%	Moderate	No	-
Leucht, 2012, 4508a	Schizophrenia	Antipsychotic maintenance therapy (12 per 100)	Placebo (33 per 100)	2,090 (16)	38 ±9	Readmission (11 ±7 months)	RR: 0.38 (0.27 to 0.55) NNT: 5 (4 to 7) I²: 45%	High	No	+
Komossa, 2013, 4123i		Olanzapine (11 per 100)	Ziprasidon (17 per 100)	766 (2)	41 ±0.1	Readmission (13 ±9 months)	RD: -0.06 (-0.01 to -0.11) NNT: 17 (9 to 100) I²: 0%	Moderate	No	?
Komossa, 2013, 4123b		Olanzapine (11 per 100)	Quetiapin (20 per 100)	876 (2)	40 ±0.4	Readmission (13 ±9 months)	RR: 0.56 (0.41 to 0.77) NNT: 11 (8 to 22) I²: 0%	Moderate	No	?

[a]Median hospitalisation event rate observed across the trials contributing to the pooled estimate. [b]Means and standard deviations, unless otherwise specified. Mean of means and median ages in trials contributing to the pooled estimate. Not all included trials reported age in a form that could be averaged. [c]Not all included trials reported follow-up in a form that could be averaged. [d]Moderate or high. quality evidence according to the Grading of Recommendations Assessment, Development and Evaluation working group criteria. [e]See Table 3 for detailed description of the summary symbols. (+) denotes a positive overall balance of benefit to harm, (-) denotes a negative overall balance of benefit to harm, and (?) denotes n unclear balance of benefit to harm. [f]Patients in normal sinus rhythm. [g]Beck (2013) showed no effect but focused on elderly patients aged 65 and over. Abbreviations: ACE= angiotensin-converting enzyme; CI= confidence interval; COPD= chronic obstructive pulmonary disease; ED= emergency department; ID No.=identification number; IV=intravenous; MI= myocardial infarction; NNT= number needed to treat to avoid one emergency hospital admission; OR= odds ratio; RCTs= randomised controlled trials; RR= risk ratio; rR= rate ratio.

Prioritised health systems interventions that reduce emergency hospital admissions

High or moderate evidence was identified for 22 unique health systems interventions that significantly reduced hospital admissions in 13 patient populations (Table 8, Table 9).

All of the interventions were classified as “delivery arrangements” according to the EPOC taxonomy, with the majority sub-categorised as “coordination of care and management of care processes”, “information and communication technology”, or “where care is provided and changes to the healthcare environment”. The interventions included: education, rehabilitation, and self-management; expanding the role of health care providers (i.e., pharmacist or nurse-led care); multi-disciplinary care; coordinating and integrating care (i.e, case management, discharge planning); outreach (i.e., home-visits); use of technology (i.e., tele-monitoring, structure telephone support); and multi-component initiatives (i.e., disease management programs).

Approximately half the interventions reduced admissions from out-patient, day procedure, or community settings in patients with chronic diseases (i.e., asthma, COPD, heart failure, chronic ischaemic heart disease, bipolar, schizophrenia) or in broad non-disease specific populations (i.e., elderly people, frequent health care users, patients presenting to primary care).

The other half of interventions reduced readmissions by targeting the transition out of hospital and the post-discharge period in patients with chronic diseases (i.e., COPD, heart failure, post-surgical gastrointestinal cancer patients) or in broad non-disease specific populations (i.e., hospitalised patients).

A favourable overall balance of benefit to harm was reported for 19 of the interventions in eight patient populations.

There were three instances of interventions with conflicting evidence:

- Education interventions for asthma patients in the emergency department were shown to be effective by Tapp et al. (2007) however, a more recent review (Villa-Roel et al. 2016) examined emergency-department directed education interventions and showed no effect on admissions.
- Self-management in patients with chronic obstructive pulmonary disease was shown to be effective by Zwerink et al. (2014) for reducing respiratory-related admissions. However, two subsequent reviews (Jordan et al. 2015 and Majothi et al. 2015) examined patients shortly after hospitalisation for a COPD exacerbation and showed that self-management had no effect on readmissions. An additional review by Jolly et al. (2016) similarly found no effect, but examined all-cause admissions, as opposed to respiratory-related admissions.
- A 2014 review by Martínez-González et al. demonstrated that nurse-led primary care was effective in reducing hospital admissions however, a previous review (Laurant et al. 2005) used a broader definition of nurse-led care and showed no effect. All of the trials in the older review (Laurant et al. 2005) were included in the updated study by Martínez-González except one large trial on nurse delivered telephone consultations. This trial was not included by Martínez-González because the intervention did not meet the authors criteria: nurses acting as the main figure with autonomous or delegated clinical responsibility for tasks that would have formerly been performed by physicians alone.

Table 8. Summary list of health systems interventions with high or moderate quality evidence that significantly reduce emergency hospital admissions

Population[a]	Health systems interventions
Reduces hospital admissions from out-patient, day procedure, or community settings	
Asthma (acute exacerbation)	• Education interventions
Angina pectoris; Acute myocardial infarction; Chronic ischaemic heart disease; or Heart failure	• Pharmacist-involved care
Bipolar disorder	• Collaborative care
Chronic obstructive pulmonary disease	• Pulmonary rehabilitation programmes • Self-management
Chronic obstructive pulmonary disease (acute exacerbations)	• Pharmacist directed care or pharmacist collaborative care
Elderly in the community or being discharged from hospital	• Community-based multifactorial interventions: geriatric assessment; community-based care; fall prevention; group education and counselling
Frequent health care users	• Self- management
Heart failure	• Multi-disciplinary care: home visits; home physiological monitoring; or televideo link • Non-invasive telemonitoring • Nurse-led titration of medication • Specialist heart-failure clinics
Schizophrenia and other types of schizophrenia-like psychoses	• Case management (intensive)
Patients presenting to primary care	• Nurse-led primary care
Reduces readmissions after an index hospital admission	
Chronic obstructive pulmonary disease	• Pulmonary rehabilitation programmes
Chronic obstructive pulmonary disease (acute exacerbations)	• Early supported discharge • Hospital at home
Heart failure	• Case management (community-based or hospital initiated) • Case management (hospital initiated) with medication review • Clinical service organisation interventions • Comprehensive disease management programmes • Comprehensive discharge planning with post discharge support • Home-visiting programs • Multidisciplinary-heart failure clinic • Multidisciplinary care post-discharge • Pre-discharge multidisciplinary patient education program • Transitional care interventions: telecare and prearranged direct patient contact • Structured telephone support: monitoring; education; or self-care management
Hospitalised patients	• Discharge planning from hospital • Nurse-led early discharge planning programmes
Severe/chronic mental disorders/illnesses	• Education/self-management

[a]Based on the 3-character coding level using the World Health Organisation's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10).

Table 9. Health systems interventions with high or moderate quality evidence that significantly reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces hospital admissions from out-patient, day procedure, or community settings										
Tapp, 2007, 7636c	Asthma (acute exacerbation)	Education interventions (12 per 100)	Usual care (19 per 100)	386 (2)	Unclear	Admission (7 ±8 months)	RR: 0.63 (0.40 to 0.97) NNT: 14 (9 to 178) I^2: 0%	Moderate	Yes[f]	+
Oud, 2016, 9309c	Bipolar disorder	Collaborative care (37 per 100)	Treatment as usual (55 per 100)	572 (2)	40 ±6	Admission (8 ±4 months)	RR: 0.68 (0.49 to 0.94) NNT: 6 (4 to 31) I^2: 0%	Moderate	No	?
Zhong, 2014, 8926a	Chronic obstructive pulmonary disease	Pharmacist directed care or pharmacist collaborative care (8 per 100)	Usual care (15 per 100)	684 (6)	64 ±5	Admission (19 ±9 months)	RR: 0.50 (0.39 to 0.64) NNT: 13 (11 to 18) I^2: 47%	High	No	+
Zwerink, 2014, 8672a		Self-management (28 per 100)	Control (39 per 100)	1365 (7)	68 ±3	Admission (11 ±6 months)	OR: 0.60 (0.40 to 0.89) NNT: 9 (5 to 37) I^2: 47%	Moderate	Yes[g]	+
Beswick, 2008 725a	Elderly patients in the community or being discharged from hospital	Community-based multifactorial intervention: geriatric assessment; community-based care; fall prevention; group education and counselling (35 per 100)	Usual care or minimum intervention (37 per 100)	20,047 (41)	78 ±3	Admission (7 ±4 months)	RR: 0.94 (0.91 to 0.97) NNT: 45 (30 to 90) I^2: 43%	Moderate	No	+
Tricco, 2014, 8899g	Frequent health care users	Self- management (37 per 100)	Usual care (46 per 100)	2,475 (12)	20 ±20	Admission (10 ±7 months)	RR: 0.80 (0.71 to 0.90) NNT: 11 (7 to 22) I^2: 0%	Moderate	No	+
Holland, 2005, 3400b	Heart failure	Home visits, home physiological monitoring, or televideo link (41 per 100)	Usual care (51 per 100)	1,519 (10)	74 ±7	Admission (9 ±4 months)	RR: 0.80 (0.71 to 0.89) NNT: 10 (7 to 18) I^2: 0%	Moderate	No	+
Feltner, 2014, 2359c		Home-visiting programs (32 per 100)	Usual care (43 per 100)	1,563 (9)	76 ±2	Readmission (6 ±3 months)	RR: 0.75 (0.68 to 0.86) NNT: 4 (7 to 17) I^2: 0%	High	No	+

Table 9 continued. Health systems interventions with high or moderate quality evidence that significantly reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces hospital admissions from out-patient, day procedure, or community settings										
Raman, 2008, 6360f	Heart failure	Multidisciplinary care post-discharge (28 per 100)	Usual care (44 per 100)	1,279 (4)	73 ±11	Readmission (14 ±4 months)	RR: 0.63 (0.44 to 0.90) NNT: 6 (4 to 23) I^2: 69%	Moderate	No	+
Feltner, 2014, 2359l		Multidisciplinary-heart failure clinic (34 per 100)	Usual care (49 per 100)	336 (2)	65 ±6	Readmission (6 months)	RR: 0.70 (0.55 to 0.89) NNT: 7 (5 to 19) I^2: 0%	High	No	+
Inglis, 2015, 8787w		Non-invasive telemonitoring (21 per 100)	Usual post-discharge care (30 per 100)	2,148 (8)	Range 18 to 80	Admission for heart failure (23 ±33 months)	RR: 0.71 (0.6 to 0.83) NNT: 12 (8 to 20) I^2: 20%	Moderate	No	+
Thomas, 2013, 7723c		Specialist heart-failure clinics (15 per 100)	Usual care (30 per 100)	1,173 (6)	69 ±8	Admission (9 ±5 months)	RR: 0.51 (0.41 to 0.63) NNT: 7 (6 to 9) I^2: 50%	High	No	+
Thomas, 2013, 7723i		Specialist heart-failure clinics with decreasing intensity of follow-up (11 per 100)	Usual care (26 per 100)	475 (3)	72 ±3	Admission (18 ±8 months)	RR: 0.42 (0.27 to 0.65) NNT: 7 (5 to 11) I^2: 4%	Moderate	No	+
Thomas, 2013, 7723m		Specialist heart-failure clinics with inpatient interventions (9 per 100)	Usual care (35 per 100)	408 (2)	69 ±1	Admission (7 ±4 months)	RR: 0.26 (0.07 to 0.92) NNT: 4 (3 to 36) I^2: 45%	Moderate	No	+
Inglis, 2015, 8787v		Structured telephone support (15 per 100)	Usual post-discharge care (18 per 100)	6,996 (15)	66 ±9	Admission for heart failure (19 ±7 months)	RR: 0.85 (0.77 to 0.93) NNT: 37 (24 to 80) I^2: 27%	Moderate	No	+
Inglis, 2015, 8787t		Structured telephone support (45 per 100)	Usual post-discharge care (50 per 100)	3,451 (7)	66 ±5	Admission (13 ±2 months)	RR: 0.89 (0.82 to 0.96) NNT: 18 (11 to 50) I^2: 37%	Moderate	No	+

Table 9 continued. Health systems interventions with high or moderate quality evidence that significantly reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces hospital admissions from out-patient, day procedure, or community settings										
Kang, 2016, 9271a	Heart failure with left ventricular dysfunction, coronary artery disease, or acute coronary syndrome	Pharmacist-involved care (41 per 100)	Usual care (48 per 100)	4,240 (13)	Unclear	Admission (9 ±5 months)	OR: 0.74 (0.58 to 0.94) NNT: 13 (8 to 65) I^2: 61%	Moderate	No	?
Driscoll, 2015, 8761a	Heart failure with reduced ejection fraction on beta-blockers, ACE inhibitors, and/or Angiotensin II receptor blocker	Nurse-led titration of medication (35 per 100)	Usual care (44 per 100)	560 (4)	Unclear	Admission (7 ±4 months)	RR: 0.80 (0.72 to 0.88) NNT: 11 (8 to 19) I^2: 0%	High	No	+
Driscoll, 2015, 8761b		Nurse-led titration of medication (14 per 100)	Usual care (27 per 100)	617 (3)	Unclear	Admission for heart failure (11 ±4 months)	RR: 0.51 (0.36 to 0.72) NNT: 7 (6 to 13) I^2: 0%	Moderate	No	+
Martínez-González, 2014, 4987a	Patients presenting to primary care	Nurse-led primary care (7 per 100)	Physician-led care (10 per 100)	3,890 (5)	50 ±18	Admission (11 ±2 months)	RR: 0.76 (0.64 to 0.91) NNT: 42 (28 to 113) I^2: 7%	Moderate	Yes[h]	?
Dieterich, 2017, 9370b	Schizophrenia, schizophrenia-like disorders, bipolar disorder, depression with psychotic features or/and personality disorder (non-acutely ill)	Case management (intensive) (51 per 100)	Standard care (60 per 100)	1,303 (5)	33 ±5	Admission (7 ±2 months)	RR: 0.85 (0.77 to 0.93) NNT: 11 (7 to 24) I^2: 0%	Moderate	No	+
Reduces readmissions after an index hospital admission										
Echevarria, 2016, 8762a	COPD (acute exacerbation)	Early supported discharge or hospital at home (27 per 100)	Traditional in-patient care (36 per 100)	688 (8)	43 ±19	Readmission (8 ±4 months)	RR: 0.74 (0.6 to 0.9) NNT: 4 (7 to 28) I^2: 26%	Moderate	No	+
Jeppesen, 2012, 3709a		Hospital at home (26 per 100)	In-hospital care (34 per 100)	870 (8)	71 ±4	Readmission (9 ±4 months)	RR: 0.76 (0.59 to 0.99) NNT: 12 (7 to 295) I^2: 34%	Moderate	No	+
Puhan, 2016, 9316a	COPD (recent exacerbation	Pulmonary rehabilitation programmes (30 per 100)	Conventional community care (49 per 100)	810 (8)	70 ±3	Readmission (3 ±2 months)	OR: 0.44 (0.21 to 0.91) NNT: 5 (3 to 42) I^2: 77%	Moderate	No	?

Table 9 continued. Health systems interventions with high or moderate quality evidence that significantly reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces readmissions after an index hospital admission										
Takeda, 2012, 7600c	Heart failure	Case management (26 per 100)	Usual care (36 per 100)	655 (3)	69 ±5	Readmission for heart failure (8 ±2 months)	OR: 0.64 (0.46 to 0.88) NNT: 11 (7 to 35) I^2: 0%	Moderate	No	+
Takeda, 2012, 7600e		Case management (19 per 100)	Usual care (36 per 100)	604 (3)	71 ±7	Readmission for heart failure (10 ±3 months)	OR: 0.42 (0.29 to 0.62) NNT: 6 (5 to 10) I^2: 9%	High	No	+
Huntley, 2016, 9178a		Case management (hospital initiated) (28 per 100)	Usual care (38 per 100)	3,066 (12)	75 ±3	Readmission (Range 3 to 18 months)	rR: 0.74 (0.6 to 0.92) NNT: 10 (7 to 33) I^2: 69%	Moderate	No	+
Huntley, 2016, 9178e		Case management (hospital initiated) (34 per 100)	Usual care (41 per 100)	2,032 (6)	75 ±2	Readmission (Range 12 to 18 months)	rR: 0.83 (0.7 to 0.98) NNT: 14 (8 to 123) I^2: 35%	Moderate	No	+
Huntley, 2016, 9178c		Case management (hospital initiated) (15 per 100)	Usual care (23 per 100)	848 (5)	75 ±4	Readmission (3 months)	rR: 0.67 (0.51 to 0.9) NNT: 13 (9 to 44) I^2: 19%	Moderate	No	+
Huntley, 2016, 9178h		Case management (hospital initiated) with medication review (Review and adjustment by experienced case manager (nurse), pharmacist, GP or consultant often using a combination of these health professionals) (33 per 100)	Usual care (45 per 100)	748 (5)	77 ±2	Readmission (Range 3 to 18 months)	rR: 0.73 (0.59 to 0.91) NNT: 8 (5 to 25) I^2: 28%	Moderate	No	+

Table 9 continued. Health systems interventions with high or moderate quality evidence that significantly reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces readmissions after an index hospital admission										
Takeda, 2012, 7600n	Heart failure	Clinical service organisation interventions (Low intensity) (37 per 100)	Usual care (51 per 100)	489 (3)	71 ±1	Readmission for heart failure (9 ±4 months)	OR: 0.56 (0.39 to 0.81) NNT: 7 (5 to 19) I^2: 0%	Moderate	No	+
Roccaforte, 2005, 6552i		Disease management programmes (comprehensive) (41 per 100)	Usual care (48 per 100)	2,071 (10)	Range 35 to 91	Readmission (11 ±9 months)	OR: 0.75 (0.63 to 0.8) NNT: 14 (9 to 18) I^2: p>0.1 heterogeneity	High	No	+
Roccaforte, 2005, 6552p		Disease management programmes (comprehensive) (23 per 100)	Usual care (34 per 100)	1,539 (8)	Range 59 to 75	Readmission for heart failure (10 ±7 months)	OR: 0.58 (0.45 to 0.75) NNT: 9 (7 to 16) I^2: p>0.1 heterogeneity	High	No	+
Roccaforte, 2005, 6552m		Disease management programmes (comprehensive, lasting 0 to 3 months) (35 per 100)	Usual care (46 per 100)	1,999 (13)	Range 35 to 91	Readmission (10 ±10 months)	OR: 0.61 (0.51 to 0.74) NNT: 8 (6 to 14) I^2: p>0.1 heterogeneity	Moderate	No	+
Lambrinou, 2012, 4305a		Disease management programme with nurse-led discharge planning (22 per 100)	Usual care (32 per 100)	2,898 (13)	71 ±4	Readmission for heart failure (94 ±36 months)	RR: 0.68 (0.53 to 0.86) NNT: 10 (7 to 22) I^2: 64%	Moderate	No	?
Lambrinou, 2012, 4305f		Disease management programme with nurse-led discharge planning (45 per 100)	Usual care (53 per 100)	3,713 (17)	72 ±4	Readmission (18 ±9 months)	RR: 0.85 (0.76 to 0.94) NNT: 13 (8 to 31) I^2: 50%	Moderate	No	?
Lambrinou, 2012, 4305i		Disease management programme with nurse-led discharge planning and home follow-up (43 per 100)	Usual care (54 per 100)	1,052 (6)	76 ±2	Readmission (18 ±6 months)	RR: 0.80 (0.70 to 0.91) NNT: 9 (6 to 21) I^2: 0%	High	No	?

Table 9 continued. Health systems interventions with high or moderate quality evidence that significantly reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces readmissions after an index hospital admission										
Phillips, 2004, 6099e	Heart failure	Discharge planning (comprehensive) with post discharge support (33 per 100)	Usual care (50 per 100)	1,153 (6)	72 ±1	Readmission for heart failure (25 ±19 months)	RR: 0.65 (0.54 to 0.79) NNT: 6 (4 to 10) I^2: 12%	Moderate	No	+
Phillips, 2004, 6099h		Discharge planning (comprehensive) with home visit and/or frequent telephone contact (40 per 100)	Usual care (50 per 100)	970 (6)	75 ±3	Readmission (8 ±3 months)	RR: 0.79 (0.69 to 0.91) NNT: 10 (6 to 22) I^2: p>0.1 heterogeneity	Moderate	No	+
Phillips, 2004, 6099f		Discharge planning (comprehensive) with single home visit (39 per 100)	Usual care (51 per 100)	476 (3)	74 ±1	Readmission (10 ±9 months)	RR: 0.76 (0.63 to 0.93) NNT: 8 (5 to 28) I^2: p>0.1 heterogeneity	Moderate	No	+
Gwadry-Sridhar, 2004, 3030a		Pre-discharge multidisciplinary patient education program (39 per 100)	Usual care (50 per 100)	1,246 (8)	75 ±5	Readmission (10 ±4 months)	RR: 0.79 (0.68 to 0.91) NNT: 10 (6 to 22) I^2: p>0.1 heterogeneity	Moderate	No	+
Feltner, 2014, 2359h		Structured telephone support: Monitoring, education, or self-care management (or various combinations) using simple telephone technology after discharge in a structured format (e.g., series of scheduled calls with a specific goal, structured questioning, or use of decision-support software). (20 per 100)	Usual care (28 per 100)	1,790 (7)	69 ±3	Readmission for heart failure (8 ±6 months)	RR: 0.74 (0.61 to 0.9) NNT: 5 (9 to 36) I^2: 0%	High	No	+

Table 9 continued. Health systems interventions with high or moderate quality evidence that significantly reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I²%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces readmissions after an index hospital admission										
Vedel, 2015, 8902i	Heart failure	Transitional care intervention (45 per 100)	Usual care (54 per 100)	1,951 (13)	77 ±2	Readmission (31 ±42 months)	RR: 0.83 (0.76 to 0.92) NNT: 11 (8 to 23) I²: 7%	Moderate	No	+
Vedel, 2015, 8902d		Transitional care intervention (high intensity): A combination of home visits and other types of follow-up (telephone and/or clinic follow-up) or telecare combined with prearranged direct contact with patients (eg, home visits, telephone follow-up, video visits) (38 per 100)	Usual care (45 per 100)	3,339 (16)	72 ±7	Readmission (9 ±10 months)	RR: 0.86 (0.78 to 0.94) NNT: 16 (10 to 37) I²: 31%	Moderate	No	+
Gonçalves-Bradley, 2016, 8776a	Hospitalised patients	Discharge planning from hospital (23 per 100)	Standard care with no individualised discharge plan (26 per 100)	4,853 (17)	71 ±12	Readmission (9 ±5 months)	RR: 0.88 (0.79 to 0.97) NNT: 32 (18 to 128) I²: 22%	Moderate	No	+
Leppin, 2014, 4494a		Peridischarge interventions: discharge planning; case management; telephone follow-up; telemonitoring; patient education; self-management; medication review; home visits; scheduled follow-up; patient-centered discharge instructions; clinician continuity; timely follow-up; timely primary care provider communication; patient hotline; rehabilitation; or streamlining services. (13 per 100)	Any comparator (16 per 100)	17,273 (42)	72 ±6	Readmission (33 ±12 months)	RR: 0.82 (0.73 to 0.91) NNT: 35 (24 to 71) I²: 31%	Moderate	No	+

Table 9 continued. Health systems interventions with high or moderate quality evidence that significantly reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces readmissions after an index hospital admission										
Zhu, 2015, 8929a	Hospitalised patients with chronic disease or rehabilitation needs	Nurse-led early discharge planning programmes (15 per 100)	Standard care (20 per 100)	3,376 (10)	67 ±14	Readmission (25 ±10 months)	RR: 0.72 (0.58 to 0.89) NNT: 18 (12 to 45) I^2: 66%	Moderate	No	+
Zhu, 2015, 8929f		Nurse-led early discharge planning programmes (30 per 100)	Standard care (62 per 100)	393 (2)	56 ±27	Readmission (14 ±3 months)	RR: 0.48 (0.37 to 0.63) NNT: 4 (3 to 4) I^2: 0%	Moderate	No	+
Zhu, 2015, 8929g		Nurse-led early discharge planning programmes (44 per 100)	Standard care (58 per 100)	1,042 (3)	53 ±22	Readmission (16 ±6 months)	RR: 0.76 (0.65 to 0.88) NNT: 7 (5 to 14) I^2: 0%	High	No	+
Zhu, 2015, 8929i		Nurse-led early discharge planning programmes (30 per 100)	Standard care (44 per 100)	768 (2)	44 ±9	Readmission (13 ±12 months)	RR: 0.69 (0.51 to 0.92) NNT: 7 (5 to 29) I^2: 0%	High	No	+
Zhu, 2015, 8929c		Nurse-led early discharge planning programmes (16 per 100)	Standard care (21 per 100)	1,638 (7)	63 ±16	Readmission (17 ±9 months)	RR: 0.78 (0.68 to 0.89) NNT: 22 (15 to 44) I^2: 0%	High	No	+
Morriss, 2013, 5399d	Schizophrenia or a nonaffective, non-organic serious or chronic mental illness	Education/self-management with training delivered to both patient and carer/health professional (23 per 100)	Usual care (36 per 100)	625 (7)	32 ±4	Readmission (8 ±5 months)	RR: 0.64 (0.51 to 0.79) NNT: 8 (6 to 13) I^2: 0%	Moderate	No	?
Morriss, 2013, 5399j		Education/self-management with training delivered to both patient and carer/health professional (30 per 100)	Usual care (49 per 100)	740 (3)	34 ±6	Time to readmission (10 ±4 months)	HR: 0.62 (0.46 to 0.83) NNT: 7 (5 to 16) I^2: 0%	Moderate	No	?

[a]Median hospitalisation event rate observed across the trials contributing to the pooled estimate. [b]Means and standard deviations, unless otherwise specified. Mean of means and median ages in trials contributing to the pooled estimate. Not all included trials reported age in a form that could be averaged. [c]Not all included trials reported follow-up in a form that could be averaged. [d]Moderate or high quality evidence according to the Grading of Recommendations Assessment, Development and Evaluation working group criteria. [e]See Table 3 for detailed description of the summary symbols. (+) denotes a positive overall balance of benefit to harm, (-) denotes a negative overall balance of benefit to harm, and (?) denotes an unclear balance of benefit to harm. [f]Villa-Roel (2016) showed no effect for ED directed educational interventions. [g]Jordan (2015) showed no effect for patients at hospital discharge or shortly after hospitalisation for an exacerbation. Majothi (2015) showed no effect for patients at hospital discharge or shortly after hospitalisation for an exacerbation. Jolly (2016) showed no effect for all-cause hospital admissions. [h]Laurant (2005) showed no effect. It was an older review with one unique trial not included in the more recent review. Martinez-Gonzalez excluded the trial because it examined nurse-led telephone consultations and did not meet the intervention criteria; nurses acting as the main figure with autonomous or delegated clinical responsibility for tasks that would have formerly been performed by physicians alone. Abbreviations: CI= confidence interval; COPD= chronic obstructive pulmonary disease; GP= general practitioner; ID No.=identification number; NNT= number needed to treat to avoid one emergency hospital admission; OR= odds ratio; RCTs= randomised controlled trials; RR= risk ratio; rR= rate ratio.

Prioritised diagnostic, medical, and surgical interventions that reduce emergency hospital admissions

High or moderate evidence was identified for four unique diagnostic, medical, and surgical interventions that significantly reduced hospital admissions in five patient populations (Table 10, Table 11).

Three of the interventions were invasive therapeutic or diagnostic procedures that require in hospital care (i.e., cardiac resynchronisation therapy for heart failure, percutaneous aspiration for pneumothorax, and early/routine coronary angiography for acute coronary syndromes).

A favourable overall balance of benefit to harm was reported for three of the interventions for use in three of the patient populations.

There was one instance of conflicting evidence:

- Wang et al. (2014) showed that fast-track recovery after laparoscopic surgery for gastrointestinal cancer reduced hospital admissions compared to fast-track recovery after open surgery however, two reviews published the following year focused on gastrectomy patients and showed no effect.

Table 10. Summary list of diagnostics, medical, and surigcal interventions with high or moderate quality evidence that significantly reduce emergency hospital admissions

Population[a]	Diagnostic, medical, and surgical interventions
Reduces hospital admissions from out-patient, day procedure, or community settings	
Atrial fibrillation	• Cardiac resynchronization therapy
Heart failure	• Cardiac resynchronization therapy • Natriuretic peptide (B-type and N-terminal Pro B-type) guided therapy
Reduces readmissions after an index hospital admission	
Angina pectoris or Acute myocardial infarction	• Early/routine coronary angiography
Angina pectoris or Acute myocardial infarction with chronic kidney diseases	• Early/routine coronary angiography
Idiopathic spontaneous pneumothorax	• Percutaneous aspiration of plural cavity
Patients receiving surgery	• Laparoscopic surgery with fast track rehabilitation

Table 11. Diagnostic, medical, and surgical interventions with high or moderate quality evidence that reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I²%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces hospital admissions from out-patient, day procedure, or community settings										
Stavrakis, 2012, 7417a	Persistent or permanent atrial fibrillation receiving atrioventricular junction ablation	Cardiac resynchronization therapy (5 per 100)	Right ventricular pacing (13 per 100)	325 (3)	69 ±4	Admission for heart failure (9 ±6 months)	RR: 0.38 (0.17 to 0.85) NNT: 12 (9 to 49) I²: 15%	Moderate	No	?
Bradely, 2003 930a	Heart failure	Cardiac resynchronization therapy (12 per 100)	Resynchronization off (16 per 100)	1,497 (3)	65 ±1	Admission for heart failure (9 ±3 months)	OR: 0.71 (0.53 to 0.96) NNT: 25 (15 to 186) I²: p>0.1 heterogeneity	Moderate	No	+
Kang, 2015, 8797a		Cardiac resynchronization therapy (14 per 100)	Left ventricular pacing (22 per 100)	7,511 (16)	64 ±3	Admission for heart failure (9 ±5 months)	OR: 0.59 (0.47 to 0.74) NNT: 13 (10 to 21) I²: 54%	Moderate	No	+
McLellan, 2016, 9300g		Natriuretic peptide (BNP or NT-proBNP) guided therapy (33 per 100)	Clinically guided therapy (40 per 100)	1,318 (6)	73 ±2	Admission for heart failure (15 ±13 months)	RR: 0.83 (0.71 to 0.98) NNT: 15 (9 to 125) I²: 38%	Moderate	No	?
McLellan, 2016, 9300l		Natriuretic peptide (BNP or NT-proBNP) guided therapy (29 per 100)	Clinically guided therapy (44 per 100)	878 (6)	72 ±8	Admission for heart failure (9 ±4 months)	RR: 0.65 (0.54 to 0.79) NNT: 7 (5 to 11) I²: 56%	Moderate	No	?
McLellan, 2016, 9300k		Natriuretic peptide (BNP or NT-proBNP) guided therapy (13 per 100)	Clinically guided therapy (36 per 100)	278 (3)	65 ±4	Admission for heart failure (14 ±3 months)	RR: 0.37 (0.23 to 0.58) NNT: 4 (4 to 7) I²: 0%	Moderate	No	?

Table 11 continued. Diagnostic, medical, and surgical interventions with high or moderate quality evidence that reduce emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Reduces readmissions after an index hospital admission										
Aguin-agal, 2010, 119a	Idiopathic spontaneous pneumothorax	Percutaneous aspiration of plural cavity (11 per 100)	Chest tube drainage of the plural cavity (29 per 100)	197 (2)	26 ±3	Readmission (5 ±2 months)	RR: 0.37 (0.18 to 0.75) NNT: 6 (4 to 14) I^2: Unclear	Moderate	No	+
Fanning, 2016, 9247a	Unstable angina or non–ST-segment elevation myocardial infarction	Early/routine coronary angiography (9 per 100)	Selective coronary angiography (symptom/stress test–driven) (12 per 100)	6,921 (6)	Unclear	Readmission (8 ±5 months)	RR: 0.77 (0.63 to 0.94) NNT: 36 (22 to 137) I^2: 54%	Moderate	No	–
Fanning, 2016, 9247c	Unstable angina or non–ST-segment elevation myocardial infarction	Early/routine coronary angiography (12 per 100)	Selective coronary angiography (symptom/stress test–driven) (17 per 100)	2,901 (3)	Unclear	Readmission (8 ±5 months)	RR: 0.71 (0.54 to 0.94) NNT: 7 (13 to 98) I^2: 30%	Moderate	No	–
Charytan, 2009, 1340a	Unstable angina or non–ST-segment elevation myocardial infarction and chronic kidney disease	Early/routine coronary angiography (10 per 100)	Selective coronary angiography (symptom/stress test–driven) (14 per 100)	7,481 (5)	63 ±3	Readmission (7 ±4 months)	RR: 0.76 (0.66 to 0.87) NNT: 31 (22 to 56) I^2: 0%	Moderate	No	+
Wang, 2014, 8910d	Gastrointestinal surgery for cancer	Laparoscopic surgery with fast track rehabilitation (7 per 100)	Open surgery with fast track rehabilitation (15 per 100)	671 (6)	67 ±6	Readmission (1 month)	RR: 0.45 (0.29 to 0.71) NNT: 12 (10 to 23) I^2: 14%	Moderate	Yes[f]	?

[a]Median hospitalisation event rate observed across the trials contributing to the pooled estimate. [b]Means and standard deviations, unless otherwise specified. Mean of means and median ages in trials contributing to the pooled estimate. Not all included trials reported age in a form that could be averaged. [c]Not all included trials reported follow-up in a form that could be averaged. [d]Moderate or high quality evidence according to the Grading of Recommendations Assessment, Development and Evaluation working group criteria. [e]See Table 3 for detailed description of the summary symbols. (+) denotes a positive overall balance of benefit to harm, (-) denotes a negative overall balance of benefit to harm, and (?) denotes an unclear balance of benefit to harm. [f]Beamish (2015) and Chen (2015) showed no effect for patients receiving gastrectomy. Abbreviations: CI= confidence interval; COPD= chronic obstructive pulmonary disease; ID No.=identification number; NNT= number needed to treat to avoid one emergency hospital admission; OR= odds ratio; RCTs= randomised controlled trials; RR= risk ratio; rR= rate ratio.

3.5.6 Prioritised interventions that increase emergency hospital admissions

While reviewing the evidence base, interventions that significantly increased hospital admissions were also found. Evidence summaries for GRADED pooled effect estimates showing a statistically significant increase in emergency hospital admissions can be found in Appendix 3.13.

There was high or moderate quality evidence for three interventions that significantly increased emergency hospital admissions (Table 12).

There was one instance of conflicting evidence:

- The review by Laurant et al. showed an increase in admissions from nurse-led primary care. However, a more recent review by Martínez-González et al. (2014) showed a reduction in admissions. The Martínez-Gonzáleze et al. (2014) review included more trials overall however, it excluded one large trial included in Laurant et al. which examining nurse delivered telephone consultations. This trial was excluded from Martínez-Gonzáleze as it did not meet the intervention criteria; nurses acting as the main figure with autonomous or delegated clinical responsibility for tasks that would have formerly been performed by physicians alone.

Table 12. Interventions with high or moderate quality evidence that increase emergency hospital admissions

Author, Year, ID No.	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Mean age[b]	Outcome (follow-up)[b,c]	Effect (95% CI) NNT (95% CI) I^2%	Quality of evidence[d]	Conflicting estimates	Overall balance of benefit to harm (+ - ?)[e]
Kew, 2014, 4004z	Moderate to severe chronic obstructive pulmonary disease	Fluticasone (with or without long acting beta2-agonist) (1.4 per 100)	Controls (placebo or long acting beta2-agonist) (0.8 per 100)	16,338 (15)	64 ±1	Admission for pneumonia (12 ±11 months)	OR: 1.82 (1.52 to 2.19) NNT: 164 (114 to 259) I^2: 0%	High	No	?
Laurant, 2005, 9181a	Patients presenting to primary care	Nurse-led primary care (12 per 100)	Physician-led primary care (11 per 100)	15,860 (3)	45	Admission (6 ±4 months)	RR: 1.17 (1.04 to 1.31) NNT: 56 (31 to 238) I^2: 40%	Moderate	Yes[f]	+
Baigent, 2013, 1653a	Patients indicated for treatment with non-steroidal anti-inflammatory drugs	Cox-2-inhibitors (59 per 100)	Placebo (26 per 100)	88,367 (184)	Unclear	Admission for heart failure (Unclear)	rR: 2.28 (1.62 to 3.2) NNT: 3 (2 to 6) I^2: Unclear	Moderate	No	?

[a]Median hospitalisation event rate observed across the trials contributing to the pooled estimate. [b]Means and standard deviations, unless otherwise specified. Mean of means and median ages in trials contributing to the pooled estimate. Not all included trials reported age in a form that could be averaged. [c]Not all included trials reported follow-up in a form that could be averaged. [d]Moderate or high quality evidence according to the Grading of Recommendations Assessment, Development and Evaluation working group criteria. [e]See Table 3 for detailed description of the summary symbols. (+) denotes a positive overall balance of benefit to harm, (-) denotes a negative overall balance of benefit to harm, and (?) denotes an unclear balance of benefit to harm. [f]Martínez-González (2014) showed a decrease in admissions. It was a newer review but excluded one of the trials included by Laurant as it did not meet the intervention criteria; nurses acting as the main figure with autonomous or delegated clinical responsibility for tasks that would have formerly been performed by physicians alone. Abbreviations: CI= confidence interval; COPD= chronic obstructive pulmonary disease; ED= emergency department; f/u= follow-up; HF= heart failure; ID No.=identification number; NNT= number needed to treat to avoid one emergency hospital admission; OR= odds ratio; RCTs= randomised controlled trials; RR= risk ratio; rR= rate ratio.

3.6 Discussion

The structure of the discussion follows a modified version of the recommendations made in the British Medical Journal by Dochery and Smith (1999).[69] A summary of findings is stated followed by a discussion of the results in the context of existing research, the strengths and limitations, implications for policy, practice, and research, and conclusions. This structure is used in all of the results chapters in this thesis and for the overall discussion and conclusions in chapter 9.

3.6.1 Summary of findings

This was a systematic review of systematic reviews to identify and prioritise evidence-based interventions that reduce emergency hospital admissions in adults. There were 306 reviews included, representing a large underlying evidence base of RCTs reporting hospital admissions outcomes (1,667 RCTs; 1,031,163 patients).

The included reviews covered a wide range of patient populations (93 unique diseases, conditions, or circumstances) and interventions (105 medications; 63 health systems intervention; and 20 diagnostic, medical, and surgical interventions). The quality of reviews was generally good according to AMSTAR criteria (mean AMSTAR score 8/11, SD 2/11).

Within the reviews were 1,431 treatment comparisons reporting hospital admissions outcomes. High or moderate quality evidence was identified for 56 unique interventions tested in 31 patient populations. Of these 56 prioritised interventions, 43 had a favourable overall balance of benefit to harm.

Approximately half of these prioritised interventions were for ongoing community-based management of patients with major chronic disease including asthma, COPD, heart failure, chronic ischaemic heart disease, and schizophrenia. There were also a few community-focused interventions for reducing admissions in broad, non-disease specific populations including elderly people, patients presenting to primary care, and frequent health care users.

The other half of the prioritised interventions were for reducing readmissions by targeting the transition out of hospital and the post-discharge period. These also focused on major chronic disease populations (i.e., asthma, COPD, heart failure, chronic ischaemic heart disease, schizophrenia) with a minority of discharge interventions for non-disease specific groups (i.e. any hospitalised patient, patients discharged with malnourishment).

3.6.2 Findings in the context of existing research

This study fills an important gap in the literature as the first systematic investigation of interventions to reduce hospital admissions without restriction by type of intervention or disease group. Previous reviews have identified few effective interventions.[23,24,70–72] The findings in this chapter expand on this previous research by identifying high or moderate quality evidence for 56 interventions that reduce admissions across 31 patient populations, including 43 interventions with a favourable overall balance of benefit to harm.

Previous reviews on interventions that reduce hospital admissions

Previously, the most comprehensive effort to summarize the literature across patient populations and interventions was a series of multiple systematic reviews on health systems-type interventions (i.e., organisational, delivery, and access to care) by Purdy et al. (2012). Purdy et al. identified a small number of effective interventions, including education and self-management for asthma and chronic obstructive pulmonary disease, exercise and rehabilitation in COPD and coronary heart disease, and specialist clinics in heart failure.

Similar to Purdy et al., this review found little evidence for effective access to care interventions. Only 17 of the 306 included studies (6%) examined interventions that targeted elements of access.[67] There were no effective access to care interventions for non-disease specific populations although there were three effective interventions with high or moderate quality evidence for heart failure patients: home visits after hospital discharge; structured telephone support; and telehealthcare and pre-arranged direct patient contact.

The findings of this review significantly expand on Purdy et al. in five ways. Firstly, this review identified 30 medications and four diagnostic, medical, and surgical interventions that significantly reduce hospital admissions.

Secondly, this review included mental health patients, an important population excluded from the Purdy et al. reviews. This review found that second generation antipsychotics, antipsychotic maintenance therapy, intensive case management, collaborative care, and education and self-management effectively reduce admissions in several patient groups with severe or chronic mental health issues (e.g., schizophrenia and related disorders, personality disorders, bipolar, and depression with psychotic features).

Thirdly, this review identified additional effective interventions within the realm of health systems interventions including: pharmacist directed or collaborative care in COPD and coronary heart disease; collaborative care for bipolar disorder; community-based multifactorial interventions for the elderly; multi-disciplinary care, non-invasive telemonitoring, hospital-initiated case management, nurse-led titration of medication, comprehensive diseases management programs, telehealth with patient outreach, and home visiting programs for heart failure; intensive case management for schizophrenia and schizophrenia-like psychosis; nurse-led primary care; early supported discharge and hospital at home for COPD; and hospital-based discharge planning for hospitalised patients.

Fourthly, this review showed that some of the interventions identified by Purdy et al. are effective in additional patient populations, specifically education and self-management interventions for frequent users of the health care system, severe or chronic mental illnesses, and heart failure.

Fifthly, this review robustly assessed the quality of evidence using GRADE criteria, while Purdy et al. relied solely on the Cochrane risk of bias tool.

Other than the Purdy et al. review, there have been two other wide-scoping reviews examining interventions to reduce hospital admissions across patient groups: Damery et al (2016) and McBain (2015).[75]

Damery et al. conducted an overview focused on integrated care interventions in chronic disease patients (i.e., interventions to coordinate care across two or more health and/or social care settings). The study included reviews of randomised controlled trial and quasi-experimental data and categorised interventions based on the direction and significance of effect estimates. The authors restricted focus to ten chronic diseases, not including mental health patients, and examined a range of hospital activity indicators including admissions, readmissions, A&E visits, length of stay, and cost. The study included 50 reviews on case management, the chronic care model, discharge management, complex interventions, multidisciplinary teams and self-management.[24] The authors found that the most effective interventions for reducing hospital admissions were discharge planning and post-discharge support for hospital inpatients, multi-disciplinary team care with condition-specific specialists or pharmacists, and interventions based on multiple components of the chronic care model, while the least effective intervention was case management.

The findings in this chapter were similar to Damery et al. with regards to discharge planning, multi-disciplinary teams, and multi-component chronic care model interventions. This review adds confidence to these findings with formal quality assessments showing that these interventions are supported by high or moderate quality evidence. There is, however, a discrepancy in the findings for case management. This review included a broader array of chronic disease patients and more recently published studies. These additional data suggest that hospital-initiated case management for heart failure and intensive case management for schizophrenia are effective.

Furthermore, Damery et al. found that interventions focusing on specific diseases were more numerous and effective than those applicable to broad groups of chronic disease patients. This review found a similar trend, with fewer effective integrated care interventions for non-disease specific groups, such as elderly people, compared to disease specific groups, such as heart failure. This trend extended

beyond the evidence for integrated care interventions and was true of all health systems interventions. This suggests that designing interventions for specific populations may produce greater benefit than interventions intended for mixed populations, such as patients being discharged from hospital.

McBain conducted an overview on the impact of self-monitoring in chronic illness on health care utilisation. The authors included studies in which patient self-monitoring was the primary focus or a key component of interventions. The authors included 17 systematic reviews and showed that self-monitoring was associated with significant reductions in hospitalisation and re-admissions to hospital for patients with heart failure and chronic obstructive pulmonary disease.

The results of this review were similar to those in the McBain study. Telemonitoring and structured telephone support were shown to reduce admission in heart failure and were supported by high or moderate quality evidence. Telehealthcare in chronic obstructive pulmonary disease was also shown to be effective in this review but was graded as low quality evidence.

Literature on medications and hospital admissions

The findings of this review complement a growing body of evidence about drug-related hospital admissions. Systematic reviews of observational studies have shown that approximately 3% of all emergency hospitalisations are related to suspected adverse drug reactions and drug-drug interactions.[76–81] Drugs often associated with hospital admissions include antiplatelet drugs, diuretics, renin-angiotensin system blockers, NSAIDs, and anticoagulants. However, these reviews have not considered the number of admissions these drugs help to avoid and therefore have not provided evidence on their net effect on admissions. This study complements this literature, as it shows a strong body of evidence supporting a beneficial reduction in admissions for renin-angiotensin system blockers (ACE inhibitors, ARBs) and aldosterone receptor antagonists.

The study also identified high or moderate quality evidence of a harmful increase in cause-specific admissions due to heart failure from the use of COX2 inhibitors and pneumonia from the use of inhaled corticosteroids in COPD patients.

Many of the other drugs commonly associated with drug-related admissions did not appear in this study. Several reviews of RCTs focusing on antiplatelet drugs and anticoagulants were excluded because they reported admissions as part of composite outcomes. The net effect of antiplatelet drugs and anticoagulants on emergency hospital admissions is therefore not clear from the published systematic review literature.

Meta-epidemiology and methodological literature

In addition to the content specific findings of this chapter, the methodology used in this systematic review of systematic reviews adds to a growing literature on meta-epidemiological approaches.[31,82–84]

To the best of the thesis author's knowledge, this was the first review of reviews to examine a single outcome with no restriction on interventions or patient disease groups. Furthermore, the method utilised in this review to prioritise interventions by conducting GRADE quality assessments on statistically significant effect estimates has not been reported elsewhere. In fact, there is little guidance on assessing the quality of evidence for outcome data in reviews of reviews.[82]

Other overview authors have relied solely on statistical evaluations of pooled effect estimates to determine the strength of a body of evidence for a particular association. For example, Professor John Ioannidis, a pioneer in meta-epidemiological research, has published several reviews of reviews (i..e umbrella reviews) and utilised a statistical method to determine the strength of evidence for an association between an exposure and outcome.[56–58,85] The method considers the size of pooled effect estimates reported in reviews, the presence of statistical significance, tests for small study effects, and agreement in the size and direction of effects between observational data and RCTs.[56]

The GRADE method used in this chapter similarly considers statistical elements including the consistency of effect between studies, the optimal information size, and tests for publication bias however, it also includes assessments of the risk of bias using the Cochrane tool and contextual elements that may affect the strength

of evidence such as the similarity of the settings, patients, interventions, comparators, and outcomes between studies.

These additional considerations of bias and contextual elements may provide a more robust assessment of the evidence. Given the large and growing volume of the evidence in many health care disciplines, novel approaches are required to identify and prioritise the highest-quality evidence. This review contributes to that methodological literature.

3.6.3 Strengths

This study has three key strengths. Firstly, it was comprehensive. Hospital admissions data on over one million patients was identified, analysed, and synthesized in order to identify the highest quality evidence for interventions that affect emergency hospital admissions. Furthermore, the inclusion of all interventions and adult patient populations sets this review apart from previous research on interventions to reduce hospital admissions.

Secondly, the methodological approach was robust. This study included formal assessments of the quality of reviews using AMSTAR criteria and assessments of the quality of evidence using GRADE criteria. To ensure the applicability of the findings for the UK context, the proportion of evidence from OECD countries was quantified and incorporated into quality assessment of pooled effect estimates. Additionally, all components of the review were completed either independently by two reviewers, or by one reviewer (thesis author) and verified by a second.

Thirdly, the impact of duplicate RCT evidence between systematic reviews was reduced by excluding outdated reviews and those with duplicate trial data sets. This required extracting and analysing over 5,000 rows of data to ultimately identify 1,667 unique randomised controlled trials that reported hospital admissions.

3.6.4 Limitations

This study has some limitations. Firstly, although data were extracted and reported for all effect estimates, quality assessments were only conducted on significant estimates. While it may be useful for decision makers and researchers to know the quality of evidence for interventions that are ineffective, the aim was to support decision making by identifying and prioritising interventions that are effective. Furthermore, evidence of no effect was considered during analysis: all treatment comparisons were analysed to identify contradictory effect estimates. It is important to note that there were few instances in which effective interventions with high or moderate quality evidence were contradicted by evidence showing no effect. Most commonly, this occurred when more recently published reviews reported different results than older reviews on the same topic. In these cases, the older reviews included a small number of trials that were not included in the more recent reviews and, therefore, the older studies contained unique trial data. This is how some older studies made it through the process designed to eliminate duplicated evidence.

Secondly, outcomes other than hospital admissions were not examined in-depth. Other outcomes of relevance for interventions that reduce hospital admissions include mortality, cost, adverse events, patient satisfaction, patient quality of life, and other types of health care utilisation (e.g., hospital length of stay). Examining all of these outcomes in-depth would not have been feasible. Hence, the overall balance of benefit to harm for each intervention was characterised based on the conclusions of the reviews. However, the reported conclusions often did not include information about the quality of evidence for other outcomes. Furthermore, the judgements about overall benefit to harm did not include input from patients or policy-makers. Further work may be needed to determine whether the overall balance of benefit to harm is acceptable according to key healthcare stakeholders. Users of this review may consider combining the results with clinical expertise and patient input when making clinical or policy decisions.

Thirdly, grouping health systems interventions into mutually exclusive categories was challenging. Although the Effective Practice and Organisation of Care Group (EPOC) taxonomy was used, many interventions were not mutually exclusive, and elements of some interventions overlapped. For example, many interventions

included a self-management component. Users of the review may assess the elements of interventions themselves using the online database.

Fourthly, reviews reporting hospital admissions as part of composite end-points were excluded. Therefore, potentially valuable interventions may have been missed. However, by eliminating composite outcomes, users of this study can be confident that the effective interventions identified have a significant effect on hospital admissions.

Fifthly, network meta-analysis was not conducted. This would have allowed a formalised comparison between interventions to prioritise the most effective interventions for reducing hospital admissions. However, this approach was not pursued due to the heterogeneity in the interventions, comparisons, patients, and settings in the reviews.

Sixthly, the tool (AMSTAR) used to assess the quality of reviews has been superseded by the AMSTAR 2 and the “Risk of Bias in Systematic Reviews” tool (ROBIS.[86,87] These tools include more criteria than AMSTAR 1 and, therefore, may provide a more comprehensive assessment. However, at the time of completing the study, AMSTAR 1 was the best tool available.

Seventhly, for feasibility reasons, only English language reviews were included. As a result, effective interventions examined in non-English reviews may have been excluded, such as potentially relevant Spanish and Scandinavian literature on reducing hospital admissions.

3.6.5 Implications for policy and practice

In this section, broad implications are discussed first, followed by implications related to different types of interventions (i.e. medications; health systems; diagnostic, medical, surgical)

Broad implications

The results of this study may inform initiatives to reduce emergency hospital admissions in the UK and other OCED countries. The findings may help to prioritise quality measurement and improvement initiatives, inform the allocation of resources for new or continuing services, and may inform the design of services to reduce hospital admissions.

Most of the effective interventions with high or moderate quality evidence identified in this review formed part of ongoing chronic disease management in ambulatory care settings and during the transition out of hospital. Therefore, implementing or optimising use of these interventions in practice may require coordination of multiple stakeholders in different settings over time. Furthermore, there were few interventions that reduced admissions from the emergency department and few follow-up times under one month. This suggests there are few “quick-fixes” for reducing emergency hospitalisations.

The results suggest that efforts that reduce admissions in specific patient populations should be prioritised over those that apply to non-specific groups. The majority of effective interventions targeted patients with specific diseases and only a minority targeted broadly defined groups, such as elderly people.

Much of the policy and grey literature on reducing hospital admissions has focused on admissions for ambulatory care sensitive conditions (ACSC). These are considered the most avoidable or preventable emergency admissions. The findings of this study provide a comprehensive summary of the effective interventions available for reducing ACSC admissions. Of the 56 prioritised interventions, 22 were shown to reduce admissions for ACSC - primarily exacerbations of heart failure and exacerbations of chronic obstructive pulmonary disease. Therefore, these findings

may help clinicians and decision-makers to achieve much needed reductions in admissions for ACSC.

Implications of results for medications, diagnostic interventions, medical procedures, and surgical interventions

This review identified 24 medications, diagnostic interventions, medical procedures, and surgical interventions that significantly reduced hospital admissions, had a favourable overall balance of benefit to harm, and were supported by high or moderate quality evidence. Although these types of interventions may not be utilised for the sole purpose of reducing hospital admissions, they represent high-value activities in the overall care of patients that should be optimally utilised in practice.

Some of these high-value interventions are already a component of routine clinical practice in OECD countries. Therefore, these interventions could be considered by clinicians, policymakers, and commissioners when auditing care and for prioritising quality measurement and improvement efforts. For example, the results include well-known medications for five major chronic diseases such as ACE inhibitors, beta-blockers, and angiotensin-ll receptor blockers in heart failure; statins for stable coronary artery disease; long-acting beta-2 agonists for chronic obstructive pulmonary disease; anticholinergics for asthma; and second-generation antipsychotic medication in schizophrenia. These diseases account for about 5% of all emergency admissions in OECD countries[88–90], and millions of hospital admissions each year globally.[91–95] Yet, there is evidence of significant variation in prescribing of some these medications in the UK and other OECD countries, including under-dosing and under-prescribing.[96–98] Therefore, improving utilisation of these medications could translate to substantial reductions in hospital admissions.

Clinicians and policymakers may focus on minimising gaps in prescribing, correcting over/under-dosing, and improving patient adherence. However, the specific target of any medicine optimisation initiatives should be driven by locally identified short-falls in care. Given that the majority of the effective medications were for reducing admissions from ambulatory care settings, it is likely that community-based health care providers (general practitioners, pharmacists, nurses) will play a central role in

these efforts, with support from commissioners and policy makers in the health service.

The results of this study reinforce the dangers of prescribing COX2 inhibitors for patients at risk of cardiovascular disease and inhaled corticosteroids for patients with moderate to severe stable COPD. It is therefore reassuring that the harms associated with the use of these drugs and steps to ensure that they are used appropriately, if at all, have been reported widely in clinical and government prescribing guidelines.[99–101]

Only three of the medical and surgical interventions were judged to have a favourable overall balance of benefit to harm: cardiac resynchronisation therapy in heart failure with reduced ejection fraction and a QRS duration $\geq$127 ms; early/routine coronary angiography in select patients with acute coronary syndromes presenting to the hospital; and percutaneous aspiration for pneumothorax. These are invasive procedures requiring in-patient hospital care. Ensuring that eligible patients receive these treatments would fall within the remit of hospital-based physicians with the support of hospital administrators and health care commissioners.

Implications of results for health systems interventions

This review identified 19 health systems interventions that significantly reduced hospital admissions, had a favourable overall balance of benefit to harm, and were supported by high or moderate quality evidence.

Some of the effective health systems interventions identified in this review may be components of routine care in certain settings. For example, hospital at home services and specialist heart failure clinics operate in parts of the UK.[102] In these settings, the findings of this study may serve to justify continued funding these initiatives in times of austerity, given their value for reducing emergency hospital admissions. The findings may also support the expansion of these services to ensure adequate coverage for relevant patient populations.

In settings where these interventions are not being utilised clinicians, policy makers, and commissioners may consider implementing them. These stakeholders may combine the results of this review with local needs assessments, clinical expertise, and patient input to determine which of the interventions would be of highest value in their setting.

Some of the interventions in this study align with NHS aims to reform health care and, therefore, may be prime candidates for implementation. For example, NHS England has started pilot projects to assess expansion of the roles of pharmacists and nurses.[103–106] The findings of this review support such an initiative and may help to orient these efforts towards populations that may gain the most benefit. Pharmacist directed or collaborative care was shown to be effective in reducing hospital admissions in patients with heart failure, chronic ischaemic heart disease, acute coronary syndromes, and chronic obstructive pulmonary disease while nurse-led medication titration for heart failure patients and nurse-led primary care in general populations were also shown to be effective.

Implications for interventions with low or very low quality evidence

In addition to high- and moderate-quality evidence, this study identified 53 interventions with low or very low quality evidence for reducing admissions (21 medications, 27 health systems interventions, and five diagnostic, medical and surgical interventions). According to the GRADE working group, these estimates for reducing admissions are likely to change if additional research were conducted. Therefore, given the uncertainty around the estimates of effects for these interventions, these are not recommended as priorities for reducing emergency admissions. However, the level of evidence required to act may vary depending on the circumstances, the stakeholders involved, and the available evidence (which may change over time). If limited evidence is available and there is a pressing need to act, lower quality evidence may be sufficient to justify cautious implementation of an intervention. The prioritisation of high and moderate quality evidence does not prevent stakeholders from using the low and very low quality evidence if justified in the context of their health care settings; however, a robust evaluation is recommended to ensure that resources are appropriately allocated to those interventions most likely to impact on practice.

3.6.6 Future research

The findings of this review highlight several areas of valuable future research.

Future research should examine efforts to promote use of the effective interventions identified in this review, including assessments of clinical practice guidelines and quality measurement and improvement frameworks in the UK. This would serve to identify useful interventions that are not yet on the "clinical radar" and interventions that may be candidates for quality improvement. This research is the focus of the next chapter.

Future research on reducing admissions should target patients with multi-morbidity, patients at the end of life, and patients with acute ambulatory care sensitive conditions. Of the 306 included reviews, only 11 (4%) included patients with multi-morbidity and one (<1%) included patients at the end of life. There were only three effective interventions for these patient groups. Given the high and increasing rates of emergency hospitalisation for patients with multi-morbidity and at the end of life there is a clear need for more research.[76,107,108]

Researchers should consider increasing the evidence base for six key acute ambulatory care sensitive conditions: urinary tract infection, diarrhoea and gastroenteritis of presumed infectious origin, cellulitis, acute upper respiratory infections, convulsions, and viral and other specified intestinal infections. Hospital admissions for these conditions are increasing at a higher rate than any other type of ACSC admission in the UK.[109] However, there were no studies in this review that reported outcomes for these conditions.

Researchers should consider reporting rates of hospital admissions, as opposed to ratio measures; 1,237 of the 1,431 (86%) treatment comparisons in this review were reported as odds or risk ratios. These are crude measures of hospitalisation as they assess admission as a binary outcome - present or absent. These effect measures therefore equate a patient who has had one admission during follow-up with a patient who has had multiple admissions. In patients with chronic diseases, such as heart failure and COPD, hospital admissions are common and rate-based measures may have greater utility in evaluating the effectiveness of interventions.

Researchers should consider defining a minimally important difference (MID) in hospital admissions. For patient reported outcomes, such as quality of life, the MID is often defined by patients' perception of what constitutes an important difference in their lives.[110] In contrast, the minimally important difference for physiological measures, such as blood pressure, is usually based on the predictive validity of affecting future events, such as stroke. Patients and health service stakeholders may be able to define a minimally important difference for hospital admissions, although it may vary by setting.

This review was effort and time intensive given the volume of included evidence. To make completion of such a review more efficient in the future, different methodological decisions could be made. Due to the requirements of the DPhil, the thesis author extracted data and analysed all 306 reviews. A group of 15 second reviewers was needed to duplicate and verify his work. It would be faster to have multiple teams of two researchers working in parallel.

Also, it is possible that the scope of the review could have been narrowed without having altered the main findings. Given the large volume of evidence for patient groups with minimal impact on emergency admissions (i.e., multiple sclerosis, hepatic encephalopathy, idiopathic spontaneous pneumothorax, lupus) it may have been more efficient to have focused on populations that contribute substantially to emergency admissions (i.e. heart failure, acute/chronic ischaemic heart disease, COPD, asthma, mental health patients, elderly people, day surgery patients); large patient groups (i.e., hospitalised patients, patients presenting to primary care); or admissions that are considered avoidable (acute and chronic ambulatory care sensitive diseases).

Another option could have been to focus on the 40% of reviews that listed hospital admissions as a primary outcome.

Given that the majority of included evidence was for patients with chronic disease, general populations, and for ambulatory care sensitive conditions, these approaches would likely have yielded the same broad findings while having increased the efficiency of the review.

Researchers should explore innovations in evidence synthesis methods in order to keep pace with the rapid rate of evidence production. Future research should explore “living” systematic reviews and automation of systematic reviews, including auto-populated results fields on up-to-date online platforms. These approaches may allow rapid and ongoing incorporation of new studies to keep clinicians and decision makers informed with the best available evidence.

3.7 Conclusions

There is strong evidence for a diverse set of interventions that significantly reduce emergency hospital admissions including medications, health systems interventions, diagnostic tests, medical procedures, and surgical interventions. Most of these effective interventions are intended to form part of ongoing chronic disease management and show benefit after several months of use, suggesting there are few “quick-fixes” for reducing emergency admissions.

These effective interventions may be considered for implementation in practice in order to reduce admission rates. In settings where the interventions are already part of routine care, this study may justify continued funding and potential expansion of services to ensure adequate coverage for relevant populations. These findings may also help to prioritise quality measurement and improvement efforts.

There is also strong evidence for small number of interventions that significantly increase emergency admissions. Use of these interventions should be avoided.

Future research should explore the extent to which effective interventions are being endorsed and used in clinical practice. Research is also needed on interventions for reducing admissions in patients with multi-morbidity, patients at the end of life, and patients with select acute ambulatory care sensitive conditions.

3.8 Chapter summary

- This systematic review of systematic reviews included 306 studies with hospital admissions data from 1,667 randomised controlled trials and 1,031,163 patients
- 1,431 treatment comparisons were extracted and analysed
- The quality of effect estimates was assessed using GRADE criteria
- High or moderate quality evidence was found for 56 interventions that reduced emergency admissions in 31 patient populations including 30 medications, 22 health systems interventions, two diagnostic interventions; and two medical and surgical procedures
- Most of the effective interventions were for patients with major chronic diseases (i.e., asthma, COPD, heart failure, chronic ischaemic heart disease, schizophrenia) while a minority targeted non-disease specific populations (i.e., elderly people, frequent health care users, patient being discharged from hospital, patient presenting to primary care)
- Most interventions formed part of ongoing disease management in ambulatory care settings, while some targeted the transition out of hospital and the post-discharge period after an acute exacerbation of disease
- Future research should explore the extent to which effective interventions are being promoted and used in clinical practice

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Chapter 3. Appendix

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Appendix 3.1 Published protocol

Open Access Protocol

BMJ Open

Protocol for an overview of systematic reviews of interventions to reduce unscheduled hospital admissions among adults

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ABSTRACT

Introduction: Unscheduled hospital admissions are an increasing burden on health systems worldwide. To date, initiatives to reduce admissions have had limited success as it is unclear which strategies effectively reduce admissions and are supported by a strong evidence-base. Therefore, we will conduct an overview to find, assess and summarise all published peer-reviewed systematic reviews of randomised controlled trials that examine the effect of an intervention on unplanned admissions among adults.

Methods and analysis: This is a protocol for a systematic overview of reviews. We will search four databases: Ovid MEDLINE, PubMed, Cochrane Database of Systematic Reviews and the Cochrane Database of Abstracts of Reviews of Effects. We will consider systematic reviews and meta-analyses of randomised controlled trials in adults (≥16 years old) evaluating the effect of any intervention on unscheduled hospital admissions including those to treat, monitor, diagnose or prevent a health problem. We will only include reviews that identified unscheduled hospitalisations as a prespecified outcome. Two authors will independently screen articles for inclusion using a priori criteria. We will assess the quality of included reviews and extract ratings of the quality of evidence from within each review. We will create a hierarchical list of interventions based on estimates of absolute admission reductions and the quality of the evidence. Presentation of results will align with guidelines in the Cochrane Handbook of Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

Ethics and dissemination: Ethics approval is not required. We will submit the results of this study for peer-review publication. The results will inform future research and could be used by healthcare managers, administrators and policymakers to guide resource allocation decisions and inform local implementation and optimisation of interventions to reduce unscheduled hospital admissions.

Strengths and limitations of this study

- We are using a novel methodology to hierarchically rank interventions to reduce unscheduled admissions.
- We anticipate this to be one of the largest overviews of systematic reviews.
- Potentially relevant studies could be missed despite use of robust search strategies.

INTRODUCTION

Over the past decade there have been dramatic increases in the number of unscheduled patient admissions to acute care hospitals in healthcare systems all over the world.[1–5] Unscheduled hospital admissions are unpredictable and occur at short notice because of a perceived need for immediate healthcare.[6] Increases in these non-elective hospitalisations have been reported in Scotland, Wales,[1] the USA,[2 3] Australia,[4] and New Zealand,[5] although the largest and most consistent increases have been in England.[1] Between 2000 and 2012 England experienced a 27% rise from 77 admissions per 1000 population to 98 admissions per 1000.[1]

These increases have seriously strained health systems, primarily due to the cost of caring for hospitalised patients.[7 8] For example, the estimated cost to the National Health Service of unscheduled admission increases in England between 2004 and 2009 was £330 million,[9] with total costs for unscheduled in-patients growing to £12.5 billion in 2013.[1] On-going increases have been deemed financially unsustainable.[1 10] However, cost is not the only issue; unscheduled admissions are problematic for the timely delivery of services as they can result in delays and cancellations for elective operations and procedures.[1]

Appendix 3.2 Search strategies

Table 1. Search strategies

Electronic databases with peer-reviewed literature	
MEDLINE Inception to February 29, 2016 for medication reviews Inception to May 17, 2017 for non-medication reviews	
1	Hospitalization/
2	Patient admission/
3	Patient readmission/
4	(admission? or admitted or readmission? or re-admission? or readmitted or re-admitted or hospitali* or rehospitali* or re-hospitali*).ti,ab.
5	1 or 2 or 3 or 4
6	Cochrane database of systematic reviews.jn. or search.tw. or meta-analysis.pt. or Medline.tw. or systematic review.tw.
7	5 and 6
Cochrane Database of Systematic Reviews Inception to February 29, 2016 for medication reviews Inception to May 17, 2017 for non-medication reviews	
1	MeSH: Hospitalization
2	MeSH: Patient Admission
3	(admission or admitted or readmission or re-admission or readmitted or re-admitted or hospitali* or rehospitali* or re-hospitali*):ti,ab
4	(#1 OR #2 OR #3)
Database of Abstracts of Reviews of Effects Inception to February 29, 2016 for medication reviews Inception to May 17, 2017 for non-medication reviews	
1	MeSH: Hospitalization
2	MeSH: Patient Admission
3	(admission or admitted or readmission or re-admission or readmitted or re-admitted or hospitali* or rehospitali* or re-hospitali*):ti,ab
4	(#1 OR #2 OR #3)
PubMed January 1, 2014 to July 1, 2014 AND August 29, 2015 to February 29, 2016 for medication reviews January 1, 2014 to July 1, 2014 AND August 29, 2015 to February 29, 2016 AND Dec 17, 2016 to May 17, 2017 for non-medication reviews	
1	((((((((admission[Title/Abstract]) OR admitted[Title/Abstract]) OR readmission[Title/Abstract]) OR re-admission[Title/Abstract]) OR readmitted[Title/Abstract]) OR re-admitted[Title/Abstract]) OR hospitali*[Title/Abstract]) OR rehospitali*[Title/Abstract]) OR re-hospitali*[Title/Abstract]
2	Date limited to six months before search date (to capture articles not yet indexed in MEDLINE)
3	Limited using built in Systematic Reviews
Grey literature	
Google scholar targeted search Inception to April 28, 2016 for medication reviews Inception to May 17, 2017 for non-medication reviews	
1	(((hospital* OR (hospital AND admi*) OR (readmi*) OR (re-admi*)) AND ((systematic review) OR (literature review) OR ((meta) AND (analy*))) AND ((random*) OR (trial) OR (RCT)))
2	Sorted by relevance
Google scholar broad search Inception to April 28, 2016 for medication reviews Inception to May 17, 2017 for non-medication reviews	
1	Hospital admissions AND interventions AND systematic review
2	Sorted by relevance

National Institutes of Health Research Website https://www.journalslibrary.nihr.ac.uk/programmes/ Journals library; ongoing research; programme studies, all statuses; health technology assessment programmes Inception to April 28, 2016 for medication reviews Inception to May 17, 2017 for non-medication reviews	
1	hospital admissions
Research Council United Kingdom Website (seven major funding agencies) http://gtr.rcuk.ac.uk/search/publication?term=admission+AND+systematic+review&fetchSize=25&selectedSortableField=score&selectedSortOrder=DESC&fields=per.on%2Cper.fn%2Cpub.a%2Cper.sn%2Cper.org.n%2Cpub.t%2Cper.pro.abs%2Cper.pro.t%2Cper.fnsn%2Cpro.t%2Corg.n%2Cpro.gr%2Cpro.a Inception to April 28, 2016 for medication reviews Inception to May 17, 2017 for non-medication reviews	
1	Hospital admissions (journal article/review)
1	Admission AND systematic review
1	Admission AND review
King's Fund Website http://kingsfund.koha-ptfs.eu Inception to April 28, 2016 for medication reviews Inception to May 17, 2017 for non-medication reviews	
1	Unplanned hospital admissions
2	Unscheduled hospital admissions
3	Emergency hospital admissions
4	1 OR 2 OR 3
5	Review
6	4 AND 5
Nuffield Trust Website http://www.nuffieldtrust.org.uk/ Inception to April 28, 2016 for medication reviews Inception to May 17, 2017 for non-medication reviews	
1	Admissions
1	Emergency
1	Unplanned
1	Unscheduled
1	Hospitalised
1	Hospitalisation
Other sources	
Experts June 2014 to April 28, 2016 for medication reviews June 2014 to May 17, 2017 for non-medication reviews	
1	Approached researchers that presented on unscheduled hospital admissions at a King's fund conference, Evidence Live 2015 conference, and the 2015 Society for Academic Primary Care Conference. I described the research and asked the researchers to identify relevant systematic reviews.
Reference lists of included reviews	
1	All included systematic reviews were assessed.

Appendix 3.3 ICD-10 codes for ambulatory care sensitive conditions

Table 2. ICD-10 codes for ambulatory care sensitive conditions in common use in the National Health Service

ACSCs in common use in the NHS (n=19)	ICD-10 codes
Angina	I20, I24.0 I24.8 I24.9 I25 R072 R073 R074 Z034 Z035
Asthma	J45, J46
Cellulitis	L03 L04 L08.0 L08.8 L08.9 L88 L98.0 I891 L010 L011 L020 to L024 L028 L029
Congestive heart failure	I11.0 I50 J81 I130 I255
Convulsions and epilepsy	G40 G41 R56 O15 G253 R568
Chronic obstructive pulmonary disease	J20 J41 J42 J43 J47 J44 J40X
Dehydration and gastroenteritis	E86 K52.2 K52.8 K52.9 A69.0 A020 A04 A059 A072 A080 A081 A083 A084 A085 A09 K520 K521
Dental conditions	A69.0 K02 K03 K04 K05 K06 K08 K09.8 K09.9 K12 K13
Diabetes complications	E10.0–E10.8 E11.0–E11.8 E12.0–E12.8 E13.0–E13.8 E14.0–E14.8 H66 E139, E149
Ear, nose, and throat infections	H66 H67 J02 J03 J06 J31.2 J040
Gangrene	R02
Hypertension	I10 I11.9
Influenza and pneumonia	J10 J11 J13 J14 J15.3 J15.4 J15.7 J15.9 J16.8 J18.1 J18 J189 J120 J121 J122 J128 J129 J160 A481 A70x
Iron-deficiency anaemia	D50.1 D50.8 D50.9 D460 D461 D463 D464 D510–D513 D518 D520 D521 D528 D529 D531 D571 D580 D581 D590–D592 D599 D601 D608 D609 D610 D611 D640 to D644 D648
Nutritional deficiency	E40 E41 E42 E43 E55.0 E64.3
Other vaccine-preventable diseases	A35 A36 A37 A80 B05 B06 B16.1 B16.9 B18.0 B18.1 B26 G00.0 M01.4
Pelvic inflammatory disease	N70 N73 N74
Perforated/bleeding ulcer	K25.0–K25.2 K25.4–K25.6 K26.0–K26.2 K26.4–K26.6 K27.0–K27.2 K27.4–K27.6 K280–282 K284–K286 K920 K921 K922 K20x K210 K219 K221 K226
Pyelonephritis	N10 N11 N12 N13.6 N300 N390 N159 N308 N309

Appendix 3.4 Revised Cochrane Effective Practice and Organisation of Care taxonomy

Table 3. Revised Cochrane Effective Practice and Organisation of Care taxonomy

Domain: Delivery Arrangements Changes in how, when and where healthcare is organized and delivered, and who delivers healthcare.		
Category: How and when care is delivered		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Group versus individual care	Comparisons of providing care to groups versus individual patients, for example intensive group therapy, group vs individual antenatal care.	
Queuing strategies	A reduction or increase in time to access a healthcare intervention, for example managed waiting lists, managing ER wait time.	
Coordination of care amongst different provider	Organizing different providers and services to ensure timely and efficient delivery of healthcare.	
Quality and safety systems	Essential standards for quality of healthcare, and reduction of poor outcomes related to unsafe healthcare.	
Triage	Management of patients attending a healthcare facility, or contacting a healthcare professional by phone, and receiving advice or being referral to an appropriate service	
Compulsory or court-ordered care	Provision of health care services when consent for care is not provided by the patient but by a legal guardian or representative or when the provision of care is legally mandated.	Sub-category added.
Category: Where care is provided and changes to the healthcare environment		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Environment	Changes to the physical or sensory healthcare environment, by adding or altering equipment or layout, providing music, art.	
Outreach services	Visits by health workers to different locations, for example involving specialists, generalists, mobile units	
Site of service delivery	Changes in where care is provided, for example home vs. healthcare facility, inpatient vs outpatient, specialized vs. non-specialized facility, walk in clinics, medical day hospital, mobile units	Includes short/brief hospital admission and early discharge.
Size of organizations	Increasing or decreasing the size of health service provider units	
Transportation services	Arrangements for transporting patients from one site to another	

Category: Who provides care and how the healthcare workforce is managed Changes in who provides care, to include the qualifications of who provides care; and the recruitment, distribution and retention of health workers		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Role expansion or task shifting	Expanding tasks undertaken by a cadre of health workers or shifting tasks from one cadre to another, to include tasks not previously part of their scope of practice.	
Self-management Education and self-management Exercise and self-management Psychosocial therapy and self-management	Shifting or promoting the responsibility for healthcare or disease management to the patient and/or their family. Education and self-management: Providing structured information in a manner conducive to improving knowledge about matters relevant to health and/or functioning and for the purpose of assisting self-management (care with assistance of health professionals) and self-care (patient engaging in activities to promote their health and well-being).[1] Exercise and self-management: A planned episode of physical activity to improve or maintain a person's health or fitness with the purpose of assisting in self-care (patient engaging in activities to promote their health and well-being). Psychosocial therapy and self-management: Providing therapeutic communication based upon the systematic application of psychological theory with the purpose of assisting self-management (care with assistance of health professionals) and self-care (patient engaging in activities to promote their health and well-being). [2]	Sub-category expanded to explicitly include education, exercise, and psychosocial therapy components as they were often included for the purpose of assisting in self-management and self-care. Exercise, rehabilitation, and psychosocial therapy were categorised separately from self-management (using the WHO ICHI framework) when they were not a component of improving a patient's self-management or self-care.
Length of consultation	Changes in the length of consultations	
Staffing models	Interventions to achieve an appropriate level and mix of staff, recruitment and retention of staff, and transitioning of healthcare workers from one environment to another, for example interventions to increase the proportion of healthcare workers in underserved areas.	
Exit interviews	A verbal exchange or written questionnaire between employees' resignation and last working day	
Movement of health workers between public and private care	Strategies for managing the movement of health workers between public and private organizations	

[1] World Health Organisation. International Classification of Health Interventions. http://www.who.int/classifications/ichi/en/. Published 2018.
[2] World Health Organisation. International Classification of Health Interventions. http://www.who.int/classifications/ichi/en/. Published 2018.

Sub-category	Definition	Notes on taxonomy revisions
Pre-licensure education	Changes in pre-licensure education of health professionals	
Recruitment and retention strategies for underserved areas	Strategies for recruiting and retaining health workers in underserved areas	
Recruitment and retention strategies for district health managers – LMIC	Interventions for hiring, retaining and training district health systems managers in LMIC	
Category: Coordination of care and management of care processes Changes in how health workers interact with each other or patients to ensure timely and efficient delivery of healthcare.		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Care pathways	Aim to link evidence to practice for specific health conditions and local arrangements for delivering care.	
Case management	Introduction, modification or removal of strategies to improve the coordination and continuity of delivery of services i.e. improving the management of one "case" (patient)	
Medication review	"A structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste."[3]	Sub-category added. Purpose of medication review is to coordinate multiple medication regimens, likely prescribed by different health care providers. Therefore, coordination of care is a key element.
Communication between providers	Systems or strategies for improving the communication between health care providers, for example systems to improve immunization coverage in LMIC	
Comprehensive geriatric assessment	A multidimensional interdisciplinary diagnostic process focused on determining a frail older person's medical, psychological and functional capability to ensure that problems are identified, quantified and managed appropriately	
Continuity of care	Interventions to reduce fragmented care and undesirable consequences of fragmented care, for example by ensuring the responsibility of care is passed from one facility to another so the patient perceives their needs and circumstances are known to the provider.	

[3] Task Force on Medicines Partnership, The National Collaborative Medicines Management Services Programme. Room for review - A guide to medication review: the agenda for patients, practitioners and managers. *Med Partnerschip*. 2002:48.

Sub-category	Definition	Notes on taxonomy revisions
Discharge planning	An individualized plan of discharge to facilitate the transfer of a patient from hospital to a post-discharge setting.	
Disease management	Programs designed to manage or prevent a chronic condition using a systematic approach to care and potentially employing multiple ways of influencing patients, providers or the process of care.	
Integration	Consolidating the provision of different healthcare services to one (or simply fewer) facilities.	
Specialist/disease focused clinics	"Out-patient clinics that aim to utilise optimal management of disease protocols focusing on optimal treatment of the condition, education of patient and family or carer about the signs and symptoms of worsening disease and medication compliance." [4]	Sub-category added. Similar to care pathways, disease management, and integration.
Packages of care	Introduction, modification, or removal of packages of services designed to be implemented together for a particular diagnosis/disease, e.g. tuberculosis management guidelines, newborn care protocols.	
Patient-initiated appointment systems	Systems that enable patients to make urgent appointments when they feel they cannot manage their condition or where something has changed unexpectedly	
Procurement and distribution of supplies	Systems for procuring and distributing drugs or other supplies.	
Referral systems	Systems for managing referrals of patients between health care providers	
Shared care	Continuing collaborative clinical care between primary and specialist care physicians	
Shared decision-making	Sharing healthcare decision making responsibilities among different individuals, potentially including the patient.	
Teams	Creating and delivering care through a multidisciplinary team of healthcare workers.	
Transition of Care	Interventions to improve transition from one care provider to another, for example adolescents moving from child to adult health services.	
Category: Information and communication technology (ICT) ICT used by healthcare organizations to manage the delivery of healthcare, and to deliver healthcare		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Health information systems	Health record and health management systems to store and manage patient health information, for example electronic patient records, or systems for recalling patients for follow-up or prevention e.g., immunization.	

[4] Purdy S Alyson H, Rebecca T, Mala M, Dyfed H, Peter B, Glyn Ee SP. Interventions to reduce unplanned hospital admission: a series of systematic reviews.

Sub-category	Definition	Notes on taxonomy revisions
The use of information and communication technology	Technology based methods to transfer healthcare information and support the delivery of care.	
Smart home technologies	Electronic assistive technologies	
Telemedicine	Exchange of healthcare information from one site to another via electronic communication	
Domain: Financial Arrangements Changes in how funds are collected, insurance schemes, how services are purchased, and the use of targeted financial incentives or disincentives		
Category: Collection of funds Mechanisms by which financial resources to pay for health care are obtained		
Sub-category	**Definition**	**Notes on taxonomy revisions**
User fees or out of pocket payments	Charges levied on any aspect of health services at the point of delivery	
Caps and co-payments for drugs of health services	Direct patient payments for part of the cost of drugs or health services	
Prepaid funding	Collection of funds through general tax revenues versus earmarked tax revenues versus employer payments versus direct payments	
Community loan funds	Funds generated from contributions of community members that families can borrow to pay for emergency transportation and hospital costs	
Health savings accounts	Prepayment schemes for individuals or families without risk pooling	
External funding	Financial contributions such as donations, loans, etc. from public or private entities from outside the national or local health financing system	
Category: Insurance schemes Risk pooling to cover all or part of the costs of health care services		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Social health insurance	Compulsory insurance that aims to provide universal coverage	
Community based health insurance	A scheme managed and operated by an organization, other than a government or private for-profit company, that provides risk pooling to cover all or part of the costs of health care services	
Private health insurance	Private for-profit health insurance	
Category: Mechanisms for the payment of health services		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Method of paying healthcare organisations	Global budgets, employer based insurance schemes, line-item budgets; case-based reimbursement; pay for performance; mixed payment	

Sub-category	Definition	Notes on taxonomy revisions
Payment methods for health workers	Fee for services, capitation, salary	
Contracting out health services	Contracting is a strategy to use public sector funds to finance the provision of healthcare services.	
Voucher schemes	Provision of vouchers that can be redeemed for health services at specified facilities	
Conditional cash transfers	Monetary transfers to households on the condition that they comply with pre-defined requirements for healthcare	
Pricing and purchasing policies	Policies that determine the price that is paid or how commercial products are purchased, for example health technologies, drugs.	
Category: Targeted financial incentives for health professionals and healthcare organisations.		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Pay for performance – target payments	Transfer of money or material goods to healthcare providers conditional on taking a measurable action or achieving a predetermined performance target, for example incentives for lay health workers.	
Fund holding	Budgets allocated to a group or individual providers to purchase services with financial rewards for underspending or penalties for overspending (includes indicative budgets).	
Incentives for career choices	Financial or material rewards for career choices; e.g. choice of profession or primary care.	
Domain: Governance Arrangements Rules or processes that affect the way in which powers are exercised, particularly with regard to authority, accountability, openness, participation, and coherence		
Category: Authority and accountability for health policies		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Decentralisation and centralisation	Decentralised versus centralised authority for health services. For example government regulation of health insurance; regional vs. national management of health budgets on efficiency and effectiveness of healthcare.	
Stakeholder involvement in policy decisions	Policies and procedures for involving stakeholders in decision-making.	
Community mobilization	Processes that enable people to organize themselves.	

Sub-category	Definition	Notes on taxonomy revisions
Patients' rights	Policies that regulate patients' rights, including access to care and information (includes regulation of information provided to patients).	
Stewardship of private health services	Policies that regulate health services provided by the private sector.	
Decision-making about what or who is covered	Processes for deciding what is reimbursed and who is covered by health insurance: Policies that regulate what drugs are reimbursed Policies that regulate what services are reimbursed Restrictions on reimbursement for health insurance Strategies for expanding health insurance coverage	
Policies to reduce corruption	Regulations that are intended to reduce corruption in the health sector.	
Policies to manage absenteeism	Regulations for managing absenteeism.	
Category: Authority and accountability for organisations		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Ownership	Policies that regulate who can own health service organizations, for example for-profit vs not-for-profit; public vs private.	
Insurance	Policies that regulate the provision of insurance, for example insurance coverage of essential drugs.	
Accreditation	Processes for accrediting healthcare providers.	
Multi-institutional arrangements	Policies for how multiple organizations work together: Policies that regulate interactions between donors and governments Social Franchising Governance arrangements for coordinating care across multiple providers Mergers Collaborations between local health and local government agencies for health improvement	
Liability of healthcare organisations	Policies that limit liability of healthcare organisations, for example risk management.	
Category: Authority and accountability for commercial products		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Registration	Procedures for registering or licensing commercial products, for example medical devices, drugs.	
Patents and profits	Policies that regulate patents and profits, for example medical devices, drugs.	
Marketing regulations	Policies that regulate marketing of commercial products, for example medical devices, drugs, the private provision of healthcare.	

Sub-category	Definition	Notes on taxonomy revisions
Sales and dispensing	Policies that regulate sales and dispensing of commercial products, for example over the counter and prescription drugs.	
Liability for commercial products	Policies that regulate liability for commercial products.	
Category: Authority and accountability for health professionals		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Training and licensing	Policies that regulate training, specialty certification and licensure requirements for health professionals.	
Prescribing	Selection of a drug, by a suitably qualified healthcare worker, to treat a patient's health condition.	
Scope of practice	Policies that regulate what health professionals can do.	
Emigration and immigration policies	Policies that regulate emigration and immigration of health professionals.	
Dual practice	Policies that regulate dual practice, e.g., working in public and privately owned healthcare settings.	
Authority and accountability for quality of practice	Policies that regulate authority and accountability for the quality of care or safety, for example implementation of clinical guidelines.	
Professional competence	Policies or procedures for assuring professional competence.	
Professional liability	Policies that regulate liability for health professionals.	
Domain: Implementation Strategies Interventions designed to bring about changes in healthcare organizations, the behaviour of healthcare professionals or the use of health services by healthcare recipients		
Category: Interventions targeted at healthcare organisations		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Organisational culture	Strategies to change organisational culture.	
Category: Interventions targeted at healthcare workers		
Sub-category	**Definition**	**Notes on taxonomy revisions**
Audit and feedback	A summary of health workers' performance over a specified period of time, given to them in a written, electronic or verbal format. The summary may include recommendations for clinical action.	
Clinical incident reporting	System for reporting critical incidents.	
Monitoring the performance of the delivery of healthcare	Monitoring of health services by individuals or healthcare organisations, for example by comparing with an external standard.	

Sub-category	Definition	Notes on taxonomy revisions
Communities of practice	Groups of people with a common interest who deepen their knowledge and expertise in this area by interacting on an ongoing basis.	
Continuous quality improvement	An iterative process to review and improve care that includes involvement of healthcare teams, analysis of a process or system, a structured process improvement method or problem solving approach, and use of data analysis to assess changes.	
Educational games	The use of games as an educational strategy to improve standards of care.	
Educational materials	Distribution to individuals, or groups, of educational materials to support clinical care, i.e., any intervention in which knowledge is distributed. For example this may be facilitated by the internet, learning critical appraisal skills; skills for electronic retrieval of information, diagnostic formulation; question formulation	
Educational meetings	Courses, workshops, conferences or other educational meetings.	
Educational outreach visits, or academic detailing	Personal visits by a trained person to health workers in their own settings, to provide information with the aim of changing practice.	
Clinical Practice Guidelines	Clinical guidelines are systematically developed statements to assist healthcare providers and patients to decide on appropriate health care for specific clinical circumstances'(US IOM).	
Inter-professional education	Continuing education for health professionals that involves more than one profession in joint, interactive learning.	
Local consensus processes	Formal or informal local consensus processes, for example agreeing a clinical protocol to manage a patient group, adapting a guideline for a local health system or promoting the implementation of guidelines.	
Local opinion leaders	The identification and use of identifiable local opinion leaders to promote good practice.	
Managerial supervision	Routine supervision visits by health staff.	
Patient-mediated interventions	The use of patients, for example by providing patient outcomes, to change practice.	
Public release of performance data	Informing the public about healthcare providers by the release of performance data in written or electronic form.	
Reminders	Manual or computerised interventions that prompt health workers to perform an action during a consultation with a patient, for example computer decision support systems.	
Routine patient-reported outcome measures	Routine administration and reporting of patient-reported outcome measures to providers and/or patients.	
Tailored interventions	Interventions to change practice that are selected based on an assessment of barriers to change, for example through interviews or surveys.	

Appendix 3.5 Formulae and calculations

Table 4. Formulae and calculations

Desired conversion	Formula		Source
Calculating the risk ratio from the odds ratio	$RR = \frac{OR}{(1 - CER) + (CER \times OR))}$		Zhang et al.[5]
Calculating the corresponding intervention group event rate per 100 from the median control group event rate from risk ratios, rate ratios, hazard ratios, odds ratios, number needed to treat, absolute difference, and mean risk difference	$Corresponding\ intervention\ group\ risk = 100 \times median\ CER \times RR$		The Cochrane Collaboration[6]
	$Corresponding\ intervention\ group\ risk = 100 \times median\ CER \times rate\ ratio$		
	$Corresponding\ intervention\ group\ risk = 100 \times median\ CER \times HR$ *At the end of follow-up or last time point		
	$Corresponding\ intervention\ group\ risk = \frac{OR \times CER}{(1 - CER) + (OR \times CER))}$		
	$Corresponding\ intervention\ group\ risk = \left(\frac{Median\ CER}{per\ 100\ patients} - \frac{NNT}{per\ 100\ patients}\right)$		Derived
	$Corresponding\ intervention\ group\ risk = 100 \times (CER + Difference\ in\ risk)$		
	$Corresponding\ intervention\ group\ risk = 100 \times (CER + Mean\ difference\ in\ risk)$		
Calculating the number needed to treat from an odds ratio	NNT =((1-(CER x (1 - OR))) / ((1 - CER) x (CER) x (1 - OR)))		The Centre for Evidence-Based Medicine[7]
Calculating the number needed to harm from an odds ratio	NNH = ((CER x (OR - 1))+1) / (CER x (OR - 1) x (1 - CER))		
Calculating the number needed to treat from a hazard ratio	NNT = $\frac{1}{((1-CER(t))^{HR})-(1-CER(t))}$	*Note: Where t is the time point of interest	Derived from Altman et al.[8]
Calculating the number needed to harm from a hazard ratio	NNH = $\frac{1}{((1-CER(t))^{HR})-(1-CER(t))} \times -1$	*Note: To be used when the hazard ratio >1 indicating an increase in hospital admissions associated with the intervention; Where t is the time point of interest	
Calculating the absolute risk difference from the risk ratio	$Absolute\ risk\ difference = \lvert CER\ x\ (RR - 1) \rvert$		Newcombe et al.[9]
Standardising follow-up times to months	30.4 days per month and 4.3 weeks per month.		
Number needed to treat from absolute risk difference	NNT = $\frac{1}{Absolute\ risk\ difference}$		The Centre for Evidence-Based Medicine[7]

Abbreviations: RR= risk ratio; OR= odds ratio; CER= control event rate; NNT= Number needed to treat; NNH= Number needed to harm; HR= Hazard ratio; t=time point of interest

[5]Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*. 1998;280(19):1690-1691. doi:10.1001/jama.280.19.1690.

[6]The Cochrane Collaboration. Chapter 11.5.5 Statistical considerations in "Summary of findings" tables. Cochrane Handbook for Systematic Reviews of Interventions. 2011. www.cochrane-handbook.org

[7]The Centre for Evidence-Based Medicine. Number Needed to Treat (NNT). http://www.cebm.net/number-needed-to-treat-nnt/. Published 2012. Accessed June 1, 2014.

[8]Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *Bmj*. 1999;319(7223):1492-1495. doi:10.1136/bmj.319.7223.1492.

[9] Newcombe RG, Bender R. Implementing GRADE: calculating the risk difference from the baseline risk and the relative risk. *Evid Based Med*. 2014;19(1):6-8. doi:10.1136/eb-2013-101340.

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Table 5. References for included reviews

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Anderson, 2015, 8714	Anderson D, Kew K, Boyter A. Long-actingmuscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma. Cochrane Database Syst Rev. 2015;(8). doi:10.1002/14651858.CD011397.pub2.
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Appendix 3.7 Information about included reviews

Table 6. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Abdelnoor, 2017, 9354	The aim of this study was to summarize the pooled effect of early discharge compared with ordinary discharge after PCI on the primary composite endpoint of re-infarction, revascularization, stroke, death, and the incidence of rehospitalization. Second, we wanted to compare costs for the two strategies.	Post-operative percutaneous coronary intervention care	Early discharge after percutaneous coronary intervention vs. Ordinary discharge after percutaneous coronary intervention	Total: 12 (2968) Admissions data: 12 (2968)	No	7	The pooled effect supports the safe use of early discharge after PCI in the treatment of a heterogeneous population of patients with coronary artery disease. There was an increased risk of rehospitalization for all subpopulations, except patients with stable angina. Clinical trials with homogeneous populations of acute coronary syndrome are needed to be conclusive on this issue.
Adams, 2007, 85	We set out to conduct a systematic review and meta-analysis of the literature to determine the following: (1) which CCM components have been implemented in patients with COPD and (2) what combination of CCM components is associated with improved outcomes.	Chronic obstructive pulmonary disease	Chronic care model: self-management; delivery system design; decision support; clinical information system. vs. Control	Total: 20 (2765) Admissions data: 16 (2573)	No	7	Limited published data exist evaluating the efficacy of CCM components in chronic obstructive pulmonary disease management. However, pooled data demonstrated that patients with chronic obstructive pulmonary disease who received interventions with 2 or more CCM components had lower rates of hospitalizations and emergency/unscheduled visits and a shorter length of stay compared with control groups. The results of this review highlight the need for well-designed trials in this population.
Afilalo, 2007, 100	We sought to determine the effect of intensive statin therapy on all-cause mortality compared with moderate statin therapy in patients with recent acute coronary syndromes and in patients with stable coronary heart disease. Secondarily, we examined the effects of intensive statin therapy on major adverse cardiovascular events admissions to hospital for heart failure, and adverse hepatic and muscular events.	Coronary artery disease	Intensive statin therapy vs. Moderate statin therapy	Total: 6 (28505) Admissions data: 4 (27548)	No	6	Compared with moderate statin therapy, intensive statin therapy reduces all-cause mortality in patients with recent ACS but not in patients with stable CHD.
Aguinagalde, 2010, 119	We performed a systematic review and meta-analysis of the effectiveness of percutaneous aspiration compared with tube drainage for treating idiopathic spontaneous pneumothorax.	Pneumothorax	Percutaneous aspiration with chest tube drainage vs. Chest tube drainage	Total: 4 (331) Admissions data: 2 (197)	No	5	As has been observed in this review, it seems that in terms of immediate results, the drainage tube may be more effective, but that this effect disappears after 1 week and does not persist in the long term. In addition, it should be pointed out that the percutaneous aspiration strategy requires less material and human resources and that the number of hospital admissions is much lower. For this reason, it would appear reasonable to begin with aspiration and to consider chest tube drainage as a backup technique.
Ahmed, 2014, 129	Our objectives were to conduct a systematic review and to grade the quality of evidence to ascertain the effect of influenza vaccination of healthcare personnel on morbidity and mortality in patients of healthcare facilities.	Patients in healthcare facilities	Influenza vaccination vs. Control	Total: 4 (8468) Admissions data: 2 (5972)	Yes	6	The quality of evidence is higher for mortality than for other outcomes. HCP influenza vaccination can enhance patient safety.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Akioyamen, 2016, 8711	The purpose of this study was to conduct a systematic review and meta-analysis assessing the long-term effects of ARBs as a class on BP control, myocardial infarction, hospitalization for heart failure, cerebrovascular events (ie, stroke), cardiovascular mortality, and all-cause mortality.	Essential hypertension	Long-term angiotensin receptor blockade vs. Placebo or placebo with second-line non-ARB antihypertensive therapy permitted	Total: 7 (16864) Admissions data: 2 (6611)	No	7	Our findings suggest that ARBs, as a class, are more effective than placebo therapy in long-term BP lowering in patients with essential hypertension. Long-term ARB treatment may also confer enhanced protection against stroke but not other cardiovascular outcomes relative to placebo. J Am Soc Hypertens 2016;10(1):55–69. 2016 American Society of Hypertension.
Al-Majed, 2011, 212	In this systematic review, we update the previous systematic review and explore the benefits and harms of cardiac resynchronization therapy in patients with less symptomatic heart failure, patients with a narrow QRS duration on electrocardiography,and the use of a left ventricular lead alone versus standard cardiac resynchronization therapy.	Heart failure	Cardiac resynchronization therapy vs. Inactive pacing, right ventricular pacing alone, left ventricular pacing alone, implantable cardioverter-defibrillator (ICD) alone (for trials of CRT plus ICD vs. ICD alone), or usual care	Total: 25 (9670) Admissions data: 16 (7193)	No	9	Cardiac resynchronization therapy is beneficial for patients with reduced left ventricular ejection fraction, symptoms of heart failure, and prolonged QRS, regardless of NYHA class.
Anderson, 2015, 8714	To assess the efficacy and safety of a long-acting muscarinic antagonist (LAMA) added to any dose of an inhaled corticosteroid (ICS) compared with the same dose of ICS alone for adults whose asthma is not well controlled.	Asthma	Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) vs. Same dose inhaled corticosteriods	Total: 5 (2563) Admissions data: 5 (2562)	No	11	For adults taking ICS for asthma without a long-acting beta - agonist (LABA), LAMA given as add-on treatment reduces the likelihood of exacerbations requiring treatment with OCS and improves lung function. The benefits of LAMA combined with ICS for hospital admissions, all-cause serious adverse events, quality of life and asthma control remain unknown. Results of this review, along with findings of related reviews conducted to assess the use of LAMA in other clinical scenarios involving asthma, can help to define the role of LAMA in the management of asthma. Trials of longer duration (up to 52 weeks) would provide a better opportunity to observe rare events such as serious adverse events and exacerbations requiring hospital admission.
Anderson, 2016, 8716	To assess the effectiveness and cost-effectiveness of exercise-based CR (exercise training alone or in combination with psychosocial or educational interventions) compared with usual care on mortality, morbidity and HRQL in patients with CHD. To explore the potential study level predictors of the effectiveness of exercise-based CR in patients with CHD.	Coronary heart disease	Exercise-based cardiac rehabilitation vs. Usual care	Total: 64 (16610) Admissions data: 17 (5505)	Yes	10	This updated Cochrane review supports the conclusions of the previous version of this review that, compared with no exercise control, exercise-based CR reduces the risk of cardiovascular mortality but not total mortality. We saw a significant reduction in the risk of hospitalisation with CR but not in the risk of MI or revascularisation. We identified further evidence supporting improved HRQL with exercise-based CR. More recent trials were more likely to be well reported and include older and female patients. However, the population studied in this review still consists predominantly of lower risk individuals following MI or revascularisation. Further well conducted RCTs are needed to assess the impact of exercise-based CR in higher risk CHD groups and also those presenting with stable angina. These trials should include validated HRQL outcome measures, explicitly report clinical event outcomes including mortality and hospital admissions, and assess costs and cost-effectiveness.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Assasi, 2009, 378	The aim of this HTA is to evaluate the comparative clinical-effectiveness of anti-TNF-α drugs in patients with CD or UC with an inadequate response to conventional therapy and to determine the economic value of anti-TNF-α drugs compared with that of conventional therapy and surgical interventions.	Crohn's Disease, Ulcerative Colitis	Anti-tumor necrosis factor alpha drugs (Infliximab or Adalimumab) vs. Intra-class drug comparison; inter-class comparison of conventional therap; immunosuppressant drugs; or surgical interventions	Total: 20 (3132) Admissions data: 4 (1137)	No	9	Although infliximab and adalimumab have been shown to provide clinical benefit, the costs associated with these treatments could be perceived as high. Based on the incremental cost-utility findings from our primary economic evaluations, adalimumab and infliximab for the treatment of IBD may not be perceived to be a cost-effective use of health care resources.
Babalola, 2014, 432	To evaluate the effect of short stay/brief admission hospital care with long stay/standard in-patient care in people with serious mental illness.	Severe mental illness	Planned short stay/brief admission vs. Long stay or standard care	Total: 6 (2044) Admissions data: 6 (2044)	No	10	The effects of hospital care and the length of stay is important for mental health policy. We found limited low and very low quality data which were all over 30 years old. Outcomes from these studies do suggest that a planned short stay policy does not encourage a 'revolving door' pattern of admission and disjointed care for people with serious mental illness. More large, well-designed and reported trials are justified especially where a short-stay policy is not routine care.
Badve, 2011, 446	The aim of this systematic review was to study the benefits and risks of beta-adrenergic antagonists (betablockers) in patients with chronic kidney disease (CKD).	Chronic Kidney Disease	Beta-blocker vs. Placebo	Total: 8 (6949) Admissions data: Unclear (Unclear)	No	5	Treatment with beta-blockers improved all-cause mortality in patients with CKD and chronic systolic heart failure. There is insufficient evidence to conclude whether people with CKD who are not known to have heart failure derive benefit from beta-blockers.
Baigent , 2013, 1653	The main objective was to characterise and quantify the cardiovascular and gastrointestinal risks of particular NSAID regimens among diff erent types of patients, particularly those at increased risk of vascular disease.	Patients at increased risk of vascular disease	Coxib vs. Placebo or another NSAID (diclofenac; ibuprofen; naproxen)	Total: 634 (192981) Admissions data: Unclear (Unclear)	Yes	6	The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs. Although NSAIDs increase vascular and gastrointestinal risks, the size of these risks can be predicted, which could help guide clinical decision making.
Baishnab, 2012, 472	To determine the effectiveness of organised asthma care delivered via primary care based asthma clinics.	Asthma	Organised care via asthma clinics in primary care vs. Non-organised care, best clinical practice, or structured primary care processes that were not another form of asthma clinic.	Total: 3 (466) Admissions data: 2 (365)	No	11	There is limited evidence of efficacy for primary care based asthma clinics, and firm conclusions cannot be formed until more good quality trials have been carried out.
Barr, 2006, 548	To determine the efficacy of tiotropium on clinical endpoints such exacerbations and hospitalisations, symptom scales and pulmonary function compared to placebo and other bronchodilators used for stable COPD.	Chronic Obstructive Pulmonary Disease	Tiotropium vs. Placebo; ipratropium bromide; long-acting ß2-agonists (salmeterol or formoterol)	Total: 9 (6584) Admissions data: 4 (4087)	Yes	10	placebo, ipratropium; ? Long acting b2 agonists) Tiotropium reduced COPD exacerbations and related hospitalisations compared to placebo and ipratropium. It also improved healthrelated quality-of-life and symptom scores among patients with moderate and severe disease, and may have slowed decline in FEV1. Additional long-term studies are required to evaluate its effect on mortality and change in FEV1 to clarify its role in comparison to, or in combination with, long-acting ß2-agonists and to assess its effectiveness in mild and very severe COPD.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Baumeister , 2011, 593	To determine the effects of psychological and pharmacological interventions for depression in coronary artery disease patients with comorbid depressive disorder.	Coronary artery disease and comorbid depressive disorder	Pharmacological intervention vs. Placebo; no intervention; usual care; other pharmacological medications	Total: 16 (unclear) Admissions data: 4 (2995)	No	11	Psychological interventions and pharmacological interventionswith SSRIsmay have a small yet clinicallymeaningful effect on depression outcomes in CAD patients. No beneficial effects on the reduction of mortality rates and cardiac events were found. Overall, however, the evidence is sparse due to the low number of high quality trials per outcome and the heterogeneity of examined populations and interventions.
Beamish, 2015, 8724	The aim of this systematic review and meta-analysis was, therefore, to evaluate all existing available evidence comparing the implementation of an ERP with conventional treatment in surgery for gastric cancer.	Gastrointestinal cancer surgery	Multimodal pathway or enhanced recovery programme vs. Usual care	Total: 8 (647) Admissions data: 6 (482)	No	6	From this review the authors concluded that multimodal, standardized perioperative gastrectomy care appears feasible, safe and cost effective.
Beck, 2013, 615	The purpose of this paper was to estimate the effectiveness of oral nutritional support compared with placebo or usual care in improving re-admissions, survival, nutritional status, functional status, quality of life and morbidity of older (65 years+) medical and surgical patients after discharge from hospital.	Older (65+) patients being discharged from the hospital to the community that are malnourished or at risk of malnourishment	Oral nutritional support vs. Placebo; usual care; standard care	Total: 6 (716) Admissions data: 4 (478)	Yes	5	Although the evidence is limited, we suggest that oral nutritional support may be considered for older malnourished medical and surgical patients after discharge from hospital.
Berghella, 2008, 696	To assess the outcome of management based on knowledge of fetal fibronectin testing results for preventing preterm birth.	Pregnant women with signs and symptoms of pre-term labour.	Fetal fibronectin testing vs. Usual care	Total: 5 (473) Admissions data: 3 (288)	No	9	Although FFN is commonly used in labor and delivery units to help in the management of women with symptoms of preterm labor, currently there is not sufficient evidence to recommend its use. Since this review found an association between knowledge of FFN results and a lower incidence of preterm birth before 37 weeks, further research should be encouraged.
Beswick, 2008, 725	We did a systematic review to assess the effectiveness of community-based complex interventions in preservation of physical function and independence in elderly people.	Elderly people	Community-based multifactorial intervention vs. Usual care or minimum intervention	Total: 88 (98937) Admissions data: 72 (82377)	No	7	Complex interventions can help elderly people to live safely and independently, and could be tailored to meet individuals' needs and preferences.
Bittencourt, 2016, 9221	We have performed a meta-analysis of randomized controlled trials comparing the use of coronary computed tomographic angiography (CTA) with usual care.	Stable chest pain	Coronary computed tomographic angiography vs. Usual care	Total: 4 (14817) Admissions data: 4 (14817)	No	9	In comparison to usual care, an initial investigation of suspected stable coronary artery disease using coronary CTA resulted in a significant reduction in myocardial infarction, an increased incidence of coronary revascularization, and no effect in all-cause mortality. Future studies should further define whether the potential reduction in myocardial infarction identified justifies the increased resource utilization associated with coronary CTA.
Blitz, 2005, 813	A systematic review of the literature was performed to examine the effect of inhaled MgSO4 in the treatment of patients with asthma exacerbations in the emergency department.	Asthma	Nebulized magnesium sulfate vs. B2-agonist alone	Total: 6 (296) Admissions data: 1 (52)	No	5	The use of nebulized MgSO4, particularly in addition to a 2-agonist, in the treatment of an acute asthma exacerbation appears to produce benefits with respect to improved pulmonary function and may reduce the number of hospital admissions.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Bond-Smith, 2016, 8728	To assess the benefits and harms of enhanced recovery protocols compared with standard care (or usual practice) in major upper gastrointestinal, liver and pancreatic surgery.	Major upper gastrointestinal, liver, and pancreatic surgery	Enhanced recovery protocols vs. Standard care	Total: 10 (1110) Admissions data: 7 (786)	No	11	Based on low quality evidence, enhanced recovery protocols may reduce length of hospital stay and costs (primarily because of reduction in hospital stay) in people undergoing major upper gastrointestinal, liver and pancreatic surgeries. However, the validity of the results is uncertain because of the risk of bias in the trials and the way the outcomes were measured. Future RCTs should be conducted with low risk of bias, and measure clinically important outcomes for including the three months to one year period.
Bonsu, 2016, 8729	This study aims to compare lipophilic and hydrophilic statin therapy on clinical outcomes of heart failure (HF) using a systematic review and an adjusted indirect comparison meta-analysis.	Heart failure	Lipophilic Statin vs. Placebo	Total: 13 (10966) Admissions data: 10 (10665)	Yes	9	Lipophilic statin treatment shows significant decreases in all-cause mortality, cardiovascular mortality and hospitalization for worsening HF compared with rosuvastatin treatment. This meta-analysis provides preliminary evidence that lipophilic statins offer better clinical outcomes in HF till data from head to head comparisons are available.
Bradely, 2003, 930	To determine whether cardiac resynchronization decreases mortality from progressive heart failure, we conducted a meta-analysis.	Heart failure with symptomatic left ventricular dysfunction	Cardiac resynchronization therapy vs. Control	Total: 4 (1555) Admissions data: 4 (1634)	No	9	Cardiac resynchronization reduces mortality from progressive heart failure in patients with symptomatic left ventricular dysfunction. This finding suggests that cardiac resynchronization may have a substantial impact on the most common mechanism of death among patients with advanced heart failure. Cardiac resynchronization also reduces heart failure hospitalization and shows a trend toward reducing all-cause mortality.
Briasoulis, 2015, 8731	The present meta-analysis was designed to systematically evaluate prospective controlled trials and observational cohorts and assess the effects of carvedilol versus metoprolol types (succinate and tartrate) on all-cause mortality and rehospitalization.	Heart failure	Carvedilol vs. Metoprolol	Total: 4 (4776) Admissions data: 2 (4544)	No	6	Neither all-cause mortality nor hospitalizations were significantly different between carvedilol and metoprolol succinatein the cohort studies. In conclusion, in patients with HFrEF, carvedilol and metoprolol succinate have similar effects in reducing all-cause mortality.
Brophy, 2001, 1021	Congestive heart failure is an important cause of patient morbidity and mortality. Although several randomized clinical trials have compared b-blockers with placebo for treatment of congestive heart failure, a meta-analysis quantifying the effect on mortality and morbidity has not been performed recently.	Congestive Heart Failure	Beta-blocker vs. Placebo	Total: 22 (10132) Admissions data: 22 (10076)	No	4	b-Blocker therapy is associated with clinically meaningful reductions in mortality and morbidity in patients withstable congestive heart failure and should be routinely offered to all patients similar to those included in trials.
Brown, 2011, 1031	To assess the effects of patient education compared with usual care on mortality, morbidity, health-related quality of life (HRQofL) and healthcare costs in patients with CHD. To explore the potential study level predictors of the effects of patient education in patients with CHD (e.g. individual versus group intervention, timing with respect to index event).	Coronary heart disease	Patient education vs. Usual care	Total: 13 (68649) Admissions data: 6 (66058)	No	9	We did not find strong evidence that education reduced all cause mortality, cardiac morbidity, revascularisation or hospitalisation compared to control. There was some evidence to suggest that education may improve HRQofL and reduce overall healthcare costs. Whilst our findings are generally supportive of current guidelines that CR should include not only exercise and psychological interventions, further research into education is needed.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Brown, 2002, 1039	The objective of this review was to assess the safety, impact and effectiveness of a policy of early discharge for healthy mothers and term infants, with respect to the health and well-being of mothers and babies, satisfaction with postnatal care, overall costs of health care and broader impacts on families.	Pregnant/Post-natal	Early postnatal discharge vs. Standard postnatal discharge timing	Total: 10 (7171) Admissions data: 9 (5817)	Yes	9	The pooled trials have inadequate power to detect increases in rare outcomes, such as infant and maternal mortality or readmissions. Policies of earlier postnatal discharge of healthy mothers and term infants do not appear to have adverse effects on breastfeeding or maternal depression when accompanied by a policy of offering women at least one nurse-midwife home visit post discharge. Large well-designed trials of early discharge programs incorporating process evaluation to assess the uptake of co-interventions, and using standardized approaches to outcome assessment are needed.
Buckley, 2015, 8733	To review the effects of supportive therapy comparedwith standard mcare, or other treatments in addition to standard care for people with schizophrenia.	Schizophrenia	Supportive therapy vs. Standard care or other psychological or psychosocial treatment	Total: 24 (2169) Admissions data: 12 (1298)	Yes	10	There are insufficient data to identify a difference in outcome between supportive therapy and standard care. There are several outcomes, including hospitalisation and general mental state, indicating advantages for other psychological therapies over supportive therapy but these findings are based on a few small studies where we graded the evidence as very low quality. Future research would benefit from larger trials that use supportive therapy as the main treatment arm rather than the comparator.
Burch, 2009, 1080	The objective of this review is to evaluate the clinical effectiveness (including adverse events) and cost-effectiveness of antivirals for the treatment of naturally acquired influenza. This evaluation considers these issues for at-risk and otherwise healthy populations. It is important to note that this health technology assessment was carried out to address the use of antiviral treatments for influenza within the context of a seasonal outbreak, not a pandemic.	Influenza	Zanamivir or oseltamivir vs. Placebo; antiviral drugs for treatment licensed in the UK (intravenous and nebulised zanamivir excluded); best symptomatic care.	Total: 34 (unclear) Admissions data: 14 (5694)	No	8	The clinical effectiveness data for population subgroups, used to inform the multiparameter evidence synthesis and cost-effectiveness modelling were, in places, limited and this should be borne in mind when interpreting the findings of this review. Trials were often not designed to determine clinical effectiveness in population subgroups and hence, although the direction of effect was clear, estimates of differences in symptom duration tended to be subject to greater uncertainty in subgroups. This limitation was more apparent for data on the rates of complications: studies with sample size and duration not designed to detect these outcomes resulted in low event rates and relatively weak evidence, even when available data were combined in meta-analyses. However, despite these concerns, the use of NIs in at-risk populations appeared to be a cost-effective approach to the treatment of influenza.
Cammarano, 2016, 8735	The goal of this review was to pool data from ivabradine studies in all patients with stable CAD to compare cardiovascular and safety-related outcomes.	Stable coronary artery disease with and without left ventricular dysfunction	Ivabradine vs. Placebo	Total: 3 (36524) Admissions data: 3 (36524)	Yes	4	Unselective use of ivabradine in patients with stable CAD is not supported by evidence and can be associated with new-onset atrial fibrillation, bradycardia,and drug-related nuisance adverse events.
Campschroer, 2014, 1164	This review aimed to answer the following question: does medical treatment with alpha-blockers compared to other pharmacotherapy or placebo impact on stone clearance rate, in adult patients presenting with symptoms of ureteral stones less than 10 mm confirmed by imaging? Other clinically relevant outcomes such as stone expulsion time, hospitalisation, pain scores, analgesic use and adverse effects have also been explored.	Ureteral stones	Alpha-blocker vs. Any other pharmacotherapy including: standard therapy (e.g. NSAIDs, corticosteroids); calcium channel blockers; placebo.	Total: 30 (6155) Admissions data: 4 (313)	No	10	The use of alpha-blockers in patients with ureteral stones results in a higher stone-free rate and a shorter time to stone expulsion. Alphablockersshould therefore be offered as part of medical expulsive therapy as one of the primary treatment modalities.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Cates, 2013, 1249	To assess the effects of holding chambers (spacers) compared to nebulisers for the delivery of beta - agonists for acute asthma.	Asthma	Treatment with beta2-agonists via Spacer (chamber) vs. Treatment with beta2-agonists via nebuliser (multiple-treatment studies)	Total: 39 (2626) Admissions data: 9 (582)	Yes	9	Nebuliser delivery produced outcomes that were not significantly better than metered-dose inhalers delivered by spacer in adults or children, in trials where treatments were repeated and titrated to the response of the participant. Spacers may have some advantages compared to nebulisers for children with acute asthma. The studies excluded people with life-threatening asthma; therefore, the results of this meta-analysis should not be extrapolated to this patient population.
Cawood, 2012, 1264	Therefore, this systematic review was undertaken to examine whether high protein ONS have beneficial effects in clinical practice and the extent to which these are associated with increased protein intake.	Patients in hospital or community settings that are malnourished or at risk of disease-related malnutrition	High protein oral nutritional supplements vs. Placebo or usual care	Total: 36 (3790) Admissions data: 2 (525)	No	7	The systematic review and meta-analysis provides evidence that high protein supplements produce clinical benefits, with economic implications.
Ceron-Litvoc, 2009, 1281	This paper reports a systematic review and metaanalysis of all randomized controlled trials (RCTs) that evaluate the use of carbamazepine in acute and maintenance phases of BD compared to lithium.	Bipolar disorder 1 and 2	Maintenance treatment with carbamazepine vs. Carbamazepine	Total: 15 (unclear) Admissions data: 2 (202)	No	5	Conclusion This review suggests that carbamazepine might be comparable to lithium in terms of efficacy and safety, and therefore a valuable option in the treatment of both manic and maintenance phases.
Chapron, 2002, , 1335	The main question addressed in this meta-analysis was whether the risk of complications with laparoscopic surgery is greater than that observed with laparotomy for patients who need to be operated for a benign gynaecological pathology.	Patients who need to be operated on for a benign gynaecological pathology.	Laparoscopic surgery vs. Laparotomy	Total: 27 (3611) Admissions data: 27 (3611)	No	6	Laparoscopic surgery is not inherently dangerous for patients presenting benign gynaecological pathologies. The potential risk of complications should no longer be advanced as an argument against using laparoscopic surgery rather than laparotomy for an operation when the indication allows the choice.
Charytan, 2009, 1340	We performed a collaborative meta-analysis in which the authors of randomized trials that compared invasive and conservative strategies in non-ST acute coronary syndromes prepared data on enrolled patients with chronic kidney disease.	Non-ST acute coronary syndromes and chronic kidney disease	Routine coronary angiography vs. Selective coronary angiography	Total: 5 (7481) Admissions data: 5 (7481)	No	7	This collaborative study suggests that the benefits of an early invasive strategy are preserved in patients with CKD and that an early invasive approach reduces the risk for rehospitalization and is associated with trends of reduction in the risk for death and nonfatal re-infarction in patients with CKD. Coronary angiography should be considered for patients who have CKD and are admitted with non–ST elevation acute coronary syndromes.
Chauhan, 2012, 1348	1. To compare the safety and efficacy of daily oral antileukotrienes with that of inhaled corticosteroids; 2. to determine the dose of inhaled corticosteroids equivalent to the effect of anti-leukotrienes in the management of asthma in adults and children; and 3. to explore different factors such as patients' age group, disease severity, anti-leukotriene used, intervention duration, hydrofluoroalkane-propelled beclomethasone or equivalent (HFA-BDP eq) dose of inhaled corticosteroids, methodological quality, publication status and funding that could influence the magnitude of effect.	Asthma	Anti-leukotriene vs. Inhaled glucocorticoids (in hydrofluorocarbon-beclomethasone dipropionate equivalent)	Total: 56 (13338) Admissions data: 12 (2715)	No	11	As monotherapy, inhaled corticosteroids display superior efficacy to anti-leukotrienes in adults and children with persistent asthma; the superiority is particularly marked in patients with moderate airway obstruction. On the basis of efficacy, the results support the current guidelines' recommendation that inhaled corticosteroids remain the preferred monotherapy.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Chauhan, 2014, 8681	To compare the safety and efficacy of adding LABA versus LTRA in children and adults with asthma who remain symptomatic in spite of regular treatment with ICS. We specifically wished to examine the relative impact of the two agents on asthma exacerbations, lung function, symptoms, quality of life, adverse health events and withdrawals.	Asthma treated with inhaled corticosteroids	Long acting beta agonists with inhaled corticosteroids vs. Leukotriene receptor antagonists plus inhaled corticosteroids	Total: 18 (7126) Admissions data: 5 (4345)	No	9	In adults with asthma that is inadequately controlled by predominantly low-dose ICS with significant bronchodilator reversibility, the addition of LABA to ICS is modestly superior to the addition of LTRA in reducing oral corticosteroid-treated exacerbations, with an absolute reduction of two percentage points. Differences favouring LABA over LTRA as adjunct therapy were observed in lung function and, to a lesser extend, in rescue medication use, symptoms and quality of life. The lower overall withdrawal rate and the higher proportion of participants satisfied with their therapy indirectly favour the combination of LABA + ICS over LTRA + ICS. Evidence showed a slightly increased risk of SAE with LABA compared with LTRA, with an absolute increase of one percentage point. Our findings modestly support the use of a single inhaler for the delivery of both LABA and low- or medium-dose ICS. Because of the paucity of paediatric trials, we are unable to draw firm conclusions about the best adjunct therapy in children.
Chen, 2013, 1389	The purpose of this meta-analysis was to systematically analyse the completed trials assessing the safety and efficacy of exercise training in elderly patients with heart failure.	Heart failure	Exercise training vs. Standard medical therapy without exercise training	Total: 7 (530) Admissions data: 4 (413)	No	8	In elderly CHF patients (mean age 70–81), exercise training increase 6MWD and improve generic HRQoL, but has no effects on mortality, hospitalisations, peakVO2 and disease-specific HRQoL. The long-term efficacy and safety of exercise training in elderly heart failure patients require further study based on large and rational-designed controlled clinical trials.
Chen, 2015, 8739	We systematically reviewed the literature for randomized controlled trials (RCTs) examining the effect of ultrafiltration in patients with cardiorenal syndrome.	Decompensated heart failure in cardiorenal syndrome	Ultrafiltration vs. Diuretics	Total: 8 (609) Admissions data: 4 (480)	No	6	Ultrafiltration is a safe and effective strategy in the treatment of cardiorenal syndrome without increasing the risk of renal deterioration.
Chen, 2015, 8740	This meta-analysis evaluated the safety and efficacy of fast track surgery (FTS) for patients with gastric cancer undergoing gastrectomy.	Gastrointestinal cancer surgery	Multimodal fast track surgery pathway vs. Conventional perioperative care	Total: 7 (527) Admissions data: 6 (485)	No	7	In patients with gastric cancer undergoing gastrectomy, the FTS pathway reduces the length and cost of postoperative hospitalisation while maintaining short-term morbidity, readmission and mortality rates comparable with those of conventional care.
Chen, 2015, 8742	We aimed to summarize the evidence for the efficacy of MRAs in patients with either heart failure with PEF (HF-PEF) or myocardial infarction with PEF (MI-PEF).	Patients with preserved ejection fraction ≥40%	Aldosterone antagonists vs. Placebo or control	Total: 14 (6428) Admissions data: 4 (4551)	Yes	8	MRA treatment in PEF patients led to reduced hospitalization for heart failure, quantifiable improvements in quality of life and diastolic function, and reversal of cardiac remodeling, but did not provide any all-cause mortality benefit.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Cheng, 2015, 8743	The aim of the present meta-analysis, therefore, was to evaluate the efficacy and safety of ultrafiltration with decompensated heart failure patients complicated by renal insufficiency.	Decompensated heart failure patients admitted with renal insufficiency: at least two signs of volume overload (lower extremity edema, pleural effusion or pulmonary edema on chest imaging, jugular venous pulsation > 10 cm H2O and patients with serum creatinine values > 1.4 mg/dL 15.	Ultrafiltration vs. Control	Total: 7 (569) Admissions data: 4 (306)	No	5	UF is an effective and safe therapeutic strategy and produces greater weight loss and fluid removal without affecting renal function, mortality, or rehospitalization in patients with decompensated heart failure complicated by renal insufficiency.
Cheyne, 2015, 8744	To compare the relative effects of tiotropium to ipratropium bromide on markers of quality of life, exacerbations, symptoms, lung function and serious adverse events in patients with COPD using available randomised controlled trial data.	Chronic obstructive pulmonary disease	Tiotropium vs. Ipratropium bromide	Total: 2 (1073) Admissions data: 2 (1073)	No	10	This review shows that tiotropium treatment, when compared with ipratropium bromide, was associated with improved lung function, fewer hospital admissions (including those for exacerbations of COPD), fewer exacerbations of COPD and improved quality of life. There were both fewer serious adverse events and disease specific events in the tiotropium group, but no significant difference in deaths with ipratropium bromide when compared to tiotropium. Thus, tiotropium appears to be a reasonable choice (instead of ipratropium bromide) for patients with stable COPD, as proposed in guidelines. A recent large double-blind trial of the two delivery devices found no substantial difference in mortality using 2.5 µg or 5 µg of tiotropium via Respimat in comparison to 18 µg via Handihaler.
Chien, 2008, 1418	The research questions for this systematic review were: 1. Is home-based exercise effective at improving exercise capacity and quality of life in people with chronic heart failure?; 2. Is it safe?	Heart failure	Home-based exercise vs. Usual activity	Total: 10 (671) Admissions data: 6 (478)	No	7	Home-based exercise increased exercise capacity safely but did not improve quality of life in patients with chronic heart failure. It could therefore be used to improve the management of people with chronic heart failure who do not have access to hospital-based exercise.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Chong, 2012, 1438	To compare the relative clinical effects of tiotropium bromide alone versus LABA alone, upon measures of quality of life, exacerbations, lung function and serious adverse events, in people with stable COPD. To critically appraise and summarise current evidence on the costs and cost-effectiveness associated with tiotropium compared to LABA in people with COPD.	Chronic obstructive pulmonary disease	Tiotropium vs. Long acting beta-agonists	Total: 7 (12223) Admissions data: 6 (12123)	No	10	In people with COPD, the evidence is equivocal as to whether or not tiotropium offers greater benefit than LABAs in improving quality of life; however, this is complicated by differences in effect among the LABA types.Tiotropium wasmore effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalisations, although there were no statistical differences between groups in overall hospitalisation rates or mortality during the study periods. There were fewer serious adverse events and study withdrawals recorded with tiotropium compared with LABAs. Symptom improvement and changes in lung function were similar between the treatment groups. Given the small number of studies to date, with high levels of heterogeneity among them, one approach may be to give a COPD patient a substantial trial of tiotropium, followed by a LABA (or vice versa), then to continue prescribing the long-acting bronchodilator that the patient prefers. Further studies are needed to compare tiotropium with different LABAs, which are currently ongoing. The available economic evidence indicates that tiotropium may be cost-effective compared with salmeterol in several specific settings, but there is considerable uncertainty around this finding.
Choudhry, 2005, 1447	Patients with unstable angina or non-ST-segment elevation myocardial infarction (MI) may be managed with either an “invasive” or “conservative” strategy. It is unclear which of these strategies is superior. We performed a systematic review and meta-analysis of these trials to clarify the advantage of one strategy over another, if such an advantage exists.	Patients in the early post-unstable angina/non-ST-segment elevation MI period	Routine coronary angiography vs. Selective coronary angiography	Total: 7 (9212) Admissions data: 5 (6482)	Yes	6	For patients with unstable angina/non-ST-segment elevation MI, an invasive strategy reduces rates of fatal or nonfatal re-infarction and hospital readmission, but not all-cause mortality, when compared with a noninvasive strategy. These results suggest that an invasive management strategy should be considered for all patients with unstable angina/non-ST-segment elevation MI and perhaps in particular those with ST-segment depression.
Christensen, 2016, 8745	We examined whether delivery of a medication review by a physician, pharmacist or other healthcare professional leads to greater improvement in health outcomes of hospitalised adult patients compared with standard care.	Hospitalised patients	In-hospital medication review vs. Standard care	Total: 10 (3826) Admissions data: 10 (3826)	No	11	We found no evidence thatmedication review reducesmortality or hospital readmissions, although we did find evidence that medication review may reduce emergency department contacts. However, because of short follow-up ranging from 30 days to one year, important treatment effects may have been overlooked. High-quality trials with long-term follow-up (i.e. at least up to a year) are needed to provide more definitive evidence for the effect of medication review on clinically important outcomes such as mortality, readmissions and emergency department contacts, and on outcomes such as adverse events. Therefore, if used in clinical practice, medication reviews should be undertaken as part of a clinical trial with long-term follow-up.
Coeytaux, 2014, 8747	We conducted a systematic review to evaluate the comparative effectiveness and safety of monotherapy or combination therapy for PAH using endothelin receptor antagonists, phosphodiesterase inhibitors, or prostanoids.	Pulmonary aterial hypertension	Combination drug therapy with endothelin receptor antagonist, phosphodiesterase inhibitors, and/or prostanoids vs. Placebo; Monotherapy	Total: 28 (3613) Admissions data: 9 (1918)	No	5	Although no studies were powered to detect a mortality reduction, monotherapy was associated with improved 6MWD and reduced hospitalization rates. Our findings also suggest an improvement in 6MWD when a second drug is added to monotherapy.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Conroy, 2011, 1575	The aim of this systematic review was to examine the evidence for services for older patients who developed a crisis and attended hospital, but who were assessed, treated and discharged, either immediately, or within a short-time period (up to 72 h) from an AMU or ED, a concept for which we have coined the phrase 'interface geriatrics'.	Elderly people	Comprehensive geriatric assessment vs. Usual care	Total: 4 (2099) Admissions data: 4 (2099)	No	6	There is no clear evidence of benefit for CGA interventions in frail older people being discharged from emergency departments or acute medical units. However, few such trials have been carried out and their overall quality was poor. Further well designed trials are justified.
Cordina, 2005, 1606	To assess the effects of pharmacological cardioversion of atrial fibrillation in adults on the annual risk of stroke, peripheral embolism, and mortality.	Paroxysmal, sustained or permanent atrial fibrillation or flutter	Rhythm (antiarrhythmic drugs) vs. Rate control (rate control drugs)	Total: 2 (4167) Admissions data: 2 (4312)	No	8	There is no evidence that pharmacological cardioversion of atrial fibrillation to sinus rhythmis superior to rate control. Rhythm control is associated with more adverse effects and increased hospitalisation. It does not reduce the risk of stroke. The conclusions cannot be generalised to all people with atrial fibrillation. Most of the patients included in these studies were relatively older (>60 years) with significant cardiovascular risk factors.
Costa, 2013, 1629	To evaluate patients with IBD treated with infliximab and providing data on the rate of complications (hospitalizations and/or surgery).	Irritable bowel disease	Infliximab vs. Placebo; no treatment; other active non-biologic drug, non-adherence to infliximab therapy and episodic/nonpersistence infliximab therapy	Total: 9 (1912) Admissions data: 6 (1736)	No	8	The best evidence available points toward a reduction of the risk of hospitalization and major surgery requirement in patients with IBD treated with infliximab. This impact is clinically and economically relevant because hospitalization and surgery are considered to be markers of disease severity and significantly contribute to the total direct costs associated with IBD.
Danchin, 2006, 1752	To provide information complementary to that provided by previous meta-analyses in patients who have CAD and either signs of heart failure or impaired systolic function	Stable coronary artery disease	Angiotensin-converting enzyme inhibitors vs. Placebo	Total: 7 (33960) Admissions data: 6 (33500)	No	8	Angiotensin-converting enzyme inhibitors reduce total mortality and major cardiovascular end points in patients who have CAD and no left ventricular systolic dysfunction or heart failure.
De Waure, 2013, 1855	The aim of this study was to assess the efficacy of nonpharmacologic interventions with multiple lifestyle components in patients with established CHD in comparison to usual care.	Coronary heart disease	Multifactorial lifestyle interventions vs. Usual care	Total: 14 (6657) Admissions data: 7 (5363)	No	7	Multifactorial lifestyle interventions aimed at improving modifiable risk factors in patients with established CHD reduce the risk for fatal cardiovascular events. Therefore, they may have added value in secondary prevention of CHD.
Deshpande, 2013, 1921	To assess the clinical effectiveness and cost-effectiveness of rapid fFN testing in predicting preterm birth (PTB) in symptomatic women.	Pregnant women with signs and symptoms of pre-term labour	Fetal fibronectin testing vs. Usual care	Total: 5 (464) Admissions data: 4 (356)	No	10	Fetal fibronectin testing has moderate accuracy for predicting PTB. The main potential role is likely to be reducing health-care resource usage by identifying women not requiring intervention. Evidence from RCTs suggests that fFN does not increase adverse outcomes and may reduce resource use. The base-case analysis showed a modest cost difference in favour of fFN testing, which is largely dependent on whether or not fFN testing reduces hospital admission. Currently, there are no high-quality studies and the existing trials were generally underpowered. Hence, there is a need for high-quality adequately powered trials using appropriate study designs to confirm the findings presented.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Dieterich, 2017, 9370	To assess the effects of ICM as a means of caring for severely mentally ill people in the community in comparison with non-ICM (caseload greater than 20) and with standard community care.We did not distinguish between models of ICM. In addition, to assess whether the effect of ICM on hospitalisation (mean number of days per month in hospital) is influenced by the intervention's fidelity to the ACT model and by the rate of hospital use in the setting where the trial was conducted (baseline level of hospital use).	Severe mental illness	Intensive case management vs. Standard care	Total: 40 (7524) Admissions data: 26 (4649)	Yes	11	Based on very low- tomoderate-quality evidence, ICMis effective in ameliorating many outcomes relevant to people with severemental illness. Compared to standard care, ICM may reduce hospitalisation and increase retention in care. It also globally improved social functioning, although ICM's effect on mental state and quality of life remains unclear. Intensive Case Management is at least valuable to people with severe mental illnesses in the subgroup of those with a high level of hospitalisation (about four days per month in past two years). Intensive Case Management models with high fidelity to the original team organisation of ACT model were more effective at reducing time in hospital. However, it is unclear what overall gain ICM provides on top of a less formal non-ICM approach. We do not think that more trials comparing current ICM with standard care or non-ICM are justified, however we currently know of no review comparing non-ICM with standard care, and this should be undertaken.
DiNicolantonio , 2013, 1991	To compare carvedilol against the most frequently prescribed b1-selective BBs.	Acute myocardial infarction (AMI) and hear tfailure (HF)	Carvedilol vs. Beta-blockers	Total: 8 (4563) Admissions data: 2 (3099)	Yes	5	Compared to b1-selective BBs used in HF (8 trials, n [4,563), carvedilol significantly reduced all-cause mortality (risk ratio 0.85, 95% confidence interval 0.78 to 0.93, p [0.0006). In 3 trials of patients with AMI (n [644), carvedilol significantly reduced all-cause mortality by 45% (fixed-effects model: risk ratio 0.55, 95% confidence interval 0.32 to 0.94, p [0.03, random-effects model: risk ratio 0.56, 95% confidence interval 0.26 to 1.12, p = 0.10), with no reduction in non-fatal MI (risk ratio 0.61, 95% confidence interval 0.31 to 1.22, p [0.16). In conclusion, carvedilol, as compared against atenolol, bisoprolol, metoprolol and nebivolol in randomized direct comparison trials, significantly reduced all-cause mortality in systolic HF patients. Additionally, carvedilol significantly reduced all-cause mortality compared with b1-selective
Donald, 2015, 8759	To determine the cost-effectiveness of nurse practitioners delivering transitional care.	Hospitalised patients	Post-discharge care by nurse practitioners vs. Usual care	Total: 5 (1171) Admissions data: 5 (1171)	Yes	7	Given the low quality evidence, weak economic analyses, small sample sizes, and small number of nurse practitioners evaluated in each study, evidence of the cost-effectiveness of nurse practitioner-transitional care is inconclusive and further research is needed.
Doyle, 2009, 2055	Investigated the effects of long-term amiodarone therapy on mortality, rhythm control, incidence of hospitalization, and drug intolerance leading to withdrawal of treatment in patients with persistent AF of more than 30 days' duration.	Persistent atrial fibrillation (>30 days' duration)	Amiodarone vs. CALCIUM CHANNEL BLOCKERS; CARDIAC THERAPY; BETA BLOCKING AGENTS	Total: 20 (5060) Admissions data: 5 (2932)	No	8	Amiodarone, as part of a strategy to achieve and maintain sinus rhythm, appears to be safe and effective in patients with persistent AF. However, some patients may not tolerate the adverse effects of this agent.
Dretzke, 2015, 8760	To assess the clinical effectiveness and cost-effectiveness of domiciliary non-invasive ventilation by systematic review and economic evaluation.	Patients with end-stage chronic obstructive pulmonary disease.	Domiciliary non-invasive ventilation vs. Usual care	Total: 22 (1221) Admissions data: 11 (915)	Yes	10	The cost-effectiveness of domiciliary NIV remains uncertain and the findings in this report are sensitive to emergent data. Further evidence is required to identify patients most likely to benefit from domiciliary NIV and to establish optimum time points for starting NIV and equipment settings.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Driscoll, 2015, 8761	We systematically reviewed the evidence from randomised controlled trials (RCTs) of NLT of ACEIs, beta-adrenergic blocking agents, and ARBs in people with HFrEF for efficacy and risk of hospitalisations and mortality.	Heart failure	Nurse-led titration of medication vs. Physician-led usual care	Total: 7 (1619) Admissions data: 6 (913)	Yes	10	Participants in theNLTgroup experienced fewer hospital admissions for any cause and an increase in survival and number of participants reaching target dose within a shorter time period. However, the quality of evidence regarding the proportion of participants reaching target dose was low and should be interpreted with caution. We found high-quality evidence supporting NLT as one strategy that may improve the optimisation of beta-adrenergic blocking agents resulting in a reduction in hospital admissions. Despite evidence of a dosedependent relationship of beta-adrenergic blocking agents, ACEIs, and ARBs with improving outcomes in patients with HFrEF, the translation of this evidence into clinical practice is poor. NLT is one strategy that facilitates the implementation of this evidence into practice.
Ducharme, 2010, 2095	To compare the relative benefit and safety profile of the combination of long-acting ß2 agonists (LABAs) and inhaled corticosteroids (ICS) with a higher dose of inhaled corticosteroids in asthmatic patients with or without previous treatment with inhaled corticosteroids.	Recurrent or chronic asthma	Long-acting beta2-agonists and inhaled corticosteroids vs. Higher dose of inhaled corticosteroids	Total: 48 (15155) Admissions data: 33 (12573)	No	11	In adolescents and adults with sub-optimal control on low dose ICS monotherapy, the combination of LABA and ICS is modestly more effective in reducing the risk of exacerbations requiring oral corticosteroids than a higher dose of ICS. Combination therapy also led to modestly greater improvement in lung function, symptoms and use of rescue ß2 agonists and to fewer withdrawals due to poor asthma control than with a higher dose of inhaled corticosteroids. Apart from an increased rate of tremor and less oral candidiasis with combination therapy, the two options appear relatively safe in adults although adverse effects associated with long-term ICS treatment were seldommonitored. In children, combination therapy did not lead to a significant reduction, but rather a trend towards an increased risk, of oral steroid-treated exacerbations and hospital admissions. These trends raised concern about the safety of combination therapy in view of modest improvement in children under the age of 12 years.
Ebell, 2013, 2148	To determine the effect of oseltamivir on the duration of illness and prevention of serious complications and hospitalizations in adults using both published and unpublished data, by a group of authors with no ties to the manufacturer and considering an appropriate definition for complications requiring antibiotics.	Influenza	Oseltamivir vs. Placebo	Total: 11 (4769) Admissions data: 8 (4327)	Yes	9	There is no evidence that oseltamivir reduces the likelihood of hospitalization, pneumonia or the combined outcome of pneumonia, otitis media and sinusitis in the ITT population.
Echevarria, 2016, 8762	A systematic review and meta-analysis was performed to assess the safety, efficacy and cost of early dupported fischarge (ESD) and hospital at home (HAH) compared to usual care (UC) for patients with acute exacerbation of COPD (AECOPD).	Chronic obstructive pulmonary disease	Early supported discharge or hospital at home vs. Traditional in-patient care	Total: 7 (762) Admissions data: 7 (762)	Yes	8	ESD/HAH is safe in selected patients with an AECOPD. Further research is required to define optimal criteria to guide patient selection and models of care.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Edmonds, 2012, 2158	To determine the effectiveness of Inhaled CorticoSteriods on outcomes in the treatment of acute asthma following discharge from the ED. To quantify the effectiveness of ICS therapy on acute asthma following ED discharge, when used in addition to, or as a substitute for, systemic corticosteroids	Acute asthma	Any inhaled corticosteroids plus oral corticosteroid vs. Placebo or standard oral corticosteroid therapy	Total: 12 (2205) Admissions data: 5 (1059)	No	9	There is insufficient evidence that ICS therapy provides additional benefit when used in combination with standard systemic corticosteroid therapy upon ED discharge for acute asthma. There is some evidence that high-dose ICS therapy alone may be as effective as oral corticosteroid therapy when used in mild asthmatics upon ED discharge; however, the confidence intervals were too wide to be confident of equal effectiveness. Further research is needed to clarify whether ICS therapy should be employed in acute asthma treatment following ED discharge. The review does not suggest any reason to stop usual treatment with ICS following ED discharge, even if a course of oral corticosteroids are prescribed.
Edmonds, 2012, 2159	To determine the benefit of ICS for the treatment of patients with acute asthma managed in the emergency department (ED).	Acute asthma	Early use of inhaled corticosteroids in the emergency department vs. Placebo or systemic corticosteroids	Total: 32 (2374) Admissions data: 5 (377)	Yes	9	ICS therapy reduces hospital admissions in patients with acute asthma who are not treated with oral or intravenous corticosteroids. They may also reduce admissions when they are used in addition to systemic corticosteroids; however, the most recent evidence is conflicting. There is insufficient evidence that ICS therapy results in clinically important changes in pulmonary function or clinical scores when used in acute asthma in addition to systemic corticosteroids. Also, there is insufficient evidence that ICS therapy can be used in place of systemic corticosteroid therapy when treating acute asthma. Further research is needed to clarify the most appropriate drug dosage and delivery device, and to define which patients are most likely to benefit from ICS therapy. Use of similar measures and reporting methods of lung function, and a common, validated, clinical score would be helpful in future versions of this meta-analysis.
El-Hayek, 2014, 8763	Therefore, we investigated the clinical impact of both RCTs and non-randomized case–control studies (CCS) comparing CCTA vs. SOC, separate and combined, on the diagnostic evaluation of lowto intermediate risk patients presenting to the ED with chest pain. Our goal was to have a better reflection and understanding of the real world practice management for these patients.	Low risk acute chest pain	Coronary computed tomography angiography vs. Standard of care	Total: 4 (3266) Admissions data: 4 (3266)	No	6	CCTA use in the ED for the triage of low to intermediate risk patients reduces the risk of future ACS and subsequent ED visits for chest pain.
Elkan, 2001, 2211	To evaluate the effectiveness of home visiting programmes that offer health promotion and preventive care to older people.	Elderly people	Preventive home visiting vs. No home visits	Total: 13 (5532) Admissions data: 11 (4284)	No	7	Home visits to older people can reduce mortality and admission to long term institutional care.
Ezekowitz, 2009, 2304	To summarize the evidence on the efficacy of spironolactone (SP), eplerenone (EP), or canrenoate (CAN) in patients with left ventricular dysfunction.	Left ventricular dysfunction (heart failure, mycardial infarction)	Aldosterone antagonists vs. Placebo or usual care or active comparator (metoprolol or ramipril)	Total: 19 (10807) Admissions data: 9 (8699)	No	6	We demonstrated a 20% reduction in all-cause mortality with the use of aldosterone blockade in a clinically heterogeneous group of clinical trial participants with heart failure and post-MI. In addition, we found a 3.1% improvement in EF. Further study in those with less severe symptoms or preserved systolic function is warranted.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Fanning, 2016, 9247	To determine the benefits and harms associatedwith the following. 1. A routine invasive versus a conservative or 'selective invasive' strategy for the management of UA/NSTEMI in the stent era. 2. A routine invasive strategy with and without glycoprotein IIb/IIIa receptor antagonists versus a conservative strategy for the management of UA/NSTEMI in the stent era.	Angina with an accelerating pattern of pain at rest (unstable angina and non-ST elevation myocardial infarction in the stent era)	Routine coronary angiography vs. Selective coronary angiography	Total: 8 (8917) Admissions data: 6 (6923)	No	11	In the all-study analysis, the evidence failed to show appreciable benefit with routine invasive strategies for unstable angina and non- ST elevation MI compared to conservative strategies in all-cause mortality and death or non-fatal MI at six to 12 months. There was evidence of risk reduction in MI, refractory angina and re-hospitalisation with routine invasive strategies compared to conservative (selective invasive) strategies at six to 12 months follow-up. However, routine invasive strategies were associated with a relatively high risk (almost double the risk) of procedure-relatedMI, and increased risk of bleeding complications. This systematic analysis of published RCTs supports the conclusion that, in patients with UA/NSTEMI, a selectively invasive (conservative) strategy based on clinical risk for recurrent events is the preferred management strategy.
Farne, 2015, 8767	To compare the relative effects on markers of quality of life, exacerbations, symptoms, lung function and serious adverse events in people with COPD randomised to LABA plus tiotropium versus tiotropium alone; or LABA plus tiotropium versus LABA alone.	Chronic obstructive pulmonary disease	Long-acting beta2-agonists (LABA) plus tiotropium vs. Tiotropium or long-acting beta2-agonist alone	Total: 10 (10894) Admissions data: 4 (4856)	Yes	10	The results from this review indicated a small mean improvement in health-related quality of life and FEV1 for participants on a combination of tiotropium and LABA compared to either agent alone, and this translated into a small increase in the number of responders on combination treatment. In addition, adding tiotropium to LABA reduced exacerbations, although adding LABA to tiotropium did not. Hospital admission and mortality were not altered by adding LABA to tiotropium, although there may not be enough data. While it is possible that this is affected by higher attrition in the tiotropium group, one would expect that participants withdrawn from the study would have had less favourable outcomes; this means that the expected direction of attrition bias would be to reduce the estimated benefit of the combination treatment. The results were largely from studies of olodaterol and there was insufficient information to assess whether the other LABAs were equivalent to olodaterol or each other.
Farrelly, 2013, 2335	To evaluate the effects of personalised, accessible, user-held clinical information for people with a severe mental illness (defined as psychotic illnesses)	Severe mental illness	User-held personalised information vs. Standard information	Total: 4 (612) Admissions data: 4 (612)	Yes	10	The evidence gap remains regarding user-held, personalised, accessible clinical information for people with psychotic illnesses for many of the outcomes of interest. However, based on moderate quality evidence, this review suggests that there is no effect of the intervention on hospital or outpatient appointment use for individuals with psychotic disorders. The number of studies is low, however, and further evidence is required to ascertain whether these results are mediated by the type of intervention, such as involvement of a clinical team or the type of information included.
Feltner, 2014, 2359	To assess the efficacy, comparative effectiveness, and harms of transitional care interventions to reduce readmission and mortality rates for adults hospitalized with HF	Heart failure	Transitional care interventions vs. Another transitional care intervention or usual care	Total: 47 (8305) Admissions data: 44 (7997)	Yes	8	Home-visiting programs and MDS-HF clinics reduced all-cause readmission and mortality; STS reduced HF-specific readmission and mortality. These interventions should receive the greatest consideration by systems or providers seeking to implement transitional care interventions for persons with HF.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Filippini, 2003, 2402	To find out whether recombinant interferons reduced the number of patients who had clinical exacerbations and disease progression, compared with placebo.	Multiple sclerosis	Interferons vs. Placebo	Total: 7 (1215) Admissions data: 2 (391)	No	7	Recombinant interferons slightly reduce the number of patients who have exacerbations during first year of treatment. Their clinical effect beyond 1 year is uncertain and new trials are needed to assess their long-term effectiveness and side-effects.
Fisher, 2014, 8769	The critical evaluation of clinical evidence on the safety and efficacy of autologous adult bone marrow-derived stemcells (BMSC) as a treatment for chronic ischaemic heart disease (IHD) and heart failure.	Chronic ischaemic heart disease and congestive heart failure	Bone marrow stem cells vs. No intervention or a placebo	Total: 23 (1255) Admissions data: 5 (402)	No	11	This systematic review and meta-analysis found moderate quality evidence that BMSC treatment improves LVEF. Unlike in trials where BMSC were administered following acute myocardial infarction (AMI), we found some evidence for a potential beneficial clinical effect in terms of mortality and performance status in the long term (after at least one year) in people who suffer from chronic IHD and heart failure, although the quality of evidence was low.
Fisher, 2015, 8770	To assess available clinical evidence on the safety and efficacy of cell-based therapies for HF.	Heart failure	Bone marrow stem cells vs. No intervention or placebo	Total: 31 (1521) Admissions data: 11 (574)	Yes	7	This study shows evidence that autologous cell therapy may be beneficial for patients having HF, but further evidence is required.
Fisher, 2015, 8771	To determine the safety and efficacy of autologous adult bone marrow stem cells as a treatment for acute myocardial infarction (AMI), focusing on clinical outcomes.	Acute myocardial infarction	Autologous adult bone marrow-derived cells following successful revascularisation by angioplasty or cardiac surgery vs. No intervention or placebo	Total: 41 (2732) Admissions data: 13 (1194)	No	11	The results of this review suggest that there is insufficient evidence for a beneficial effect of cell therapy for AMI patients. However, most of the evidence comes from small trials that showed no difference in clinically relevant outcomes. Further adequately powered trials are needed and until then the efficacy of this intervention remains unproven.
Fox, 2011, 2496	To examine whether combination therapy is more efficacious than monotherapy therapy for treatment of pulmonary artery hypertension.	Pulmonary arterial hypertension (PAH)	Combination therapy (Tadalafil and Bosentan; INH treprostinil and Bosentan or sildenafil; Sildenafil and Epoprostenol; INH iloprost and Bosentan) vs. Placebo (Monotherapy when combined with co-intervention)	Total: 6 (729) Admissions data: 5 (634)	No	5	CT did not decrease the combined end point of mortality, admission for worsening PAH, lung transplantation, or escalation of PAH therapy (RR 0.42, 95% CI 0.17 to 1.04). In conclusion, this meta-analysis suggests that in PAH CT doesnot offer an advantage over MT apart from modestly increasing exercise capacity. However, given the paucity of good-quality data, more studies are required to define the efficacy of CT in this population before establishing final guidelines.
Fox, 2012, 2500	To compare the effectiveness of acute geriatric unit care, based on all or part of the Acute Care for Elders (ACE) model and introduced in the acute phase of illness or injury, with that of usual care.	Elderly people	Acute geriatric unit care vs. Usual care	Total: 9 (5869) Admissions data: 5 (4426)	No	7	Acute geriatric unit care, based on all or part of the ACE model and introduced during the acute phase of older adults' illness or injury, improves patient and system-level outcomes.
Fredericks, 2017, 9375	The aim of this systematic review was to determine the effects of individualized patient education interventions compared to standardized education on rate of re-hospitalizations, performance of self-care behaviors, changes in mood (depression/anxiety), and cognitive states during the post-hospital discharge recovery period following cardiovascular surgery.	Heart surgery	Individualized patient education intervention vs. Standard care	Total: 19 (3330) Admissions data: 4 (930)	Yes	9	The findings from this systematic review suggest favorable effects on the readmission rates. However, a major limitation notes in the current body of evidence relates to the small number of or even lacking number of trials for clinically important outcomes. As well, the individualized patient education intervention is effective in promoting statistically significant changes in quality of life, performance of health behaviours, depression, and anxiety.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Fu, 2012, 2549	The aim of this meta-analysis was to assess the efficacy of ACE inhibitors in HFPEF patients, based on the results of the most recently published prospective studies.	Heart failure with preserved left ventricular ejection fraction defined as signs or symptoms of heart failure and EF≥40%)	Angiotensin converting enzyme inhibitor vs. Placebo or 'other classes of drugs such as monotherapy or first line therapy' for heart failure with preserved ejection fraction.	Total: 7 (2554) Admissions data: 4 (1803)	No	7	In patients with chronic heart failure with preserved ejection fraction, ACE inhibitors reduced all-cause mortality without affecting mortality due to heart failure and any-cause rehospitalization.
Gandhi, 2014, 2599	We have performed a systematic review of studies assessing the efficacy of HSS in combination with furosemide for the treatment of acute advanced CHF.	Heart Failure	Hypertonic saline and furosemide vs. Furosemide alone	Total: 10 (2845) Admissions data: 4 (1012)	Yes	8	The results of this meta-analysis demonstrate that in patients with advanced CHF concomitant hypertonic saline administration improved weight loss, preserved renal function, and decreased length of hospitalization, mortality and heart failure rehospitalization. Pending further validation, there is promise for hypertonic saline as an advanced therapy for the management of acute advanced CHF.
Gandhi, 2017, 9376	The objective of our study was to provide further insight as to whether mhealth technology can provide added benefit in the contemporary management of CVD.	Cardiovascular disease	Mobile health interventions vs. Usual care	Total: 27 (6041) Admissions data: 7 (2843)	No	8	The mhealth group compared with the usual care group had increased adherence to medical therapy, ability to reach blood pressure targets, exercise goals, and showed less anxiety and increased awareness of diet and exercise. There was no difference in smoking cessation, ability to meet low-density lipoprotein cholesterol targets, and hospital readmission.
Gao, 2014, 8775	We conducted a systematic review and meta-analysis to evaluate the impacts of macrolides on the number of bronchiectasis exacerbations and other clinical measures, i.e. admission for exacerbations, QoL, spirometric indices and adverse events.	Non-cystic fibrosis bronchiectasis	Macrolide vs. Placebo	Total: 9 (559) Admissions data: 2 (224)	No	6	Macrolide maintenance therapy, both in adults and children, was effective and safe in reducing bronchiectasis exacerbations, but not the admissions for exacerbations. In addition, macrolide administration in adults was associated with improvement in QoL and spirometry, but not 6WMT. Future studies are warranted to verify the optimal populations and clarify its potential effects on antimicrobial resistance.
Garside, 2007, 2640	To establish the effectiveness and cost-effectiveness of cinacalcet for the treatment of SHPT for people on dialysis due to ESRD.	Hyperparathyroidism secondary to ESRD	Cinacalcet vs. Placebo or ‘standard care’, which may include: phosphate binders, vitamin D and/or parathyroidectomy	Total: 7 (846) Admissions data: 4 (1184)	No	10	Cinacalcet in addition to standard care is more effective than placebo plus standard care at reducing PTH levels without compromising calcium levels. However, there is limited information about the impact of this reduction on patient-relevant clinical outcomes. Given the short follow-up in the trials, it is unclear how data should be extrapolated to the long term.
Gibson, 2002, 2715	Specific questions asked were: 1. Does limited (information only) asthma education lead to improved health outcomes in adults with asthma? 2. What are the characteristics of those education programmes which lead to measurable changes in health outcomes?	Asthma	Limited (information only) patient education programs vs. Usual care	Total: 11 (1918) Admissions data: 9 (1306)	No	7	Use of limited asthma education as it has been practiced does not appear to improve health outcomes in adults with asthma although perceived symptoms may improve. Provision of information in the emergency department may be effective, but this needs to be confirmed.
Goffinet, 1997, 2780	Our objective was to evaluate the effect of routine use of the umbilical Doppler in unselected or low risk pregnancies by reviewing all published and unpublished randomised controlled trials.	Unselected or a low risk pregnancy population	Umbilical Doppler testing vs. Usual care	Total: 4 (11357) Admissions data: 3 (9359)	No	5	Based on the results of the published trials, routine use of the umbilical Doppler cannot be recommended.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Gonçalves-Bradley, 2016, 8776	The main objective was to assess the effectiveness of planning the discharge of individual patients moving from hospital.	Hospitalised patients	Discharge planning from hospital vs. Standard care with no individualised discharge plan	Total: 30 (12387) Admissions data: 24 (9388)	Yes	10	A discharge plan tailored to the individual patient probably brings about a small reduction in hospital length of stay and reduces the risk of readmission to hospital at three months follow-up for older people with a medical condition. Discharge planning may lead to increased satisfaction with healthcare for patients and professionals. There is little evidence that discharge planning reduces costs to the health service.
Gonseth, 2004, 2811	To systematically evaluate the published evidence regarding the effectiveness of disease management programmes (DMPs) reducing hospital re-admissions among elderly patients with heart failure (HF).	Heart failure	Disease management programs vs. Control	Total: 27 (11583) Admissions data: 27 (11583)	Yes	9	DMPs are effective at reducing re-admissions among elderly patients with HF. Their effectiveness is close to that observed in clinical trials evaluating drugs for HF, such as angiotensin-converting enzyme inhibitors, beta-blockers or digoxin. However, since none of the DMP studies compared different interventions directly, we do not know the relative effectiveness of types of healthcare delivery within the DMP.
Greco, 2014, 2894	The aim of the present meta-analysis is to assess the impact of the ERAS pathway on short-term outcome, particularly on single postoperative complications, following colorectal surgery.	Post-operative colorectal surgical patients	Enhanced recovery program vs. Standard care	Total: 16 (2377) Admissions data: 15 (1780)	No	9	The ERAS pathway reduced overall morbidity rates and shortened the length of hospital stay, without increasing readmission rates. A significant reduction in nonsurgical complications was evident, while no significant reduction was found for surgical complications.
Griffiths, 2007, 2924	The review aims to determine whether nursing-led inpatient units are effective in preparing patients for discharge from hospital. Effectiveness of the NLU will be compared to 'usual care' (inpatient care in general acute hospital wards). In order to achieve this, the objectives of the review are as follows: (1) to identify patient outcomes for the NLU compared to usual care; (2) to identify resource use/cost of the NLU compared to usual care.	Hospitalised patients	Intermediate care in nursing-led inpatient units for discharge preparation vs. Usual inpatient care for discharge preparation	Total: 8 (1154) Admissions data: 4 (712)	No	9	There is some evidence that patients discharged from a NLU are better prepared for discharge but it is unclear if this is simply a product of an increased length of inpatient stay. No statistically significant adverse effects were noted but the possibility of increased early mortality cannot be discounted. More research is needed.
Grimwade, 2003, 2933	To assess the effects of routinely administered cotrimoxazole on death and illness episodes in HIV infected adults.	Human immunodeficiency virus	Cotrimoxazole vs. Placebo or usual treatment	Total: 4 (1476) Admissions data: 3 (764)	No	9	In the trials included in the review, cotrimoxazole prophylaxis had a beneficial effect in preventing death and illness episodes in adults with both early and advanced HIV disease. However, the wider applicability of these findings is unclear, in particular to areas with higher background bacterial resistance to cotrimoxazole. Further trials would be required in differing settings to widen applicability.
Grooten, 2015, 8780	The aim of the present systematic review and meta-analysis is to summarize the available evidence on the effectiveness of CCS therapy for HG.	Pregnant women with hyperemesis gravidarum	Corticosteroids (Prednisolone; Methylprednisolone; Hydrocortisone) vs. Prevailing treatment or a placebo	Total: 5 (310) Admissions data: 4 (214)	No	7	Meta-analysis yielded no effect of CCS therapy on readmission rates. Single small studies indicated possible beneficial effects on other outcomes. Future high-quality trials are necessary and would benefit from consensus on HG definition and core outcomes of HG therapy.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Gupta, 2014, 8688	To review the benefits and risks of uterine artery embolization (UAE) versus other medical or surgical interventions for symptomatic uterine fibroids.	Symptomatic uterine fibroids	Uterine artery embolization vs. Surgery	Total: 7 (840) Admissions data: 2 (298)	No	10	When we compared patient satisfaction rates at up to two years following UAE versus surgery (myomectomy or hysterectomy) our findings are that there is no evidence of a difference between the interventions. Findings at five year follow-up were similarly inconclusive. There was very low quality evidence to suggest that myomectomy may be associated with better fertility outcomes than UAE, but this information was only available from a selected subgroup in one small trial. We found no clear evidence of a difference between UAE and surgery in the risk of major complications, but UAE was associated with a higher rate of minor complications and an increased likelihood of requiring surgical intervention within two to five years of the initial procedure. If we assume that 7% of women will require further surgery within two years of hysterectomy or myomectomy, between 15% and 32% will require further surgery within two years of UAE. This increase in the surgical re-intervention rate may balance out any initial cost advantage of UAE. Thus although UAE is a safe, minimally invasive alternative to surgery, patient selection and counselling are paramount due to the much higher risk of requiring further surgical intervention.
Gwadry-Sridhar, 2004, 3030	The present study addresses the following question: Do patients with HF participating in a peridischarge multidisciplinary patient treatment program have a reduced rate of readmission and mortality compared with patients who receive usual care?	Heart failure	Pre-discharge multidisciplinary patient education program vs. Usual care	Total: 8 (1239) Admissions data: 8 (1239)	Yes	9	This systematic review suggests that specific heart failure–targeted interventions significantly decrease hospital readmissions but do not affect mortality rates.
Handoll, 2009, 3116	This review aims to examine the effectiveness and cost effectiveness of specialised multidisciplinary rehabilitation supervised by a geriatrician or rehabilitation physician/clinician compared with usual care, for older people with hip fracture.	Elderly people	Multidisciplinary post-surgical rehabilitation programme vs. Usual care	Total: 13 (2498) Admissions data: 9 (1746)	No	10	While there was a tendency to a better overall result in patients receiving multidisciplinary inpatient rehabilitation, these results were not statistically significant. Future trials of multidisciplinary rehabilitation should aim to establish both effectiveness and cost effectiveness of multidisciplinary rehabilitation overall, rather than evaluate its components.
Harrison, 2015, 8782	The objectives of this review were to describe SM interventions delivered immediately following an AE of COPD (AECOPD) and to conduct a systematic review with meta-analysis of its impact on health-care utilization and health outcomes.	Chronic obstructive pulmonary disease	Self-management vs. Usual care	Total: 7 (1115) Admissions data: 6 (1075)	No	5	SM interventions delivered immediately post-AE vary widely and outcome measures are inconsistent, making it difficult to draw strong recommendations regarding its effectiveness. The evaluation of SM interventions, delivered by trained health-care professionals to selected patients and which off er structured follow-up, appears necessary.
Hatah, 2013, 3183	The current study therefore aimed to examine the impact of fee-for-service pharmacist-led medication review on patient outcomes and quantify these according to the type of review undertaken. The specific objectives were to evaluate and quantify (i) the primary outcomes of such services (such as hospitalization, mortality rate, clinical biomarkers or marker of disease progress) and (ii) any secondary outcomes (such as medication adherence, economic implications and quality of life).	Patients on medication	Pharmacist-led fee-for-services medication review vs. Usual care	Total: 18 (6367) Admissions data: 8 (2022)	Yes	5	The majority of the studies (57.9%) showed improvement in medication adherence. Fee-for-service pharmacist-led medication reviews showed positive benefits on patient outcomes. Interventions that include a clinical review had a significant impact on patient outcomes by attainment of target clinical biomarkers and reduced hospitalization.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Hemkens, 2016, 8784	To evaluate potential cardiovascular benefits and harms of a continuous long-term treatment with colchicine in any population, and specifically in people with high cardiovascular risk.	Any condition or disease	Colchicine vs. Placebo, inactive control, or active control	Total: 39 (4992) Admissions data: 2 (599)	No	11	Overall, we found that further research would probably change our assessment of the benefits and harms of colchicine. Our findings should therefore be interpreted with caution. However, new treatments in heart diseases are urgently needed. Although there is much uncertainty around the benefits and harms of colchicine treatment, it may be associated with cardiovascular benefits, especially on myocardial infarction. We therefore think that large high-quality clinical trials should be conducted to further investigate colchicine in heart disease.
Heran, 2012, 3275	To assess the benefit and harm of ARBs compared with ACE inhibitors (ACEIs) or placebo on mortality, morbidity and withdrawals due to adverse effects in patients with symptomatic HF and left ventricular systolic dysfunction or preserved systolic function.	Heart failure with and without preserved ejection fraction	Angiotensin II receptor blocker with or without angiotensin converting enzyme inhibitor vs. Placebo, in addition to standard therapy (ACE-inhibitors)	Total: 24 (25051) Admissions data: 9 (14337)	Yes	10	Monotherapy; - dual therapy)In patients with symptomatic HF and systolic dysfunction or with preserved ejection fraction, ARBs compared to placebo or ACEIs do not reduce total mortality or morbidity Adding an ARB in combination with an ACEI does not reduce total mortality or total hospital admission but increases withdrawals due to adverse effects compared with ACEI alone.
Ho, 2014, 3350	We sought to perform a meta-analysis on the effect of sham feeding in colorectal surgery, with a separate analysis on trials that used rapid postoperative feeding.	Post-surgical colorectal resection patients	Sham feeding by means of chewing gum vs. Standard postoperative management	Total: 10 (620) Admissions data: 3 (Unclear)	No	9	Sham feeding following colorectal surgery is safe, results in small improvements in GI recovery, and is associated with a reduction in the length of hospital stay. It confers no advantage if patients are placed on a rapid postoperative feeding regime.
Hodnett, 2010, 3362	The primary objective was to assess the effects of programs offering additional social support compared with routine care for pregnant women who are believed to be at high risk for giving birth to babies that are either preterm or weigh less than 2500 gm, or both, at birth. Secondary objectives were to determine whether effectiveness of support was mediated by timing of onset (early versus later in pregnancy) or type of provider (a healthcare professional or a lay woman).	Pregnancy	Family or psychosocial support vs. Usual care	Total: 17 (12267) Admissions data: 5 (1004)	No	9	Pregnant women need the support of caring family members, friends, and health professionals. While programs which offer additional support during pregnancy are unlikely to prevent the pregnancy from resulting in a low birthweight or preterm baby, they may be helpful in reducing the likelihood of antenatal hospital admission and caesarean birth.
Holland, 2005, 3400	To determine the impact of multidisciplinary interventions on hospital admission and mortality in heart failure.	Heart failure	Multidisciplinary interventions vs. Usual care	Total: 30 (10452) Admissions data: 29 (10432)	Yes	7	Multidisciplinary interventions for heart failure reduce both hospital admission and all-cause mortality. The most effective interventions were delivered at least partly in the home.
Holland, 2007, 3401	We therefore aimed systematically to evaluate and quantify the effects of medication review by pharmacists on substantive clinical outcomes (namely, hospital admissions and mortality) for older people across all care settings.We also aimed to evaluate, as secondary outcomes, the effects of medication review on qualitative outcomes such as quality of life and patient satisfaction.	Elderly people	Pharmacist-led medication review vs. Control	Total: 32 (18761) Admissions data: 19 (11661)	Yes	6	Pharmacist-led medication review interventions do not have any effect on reducing mortality or hospital admission in older people, and can not be assumed to provide substantial clinical benefit. Such interventions may improve drug knowledge and adherence, but there are insufficient data to know whether quality of life is improved.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Hood, 2014, 3415	To examine the effectiveness of digitalis glycosides in treating HF in patients with normal sinus rhythm. To examine the effects of digitalis in patients taking diuretics and angiotensin-converting enzyme inhibitors; in patients with varying severity and duration of disease; in patients with prior exposure to digitalis versus no prior exposure; and in patients with "HF due to systolic dysfunction" versus "HF with preserved ejection fraction."	Heart failure	Digitalis (digoxin or digitoxin) vs. Placebo	Total: 13 (7896) Admissions data: 4 (7262)	Yes	7	The literature indicates that digitalis may have a useful role in the treatment of patients with HF who are in normal sinus rhythm. New trials are needed to elucidate the importance of the dosage of digitalis and its usefulness in the era of beta-blockers and other agents shown to be effective in treating HF.
Howcroft, 2016, 9261	To compare effects of an action plan for COPDexacerbations provided with a single short patient education component and without a comprehensive self-management programme versus usual care. Primary outcomes were healthcare utilisation, mortality and medication use. Secondary outcomes were health-related quality of life, psychological morbidity, lung function and cost-effectiveness.	Chronic obstructive pulmonary disease	Action plans with brief patient education vs. Usual care	Total: 7 (1630) Admissions data: 7 (1630)	Yes	11	Use of COPD exacerbation action plans with a single short educational component along with ongoing support directed at use of the action plan, but without a comprehensive self management programme, reduces in-hospital healthcare utilisation and increases treatment of COPDexacerbations with corticosteroids and antibiotics. Use of COPDaction plans in this context is unlikely to increase or decrease mortality. Whether additional benefit is derived from periodic ongoing support directed at use of an action plan cannot be determined from the results of this review.
Hulten, 2013, 3492	To systematically review and perform a meta-analysis of randomized, controlled trials of coronary computed tomography angiography (CCTA) versus usual care (UC) triage of acute chest pain in the emergency department (ED).	Acute chest pain syndromes	Coronary computed tomography angiography vs. Usual care	Total: 4 (3266) Admissions data: 4 (3266)	No	5	Compared with usual care the use of coronary computed tomography angiography in the ED is associated with decreased ED cost and length of stay but increased invasive coronary angiography and revascularization.
Huntley, 2013, 3507	To systematically review evidence from randomized controlled trials regarding the effectiveness of case management in reducing the risk of unplanned hospital admissions in older people.	Elderly people	Case management vs. Usual care	Total: 11 (4247) Admissions data: 11 (4247)	Yes	8	The identified trials included a range of case management interventions. Nine of the 11 trials showed no reduction of unplanned hospital admissions with case management compared with the same with usual care.
Huntley , 2016, 9178	The aim of this systematic review of randomised controlled trials (RCTs) and controlled trials (non-RCTs, NRCTs) is to nvestigate the effectiveness and related costs of case management (CM) for patients with heart failure (HF) predominantly based in the community in reducing unplanned readmissions and length of stay (LOS).	Heart failure	Case management vs. Usual care	Total: 17 (6468) Admissions data: 16 (4268)	Yes	7	Hospital-initiated CM can be successful in reducing unplanned hospital readmissions for HF and length of hospital stay for people with HF. 9 trials described cost data; no clear difference emerged between CM and usual care. There was limited evidence for community initiated CM which suggested it does not reduce admission.
Inglis, 2015, 8787	To review randomised controlled trials (RCTs) of structured telephone support or non-invasive home telemonitoring compared to standard practice for people with heart failure, in order to quantify the effects of these interventions over and above usual care.	Heart failure	Structured telephone support or non-invasive telemonitoring vs. Usual post-discharge care	Total: 41 (13262) Admissions data: 36 (11799)	Yes	11	For people with heart failure, structured telephone support and non-invasive home telemonitoring reduce the risk of all-cause mortality and heart failure-related hospitalisations; these interventions also demonstrated improvements in health-related quality of life and heart failure knowledge and self-care behaviours. Studies also demonstrated participant satisfaction with the majority of the interventions which assessed this outcome.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Inglis, 2015, 8788	We conducted a post-hoc sub-analysis of a previously published large Cochrane systematic review and meta-analysis of relevant randomized controlled trials to determine whether structured telephone support and telemonitoring were effective in this population.	Heart failure	Telemonitoring and structured telephone support vs. Usual care	Total: 12 (3777) Admissions data: 10 (2688)	Yes	8	Despite a systematic bias towards recruitment of individuals younger than the epidemiological average into the randomized controlled trials, older people with heart failure did benefit from structured telephone support and telemonitoring. These post-hoc sub-analysis results were similar to overall effects observed in the main metaanalysis. While further research is required to confirm these observational findings, the evidence at hand indicates that discrimination by age alone may be not be appropriate when inviting participation in a remote monitoring service for heart failure.
Jaeschke, 2008, 3639	To determine the safety of long-acting b-agonists among patients with asthma using corticosteroids.	Asthma	Long acting beta agonists with inhaled corticosteroids vs. Inhaled corticosteroids	Total: 62 (29401) Admissions data: 44 (22396)	No	5	In patients with asthma using ICS, LABA did not increase the risk of asthma-related hospitalizations. There were very few asthma-related deaths and intubations, and events were too infrequent to establish LABA's relative effect on these outcomes.
Jaeschke, 2008, 3640	To assess the safety of formoterol in patients with asthma using inhaled corticosteriods.	Asthma	Long acting beta agonists with inhaled corticosteroids vs. Inhaled corticosteroids	Total: 16 (10638) Admissions data: 16 (10638)	No	4	In patients with asthma using inhaled corticosteroids formoterol decreased the risk of asthma-related hospitalizations. There were too few asthma-related deaths and intubations to establish formoterol's relative impact on these outcomes.
James, 2008, 3657	To examine whether topical or intraluminal antibiotics reduce catheter-related bloodstream infection compared with no antibiotic therapy in adults undergoing hemodialysis.	Long-term hemodialysis using a central venous catheter	Topical prophylaxtic antibiotics vs. Another or no antimicrobial agent	Total: 16 (1395) Admissions data: 2 (305)	No	7	Both topical and intraluminal antibiotics reduced the rate of bacteremia as well as the need for catheter removal secondary to complications. Whether these strategies will lead to antimicrobial resistance and loss of efficacy over longer periods remains unclear.
Jankowska, 2016, 8790	The aim of our study was to summarize the evidence in the form of a meta-analysis of all randomized controlled trials that investigated the effects of i.v. iron therapy in iron-deficient patients with systolic HF (also analysed separately in anaemic and non-anaemic subjects).	Iron-deficient patients with systolic heart failure	Intravenous iron therapy vs. Placebo	Total: 5 (509) Admissions data: 4 (835)	No	6	The evidence indicates that i.v. iron therapy in iron-deficient patients with systolic HF improves outcomes, exercise capacity, and quality of life, and alleviates HF symptoms.
Jefferson, 2014, 3696	To describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all clinical study reports of published and unpublished randomised, placebo-controlled trials and regulatory comments.	Influenza	Oseltamivir for influenza prophylaxis or treatment vs. Placebo	Total: 46 (24251) Admissions data: 11 (7828)	No	11	Oseltamivir and zanamivir have small, non-specific effects on reducing the time to alleviation of influenza symptoms in adults, but not in asthmatic children. Using either drug as prophylaxis reduces the risk of developing symptomatic influenza. Treatment trials with oseltamivir or zanamivir do not settle the question of whether the complications of influenza (such as pneumonia) are reduced, because of a lack of diagnostic definitions. The use of oseltamivir increases the risk of adverse effects, such as nausea, vomiting, psychiatric effects and renal events in adults and vomiting in children. The lower bioavailability may explain the lower toxicity of zanamivir compared to oseltamivir. The balance between benefits and harms should be considered when making decisions about use of both NIs for either the prophylaxis or treatment of influenza. The influenza virus-specific mechanism of action proposed by the producers does not fit the clinical evidence.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Jeppesen, 2012, 3709	To evaluate the efficacy of hospital at home compared to hospital inpatient care in acute exacerbations of COPD.	Chronic obstructive pulmonary disease	Hospital at home vs. In-hospital care	Total: 8 (870) Admissions data: 8 (870)	Yes	10	Selected patients presenting to hospital emergency departments with acute exacerbations of COPDcan be safely and successfully treated at home with support from respiratory nurses.We found evidence of moderate quality that hospital at home may be advantageous with respect to readmission rates in these patients. Treatment of acute exacerbation of COPD in hospital at home also show a trend towards reduced mortality rate when compared with conventional inpatient treatment, but these results did not reach statistical significance (moderate quality evidence). For other outcomes than readmission and mortality rate, we assessed the evidence to be of low or very low quality.
Johnstone, 1999, 3761	To determine the effectiveness of planned short hospital stays versus standard care for people with serious mental illness.	Severe mental illness	Planned short hospital stay vs. Long hospital stay or standard care	Total: 4 (628) Admissions data: 4 (628)	No	8	The effectiveness of care in mental hospitals is important to patients, carers, and policy makers. Despite inadequacies in the data, this review suggests that planned short hospital stays do not encourage a “revolving door” pattern of care for people with serious mental illness and may be more effective than standard care. Further pragmatic trials are needed on the most effective organisation and delivery of care in mental hospitals.
Jolly, 2016, 9198	We undertook a wide systematic review of interventions which included supported self-management for COPD to explore the effectiveness of various configurations on all-cause hospital admissions and health-related quality of life (HRQoL).	Chronic obstructive pulmonary disease	Self-management vs. Usual care, control or another active intervention	Total: 19 (2997) Admissions data: 18 (2997)	Yes	8	While many self-management interventions increased HRQoL, little effect was seen on hospital admissions. More trials should report admissions and follow-up participants beyond the end of the intervention.
Jones, 2012, 3769	To review the effects of CBT for people with schizophrenia when compared with other psychological therapies.	Schizophrenia	Cognitive behavioural therapy adjunct to standard care vs. Standard care	Total: 20 (1927) Admissions data: 8 (1137)	No	10	Trial-based evidence suggests no clear and convincing advantage for cognitive behavioural therapy over other - and sometime much less sophisticated - therapies for people with schizophrenia.
Jong, 2002, 3781	To determine the effect of ARBs on the survival and hospitalization rates in patients with HF.	Heart failure	Angiotensin receptor blockers (Angiotensin II receptor blocker and angiotensin converting enzyme inhibitor) vs. Angiotensin converting enzyme inhibitors alone	Total: 17 (12469) Admissions data: 6 (10031)	No	6	This meta-analysis cannot confirm that ARBs are superior in reducing all-cause mortality or HF hospitalization in patients with symptomatic HF, particularly when compared with ACEIs. However, the use of ARBs as monotherapy in the absence of ACEIs or as combination therapy with ACEIs appears promising.
Jonkman, 2016, 8795	This IPD meta-analysis aimed to evaluate the effectiveness of self-management interventions on HF-related QoL (HF-QoL) or generic QoL, HF-related or all-cause hospitalization, and all-cause mortality and to identify subgroups of patients with HF who respond differently to such interventions.	Heart failure	Self-management vs. Usual care	Total: 20 (5650) Admissions data: 14 (4460)	Yes	8	This study shows that self-management interventions had a beneficial effect on time to HF-related hospitalization or all-cause death and HF-related hospitalization alone and elicited a small increase in HF-related quality of life. The findings do not endorse limiting self-management interventions to subgroups of patients with HF, but increased mortality in depressed patients warrants caution in applying self-management strategies in these patients.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Jordan, 2015, 8796	The aim of this chapter is to present the findings of a systematic review of the evidence for the effectiveness of SM support evaluating health behaviour change, self-efficacy, health service utilisation and patient-reported outcomes, such as quality of life (QoL).	Chronic obstructive pulmonary disease	Supported self-management vs. Usual care, control, sham or other self-management interventions	Total: 175 (14387) Admissions data: 54 (6968)	Yes	10	(Self-management support delivered shortly after an acute exacerbation may have some benefit in terms of HRQoL and possibly admissions but the evidence is thin and unconvincing. Exercise may play an important role but there are not enough data to explore this. Any future trials should address issues of bias, particularly loss to follow-up, but this may be inherent in the nature of the intervention and the fact that patients are still trying to recover from an exacerbation. The evidence is not in support of SM interventions to be put into practice for patients with COPD at, or recently after, hospital discharge.
Kang, 2007, 3877	The aim of this study was to investigate the effectiveness and tolerability of G-CSF treatment with regard to global left ventricular function in patients with myocardial infarction (MI).	Myocardial infarction	Granulocyte colony-stimulating factor (G-CSF) treatment vs. Placebo or blank control	Total: 7 (364) Admissions data: 8 (364)	No	6	Based on the studies included in this meta-analysis, G-CSF treatment improved the LVEF in AMI (but not OMI) at 3 to 12 months follow-up. Treatment with G-CSF was generally well tolerated.
Kang, 2008, 3879	Therefore, we conducted a systematic review and metaanalysis of available prospective randomized controlled trials (RCTs) to analyze the efficacy and safety of bone marrow-derived stem/progenitor cells (BMC) treatment with global left ventricular function in acute myocardial infarction.	Acute myocardial infarction	intracoronary bone marrow-derived stem/progenitor cells vs. Placebo or blank control	Total: 6 (517) Admissions data: 6 (517)	No	7	On the basis of present evidence, intracoronary BMC infusion in patients with AMI seems to be safe and associated with slight improvement of the left ventricular ejection fraction at 3–6 months' follow-up.
Kang, 2015, 8797	In this study, we conducted a comprehensive systematic review, meta-analysis, and meta-regression of data from contemporary randomized controlled trials (RCT) to determine which factors may determine the outcome of cardiac resynchronization therapy.	Patients with systolic heart failure with a left ventricular ejection fraction (LVEF) less than or equal to 40%.	Cardiac resynchronization therapy vs. Medical treatment or implantable cardioverter-defibrillator	Total: 23 (10103) Admissions data: 17 (7697)	No	8	This meta-regression analysis implies that patients with a QRS duration ≥ 150 ms would most benefit from CRT, and in those with a QRS duration < 130 ms CRT implantation may be potentially harmful.
Kang, 2016, 9271	We performed a qualitative evaluation for all positive and negative effects of pharmacist services for the two major CVD of HF and ACS. Second, to identify the effects of pharmaceutical care quantitatively, a meta-analysis was carried out for all-cause mortality, all-cause hospitalization and cardiac-related hospitalization and key medication prescription rates as direct effects of pharmaceutical care.	Heart failure and acute coronary syndrome	Pharmacist-involved care vs. Usual care	Total: 24 (9286) Admissions data: 15 (4595)	Yes	6	All-cause hospitalization showed improvement in the pharmaceutical care group. However, the strength of evidence for the majority of outcomes with pharmaceutical care, except direct performance measures such as prescription rates, was either insufficient or low. This could be explained by the presence of imprecision and inconsistency derived from the diversity of pharmaceutical care, the heterogeneity of patient populations or clinical settings. Moreover, it may indicate the necessity for homogeneous applicable criteria for assessment. A standardized consensus of the guidelines for pharmaceutical care service should be considered to improve homogeneity.
Kansagara, 2013, 3885	To evaluate the benefits and harms of treatments for anemia in adults with heart disease.	Heart disease	Erythropoiesis stimulating agent vs. Placebo or those comparing more intensive with less intensive interventions	Total: 26 (9695) Admissions data: 4 (3901)	No	8	Higher transfusion thresholds do not consistently improve mortality rates, but large trials are needed. Intravenous iron may help to alleviate symptoms in patients with heart failure and iron deficiency and also warrants further study. Erythropoiesisstimulating agents do not seem to benefit patients with mild to moderate anemia and heart disease and may be associated with serious harms.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Karner, 2011, 3908	To assess the relative effects of inhaled corticosteroid and long-acting beta2-agonist combination therapy in addition to tiotropium compared to tiotropium or combination therapy alone in patients with chronic obstructive pulmonary disease.	Chronic obstructive pulmonary disease	Tiotropium plus long acting beta 2 agonists and or inhaled corticosteroid vs. Inhaled tiotropium bromide alone or inhaled combination corticosteroid and long-acting beta2- agonist	Total: 3 (1051) Admissions data: 2 (961)	Yes	10	To date there is uncertainty regarding the long-termbenefits and risks of treatment with tiotropium in addition to inhaled corticosteroid and long-acting beta2-agonist combination therapy onmortality, hospitalisation, exacerbations of COPDand pneumonia. The addition of combination treatment to tiotropium has shown improvements in average health-related quality of life and lung function.
Karner, 2014, 8692	To evaluate data from randomised controlled trials (RCTs) comparing the efficacy of tiotropium and placebo in patients with chronic obstructive pulmonary disease (COPD), upon clinically important endpoints.	Chronic obstructive pulmonary disease	Tiotropium vs. Placebo	Total: 22 (23309) Admissions data: 21 (22852)	Yes	10	This review shows that tiotropium treatment was associated with a significant improvement in patients' quality of life and it reduced the risk of exacerbations, with a number needed to treat to benefit (NNTB) of 16 to prevent one exacerbation. Tiotropium also reduced exacerbations leading to hospitalisation but no significant difference was found for hospitalisation of any cause or mortality. Thus, tiotropium appears to be a reasonable choice for the management of patients with stable COPD, as proposed in guidelines. The trials included in this review showed a difference in the risk of mortality when compared with placebo depending on the type of tiotropium delivery device used. However, these results have not been confirmed in a recent trial when 2.5mcg or 5mcg of tiotropium via Respimat was used in a direct comparison to the 18 mcg Handihaler.
Kaur, 2014, 3937	To determine whether raising HDL-C with pharmacologic therapies translates into beneficial cardiovascular outcomes and to find out if this change was proportional to the percentage change in HDL levels.	Cardiovascular disease	High density lipoprotein raising therapeutic agents as monotherapy or co-administered with statins vs. The control arm should have had an intervention which would permit appropriate attribution of the results to HDL targeting drug.	Total: 12 (53721) Admissions data: 7 (40155)	No	7	Increasing HDL levels via pharmacological manipulation beyond optimal lipid lowering therapy for secondary prevention is not beneficial.
Kew, 2014, 4002	To assess the safety and efficacy of IVMgSO4 in adults treated for acute asthma in the emergency department.	Acute asthma	Intravenous magnesium sulfate vs. Placebo	Total: 14 (2313) Admissions data: 11 (972)	Yes	10	This review provides evidence that a single infusion of 1.2 g or 2 g IV MgSO4 over 15 to 30 minutes reduces hospital admissions and improves lung function in adults with acute asthma who have not responded sufficiently to oxygen, nebulised short-acting beta2-agonists and IV corticosteroids. Differences in the ways the trials were conducted made it difficult for the review authors to assess whether severity of the exacerbation or additional co-medications altered the treatment effect of IV MgSO4. Limited evidence was found for other measures of benefit and safety. Studies conducted in these populations should clearly define baseline severity parameters and systematically record adverse events. Studies recruiting participants with exacerbations of varying severity should consider subgrouping results on the basis of accepted severity classifications.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Kew, 2013, 4003	To assess the effects of twice-daily long-acting beta2-agonists compared with placebo for patients with COPD on the basis of clinically important endpoints, primarily quality of life and COPD exacerbations.	Chronic obstructive pulmonary disease	Long-acting beta2-agonists vs. Not reported	Total: 26 (14939) Admissions data: 7 (3804)	Yes	11	Moderate-quality evidence from 26 studies showed that inhaled long-acting beta2-agonists are effective over the medium and long term for patients with moderate to severe COPD. Their use is associated with improved quality of life and reduced exacerbations, including those requiring hospitalisation. Overall, findings showed that inhaled LABAs did not significantly reduce mortality or serious adverse events.
Kew, 2014, 4004	To assess the risk of pneumonia associated with the use of fluticasone and budesonide for COPD.	Chronic obstructive pulmonary disease	Fluticasone (with or without long acting beta2-agonist) vs. Placebo or long acting beta2-agonist	Total: 43 (31397) Admissions data: 24 (25976)	Yes	10	Budesonide and fluticasone, delivered alone or in combination with a LABA, are associated with increased risk of serious adverse pneumonia events, but neither significantly affected mortality compared with controls. The safety concerns highlighted in this review should be balanced with recent cohort data and established randomised evidence of efficacy regarding exacerbations and quality of life. Comparison of the two drugs revealed no statistically significant difference in serious pneumonias, mortality or serious adverse events. Fluticasone was associated with higher risk of any pneumonia when compared with budesonide (i.e. less serious cases dealt with in the community), but variation in the definitions used by the respectivemanufacturers is a potential confounding factor in their comparison. Primary research should accurately measure pneumonia outcomes and should clarify both the definition and the method of diagnosis used, especially for new formulations and combinations for which little evidence of the associated pneumonia risk is currently available. Similarly, systematic reviews and cohorts should address the reliability of assigning 'pneumonia' as an adverse event or cause of death and should determine how this affects the applicability of findings.
Kew, 2016, 8802	To assess the effects of adding a long-acting muscarinic antagonist (LAMA) to combination long-acting beta2-agonists (LABA) and inhaled corticosteroids (ICS) in adults whose asthma is not well controlled by LABA/ICS.	Asthma	Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) vs. Long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS)	Total: 4 (1197) Admissions data: 3 (1191)	No	10	Tiotropium add-on may have additional benefits over LABA/ICS alone in reducing the need for rescue oral steroids in people with severe asthma. The effect was imprecise, and there was no evidence for other LAMA preparations. Possible benefits on quality of life were negligible, and evidence for the effect on serious adverse events was inconsistent. There are likely to be small added benefits for tiotropium Respimat 5 µg daily on lung function and asthma control over LABA/ICS alone and fewer non-serious adverse events. The benefit of tiotropium add-on on the frequency of hospital admission is still unknown, despite year-long trials. Ongoing and future trials should clearly describe participants' background medications to help clinicians judge how the findings relate to stepwise care. If studies test LAMAs other than tiotropium Respimat for asthma, they should be at least six months long and use accepted and validated outcomes to allow comparisons of the safety and effectiveness between different preparations.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Kew, 2015, 8803	To assess the efficacy and safety of adding a LAMA to ICS compared with adding a LABA for adults whose asthma is not well controlled on ICS alone.	Asthma not well controlled with inhaled corticosteroids alone	Long acting muscarinic antagonists added to inhaled corticosteroids vs. Long-acting beta2-agonists (LABA) added to inhaled corticosteroids (ICS)	Total: 8 (unclear) Admissions data: 4 (2022)	No	11	Direct evidence of LAMA versus LABA as add-on therapy is currently limited to studies of less than six months comparing tiotropium (Respimat) to salmeterol, and we do not know how they compare in terms of exacerbations and serious adverse events. There was moderate quality evidence that LAMAs show small benefits over LABA on some measures of lung function, and high quality evidence that LABAs are slightly better for quality of life, but the differences were all small. Given the much larger evidence base for LABA versus placebo for people whose asthma is not well controlled on ICS, the current evidence is not strong enough to say that LAMA can be substituted for LABA as add-on therapy. The results of this review, alongside pending results from related reviews assessing the use of LAMA in other clinical scenarios, will help to define the role of these drugs in asthma and it is important that they be updated as results from ongoing and planned trials emerge.
Kew, 2015, 8805	To assess the effects of macrolides for managing chronic asthma.	Chronic asthma	Macrolides vs. Placebo	Total: 23 (1513) Admissions data: 2 (143)	No	11	Existing evidence does not show macrolides to be better than placebo for the majority of clinical outcomes. However, they may have a benefit on some measures of lung function, and we cannot rule out the possibility of other benefits or harms because the evidence is of very low quality due to heterogeneity among patients and interventions, imprecision and reporting biases. The reviewhighlights the need for researchers to report clinically relevant outcomes accurately and completely using guideline definitions of exacerbations and validated scales. The possible benefit of macrolides in patients with non-eosinophilic asthma based on subgroup analyses in two of the included studies may require further investigation.
Kim, 2005, 4041	The purpose of this study was to investigate the effect of hospital-based CM compared with usual care on length of hospital stay and readmission rate.	Hospitalised patients	Hospital-based case management vs. Usual care	Total: 12 (2876) Admissions data: 10 (2603)	Yes	7	The findings of this meta-analysis demonstrate a 6% decrease in readmission rate for patients who received hospital-based CM interventions. Further meta-analytic studies are needed to investigate the effectiveness of CM on other outcomes.
Kisely, 2017, 9387	To examine the effectiveness of compulsory community treatment (CCT) for people with severe mental illness (SMI).	Severe mental illness	Compulsory community treatment vs. Entirely voluntary care; supervised discharge; or standard care.	Total: 3 (752) Admissions data: 3 (752)	Yes	10	These review data show CCT results in no clear difference in service use, social functioning or quality of life compared with voluntary care or brief supervised discharge. People receiving CCT were, however, less likely to be victims of violent or non-violent crime. It is unclear whether this benefit is due to the intensity of treatment or its compulsory nature. Short periods of conditional leave may be as effective (or non-effective) as formal compulsory treatment in the community. Evaluation of a wide range of outcomes should be considered when this legislation is introduced. However, conclusions are based on three relatively small trials, with high or unclear risk of blinding bias, and low- to moderate-quality evidence. In addition, clinical trials may not fully reflect the potential benefits of this complex intervention.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Kishimoto, 2013, 4065	Few controlled trials compared second-generation antipsychotics (SGAs) with first-generation antipsychotics (FGAs) regarding relapse prevention in schizophrenia. We conducted a systematic review/meta-analysis of randomized trials, lasting >6 months comparing SGAs with FGAs in schizophrenia.	Schizophrenia	Second generation antipsychotics vs. First generation antipsychotics	Total: 23 (4504) Admissions data: 11 (2869)	No	6	In conclusion, results from this meta-analysis suggest that, whereas individually SGAs were not consistently superior to FGAs, as a group, SGAs were associated with less study-defined relapse, overall treatment failure and hospitalization than FGAs, having a modest but clinically relevant effect size. Future relapse prevention studies should carefully assess EPS and adherence. Moreover, additional studies with a variety of SGAs using non-haloperidol FGA comparators at low-medium doses that do not produce significantly greater EPS than SGAs47 are needed to extend these findings. In particular, sufficiently large data sets are needed to allow examination of the relative merits of individual SGAs, and to guide an individualized and evidence-based maintenance treatment selection in schizophrenia.
Kishimoto, 2014, 4067	While long-acting injectable antipsychotics (LAIs) are hoped to reduce high relapse rates in schizophrenia, recent randomized controlled trials (RCTs) challenged the benefits of LAIs over oral antipsychotics (OAPs).	Schizophrenia	Long-acting injectable antipsychotics vs. Oral Antipsychotics	Total: 21 (5176) Admissions data: 10 (2341)	No	8	In RCTs, which are less representative of real-world patients than naturalistic studies, pooled LAIs did not reduce relapse compared with OAPs in schizophrenia patients. The exceptions were FGA-LAIs, mostly consisting of fluphenazine-LAI studies, which were all conducted through 1991. Because this finding is vulnerable to a cohort bias, studies comparing FGA-LAI vs second-generation antipsychotics-LAI and LAI vs OAP RCTs in real-world patients are needed.
Komossa, 2010, 4123	To evaluate the effects of olanzapine compared to other atypical antipsychotics for people with schizophrenia and schizophrenia-like psychosis.	Schizophrenia and schizophrenia-like psychosis	Olanzapine or other atypical antipsychotic drugs vs. Second generation (atypical) antipsychotics	Total: 50 (9100) Admissions data: 4 (1932)	No	9	Olanzapine may be a somewhat more efficacious drug than some other second generation antipsychotic drugs. This small superiority in efficacy needs to be weighed against a larger weight gain and associated metabolic problems than most other second generation antipsychotic drugs, except clozapine. These conclusions are tentative due to the large number of people leaving the studies early which possibly limits the validity of the findings. Further large, well-designed trials are necessary to establish the relative effects of different second generation antipsychotic drugs.
Koshman, 2008, 4147	We conducted a systematic review to evaluate the impact of pharmacist care on the management of patients with HF and, in particular, contacted the primary study authors of multidisciplinary intervention trials that incorporated a pharmacist in an attempt to define the precise role of the pharmacist in these interventions.	Heart failure	Pharmacist directed care or pharmacist collaborative care vs. No pharmacist care	Total: 12 (2060) Admissions data: 12 (2060)	Yes	5	Pharmacist care in the treatment of patients with HF greatly reduces the risk of all-cause and HF hospitalizations. Since hospitalizations associated with HF are a major public health problem, the incorporation of pharmacists into HF care teams should be strongly considered.
Kotb, 2014, 4154	To determine the effect of telephone support interventions compared with standard post-discharge care on coronary artery disease patient outcomes.	Coronary heart disease	Structured telephone support after hospital discharge vs. Standard post-discharge care	Total: 26 (6421) Admissions data: 5 (1046)	Yes	5	Compared to standard post-discharge care, regular telephone support interventions may help reduce feelings of anxiety and depression as well as, improve systolic blood pressure control and the likelihood of smoking cessation.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Kruis, 2013, 4192	To evaluate the effects of integrated disease management (IDM) programs or interventions in people with COPD on health-related QoL, exercise tolerance and number of exacerbations.	Chronic obstructive pulmonary disease	Integrated disease management interventions vs. Control	Total: 26 (3006) Admissions data: 16 (2488)	Yes	10	In these COPD participants, IDM not only improved disease-specific QoL and exercise capacity, but also reduced hospital admissions and hospital days per person.
Kuenzli, 2010, 4206	To investigate the effect of adding ARBs to ACE inhibitor therapy alone in terms of clinically relevant beneficial and adverse patient important outcomes including hospital readmissions for any reason.	Left ventricular dysfunction or congestive heart failure and background therapy with ACE inhibitor therapy in at least 90% of patients (i.e. patients on ACE inhibitors)	Angiotensin II receptor blocker and angiotensin converting enzyme inhibitor vs. Angiotensin enzyme converting inhibitors alone	Total: 8 (18061) Admissions data: 6 (17948)	No	7	Combination therapy with ARBs and ACE inhibitors reduces admissions for heart failure in patients with congestive heart failure when compared to ACE inhibitor therapy alone, but does not reduce overall mortality or all-cause hospitalization and is associated with more adverse events. Thus, based on current evidence, combination therapy with ARBs and ACE inhibitors may be reserved for patients who remain symptomatic on therapy with ACE inhibitors under strict monitoring for any signs of worsening renal function and/or symptomatic hypotension.
Kul, 2012, 4210	To determine how care pathways in the hospital treatment of heart failure affect in-hospital mortality, length of in-hospital stay, readmission rate and hospitalisation cost when compared with standard care.	Heart failure	In-hospital care pathways vs. Usual care	Total: 3 (3426) Admissions data: 3 (3426)	Yes	9	By combining all possible results, it can be concluded that care pathways for treatment of heart failure decrease mortality rates and length of hospital stay, but no statistically significant difference was observed in the readmission rates and hospitalisation costs. However, one should be cautious with overall conclusions: what works for one organization may not work for another because of the subtle differences in processes and bottlenecks.
Kumar, 2014, 8815	We undertook a systematic review and metaanalysis to assess whether the maintenance of anaesthesia using propofol TIVA is associated with fewer unplanned hospital admissions than maintenance with the inhalational agents sevoflurane or desflurane.	Ambulatory surgery	Total intravenous anaesthesia using propofol with sevoflurane vs. Inhalational agents sevoflurane or desflurane	Total: 18 (1621) Admissions data: 10 (1621)	Yes	6	Therefore, based on the published evidence to date, maintenance of anaesthesia using propofol appeared to have no bearing on the incidence of unplanned admission to hospital and was more expensive, but was associated with a decreased incidence of early postoperative nausea and vomiting compared with sevoflurane or desflurane in patients undergoing ambulatory surgery.
Kuswardhani, 2011, 4239	To confirm the beneficial effect of BMCs therapy over placebo in AMI patients with inclusion only to the randomized double blind placebo-controlled trials	Acute myocardial infarction	Bone Marrow-derived Stem Cells vs. Control/placebo	Total: 10 (686) Admissions data: 3 (319)	No	6	The resulting meta-analysis concluded that BMCs therapy consistently improves cardiac performance parameters (LVEF, LVESV, and LVEDV) when compared to placebo, even after the establishment of primary intervention. It is also safe to use and prevents the development of recurrent MI and HF.
Kwong, 2014, 4254	Systematic review and meta-analysis of randomized studies exploring the efficacy and safety of ultrafiltration in patients with acute decompensated heart failure.	Acute decompensated heart failure	Extracorporeal ultrafiltration vs. Standard care	Total: 12 (659) Admissions data: 4 (436)	Yes	5	For patients with ADHF, UF is effective in reducing fluid retention and body weight, with no significant benefits in mortality or rehospitalization. The current limited randomized evidence highlights the need for further well-conducted randomized studies of adequate power to establish the role of UF in ADHF patients for whom conventional HF treatment is unsuccessful or contraindicated.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Kwong, 2012, 4255	This meta-analysis aimed to systematically review the latest available randomized evidence on the effectiveness and safety of cardiac contractility modulation in HF.	Heart failure	Cardiac contractility modulation vs. Sham treatment or standard care	Total: 3 (641) Admissions data: 2 (477)	Yes	7	Meta-analysis of data from small randomized trials suggests that CCM, although with no clear benefits in improving clinical outcomes, is not associated with worsening prognosis. Large, well- designed trials are needed to confirm its role in HF patients for whom cardiac resynchronization therapy is contraindicated or unsuccessful.
La Mantia, 2010, 4260	To verify the clinical efficacy of glatiramer acetate in the treatment of MS patients with relapsing remitting (RR) and progressive (P) course.	Multiple sclerosis	Glatiramer acetate vs. Placebo	Total: 6 (3233) Admissions data: 2 (449)	No	9	Glatiramer acetate did show a partial efficacy in RR MS in term of relapse -related clinical outcomes, without any significant effect on clinical progression of disease measured as sustained disability. The drug is not effective in progressive MS patients.
Lam, 2010, 4296	To investigate whether B-Type Natriuretic Peptide testing of patients presenting with acute dyspnea in the emergency department leads to fewer admissions, shorter length of stay, and improved short-term survival compared with usual care without BNP testing.	Patients presenting to the emergency department with acute dyspnea.	BNP or NT-proBNP testing vs. Usual care	Total: 5 (2513) Admissions data: 5 (2513)	Yes	7	B-type natriuretic peptide testing in the emergency department for patients presenting with acute dyspnea decreased length hospital of stay by about 1 day and possibly reduced admission rates but did not conclusively affect hospital mortality rates.
Lambrinou, 2012, 4305	A meta-analysis was undertaken to estimate the effect of Heart Failure -Management Programmes with a nurse driven pre-discharge phase on the outcomes of HF and all-cause re-admission	Heart failure	Disease management programme vs. Usual care	Total: 19 (4197) Admissions data: 19 (4197)	Yes	6	The results of the current meta-analysis highlight the potential of HF-MPs with nurse-driven pre-discharge interventions to reduce hospital re-admissions. Essential characteristics or components of a successful HF-MP are still to be determined; thus more studies are required to solve this issue.
Lasserson, 2011, 4362	To assess the relative effects of fluticasone/salmeterol and budesonide/formoterol in people with asthma.	Chronic asthma	Long acting beta agonists with inhaled corticosteroids vs. Fixed dose combination budesonide and formoterol	Total: 5 (5537) Admissions data: 4 (4879)	Yes	9	Statistical imprecision in the effect estimates for exacerbations and serious adverse events do not enable us to conclude that either therapy is superior. The uncertainty around the effect estimates justify further trials to provide more definitive conclusions; the overall quality of evidence based on GRADE recommendations for the three primary outcomes and withdrawals due to serious adverse events was moderate.We rated the quality of evidence for mortality to be low. Results for lung function outcomes showed that the drugs were sufficiently similar that further research is unlikely to change the effects. No trials were identified in the under-12s and research in this population is a high priority. Evaluation of quality of life is a priority for future research.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Laurant, 2005, 9181	Our aim was to evaluate the impact of doctor-nurse substitution in primary care on patient outcomes, process of care, and resource utilisation including cost.	Patients presenting to primary care	Nurse led primary care vs. Doctor led primary care	Total: 13 (23304) Admissions data: 6 (13491)	No	8	The findings suggest that appropriately trained nurses can produce as high quality care as primary care doctors and achieve as good health outcomes for patients. However, this conclusion should be viewed with caution given that only one study was powered to assess equivalence of care, many studies had methodological limitations, and patient follow-up was generally 12 months or less. While doctor-nurse substitution has the potential to reduce doctors' workload and direct healthcare costs, achieving such reductions depends on the particular context of care. Doctors' workload may remain unchanged either because nurses are deployed to meet previously unmet patient need or because nurses generate demand for care where previously there was none. Savings in cost depend on the magnitude of the salary differential between doctors and nurses, and may be offset by the lower productivity of nurses compared to doctors.
Le, 2016, 8817	Our study aimed to assess the efficacy of AA on SCD, hospitalization admission and several common adverse events in patients with HF or post MI.	Heart failure and post-myocardial infarction	Aldosterone Antagonists vs. Placebo or routine treatment	Total: 25 (19333) Admissions data: 14 (8151)	No	8	Aldosterone antagonists appear to be effective in reducing SCD and other mortality events, compared with placebo or standard medication in patients with HF and/or after a MI.
Lei, 2015, 8819	The purpose of this present meta-analysis of RCTs is to examine the latest substantive evidence of safety and efficacy for laparoscopic colorectal surgery when compared with the open operation within FT programs.	Patients with malignant or benign colorectal diseases receiving fast track surgical recovery protocols.	Laparoscopic colorectal surgery vs. Open colorectal resection	Total: 7 (1004) Admissions data: 6 (678)	No	6	The laparoscopic colorectal surgery combined with FT programs shows high-level evidence on shortening postoperative and total hospital stay, reducing overall complications without `compromising patients' safety.
Leppin, 2014, 4494	To synthesize the evidence of the efficacy of interventions to reduce early hospital readmissions and identify intervention features—including their impact on treatment burden and on patients' capacity to enact postdischarge self-care—that might explain their varying effects.	Hospitalised patients	Peridischarge interventions vs. Any comparator	Total: 46 (17312) Admissions data: 46 (17312)	Yes	10	Tested interventions are effective at reducing readmissions, but more effective interventions are complex and support patient capacity for self-care. Interventions tested more recently are less effective.
Lethaby, 2012, 4502	To compare short term and long term outcomes of subtotal hysterectomy with total hysterectomy for benign gynaecological conditions.	Women undergoing hysterectomy for benign gynaecological conditions	Subtotal hysterectomy by any approach vs. Total hysterectomy by any approach	Total: 9 (1553) Admissions data: 5 (1074)	No	11	This review has not confirmed the perception that subtotal hysterectomy offers improved outcomes for sexual, urinary or bowel function when compared with total abdominal hysterectomy.Women are more likely to experience ongoing cyclical bleeding up to a year after surgery with subtotal hysterectomy compared to total hysterectomy.
Leucht, 2011, 4505	Non-adherence is a major problem in the treatment of schizophrenia. Depot antipsychotic drugs are thought to reduce relapse rates by improving adherence, but a systematic review of long-term studies in outpatients is not available.	Schizophrenia	Depot antipsychotic drugs vs. Oral formulations of antipsychotic drugs	Total: 10 (1700) Admissions data: 7 (1476)	No	7	Depot antipsychotic drugs significantly reduced relapse. Due to a number of methodological problems in the single trials the evidence is, nonetheless, subject to possible bias.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Leucht, 2012, 4508	To review the effects of maintaining antipsychotic drug treatment for people with schizophrenia compared to withdrawing these agents.	Schizophrenia	Maintenance/continous treatment with antipsychotic drugs vs. Active or inactive placebo, or no treatment	Total: 65 (6493) Admissions data: 16 (2090)	No	11	The results clearly demonstrate the superiority of antipsychotic drugs compared to placebo in preventing relapse. This effect must be weighed against the side effects of antipsychotic drugs. Future studies should focus on outcomes of social participation and clarify the long-term morbidity and mortality associated with these drugs.
Levy, 2010, 4518	Aim of this systematic review was to examine the current published evidence concerning the impact of differing perioperative analgesic regimens on the shortterm outcomes following laparoscopic colorectal surgery.	Patients getting a colorectal resection	Patient controlled analgesia vs. Epidural	Total: 6 (227) Admissions data: 3 (132)	No	3	There is a paucity of data assessing the benefits of postoperative analgesic regimes following laparoscopic colorectal surgery and none of the protocols were shown to be clearly superior. Further studies, including the assessment of spinal analgesia are required to determine the most appropriate analgesic regime following laparoscopic colorectal surgery.
Li, 2016, 8822	To examine the association between dipeptidyl peptidase-4 (DPP-4) inhibitors and the risk of heart failure or hospital admission for heart failure in patients with type 2 diabetes.	Type 2 diabetes	Dipeptidyl peptidase-4 inhibitors vs. Placebo or active antidiabetic drugs (glimepiride)	Total: 38 (31680) Admissions data: 5 (37095)	Yes	9	The relative effect of DPP-4 inhibitors on the risk of heart failure in patients with type 2 diabetes is uncertain, given the relatively short follow-up and low quality of evidence. Both randomised controlled trials and observational studies, however, suggest that thes drugs may increase the risk of hospital admission for heart failure in those patients with existing cardiovascular diseases or multiple risk factors for vascular diseases, compared with no use.
Liew, 2014, 4577	We performed a meta-analysis of all these trials in order to obtain best estimates of the efficacy and safety of warfarin as compared with antiplatelet therapy, in patients with systolic heart failure who are in sinus rhythm.	Heart failure	Warfarin vs. Antiplatelet therapy	Total: 4 (4187) Admissions data: 4 (4187)	No	4	Warfarin as compared with antiplatelet therapy reduces risk of ischemic stroke, does not significantly affect death, myocardial infarction, hospitalization due to heart failure or intracranial hemorrhage and increases major hemorrhage in heart failure patients who are in sinus rhythm.
Lipinski, 2009, 4615	The goal of this study was to systematically review randomized trials comparing statins to placebo for HF and compare the impact of different statins.	Heart failure	Statins vs. Placebo	Total: 10 (10203) Admissions data: 10 (10193)	No	7	In conclusion, meta-analysis of randomized controlled trials demonstrated that statins are safe and improve LVEF and decrease hospitalization for worsening HF.
Liu, 2014, 4629	Given the limited evidence and uncertain effects of betablockers in the patients with HFpEF, this meta-analysis summarized the current data from randomized controlled trials (RCTs) and observational studies (OSs) to determine the impact of the beta-blockers treatment on mortality and hospitalization in the patients with HFpEF (an EF < 40%).	Heart failure with preserved ejection fraction (an EF >/= 40%).	Beta-blockers vs. Non-beta-blocker control	Total: 2 (888) Admissions data: 2 (888)	Yes	4	The beta-blockers treatment for the patients with HFpEF was associated with a lower risk of all-cause mortality, but not with a lower risk of hospitalization. These finding were mainly obtained from observational studies, and further investigations are needed to make an assertion.
Liu, 2014, 8826	Therefore, we performed a meta-analysis of all prospective RCTs to assess the effects of lipophilic statins, including simvastatin, atorvastatin, and pitavastatin, on mortality, hospitalisation for worsening HF, LVEF, and low-density lipoprotein (LDL) cholesterol in HF patients.	Heart failure: (left ventricular ejection fraction < 45%)	Lipophilic Statins vs. No statin or placebo	Total: 13 (1532) Admissions data: 9 (1087)	Yes	7	It appears that further studies are needed to determine if lipophilic statins are beneficial for HF patients.
Liu, 2014, 8827	To assess the feasibility and safety of early oral feeding (EOF) after gastrectomy for gastric cancer through a systematic review and meta-analysis based on randomized controlled trials.	Gastrointestinal cancer surgery	Early oral feeding vs. Traditional postoperative oral feeding	Total: 6 (454) Admissions data: 5 (372)	Yes	7	The result of this meta-analysis showed that EOF after gastric cancer surgery seems feasible and safe, even started at the day of surgery irrespective of the extent of the gastric resection and the type of surgery. However, more prospective, well-designed multicenter RCTs with more clinical outcomes are needed for further validation.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Lopez, 2015, 8829	The aim of this meta-analysis was to evaluate the clinical efficacy (clinical response, clinical remission, and mucosal healing rates), and for the first time the need for colectomy and UC-related hospitalisations of all TNF antagonists (infliximab, adalimumab and golimumab) that have been evaluated in randomised, placebocontrolled phase III trials in adults with moderately to severely active UC. Safety was also evaluated.	Ulcerative colitis	Tumour necrosis factor antagonists (anti-TNF): Infliximab, Adalimumab vs. Placebo	Total: 5 (3654) Admissions data: 2 (1691)	No	8	Anti-tumour necrosis factor therapy is more effective than placebo to induce and maintain clinical remission and mucosal healing. Both infliximab and adalimumab are associated with less hospitalisations. Infliximab reduces the need for colectomy. Anti-tumour necrosis factor therapy does not increase the risk of adverse events.
Lowthian, 2015, 8830	This study is part of the Safe Elderly Emergency Discharge (SEED) project aimed to develop a best practice model of care for older patients discharged from ED.	Elderly people	Emergency department to community transition strategies vs. Usual care	Total: 4 (3092) Admissions data: 4 (3092)	No	6	There is limited high-quality data to guide confident recommendations about optimal ED community transition strategies, highlighting a need to encourage better integration of researchers and clinicians in the design and evaluation process, and increased reporting, including appropriate robust evaluation of efficacy and effectiveness of these innovative models of care.
Magee, 2003, 4812	To assess whether oral beta-blockers are better than placebo, or no beta-blocker, and have advantages over other antihypertensives, for women with mild to moderate pregnancy hypertension.	Mild to moderate hypertension during pregnancy	Beta-blockers vs. Placebo, no therapy, or other antihypertensive drug therapy	Total: 29 (2500) Admissions data: 5 (563)	No	9	Improvement in control of maternal blood pressure with use of beta-blockers would be worthwhile only if it were reflected in substantive benefits for mother and/or baby, and none have been clearly demonstrated. The effect of beta-blockers on perinatal outcome is uncertain; the worrying trend to an increase in SGA infants is partly dependent on one small outlying trial. Large randomised trials are needed to determine whether antihypertensive therapy in general (rather than beta-blocker therapy specifically) results in greater benefit than risk, for treatment of mild-moderate pregnancy hypertension. If so, then it would be appropriate to consider which antihypertensive is best, and beta-blockers should be evaluated.
Magee, 2000, 4815	This overview was undertaken to relate measurable characteristics of participants, interventions, and outcome definitions to demonstrated effects of b-blockers for pregnancy hypertension.	Pregnancy hypertension	Beta-blockers vs. Non-b-blocker or no therapy (placebo, no treatment)	Total: 32 (2474) Admissions data: 5 (563)	No	9	It is not clear that the benefits outweigh the risks when b-blockers are used to treat mild to moderate chronic or pregnancy-induced hypertension, given the unknown overall effect on perinatal outcomes. For severe 'late-onset' pregnancy hypertension, i.v. labetalol is safer than i.v. hydralazine or diazoxide.
Maggio, 2008, 4817	We undertook a systematic review and meta-analysis of randomised controlled trials to determine the role of early laparoscopy in patients with acute un-differentiated abdominal pain.	Acute abdominal pain	Early laparoscopy (laparoscopy within 24 h of admission) vs. Active observation	Total: 4 (811) Admissions data: 2 (642)	No	6	There is insufficient evidence to recommend routine use of early laparoscopy as the gold standard in patients with undifferentiated acute abdominal pain. Conversely, there is no evidence of harm. Further large clinical trials are required to determine the role of laparoscopy in this clinical situation.
Majothi, 2015, 8833	We therefore report a systematic review undertaken to assess the clinical effectiveness of interventions to support self-management among patients with COPD who have recently been discharged from hospital following an acute exacerbation.	Chronic obstructive pulmonary disease	Self-management vs. Usual care, control, sham intervention or other self-management intervention comparator	Total: 9 (1446) Admissions data: 9 (1446)	Yes	8	There is insufficient evidence to support self-management interventions post-discharge. There is a need for good quality primary research to identify effective approaches.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Makani, 2013, 4838	We compared the long term efficacy of dual blockade of the renin-angiotensin system (any two of ACE inhibitors, angiotensin receptor blockers, or aliskiren) with monotherapy and evaluated adverse events in patients receiving dual therapy compared with monotherapy.	Not reported	Dual blockade of the renin-angiotensin system (any two of ACE inhibitors, angiotensin receptor blockers, or aliskiren) vs. Single renin-angiotensin blockade (Angiotensin converting enzyme inhibitor or angiotensin receptor blockers or direct renin inhibitors)	Total: 33 (68405) Admissions data: 5 (42071)	No	6	Although dual blockade of the renin-angiotensin system may have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy. The risk to benefit ratio argues against the use of dual therapy.
Makrides, 2014, 4844	To assess the effects of magnesium supplementation during preg- nancy on maternal, neonatal/infant and paediatric outcomes, us- ing the best available evidence.	Pregnancy	Magnesium vs. Not specified	Total: 10 (9090) Admissions data: 3 (1158)	No	9	There is not enough high-quality evidence to show that dietary magnesium supplementation during pregnancy is beneficial.
Malone, 2007, 4860	To evaluate the effects of community mental health team (CMHT) treatment for anyone with serious mental illness compared with standard non-team management.	Severe mental illness	Community mental health teams vs. Standard or usual care	Total: 3 (587) Admissions data: 3 (587)	No	10	Community mental health team management is not inferior to non-team standard care in any important respects and is superior in promoting greater acceptance of treatment. It may also be superior in reducing hospital admission and avoiding death by suicide. The evidence for CMHT based care is insubstantial considering themassive impact the drive toward community care has on patients, carers, clinicians and the community at large.
Mannucci, 2008, 4889	The aim of this meta-analysis of randomized clinical trials (RCT) was to assess whether pioglitazone is also associated with increased cardiovascular risk, as recently reported for rosiglitazone.	Patients at relatively low risk of cardiovascular risk, such as those with metabolic end-points	Pioglitazone vs. Any other treatment with a duration of at least 4 weeks (Placebo, sulphonylureas, or dual peroxisome proliferator-activated receptor-alpha, gamma agonists (glitazars))	Total: 94 (21180) Admissions data: 40 (10322)	No	5	The use of pioglitazone does not appear to be harmful in terms of cardiovascular events and all-cause deaths.
Marshall, 2011, 4965	To assess the effects of day hospital versus inpatient care for people with acute psychiatric disorders.	Psychiatric disorders	Acute psychiatric day hospitals vs. In-patient care	Total: 10 (2686) Admissions data: 7 (1206)	Yes	11	Caring for people in acute day hospitals is as effective as inpatient care in treating acutely ill psychiatric patients. However, further data are still needed on the cost effectiveness of day hospitals.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Marshall, 1998, 4966	To determine the effects of case management as an approach to caring for severely mentally ill people in the community. Case management was compared against standard care on four main indices: (i) numbers remaining in contact with the psychiatric services; (ii) extent of psychiatric hospital admissions; (iii) clinical and social outcome; and (iv) costs.	Severe mental illness	Case management vs. Standard care	Total: 10 (1794) Admissions data: 7 (1382)	Yes	8	Case management ensures that more people remain in contact with psychiatric services (one extra person remains in contact for every 15 people who receive case management), but it also increases hospital admission rates. Present evidence suggests that case management also increases duration of hospital admissions, but this is not certain. Whilst there is some evidence that case management improves compliance, it does not produce clinically significant improvement in mental state, social functioning, or quality of life. There is no evidence that case management improves outcome on any other clinical or social variables. Present evidence suggests that case management increases health care costs, perhaps substantially, although this is not certain. In summary, therefore, case management is an intervention of questionable value, to the extent that it is doubtful whether it should be offered by community psychiatric services. It is hard to see how policymakers who subscribe to an evidence-based approach can justify retaining casemanagement as 'the cornerstone' of community mental health care. Case management is compared to the main alternative approach (ACT) in a forthcoming Cochrane review.
Marshall, 1998, 4968	The objectives are to determine the effectiveness of ACT as an alternative to: i. standard community care; ii. traditional hospitalbased rehabilitation; and iii. case management. For each of the three comparisons the main outcome indices were: i. numbers remaining in contact with the psychiatric services; ii. extent of psychiatric hospital admissions; iii. clinical and social outcome; and iv. costs.	Severe mental illness	Assertive community treatent vs. Standard care	Total: 20 (3376) Admissions data: 11 (1405)	Yes	8	ACT is a clinically effective approach to managing the care of severely mentally ill people in the community. ACT, if correctly targeted on high users of in-patient care, can substantially reduce the costs of hospital care whilst improving outcome and patient satisfaction. Policy makers, clinicians, and consumers should support the setting up of ACT teams.
Marshall, 2011, 4972	To evaluate the effects of: (a) early detection; (b) phase-specific treatments; and (c) specialised early intervention teams in the treatment of people with prodromal symptoms or first-episode psychosis.	Psychiatric disorders	Early intervention for psychosis: early detection and phase-specific treatment. vs. Standard care	Total: 18 (1808) Admissions data: 5 (911)	Yes	11	There is emerging, but as yet inconclusive evidence, to suggest that people in the prodrome of psychosis can be helped by some interventions. There is some support for specialised early intervention services, but further trials would be desirable, and there is a question of whether gains are maintained. There is some support for phase-specific treatment focused on employment and family therapy, but again, this needs replicating with larger and longer trials.
Martínez-González, 2014, 4987	In many countries, substitution of physicians by nurses has become common due to the shortage of physicians and the need for high-quality, affordable care, especially for chronic and multi-morbid patients. We examined the evidence on the clinical effectiveness and care costs of physician-nurse substitution in primary care.	Any patient presenting to primary care	Nurse-led primary care vs. Physician-led care	Total: 23 (22427) Admissions data: 9 (16690)	No	10	The available evidence continues to be limited by the quality of the research considered. Nurse-led care seems to have a positive effect on patient satisfaction, hospital admission and mortality. This important finding should be confirmed and the determinants of this effect should be assessed in further, larger and more methodically rigorous research.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Mayo-Wilson, 2014, 5047	Home visits for older adults aim to prevent cognitive and functional impairment, thus reducing institutionalization and mortality. Visitors may provide information, investigate untreated problems, encourage medication compliance, and provide referrals to services	Elderly people	Preventative home visits vs. Usual care	Total: 63 (28836) Admissions data: 27 (12642)	No	9	Home visiting is not consistently associated with differences in mortality or independent living, and investigations of heterogeneity did not identify any programs that are associated with consistent benefits. Due to poor reporting of intervention components and delivery, we cannot exclude the possibility that some programs may be effective.
McLean, 2010, 5145	To assess the effectiveness of telehealthcare interventions in people with asthma.	Asthma	Telehealthcare vs. Usual care or any other control intervention	Total: 21 (10839) Admissions data: 12 (9320)	Yes	10	Telehealthcare interventions are unlikely to result in clinically relevant improvements in health outcomes in those with relatively mild asthma, but they may have a role in those with more severe disease who are at high risk of hospital admission. Further trials evaluating the effectiveness and cost-effectiveness of a range of telehealthcare interventions are needed.
McLean, 2011, 5147	To review the effectiveness of telehealthcare for COPD compared with usual face-to-face care.	Chronic obstructive pulmonary disease	Telehealthcare vs. Control	Total: 10 (1307) Admissions data: 5 (803)	Yes	11	Telehealthcare in COPD appears to have a possible impact on the quality of life of patients and the number of times patients attend the emergency department and the hospital. However, further research is needed to clarify precisely its role since the trials included telehealthcare as part of more complex packages.
McLellan, 2016, 9300	To assess whether treatment guided by serial BNP or NT-proBNP (collectively referred to as NP) monitoring improves outcomes compared with treatment guided by clinical assessment alone.	Heart failure	BNP- or NT-proBNP-guided (collectively NP-guided) treatment of heart failure vs. Usual care	Total: 18 (3660) Admissions data: 16 (3215)	No	11	In patients with heart failure low-quality evidence showed a reduction in heart failure admission with NP-guided treatment while lowquality evidence showed uncertainty in the effect of NP-guided treatment for all-cause mortality, heart failure mortality, and all-cause admission. Uncertainty in the effect was further shown by very low-quality evidence for patient's quality of life. The evidence for adverse events and cost of treatment was low quality and we were unable to pool results.
Mead, 2005, 5161	To assess the effects of electrical cardioversion of atrial fibrillation or flutter on the risk of thromboembolic events, strokes and mortality (primary outcomes), the rate of cognitive decline, quality of life, the use of anticoagulants and the risk of re hospitalisation (secondary outcomes) in adults (>18 years).	Adults (more than 18 years) with paroxysmal, sustained or permanent atrial fibrillation or atrial flutter.	Electrical cardioversion used as a first intervention for rhythm control vs. Usual care including any combination of drugs for 'rate control', anticoagulants or antiplatelet drugs.	Total: 3 (927) Admissions data: 2 (405)	No	8	Electrical cardioversion (rhythm control) led to a non-significant increase in stroke risk but improved three domains of quality of life.
Meads, 2007, 5165	The aim of this review of to identify and systematically map the evidence base of the clinical and cost-effectiveness of therapy programmes involving family and friends in the treatment of alcohol misuse.	Problem drinkers	Psychological therapy involving family and friends vs. Any	Total: 34 (3531) Admissions data: 4 (173)	No	8	The evidence suggests that therapy involving family and friends can reduce alcoholrelated outcomes and may be cost-saving to the NHS. It would be useful to know whether different forms of therapy involving family and friends are equally effective, particularly those from the different theoretical models of the family and using different psychotherapeutic approaches. More research is needed on the long-term effectiveness of different treatment strategies and their cost implications. There may need to be more specialist alcohol treatment service provision and more targeted health promotion to encourage problem drinkers to seek help.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Medic, 2016, 8842	The objective of this study was to estimate the relative efficacy and safety of fixed-dose combination aclidinium/formoterol 400/12 lg twice daily compared to tiotropium 18 lg once daily in adult patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).	Moderate-to-severe chronic obstructive pulmonary disease	Aclidinium, Formoterol, Tiotropium vs. Placebo; tiotropium	Total: 17 (21954) Admissions data: unclear (unclear)	No	7	Based on the ITC, aclidinium/formoterol is expected to be more efficacious than tiotropium in terms of lung function and symptom control while providing comparable HRQoL results and safety profile.
Mehta, 2005, 5183	To conduct a meta-analysis that compares benefits and risks of routine invasive vs selective invasive strategies.	Patients with unstable angina or non–ST-segment elevation myocardial infarction	Routine coronary angiography vs. Selective coronary angiography	Total: 7 (9212) Admissions data: 7 (9147)	No	7	A routine invasive strategy exceeded a selective invasive strategy in reducing MI, severe angina, and rehospitalization over a mean follow-up of 17 months. But routine intervention was associated with a higher early mortality hazard and a trend toward a mortality reduction at follow-up. Future strategies should explore ways to minimize the early hazard and enhance later benefits by focusing on higher-risk patients and optimizing timing of intervention and use of proven therapies.
Mekonnen, 2016, 8844	Thus, the aim of this study was to systematically investigate the effect of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions	Hospitalised patients	Pharmacist-led medication reconciliation programmes vs. Usual care	Total: 8 (2870) Admissions data: 8 (2870)	Yes	7	Pharmacist-led medication reconciliation programmes are effective at improving post-hospital healthcare utilisation. This review supports the implementation of pharmacist-led medication reconciliation programmes that include some component aimed at improving medication safety.
Mohammed, 2007, 5325	To estimate the effect of intravenous and nebulised magnesium sulphate upon hospital admissions and pulmonary function in adults and children with acute asthma.	Acute asthma	Intravenous or nebulised magnesium sulphate vs. Not pre-specified: Saline solution used in most included studies	Total: 24 (1669) Admissions data: 18 (1359)	Yes	6	Intravenous magnesium sulphate appears to be an effective treatment in children. Further trials are needed of intravenous and nebulised magnesium sulphate in adults and nebulised magnesium sulphate in children.
Møiniche, 2003, 5330	The aim of this systematic review was to critically appraise the existing data on the incidence of perioperative bleeding complications caused by NSAIDs and to quantify the potential impact of NSAIDs on bleeding.	Post-operative tonsillectomy	Nonsteroidal antiinflammatory drugs vs. Non-NSAID treatment	Total: 25 (1853) Admissions data: 8 (506)	Yes	3	Of four bleeding end points (intraoperative blood loss, postoperative bleeding, hospital admission, and reoperation because of bleeding), only reoperation happened significantly more often with NSAIDs: Petoodds ratio, 2.33 (95% confidence interval [CI], 1.12– 4.83) and number-needed-to-treat, 60 (95% CI, 34–277). Compared with opioids, NSAIDs were equianalgesic, and the risk of emesis was significantly decreased (relative rate 0.73; 95% CI, 0.63– 0.85; numbers-needed-totreat, 9; 95% CI, 5–19).
Moore, 2006, 5371	The aim of this review was to systematically examine the available evidence concerning MMF in lupus nephritis from randomised trials and observational studies.	Lupus nephritis	Mycophenolate mofetil vs. Cyclophosphamide and steroid	Total: 6 (370) Admissions data: 2 (220)	No	6	The results form a basis on which to plan future studies and provide a guide for the use of MMF in lupus nephritis until results of larger studies are available. At least one such study is under way.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Morriss, 2007, 5398	The overall aim was to conduct a systematic review of all intervention studies that included systematically teaching the recognition of early warning signs (EWS) of recurrence to people diagnosed with bipolar disorder and/or their carers. The objectives were: 1. To compare the effectiveness of an EWSintervention plus treatment as usual (TAU) versus TAU not involving a psychological therapy on time to manic, depressive and all bipolar episodes. 2. To compare the effectiveness of an EWS intervention plus TAU versus TAU plus another psychological therapy on time to manic, depressive and all bipolar episodes. 3. To compare the effectiveness of intermittent medication used on recognition of EWS without continued mood stabilising medication versus TAU involving continued mood stabilising medication on time to manic, depressive and all bipolar episodes.	Bipolar disorder	Interventions to recognise early warning signs of bipolar recurrence vs. Treatment as usual	Total: 11 (1307) Admissions data: 5 (782)	No	10	This review shows a beneficial effect of EWS in time to recurrence, percentage of people hospitalised and functioning in people with bipolar disorder. However, the absence of data on the primary outcome measure in so many included studies is a source of concern and a potential source of bias. Mental health services should consider routinely providing EWS interventions to adults with bipolar disorder, as they appear to reduce hospitalisation and therefore may be cost-effective.
Morriss, 2013, 5399	The primary objective was to compare the effectiveness of early warning signs intervention plus treatment as usual versus treatment as usual for those with schizophrenia. Treatment as usual could involve medication plus psychological therapy which did not incorporate early warning signs principles or only medication as part of its care plan. Another objective was to compare the effectiveness of intermittent medication used on recognition of early warning signs in people not taking maintenance neuroleptic medication with treatment as usual involving maintenance neuroleptic medication. Other areas of interest were early warning signs as the primary focus of the intervention or as part of another intervention; early warning signs intervention delivered to patient only or patient and carer or health professional; early warning signs intervention delivered to carer only versus carer and patient; early warning signs intervention delivered individually versus group intervention.	Schizophrenia	Education/self-management vs. Usual care	Total: 34 (3686) Admissions data: 20 (2652)	Yes	11	This review indicates that early warning signs interventions may have a positive effect on the proportions of people re-hospitalised and on rates of relapse, but not on time to recurrence. However, the overall quality of the evidence was very low, indicating that we do not know if early warning signs interventions will have similar effects outside trials and that it is very likely that further research will alter these estimates. Moreover, the early warning signs interventions were used along side other psychological interventions, and we do not know if they would be effective on their own. They may be cost-effective due to reduced hospitalisation and relapse rates, but before mental health services consider routinely providing psychological interventions involving the early recognition and prompt management of early warning signs to adults with schizophrenia, further research is required to provide evidence of high or moderate quality regarding the efficacy of early warning signs interventions added to usual care without additional psychological interventions, or to clarify the kinds of additional psychological interventions that might aid its efficacy. Future RCTs should be adequately-powered, and designed to minimise the risk of bias and be transparently reported. They should also systematically evaluate resource costs and resource use, alongside efficacy outcomes and other outcomes that are important to people with serious mental illness and their carers.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Murphy, 2015, 8847	To review the effects of crisis-intervention models for anyone with serious mental illness experiencing an acute episode compared to the standard care they would normally receive. If possible, to compare the effects of mobile crisis teams visiting patients' homes with crisis units based in home-like residential houses.	Severe mental illness	Crisis intervention vs. Standard care	Total: 8 (1184) Admissions data: 7 (1143)	Yes	10	Care based on crisis-intervention principles, with or without an ongoing homecare package, appears to be a viable and acceptable way of treating people with serious mental illnesses. However only eight small studies with unclear blinding, reporting and attrition bias could be included and evidence for the main outcomes of interest is low to moderate quality. If this approach is to be widely implemented it would seem that more evaluative studies are still needed.
Nair, 2012, 5515	To determine whether intravenous aminophylline has an additional bronchodilation effect in adult patients with acute asthma when used in conjunction with inhaled beta2-agonists with or without systemic corticosteroids (intravenous, oral, inhaled or combinations of these).	Acute asthma	Aminophylline vs. Placebo or inhaled beta2-agonists alone	Total: 19 (817) Admissions data: 6 (315)	No	9	The use of intravenous aminophylline did not result in significant additional bronchodilation compared to standard care with inhaled beta2-agonists in patients experiencing an asthma exacerbation in the ED setting, or in a significant reduction in the risk of hospital admission.
Nannini, 2013, 5533	To determine the efficacy and safety of combined ICS and LABA for stable COPD in comparison with placebo.	Chronic obstructive pulmonary disease	Combined inhalers vs. Placebo	Total: 19 (10400) Admissions data: 12 (9492)	Yes	10	Combined inhaler therapy led to around a quarter fewer COPD exacerbations than were seen with placebo. A significant reduction in all-cause mortality was noted, but this outcome was dominated by one trial (TORCH), emphasising the need for further trials of longer duration. Increased risk of pneumonia is a concern; however, this did not translate into increased exacerbations, hospitalisations or deaths.
Nannini, 2013, 8694	To assess the efficacy and safety of combined long-acting beta2- agonist and inhaled corticosteroid (LABA/ICS) preparations, as measured by clinical endpoints and pulmonary function testing, compared with inhaled corticosteroids (ICS) alone, in the treatment of adults with chronic obstructive pulmonary disease (COPD).	Chronic obstructive pulmonary disease	Combined corticosteroid and long-acting beta2-agonist in one inhaler vs. Inhaled corticosteroids alone	Total: 15 (7814) Admissions data: 10 (7060)	Yes	10	Combination ICS and LABA offer some clinical benefits in COPDcompared with ICS alone, especially for reduction in exacerbations. This review does not support the use of ICS alone when LABAs are available. Adverse events were not significantly different between treatments. Further long-term assessments using practical outcomes of current and new 24-hour LABAs will help determine their efficacy and safety. For robust comparisons as to their relative effects, long-term head-to-head comparisons are needed.
Ngo, 2010, 5606	To assess the benefit and risk of ESAs for chronic heart failure patients with anaemia.	Chronic heart failure and anaemia of chronic disease	Erythropoiesis stimulating agent vs. Placebo or no treatment	Total: 11 (794) Admissions data: 9 (734)	No	10	Meta-analysis of small RCTs suggests that ESA treatment in patients with symptomatic CHF and mild anaemia (haemoglobin more than 10g/dL) can improve anaemia and exercise tolerance, reduce symptoms and have benefits on clinical outcomes. Confirmation requires well-designed studies with careful attention to dose, haemoglobin treatment target and associated iron therapy.
Ni, 2009, 5611	To examine the safety and efficacy of initiating a combination of long-acting ß2-agonists and inhaled corticosteroids compared to a similar dose or a higher dose of inhaled corticosteroids alone, in steroid-naive children and adults with persistent asthma.	Asthma	Addition of long-acting beta2-agonists to inhaled corticosteroids as first line therapy vs. Same dose of inhaled corticosteroids alone	Total: 28 (8050) Admissions data: 12 (4872)	No	9	In patients with asthma who require daily anti-inflammatory therapy, there is insufficient evidence to support initiating therapy with a combination of inhaled corticosteroids (ICS) and long-acting ß2-agonist (LABA) rather than with inhaled corticosteroids alone.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Ni, 2014, 8850	To assess the efficacy and safety of aclidinium bromide in stable COPD.	Stable chronic obstructive pulmonary	Aclidinium bromide vs. Placebo; long-acting muscarinic antagonist	Total: 12 (9547) Admissions data: 10 (5624)	No	11	Aclidinium is associated with improved quality of life and reduced hospitalisations due to severe exacerbations in patients with moderate to severe stable COPD compared to placebo. Overall, aclidinium did not significantly reduce mortality, serious adverse event or exacerbations requiring oral steroids or antibiotics, or both. Currently, the available data are insufficient and of very low quality in comparisons of the efficacy of aclidinium versus tiotropium. The efficacy of aclidinium versus LABAs cannot be assessed due to inaccurate data. Thus additional trials are recommended to assess the efficacy and safety of aclidinium compared to other LAMAs or LABAs.
Ni, 2015, 9197	Hence, in order to add more information and evidence to clinical practice, we performed an updated meta-analysis to evaluate the efficacy and safety of prophylactic macrolide therapy on the prevention of acute exacerbations of chronic obstructive pulmonary disease.	Chronic obstructive pulmonary disease	Prophylactic use of macrolide antibiotics vs. Placebo	Total: 9 (1666) Admissions data: 5 (1424)	No	6	Our results suggest 6-12 months erythromycin or azithromycin therapy could effectively reduce the frequency of exacerbations in patients with COPD. However, Long-term treatment may bring increased adverse events and the emergence of macrolide-resistance. A recommendation for the prophylactic use of macrolide therapy should weigh both the advantages and disadvantages
Nicholson, 2014, 5620	Using data from randomized clinical trials (RCTs), this systematic review aimed to describe the impact of enhanced recovery programmes compared with standard care in adult elective surgical patients on a range of outcomes, including mortality, complications and time to discharge from hospital. Specific research questions were whether the effect of ERPs is dependent on the type of surgical procedure or the components of the specific protocol.	Elective surgical patients	Enhanced recovery programmes vs. Comparison programme	Total: 36 (4911) Admissions data: 22 (1992)	No	10	ERPs are effective in reducing length of hospital stay and overall complication rates across surgical specialties. It was not possible to identify individual components that improved outcome. Qualitative synthesis may be more appropriate to investigate the determinants of success.
Nistor, 2015, 8854	To compare convective (HF, HDF, or AFB) with diffusive (HD) dialysis modalities on clinical outcomes (mortality, major cardiovascular events, hospitalisation and treatment-related adverse events) in men and women with end-stage kidney disease.	End-stage kidney disease on dialysis	Haemodiafiltration, haemofiltration and haemodialysis. vs. Diffusive therapy or comparative effectiveness with haemodiafiltration, haemofiltration and haemodialysis	Total: 40 (4155) Admissions data: 7 (2731)	No	11	Convective dialysismay reduce cardiovascular but not all-causemortality and effects on nonfatal cardiovascular events and hospitalisation are inconclusive. However, any treatment benefits of convective dialysis on all patient outcomes including cardiovascular death are unreliable due to limitations in study methods and reporting. Future studies which assess treatment effects of convection dose on patient outcomes including mortality and cardiovascular events would be informative.
Nyong, 2016, 9307	To determine the efficacy and safety of ablation (catheter and surgical) in people with non-paroxysmal (persistent or long-standing persistent) atrial fibrillation compared to antiarrhythmic drugs.	Persistent atrial fibrillation or long-standing persistent atrial fibrillation	Radiofrequency catheter ablation (RFCA) technique vs. Antiarrhythmic drugs	Total: 3 (353) Admissions data: 2 (216)	Yes	10	In people with non-paroxysmal atrial fibrillation, evidence suggests a superiority of RFCA to antiarrhythmic drugs in achieving freedom from atrial arrhythmias, reducing the need for cardioversion, and reducing cardiac-related hospitalisations. There was uncertainty surrounding the effect of RFCA with significant bradycardia (or need for a pacemaker), periprocedural complications, and other safety outcomes. Evidence should be interpreted with caution, as event rates were low and quality of evidence ranged from moderate to very low.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Oud, 2016, 9309	To evaluate the efficacy of psychological interventions for adults with bipolar disorder.	Bipolar disorder	Individual, group and family psychological interventions or service-level interventions vs. Treatment as usual, waiting list or attention control	Total: 58 (6145) Admissions data: 12 (1501)	No	8	There is evidence that psychological interventions are effective for people with bipolar disorder. Much of the evidence was of low or very low quality thereby limiting our conclusions. Further research should identify the most effective (and cost-effective) interventions for each phase of this disorder.
Parker, 2002, 5937	This review was conducted to test the following general hypotheses: there is an inadequate number of comparable randomised controlled trials (RCTs) to allow a definitive analysis; hospital discharge process, outcome and cost effectiveness can be improved through the use of a variety of interventions; some interventions are more effective than others; there are priority areas for future research.	Elderly people	Discharge arrangements vs. Usual care	Total: 54 (16851) Admissions data: 36 (11940)	No	10	The evidence from these trials does not suggest that discharge arrangements have effects on mortality or length of hospital stay. This review supports the concept that arrangements for discharging older people from hospital can have beneficial effects on subsequent readmission rates. Interventions provided across the hospital-- community interface, both in hospital and in the patient's home, showed the largest effect. Evidence from RCTs is not available to support the general adoption of discharge planning protocols, geriatric assessment processes or discharge support schemes as means of improving discharge outcomes.
Parthiban, 2015, 8859	This study sought to conduct a systematic published data review and meta-analysis of RCTs comparing RM with IO follow-up.	People with implantable cardioverter-defibrillators devices	Remote monitoring with conventional in-office follow-up vs. Conventional in-office follow-up	Total: 9 (6469) Admissions data: 7 (4304)	No	5	Meta-analysis of RCTs demonstrates that RM and IO follow-up showed comparable overall outcomes related to patient safety and survival, with a potential survival benefit in RCTs using daily transmission verification. RM benefits include more rapid clinical event detection and a reduction in inappropriate shocks.
Pharoah, 2010, 6091	To estimate the effects of family psychosocial interventions in community settings for the care of people with schizophrenia or schizophrenia-like conditions.	Schizophrenia	Family psychosocial interventions vs. Standard care	Total: 50 (5326) Admissions data: 23 (2159)	Yes	10	Family intervention may reduce the number of relapse events and hospitalisations and would therefore be of interest to people with schizophrenia, clinicians and policy makers. However, the treatment effects of these trials may be overestimated due to the poor methodological quality. Further data from trials that describe the methods of randomisation, test the blindness of the study evaluators, and implement the CONSORT guidelines would enable greater confidence in these findings.
Phillips, 2004, 6099	To evaluate the effect of comprehensive discharge planning plus post discharge support on the rate of readmission in patients with CHF, all-cause mortality, length of stay (LOS), quality of life (QOL), and medical costs.	Heart failure	Comprehensive discharge planning with postdischarge support vs. Usual care	Total: 18 (3438) Admissions data: 18 (3438)	Yes	5	Comprehensive discharge planning plus postdischarge support for older patients with CHF significantly reduced readmission rates and may improve health outcomes such as survival and QOL without increasing costs.
Piccini, 2009, 6110	The goal of this meta-analysis was to determine whether pulmonary vein isolation is more efficacious than medical therapy alone and whether its safety profile is comparable to other invasive procedures.	Atrial fibrillation	Catheter-based pulmonary vein isolation or left atrial ablation vs. Control or antiarrhythmic drug therapy	Total: 6 (693) Admissions data: 3 (405)	No	9	Compared with a nonablation treatment strategy, PVI results in dramatically increased freedom from AF at 1 year. Although the procedure can be associated with major complications, the risk of these complications is comparable to other interventional procedures.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Pizzi, 2011, 6161	We carried out a meta-analysis to summarize evidence on the effects of SSRI versus placebo or no antidepressants in all-cause mortality and readmission for CHD in patients with CHD and depression.	Cardiovascular disease and depression	Selective serotonin reuptake inhibitors vs. Placebo or no anti-depressant	Total: 4 (2461) Admissions data: 3 (707)	Yes	9	When only properly randomized trials were considered (n 734 patients), patients on SSRIs showed no significant differences in mortality (risk ratio 0.39, 95% confidence interval 0.08 to 2.01) or CHD readmission rates (0.74, 0.44 to 1.23) compared to controls. Conversely, when all studies were included, SSRI use was associated with a significant decrease in CHD readmission (0.63, 0.46 to 0.86) and mortality rates (0.56, 0.35 to 0.88). A significantly greater improvement in depression symptoms was always apparent in patients on SSRIs with all selected indicators. In conclusion, in patients with CHD and depression, SSRI medication decreases depression symptoms and may improve CHD prognosis.
Poole, 2015, 8867	Primary objective: To determine whether treatment with mucolytics reduces frequency of exacerbations and/or days of disability in patients with chronic bronchitis or COPD. Secondary objectives: To assess whether mucolytics lead to improvement in lung function or quality of life. To determine the frequency of adverse effects associated with use of mucolytics.	Chronic bronchitis or chronic obstructive pulmonary disease	Mucolytic agents vs. Placebo	Total: 26 (6233) Admissions data: 4 (1788)	No	10	In participants with chronic bronchitis or COPD, we are moderately confident that treatment with mucolytics may produce a small reduction in acute exacerbations and a small effect on overall quality of life. Our confidence in the results is reduced by the fact that effects on exacerbations shown in early trials were larger than those reported by more recent studies, possibly because the earlier smaller trials were at greater risk of selection or publication bias, thus benefits of treatment may not be as great as was suggested by previous evidence.
Powell, 2002, 6220	The specific questions addressed are: (1) Is optimisation of asthma control through the use of inhaled corticosteroid treatment, by regular medical review, equivalent to optimisation of asthma control by an individualised written self management plan in improving health outcomes? (2) Are there differences in health outcomes for programmes using written self-management plans based on peak expiratory flow selfmonitoring and symptom self-monitoring? (3) What are the characteristics of optimal self-management programme delivery, which lead to changes in health outcomes?	Asthma	Self-management education interventions vs. Other self-management education interventions or non-self management interventions	Total: 15 (2465) Admissions data: 9 (1559)	No	9	Optimal self-management allowing for optimisation of asthma control by adjustment of medications may be conducted by either selfadjustment with the aid of a written action plan or by regular medical review. Individualised written action plans based on PEF are equivalent to action plans based on symptoms. Reducing the intensity of self-management education or level of clinical review may reduce its effectiveness.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Powell, 2015, 8868	To compare the effects of mepolizumab with placebo on exacerbations and HRQoL in adults and children with chronic asthma.	Asthma	Mepolizumab vs. Placebo	Total: 8 (1707) Admissions data: 2 (690)	Yes	11	It is not possible to draw firm conclusions from this review with respect to the role of mepolizumab in patients with asthma. Our confidence in the results of this review are limited by the fact that the intravenous route is not currently licensed for mepolizumab, and the evidence for the currently licenced subcutaneous route is limited to a single study in participants with severe eosinophilic asthma. The currently available studies provide evidence that mepolizumab can lead to an improvement in health-related quality of life scores and reduce asthma exacerbations in people with severe eosinophilic asthma. Further research is needed to clarify which subgroups of patients with asthma could potentially benefit from this treatment. Dosage, ideal dosing regimens and duration of treatment need to be clarified, as the studies included in this review differed in their protocols. There are no studies reporting results from children, so we cannot comment on treatment for this age group. At the present time, larger studies using licenced treatment regimens are required to establish the role of mepolizumab in the treatment of severe asthma.
Puhan, 2016, 9316	To assess effects of pulmonary rehabilitation after COPD exacerbations on hospital admissions (primary outcome) and other patient-important outcomes (mortality, HRQL and exercise capacity).	Chronic obstructive pulmonary disease	Pulmonary rehabilitation programmes vs. Conventional community care	Total: 20 (1563) Admissions data: 8 (909)	Yes	11	Overall, evidence of high quality shows moderate to large effects of rehabilitation on health-related quality of life and exercise capacity in patients with COPD after an exacerbation. Some recent studies showed no benefit of rehabilitation on hospital readmissions and mortality and introduced heterogeneity as compared with the last update of this review. Such heterogeneity of effects on hospital readmissions and mortality may be explained to some extent by the extensiveness of rehabilitation programmes and by the methodological quality of the included studies. Future researchers must investigate how the extent of rehabilitation programmes in terms of exercise sessions, self-management education and other components affects the outcomes, and how the organisation of such programmes within specific healthcare systems determines their effects after COPD exacerbations on hospital readmissions and mortality.
Rabindranath, 2007, 6325	We evaluated the comparative clinical efficacy of continuous ambulatory peritoneal dialysis with all forms of automated peritoneal dialysis.	Patients undergoing peritoneal dialysis for end-stage renal disease	Continuous ambulatory peritoneal dialysis vs. Automated peritoneal dialysis	Total: 3 (130) Admissions data: 2 (122)	No	9	APD has not been shown to have significant advantages over CAPD in terms of important clinical outcomes. APD may however be considered advantageous in select group of patients such as in the younger PD population and those in employment or education due to its psychosocial advantages. There is a need for a RCT comparing CAPD with APD with sufficiently large patient numbers looking at important clinical outcomes including residual renal function, accompanied by an economic evaluation to clarify the relative clinical and cost-effectiveness of both modalities.
Rajagopalan, 2011, 6347	Hence, we planned to conduct a systematic review to answer the question whether pharmacotherapy has any beneficial role in the management of HFNEF.	Heart failure with normal ejection fraction (EF of 40%)	Angiotensin II receptor blocker or angiotensin converting enzyme inhibitor; Digoxin vs. Placebo	Total: 6 (8410) Admissions data: 4 (4857)	No	8	There was no significant benefit of pharmacotherapy in HFNEF. This might have been because of a lack of stringent inclusion criteria for patients in the trials and lower power of the studies. Hence trials with well defined inclusion criteria, better power, longer follow-up periods and with echocardiographic parameters as endpoints are required to shed further light on this topic.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Ram, 2004, 6355	To evaluate the efficacy of hospital at home schemes compared with inpatient care in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD).	Chronic obstructive pulmonary disease	Hospital at home vs. Usual in-patient care	Total: 7 (754) Admissions data: 7 (754)	Yes	7	Hospital at home schemes can be safely used to care for patients with acute exacerbations of COPD who would otherwise be admitted to hospital. Clinicians should consider this form of management, especially as there is increasing pressure for inpatient beds in the United Kingdom.
Raman, 2008, 6360	To conduct a technology assessment on the effectiveness of non-pharmacological interventions for post-discharge care in heart failure patients.	Heart failure	Non-pharmacological interventions vs. Usual care, routine care, or standard care.	Total: 50 (11367) Admissions data: 50 (11367)	No	7	Interventions that utilized increased clinic visits, home visits, and multidisciplinary care reduced the risk of readmissions. Studies with intermediate- to long-term followup, interventions initiated in the inpatient setting, and patient ages greater than 75 years were associated with significant reduction of all cause readmissions in the intervention group. These interventions often utilized a combination of components. There was no distinct combination of intervention components that was associated with improved clinical outcomes. The evidence was sparse for interventions beginning in the outpatient clinics.
Randall, 2015, 8875	To review and synthesize the currently available research on whether early intervention for psychosis programs reduce the use of inpatient services.	Psychiatric disorders	Early intervention program vs. Standard care	Total: 3 (733) Admissions data: 3 (733)	Yes	6	These results suggest that early intervention programs are superior to standard of care, with respect to reducing inpatient service usage. Wider use of these programs may prevent the occurrence of admission for patients experiencing the onset of psychotic symptoms.
Reilly, 2015, 8880	Primary objective: To evaluate the effectiveness of case management approaches to home support for people with dementia from the perspective of the different people involved (patients, carers, and staff) compared with other forms of treatment, including 'treatment as usual', standard community treatment and other non-case management interventions. Secondary objective: To study whether other potential mediating variables affect case management outcomes (e.g. key structural and organisational features of case management interventions and also the methodological characteristics of studies).	Dementia	Case management approaches to home support vs. Usual care	Total: 13 (9615) Admissions data: 6 (8961)	Yes	11	There is some evidence that case management is beneficial at improving some outcomes at certain time points, both in the person with dementia and in their carer. However, there was considerable heterogeneity between the interventions, outcomes measured and time points across the 13 included RCTs. There was some evidence from good-quality studies to suggest that admissions to care homes and overall healthcare costs are reduced in the medium term; however, the results at longer points of follow-up were uncertain. There was not enough evidence to clearly assess whether case management could delay institutionalisation in care homes. There were uncertain results in patient depression, functional abilities and cognition. Further work should be undertaken to investigate what components of case management are associated with improvement in outcomes. Increased consistency in measures of outcome would support future meta-analysis.
Renner, 2012, 6442	To identify, assess, meta-analyze and summarize the evidence concerning the efficacy and safety of primary prophylactic CSFs (GCSFs or GM-CSFs) compared to placebo or no treatment for the prevention of FN, early mortality and infection-related mortality in patients with breast cancer undergoing chemotherapy.	Breast cancer undergoing chemotherapy	Primary prophylactic colony-stimulating factors vs. No treatment or placebo	Total: 8 (2156) Admissions data: 4 (1149)	No	11	In patients with breast cancer receiving chemotherapy,CSFs have shown evidence of bene t in the prevention of FN. There is evidence, though less reliable, of a decrease of all-cause mortality during chemotherapy and a reduced need for hospital care. No reliable evidence was found for a reduction of infection-related mortality, a higher dose intensity of chemotherapy with CSFs or diminished rates of severe neutropenia and infections. The majority of adverse events reported from CSF use were bone pain and injection-site reactions but no conclusions could be drawn regarding late-term side effects.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Roberts, 2009, 6536	To review the effects of intercessory prayer as an additional intervention for people with health problems already receiving routine health care.	Hospitalised patients	Intercessory prayer vs. Routine care	Total: 9 (7646) Admissions data: 4 (3034)	No	9	These findings are equivocal and, although some of the results of individual studies suggest a positive effect of intercessory prayer, the majority do not and the evidence does not support a recommendation either in favour or against the use of intercessory prayer.We are not convinced that further trials of this intervention should be undertaken and would prefer to see any resources available for such a trial used to investigate other questions in health care.
Roccaforte, 2005, 6552	To summarise the evidence supporting disease management programmes effectiveness in improving heart failure clinical outcomes.	Heart failure	Comprehensive disease management programmes vs. Usual care	Total: 33 (8697) Admissions data: 33 (8697)	Yes	7	Disease management programmes reduce mortality and hospitalisations in heart failure patients. Because various types of disease management programmes appear to be similarly effective, the choice of a specific programme depends on local health services characteristics, patient population, and resources available.
Rodrigo, 1999, 6564	The objective of this review was to reevaluate the literature on the effectiveness of CCS administration in the treatment of adult patients with acute asthma presenting to an acute-care setting (ie, usually the ED).	Acute asthma	Parenteral or inhaled corticosteroids vs. Parenteral (IV, IM), oral, or inhaled administration of CCSs or placebo	Total: 21 (1049) Admissions data: 6 (480)	Yes	8	This evidence-based evaluation suggests that the administration of parenteral CCSs to the patient on arrival at the emergency department (ED) neither improves airflow obstruction nor reduces the need for hospitalization. Parenteral CCSs probably require > 6 to 24 h to begin to act. Comprehensible conclusions about admission rates in the ED setting are difficult to make. At the 3-h assessment, only high doses of inhaled CCSs (in one study) significantly improved pulmonary function compared with placebo. IV and oral CCSs appear to have equivalent effects, and there is a tendency toward improvement in pulmonary function with medium or high doses.
Rodrigo, 2000, 6566	The purpose of this article was to review the literature to determine whether MgSO 4 provides an additive improvement in adults with acute asthma.	Acute asthma	Nebulised or parenteral magnesium sulfate vs. Placebo	Total: 5 (374) Admissions data: 4 (326)	No	7	The existing evidence reveals that the addition of MgSO4 to ED patients with moderate to severe asthmatic exacerbations does not alter treatment outcomes. Nevertheless, the number and size of studies being pooled remain small.
Rodrigo, 2005, 6568	A review was undertaken to incorporate the more recent evidence available about the effectiveness of treatment with a combination of b2 agonists and anticholinergics compared with b2 agonists alone in the treatment of acute asthma.	Acute asthma	Single or repeated doses of inhaled anticholinergic agents given in combination with inhaled b2 agonists vs. Inhaled b2 agonists alone	Total: 32 (3611) Admissions data: 9 (1556)	Yes	6	This review strongly suggests that the addition of multiple doses of inhaled ipratropium bromide to b2 agonists is indicated as the standard treatment in children, adolescents, and adults with moderate to severe exacerbations of asthma in the emergency setting.
Rodrigo, 2002, 6576	To determine whether continuous nebulization offered an advantage over intermittent nebulization for the treatment of adults with acute asthma in the emergency department (ED).	Acute asthma	Continuous nebulization of B-agonists vs. Intermittent nebulization of B-agonists	Total: 6 (393) Admissions data: 2 (80)	No	6	Overall, this review supports the equivalence of continuous and intermittent albuterol nebulization in the treatment of acute adult asthma.
Rodrigo, 2003, 6578	To determine the effect of the addition of heliox to standard medical care on the course of acute asthma.	Acute asthma presenting to an emergency department (ED) or equivalent care settings	Helium-oxygen gas mixture vs. Oxygen/air	Total: 6 (347) Admissions data: 4 (306)	No	7	The existing evidence does not provide support for the administration of heliumoxygen mixtures to emergency department patients with moderate-to-severe acute asthma. However, these conclusions are based on between-group comparisons and small studies, and these results should be interpreted with caution.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Rowe, 2000, 6670	This systematic review examined the effect of intravenous magnesium sulfate used for patients with acute asthma managed in the emergency department.	Acute asthma presenting to an emergency department	Intravenous magnesium sulfate vs. Placebo	Total: 7 (668) Admissions data: 5 (590)	Yes	8	Current evidence does not clearly support routine use of intravenous magnesium sulfate in all patients with acute asthma presenting to the ED. However, magnesium sulfate appears to be safe and beneficial for patients who present with severe acute asthma. Practice guidelines need to be changed to reflect these results.
Rowe, 1992, 6672	The objective of this study was to determlne the effect of steroid therapy on pulmonary function, admission rates, and relapse rates in patients presenting with acute exacerbations of asthma.	Acute exacerbations of asthma	Parenteral or oral glucocoritcoids vs. Not specified	Total: 30 (unclear) Admissions data: 3 (252)	No	6	The authors conclude that overall, steroid therapy provides Important benefits to patients presenting to emergency departments with acute exacerbations of asthma. Further research into dosage, alternative routes of adminlstratien, and alternative outcome measures is needed.
Rowe, 2001, 6676	To determine the benefit of treating patients with acute asthma with systemic corticosteroids within an hour of presenting to the emergency department (ED).	Acute asthma in the emergency department	Systemic corticosteroids vs. IV saline or placebo	Total: 12 (863) Admissions data: 12 (863)	Yes	9	Use of corticosteroids within 1 hour of presentation to an ED significantly reduces the need for hospital admission in patients with acute asthma. Benefits appear greatest in patients with more severe asthma, and those not currently receiving steroids. Children appear to respond well to oral steroids.
Rowe, 2007, 6677	To determine the benefit of corticosteroids (oral, intramuscular, or intravenous) for the treatment of asthmatic patients discharged from an acute care setting (i.e. usually the emergency department) after assessment and treatment of an acute asthmatic exacerbation.	Asthmatic exacerbations	Outpatient oral or Intramuscular corticosteroid vs. Placebo	Total: 6 (374) Admissions data: 4 (210)	No	8	A short course of corticosteroids following assessment for an asthma exacerbation significantly reduces the number of relapses to additional care, hospitalizations and use of short-acting beta2-agonist without an apparent increase in side effects. Intramuscular and oral corticosteroids are both effective.
Royal, 2006, 6681	To identify and evaluate studies of interventions in primary care aimed at reducing medication related adverse events that result in morbidity, hospital admission, and/or mortality.	Patients on medication	Pharmacist-led medication review in primary care vs. Usual care	Total: 29 (27898) Admissions data: 19 (23872)	Yes	7	There is relatively weak evidence to indicate that pharmacist-led medication reviews are effective in reducing hospital admissions. There is currently no evidence for the effectiveness of other interventions which aim at reducing admissions or preventable drug related morbidity. More randomised controlled trials of primary care based pharmacist-led interventions are needed to decide whether or not this intervention is effective in reducing hospital admissions.
Saab, 2015, 8884	The aim of this study was to evaluate the efficacy of probiotics in the management of minimal hepatic encephalopathy HE (MHE) and overt HE (OHE) in comparison to no treatment/placebo and lactulose.	Hepatic encephalopathy	Probiotics vs. No treatment, placebo, or lactulose	Total: 14 (1152) Admissions data: 5 (524)	Yes	4	Overall the use of probiotics was more effective in decreasing hospitalization rates, improving MHE and preventing progression to OHE in patients with underlying MHE than placebo, but similar to that seen with lactulose. The use of probiotics did not affect mortality rates.
Saha, 2007, 6746	We, therefore, conducted a systematic review and meta-analysis of randomized placebo-controlled clinical trials to evaluate the role of tissue ACE inhibitors for secondary prevention of cardiovascular events in patients with preserved ventricular function.	Patients with preserved left ventricular function	Tissue angiotensin-converting enzyme inhibitors vs. Placebo	Total: 4 (31555) Admissions data: 4 (31555)	No	4	Tissue ACE inhibitors have demonstrated benefit when used for secondary prevention of cardiovascular disease in patients with preserved left ventricular function in randomized placebo-controlled clinical trials.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Saha , 2008, 6747	The aim of this study was to determine the role of tissue angiotensin-converting enzyme (ACE) inhibitors in the prevention of cardiovascular disease in patients with diabetes mellitus without left ventricular systolic dysfunction or clinical evidence of heart failure in randomized placebo-controlled clinical trials using pooled meta-analysis techniques.	Patients with diabetes mellitus without left ventricular systolic dysfunction or clinical evidence of heart failure	Tissue angiotensin-converting enzyme inhibitors vs. Placebo	Total: 4 (10328) Admissions data: 4 (9991)	No	4	Pooled meta-analysis of randomized placebo-controlled trials suggests that tissue ACE inhibitors modestly reduce the risk of myocardial infarction and cardiovascular death and tend to reduce overall mortality in diabetic patients without left ventricular systolic dysfunction or heart failure.
Sajid, 2012, 6764	The objective of this review was to systemically analyse the published randomised controlled trials evaluating the efficacy of routine on-table cholangiography (R-OTC) versus no on-table cholangiography (NOTC) in patients undergoing laparoscopic, laparoscopic converted to open and open cholecystectomy using the principles of meta-analysis.	Cholecystectomy	Routine on-table cholangiography vs. No on-table cholangiography	Total: 4 (860) Admissions data: 4 (860)	No	5	N-OTC is associated with shorter operative time and fewer peri-operative complications, and it is comparable to R-OTC in terms of CBD injury risk during cholecystectomy. R-OTC is helpful for peri-operative CBD stone detection and there is therefore reduced readmission for retained CBD stones. The N-OTC approach may be adopted routinely for patients undergoing laparoscopic cholecystectomy providing there are no clinical, biochemical or radiological features suggestive of CBD stones. However, a major multicentre randomised controlled trial is required to validate this conclusion.
Salpeter, 2006, 6795	The objective of our study was to assess the effect of long-acting -agonists on severe asthma exacerbations requiring hospitalization, life-threatening asthma attacks, and asthma-related deaths. We used subgroup analyses to compare results for salmeterol and formoterol and for children and adults.	Asthma	Long acting beta agonists vs. Placebo	Total: 47 (unclear) Admissions data: 9 (3772)	Yes	6	Long-acting beta-agonists have been shown to increase severe and life-threatening asthma exacerbations, as well as asthma related deaths.
Salpeter, 2006, 6797	The objective of this meta-analysis is to compare the effects of b2-agonists and anticholinergics on exacerbations requiring withdrawal from the trial, severe exacerbations requiring hospitalization, and respiratory deaths in patients with COPD.	Chronic obstructive pulmonary disease	B2-agonists or anticholinergics vs. Placebo or anticholinergics	Total: 22 (15276) Admissions data: unclear (unclear)	Yes	6	Inhaled anticholinergics significantly reduced severe exacerbations and respiratory deaths in patients with COPD, while b2-agonists were associated with an increased risk for respiratory deaths. This suggests that anticholinergics should be the bronchodilator of choice in patients with COPD, and b2-agonists may be associated with worsening of disease control
Sampson, 2013, 6806	To review the effects of different intermittent drug techniques compared with maintenance treatment (as defined by the trial authors) in people with schizophrenia or related disorders.	Schizophrenia and other types of schizophrenia-like psychoses	Any intermittent drug technique vs. Maintenance therapy	Total: 17 (2252) Admissions data: 6 (661)	Yes	11	Results of this reviewsupport the existing evidence that intermittent antipsychotic treatment is not as effective as continuous,maintained antipsychotic therapy in preventing relapse in people with schizophrenia. More research is needed to assess any potential benefits or harm of intermittent treatment regarding adverse effects typically associated with maintained antipsychotic treatment, as well as any cost-effectiveness of this experimental treatment.
Shah, 2015, 8887	Our aim was to perform a meta-analysis of all randomized controlled trial (RCTs) and to evaluate the effect of implantable CRT defibrillator (CRTD) on all-cause mortality, HF mortality, and HF hospitalization in patients with QRSd less than 130 ms.	Patients with systolic heart failure and QRS interval less than or equal to 130 ms (ejection fraction less than or equal to 35%)	Cardiac-resynchronization therapy defibrillator vs. Implantable cardiac defibrillator	Total: 4 (1186) Admissions data: 4 (1186)	Yes	4	Cardiac-resynchronization therapy defibrillator has no impact on SHF mortality and SHF hospitalization in patients with systolic HF with QRS duration ≤130 ms and is associated with higher all-cause mortality in comparison with ICD therapy.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Shan, 2013, 7029	We therefore aimed to undertake a systematic review and meta-analysis of both intravenous and nebulized magnesium sulfate to determine their roles in adults and children with acute asthma.	Asthma	Intravenous or nebulized magnesium sulfate as an adjuvant in combination with b2-agonists vs. B2-agonists & placebo	Total: 25 (1754) Admissions data: 6 (383)	Yes	6	The use of intravenous magnesium sulfate, in addition to b2-agonists and systemic steroids, in the treatment of acute asthma appears to produce benefits with respect to improve pulmonary function and reduce the number of hospital admissions for children, and only improve pulmonary function for adults. However, the use of nebulized magnesium sulfate just appears to produce benefits for adults.
Shek, 2009, 7053	To assess the effects of day hospital care as an alternative to continuing outpatient care for people with schizophrenia.	Schizophrenia	Day hospital vs. Outpatient care	Total: 4 (351) Admissions data: 4 (351)	No	11	Evidence is limited and dated. Day hospital care may help avoid inpatient care but data are lacking on missing on a raft of outcomes that are now considered important, such as quality of life, satisfaction, healthy days, and cost.
Shepperd, 2016, 8888	To determine if providing home-based end-of-life care reduces the likelihood of dying in hospital and what effect this has on patients' symptoms, quality of life, health service costs, and caregivers compared with inpatient hospital or hospice care.	Patients at end of life that require terminal care	Home-based end-of-life care vs. Routine (not specialised) home care, acute inpatient care, primary care services, and/or hospice care	Total: 4 (1057) Admissions data: 3 (747)	Yes	10	The evidence included in this review supports the use of home-based end-of-life care programmes for increasing the number of people who will die at home, although the numbers of people admitted to hospital while receiving end-of-life care should be monitored. Future research should systematically assess the impact of home-based end-of-life care on caregivers.
Shepperd, 2016, 9327	To determine the effectiveness and cost of managing patients with admission avoidance hospital at home compared with inpatient hospital care.	Patients requiring hospital admission for a medical condition	Admission avoidance hospital at home schemes vs. Acute hospital inpatient care	Total: 16 (1966) Admissions data: 12 (1639)	Yes	10	Admission avoidance hospital at home, with the option of transfer to hospital, may provide an effective alternative to inpatient care for a select group of elderly patients requiring hospital admission. However, the evidence is limited by the small randomised controlled trials included in the review, which adds a degree of imprecision to the results for the main outcomes.
Sin, 2003, 7186	To systematically review the impact of long-acting bronchodilators, inhaled corticosteroids, nocturnal noninvasive mechanical ventilation, pulmonary rehabilitation, domiciliary oxygen therapy, and disease management programs on clinical outcomes in patients with COPD.	Chronic obstructive pulmonary disease	Disease management programs vs. Usual care	Total: 41 (19653) Admissions data: 9 (3071)	No	7	A significant body of evidence supports the use of long-acting bronchodilators and inhaled corticosteroids in reducing exacerbations in patients with moderate to severe COPD. Domiciliary oxygen therapy is the only intervention that has been demonstrated to prolong survival, but only in patients with resting hypoxia.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Smith, 2005, 7279	Prior research has highlighted the importance of psychosocial factors in 'difficult' asthma. This study aimed to review the content, effectiveness and cost-effectiveness of psycho-educational interventions designed to address these factors in patients with severe and difficult asthma.	Asthma	Psycho-educational interventions vs. Other psycho-educational interventions	Total: 14 (1822) Admissions data: 12 (1669)	No	11	There was some evidence of overall positive effects of psycho-educational interventions on hospital admissions in adults and children, and on symptoms in children, but limited evidence of effects on other outcomes. The majority of research and greatest effects, especially in adults, were confined to patients with severe disease but who lacked other characteristics indicative of difficult asthma or likely to put them at risk. A lack of good-quality research limited conclusions about cost-effectiveness. Although psycho-educational interventions may be of some benefit to patients with severe disease, there is currently a lack of evidence to warrant significant changes in clinical practice with regard to the care of patients with more difficult asthma. Further research is needed to: (1) standardise reporting of complex interventions; (2) extend and update this review; (3) improve identification of patients at risk from their asthma; (4) develop and test appropriate outcome measures for this group; and (5) design and evaluate, via the conduct of high-quality pragmatic RCTs, more powerful psycho-educational interventions that are conceptualised in terms of the ways in which psychosocial factors and asthma interact.
Stavrakis, 2012, 7417	We performed a meta-analysis of randomized controlled trials to examine whether cardiac resynchronization therapy (CRT) is superior to right ventricular (RV) pacing in this patient population.	Patients with persistent or permanent atrial fibrillation receiving atrioventricular junction ablation	Cardiac resynchronization therapy vs. Right ventricular pacing	Total: 5 (622) Admissions data: 3 (301)	No	6	Cardiac resynchronization therapy may be superior to RV pacing in patients undergoing AVJ ablation for AF. Further studies, adequately powered to detect clinical outcomes, are required.
Stratton, 2013, 7484	Therefore, this systematic review aimed to critically reviewand synthesise the literature to assess the impact of oral nutri-tional supplements used in the community setting across all patientgroups on hospital admissions and readmissions (indicated as (re)admissions).	Malnourished patients being discharged from the hospital to the community	Oral nutritional supplements vs. Usual care or dietary counselling	Total: 9 (1190) Admissions data: 6 (852)	Yes	6	This systematic review shows that ONS significantly reduce hospital (re)admissions, particularly in older patient groups, with economic implications for health care.
Su, 2014, 7504	In order to provide a scientific basis for clinical use of nitroprusside, it is necessary to evaluate the drug efficacy and safety in preventing no-flow using the method of the Cochrane systematic review.	Acute myocardial infarction	Nitroprusside vs. Placebo (including the blank control, saline, and nitroglycerin)	Total: 4 (169) Admissions data: 2 (190)	No	6	The results of the meta-analyses showed that intracoronary nitroprusside is beneficial in preventing no-reflow/slow-flow, in reducing corrected TIMI frame count, and in improving left ventricular ejection fraction. It also likely reduces adverse reactions in patients after PCI and rehospitalization due to cardiovascular events.
Susantitaphong, 2013, 7543	The Canadian Heart and Stroke Foundation clinical guidelines now recommend that combined RAAS blockade therapy be discontinued for the treatment of hypertension.21 In light of scarce data on the potentially deleterious effect of combined RAAS blockade therapy on kidney-related endpoints in patients with CKD, we conducted a meta-analysis of all randomized controlled trials (RCTs) comparing the efficacy and safety of combined vs. single RAAS blockade therapy in patients with CKD.	Chronic kidney disease	Combined renin angiotensin aldosterone system blockade therapy vs. Single renin-angiotensin aldosterone system blockade	Total: 59 (4975) Admissions data: 5 (326)	No	7	Although combined RAAS blockade therapy in CKD is associated with a decrease in albuminuria and proteinuria, it is associated with a decrease in GFR and a higher incidence of hyperkalemia and hypotension relative to monotherapy. The potential long-term kidne benefits of combined RAAS blockade therapy require further study.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Takeda, 2012, 7600	To update the previously published review which assessed the effectiveness of disease management interventions for patients with CHF.	Heart failure	Clinical service organisation interventions vs. Usual care	Total: 25 (5885) Admissions data: 25 (5885)	Yes	10	Amongst CHF patients who have previously been admitted to hospital for this condition there is now good evidence that case management type interventions led by a heart failure specialist nurse reduces CHF related readmissions after 12 months follow up, all cause readmissions and all cause mortality. It is not possible to say what the optimal components of these case management type interventions are, however telephone follow up by the nurse specialist was a common component. Multidisciplinary interventions may be effective in reducing both CHF and all cause readmissions. There is currently limited evidence to support interventions whose major component is follow up in a CHF clinic.
Tan, 2012, 7624	To test our hypothesis and evaluate the effectiveness and influence of disease-specific education programs on the health of COPD patients, we performed a meta-analysis on published research in this area. Using randomized controlled trials, we investigated the reported differences between COPD patients who received disease specific education programming (intervention group) and COPD patients who received usual care, which did not include educational programming (control group).	Chronic obstructive pulmonary disease	Disease-specific education program plus usual care vs. Usual care	Total: 12 (2113) Admissions data: 9 (1861)	No	8	Although significant effects were not detected across all HRQoL variables and health measures, our findings suggest that education programs have the potential to be a valuable intervention for COPD patients. Our results provide a foundation for future research in this area, which we recommend as including more rigorously designed, large, randomized studies.
Tan, 2014, 7626	To assess the efficacy and safety of fast track (FT) programmes in laparoscopic colorectal surgery by comparing FT programmes with traditional care in randomized controlled trials	Elective laparoscopic colorectal surgery	Fast track surgical programmes vs. Traditional care	Total: 4 (677) Admissions data: 4 (677)	No	5	FT programmes in elective laparoscopic colorectal surgery could significantly reduce primary hospital stay and overall hospital stay, and with no significant difference in readmission rate, morbidity, and mortality compared with traditional care.
Tapp, 2007, 7636	The aim of this study is to conduct a systematic review of the literature in order to determine whether asthma education provided to adults while attending the emergency department for asthma exacerbation management leads to improved health outcomes. A secondary aim is to identify the characteristics of the asthma education programs that had the greatest positive effect on health outcomes.	Asthma	Education interventions vs. Usual care	Total: 13 (2157) Admissions data: 9 (1445)	Yes	9	Our findings support educational interventions applied in the emergency department as a means of reducing subsequent asthma admissions to hospital. Whilst the direction of the effect on EDpresentations was consistent with the reduction in risk of admission, the results were not definitive.. Outcomes were measured on average at 6 months after index ED presentation. The impact of educational intervention in this context on longer term outcomes relating to asthma morbidity is unclear. Priorities for additional research in this area include assessment of health-related quality of life, lung function assessment, exploration of the relationship between socioeconomic status and asthma morbidity, and better description of the intervention assessed.
Taylor, 2001, 7647	To examine the benefits and risks of long term anticoagulation (warfarin) compared with antiplatelet treatment (aspirin/indoprofen) in patients with non-rheumatic atrial fibrillation.	Nonrheumatic atrial fibrillation	Long term anticoagulation vs. Antiplatelet treatment	Total: 5 (3298) Admissions data: 5 (3298)	No	6	The heterogeneity between the trials and the limited data result in considerable uncertainty about the value of long term anticoagulation compared with antiplatelet treatment. The risks of bleeding and the higher cost of anticoagulation make it an even less convincing treatment option.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Taylor, 2014, 7651	To determine the effectiveness of exercise-based rehabilitation on themortality, hospitalisation admissions, morbidity and health-related quality of life for people with HF. Review inclusion criteria were extended to consider not only HF due to reduced ejection fraction (HFREF or 'systolic HF') but also HF due to preserved ejection fraction (HFPEF or 'diastolic HF').	Heart failure	Exercise-based rehabilitation vs. Usual care or active intervention but no exercise training	Total: 35 (5507) Admissions data: 22 (4930)	Yes	9	This updated Cochrane review supports the conclusions of the previous version of this review that, compared with no exercise control, exercise-based rehabilitation does not increase or decrease the risk of all-cause mortality in the short term (up to 12-months' follow-up) but reduces the risk of hospital admissions and confers important improvements in health-related quality of life. This update provides further evidence that exercise training may reduce mortality in the longer term and that the benefits of exercise training on appear to be consistent across participant characteristics including age, gender and HF severity. Further randomised controlled trials are needed to confirm the small body of evidence seen in this review for the benefit of exercise in HFPEF and when exercise rehabilitation is exclusively delivered in a home-based setting.
Teuffel, 2011, 7687	Our objective was to evaluate the current level of evidence before supporting widespread adoption of outpatient management for this population.	Cancer patients with febrile neutropenia	Outpatient antibiotic therapy vs. In-patient antibiotic therapy	Total: 7 (688) Admissions data: 2 (177)	No	8	Based on the current literature, outpatient treatment of FN is a safe and efficacious alternative to inpatient management. Variation between studies in terms of time to discharge, choice of antibiotic class, and age of study population may limit the interpretation of the data.
Thomas, 2013, 7723	Undertake a systematic literature review and meta-analysis to evaluate the effectiveness of specialist clinics in reducing unplanned hospital admissions in people with heart failure.	Heart failure	Specialist heart-failure clinics vs. Usual care	Total: 10 (2811) Admissions data: 10 (2811)	Yes	7	Specialist clinics for patients with heart failure can reduce the risk of unplanned admissions; these were most effective when there was a high intensity of clinic appointments close to the time of discharge which then reduced over the follow-up period.
Thomas, 2014, 7724	This systematic review aimed to evaluate the effectiveness of interventions led by hospital or community pharmacists in reducing unplanned hospital admissions for older people.	Elderly people	Interventions led by hospital or community pharmacists vs. Usual care	Total: 20 (9884) Admissions data: 20 (9884)	Yes	6	Evidence from three randomised controlled trials suggests that interventions led by hospital pharmacists reduce unplanned hospital admissions in older patients with heart failure, although these trials were heterogeneous. Data from trials do not support the concept that interventions led by hospital or community pharmacists for the general older population reduces unplanned admissions.
Toelle, 2004, 7778	The primary objective of this review was to determine whether providing a person who has asthma with an individualised written asthma management plan increases adherence to specified asthma management behaviours, as detailed in the individual components of the written plan (i.e. primary outcome measures). A secondary objective was to observe the effect of individualised management plans on clinical outcomes (i.e. secondary outcome measures).	Asthma	Individualised written asthma management plan vs. No written instructions	Total: 7 (1098) Admissions data: 4 (606)	No	10	The available trials are too small and the results too few and inconsistent to form any firm conclusions as to the contribution of written self management plans in the known beneficial effects of a comprehensive asthma care programme.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Tonelli, 2008, 7787	The aim of this review was to assess the evidence for clinical efficacy and harms and the economic implications of ESA use in adult patients with anemia of CKD.	Patients with anemia of chronic kidney disease	Erythropoiesis-Stimulating Agents (Epoetin (alpha and beta) or darbepoetin) targeting high haemoglobin vs. Intermediate or low target haemoglobin protocols	Total: 10 (1553) Admissions data: 4 (3143)	No	11	In an environment where decision makers are willing to reimburse ESA, our base case analysis suggests that treatment to a target Hb of 110 g/L is most likely to be cost-effective. This strategy, however, will lead to higher costs (mainly due to ESA acquisition) compared to the low Hb target strategy, and it is based on the assumption that the intermediate target will improve QoL compared with the low target, which is unproven. Given the generally modest clinical benefit of ESA and the direct relationship between dose and cost, it may be prudent to consider a maximum ESA dose (above which the dose would not be increased further, even if the Hb target were not reached). Future research should focus on this comparison. In the interim, decision makers might reasonably choose to reimburse only the low Hb strategy because of the uncertainty in the quality-of-life gains associated with the intermediate strategy. Because of the higher cost of IV epoetin, the merits of reimbursing only SC epoetin (or darbopoetin by either route) should be explored. Lastly, because even small differences in potency per unit cost of ESA can translate into large differences in total costs, head-tohead comparisons of epoetin and darbepoetin should be considered.
Torloni, 2009, 7800	In the context of the planned International Society of Ultrasound in Obstetrics and Gynecology– World Health Organization multicenter study for the development of fetal growth standards for international application, we conducted a systematic review and meta-analysis to evaluate the safety of human exposure to ultrasonography in pregnancy.	Pregnant women	Ultrasonography vs. No exposure or less exposure to ultrasonography	Total: 9 (25200) Admissions data: 9 (25200)	No	7	According to the available evidence, exposure to diagnostic ultrasonography during pregnancy appears to be safe.
Tran, 2008, 7820	The aim of this review was to systematically evaluate the clinical benefit and to review the costeffectiveness of home telehealth versus usual care or no care for the management of diabetes, heart failure, and chronic obstructive pulmonary disease (COPD).	Chronic disease	Home telehealth vs. Usual care or no care	Total: 48 (12048) Admissions data: 26 (6280)	Yes	11	Despite the limited evidence, this assessment indicates that, overall, home telehealth is effective and that it can reduce health resource use. The economic studies were highly heterogeneous. More studies of a higher methodological quality are needed to give greater insights into the potential cost-effectiveness of home telehealth interventions. A framework for such studies is suggested. Home telehealth is a useful addition to Canadian health care delivery. It has been applied in the management of several chronic diseases. Many ethical, legal, and psychosocial issues that may arise can be solved using existing models. Some issues regarding the criteria for identifying suitable patients, liability, reimbursement, and unique patient identifiers, which are crucial to home telehealth implementation, require further discussion.
Tricco, 2014, 8899	We conducted a metaanalysis of the effectiveness of interventions to improve the coordination of care to reduce health care utilization in this patient group.	Frequent health care users	Coordination of care quality improvement strategies vs. Usual care, no intervention or other quality improvement strategies.	Total: 36 (7634) Admissions data: 29 (6746)	Yes	8	We found that quality improve- ment strategies for coordination of care reduced hospital admissions among patients with chronic conditions other than mental ill- ness and reduced emergency department visits among older patients. Our results may help cli- nicians and policy-makers reduce utilization through the use of strategies that target the system (team changes, case management) and the patient (promotion of self-management).

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Trinquart, 2011, 7841	The aim of the study was to assess the usefulness of systematic natriuretic peptide testing in the management of patients presenting with acute dyspnea to emergency departments (EDs).	Acute dyspnea	Natriuretic peptide (BNP or NT-proBNP) testing vs. Usual care	Total: 4 (2041) Admissions data: 4 (2041)	Yes	9	Four randomized controlled trials, representing 2041 patients, were selected. In 4 trials, there was a tendency for hospital admission to be reduced in the intervention group (combined risk ratio, 0.95; 95% confidence interval, 0.89-1.01). Time to discharge was significantly reduced in 2 trials, whereas there was no significant reduction in hospital length of stay in 3 trials. There was no significant effect on in-hospital and 30-day mortality rates or rehospitalization rates (3 trials reporting each outcome). Two trials found significant reduction in direct costs.
Vaughan, 2013, 8026	To assess the impact of day-surgery versus overnight stay laparoscopic cholecystectomy on patient-oriented outcomes such as mortality, severe adverse events, and quality of life.	Laparoscopic cholecystectomy surgery	Day-surgery vs. Overnight stay	Total: 6 (559) Admissions data: 5 (459)	No	9	Day-surgery appears just as safe as overnight stay surgery in laparoscopic cholecystectomy. Day-surgery does not seem to result in improvement in any patient-oriented outcomes such as return to normal activity or earlier return to work. The randomised clinical trials backing these statements are weakened by risks of systematic errors (bias) and risks of random errors (play of chance). More randomised clinical trials are needed to assess the impact of day-surgery laparoscopic cholecystectomy on the quality of life as well as other outcomes of patients.
Vedel, 2015, 8902	We aimed to determine the impact of transitional care interventions (TCIs) on acute health service use by patients with congestive heart failure in primary care and to identify the most effective TCIs and their optimal duration.	Heart failure	Transitional care intervention vs. Usual care	Total: 41 (10814) Admissions data: 41 (10814)	Yes	8	Clinicians and managers who implement TCIs in primary care can incorporate these results with their own health care context to determine the optimal balance between intensity and duration of TCIs. High-intensity interventions seem to be the best option. Moderate-intensity interventions implemented for 6 months or longer may be another option.
Villa-Roel, 2016, 9339	The objective of this review was to assess and describe the evidence from randomized controlled trials (RCTs) on the effectiveness of ED-directed educational interventions to improve office follow-up visits with PCPs in adults who were discharged from the ED after being treated for acute asthma.	Asthma	Emergency department directed patient education vs. Provision of usual or standard care following the ED presentation	Total: 5 (885) Admissions data: 3 (568)	No	9	ED-directed educational interventions targeting either patients or providers increase the chance of having office follow-up visits with PCPs after asthma exacerbations. Their impact on health related outcomes (e.g., relapse and admissions) remains unclear.
Viswanathan, 2015, 8904	To assess the effect of Medication therapy management interventions among outpatients with chronic illnesses.	Chronic disease	Medication therapy management interventions vs. No medication therapy management interventions	Total: 16 (4815) Admissions data: 7 (3599)	No	7	We graded the evidence as insufficient for most outcomes because of inconsistency and imprecision that stem in part from underlying heterogeneity in populations and interventions. Medication therapy management interventions may reduce the frequency of some medication-related problems, including nonadherence, and lower some health care use and costs, but the evidence is insufficient with respect to improvement in health outcomes.
Wallerstedt, 2014, 8176	Medication reviews by a third party have been introduced as a method to improve drug treatment in older people. We assessed whether this intervention reduces mortality and hospitalization for nursing home residents.	Patients on medication	Medication review vs. Standard care or other type of medication review	Total: 7 (11192) Admissions data: 4 (4185)	Yes	7	Our findings indicate that medication reviews for nursing home residents do not reduce mortality or hospitalization. More research in the setting of controlled trials remains to be done in order to clarify how drug treatment can be optimized for these patients.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Walters, 2014, 8704	To assess the effects of corticosteroids administered orally or parenterally for treatment of acute exacerbations of COPD, and to compare the efficacy of parenteral versus oral administration	Chronic obstructive pulmonary disease	Intravenous corticosteroid vs. Oral corticosteroid	Total: 20 (2078) Admissions data: 5 (unclear)	Yes	10	There is high-quality evidence to support treatment of exacerbations of COPD with systemic corticosteroid by the oral or parenteral route in reducing the likelihood of treatment failure and relapse by one month, shortening length of stay in hospital inpatients not requiring assisted ventilation in ICU and giving earlier improvement in lung function and symptoms. There is no evidence of benefit for parenteral treatment compared with oral treatment with corticosteroid on treatment failure, relapse or mortality. There is an increase in adverse drug effects with corticosteroid treatment, which is greater with parenteral administration compared with oral treatment.
Wang, 2015, 8908	This meta-analysis aimed to determine whether HF patients with narrow QRS complexes may benefit from CRT.	Patients with heart failure and narrow QRS complexes	Cardiac resynchronization therapy vs. Optimal pharmacological treatment or implantable cardioverter-defibrillator	Total: 5 (1134) Admissions data: 4 (1074)	No	5	In HF patients with reduced left ventricular ejection fraction (less than or equal to 35 %) and narrow QRS complexes (less than 130 ms), CRT did not improve clinical or functional outcomes and may actually increase all-cause mortality.
Wang, 2014, 8910	To compare the safety of fast-track rehabilitation protocols (FT) and conventional care strategies (CC), or FT and laparoscopic surgery (LFT) and FT and open surgery (OFT) after gastrointestinal surgery.	Gastrointestinal cancer surgery	Fast-track post-surgical rehabilitation vs. Conventional post-surgical care	Total: 24 (3083) Admissions data: 20 (2302)	No	7	Fast-tracks are safe after gastrointestinal surgery. Additional large, prospective RCTs should be conducted to establish further the safety of this approach.
Willcutts , 2016, 9138	The purpose of this systematic reviewandmeta-analysis is to compare early postoperative oral feeding, as the sole intervention, to traditional timing of oral feeding after any type of upper GI surgery.	Upper gastrointestinal surgery	Early feeding vs. Late or traditional feeding	Total: 8 (980) Admissions data: 4 (698)	No	6	Early postoperative oral feeding as compared with traditional (or late) timing is associated with shorter hospital length of stay and is not associated with an increase in clinically relevant complications.
Wilt, 2007, 8367	To evaluate the effectiveness of COPD management strategies.	Stable chronic obstructive pulmonary disease	1) inhaled medications (2-agonists, anticholinergics, combination 2-agonists and anticholinergics, inhaled corticosteroids, and combination inhaled corticosteroids and long-acting 2-agonists or anticholinergics), 2) pulmonary rehabilitation, 3) disease management programs, and 4) oxygen therapy. vs. Placebo; long-acting beta2-agonists; inhaled corticosteroids; tiotropium	Total: 42 (41932) Admissions data: 12 (20540)	No	8	Long-acting inhaled therapies, supplemental oxygen, and pulmonary rehabilitation are beneficial in adults who have bothersome respiratory symptoms, especially dyspnea, and FEV1 less than 60% predicted.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Wong, 2012, 8404	To evaluate the effectiveness of outreach respiratory health care worker programmes for Chronic obstructive pulmonary disease (COPD) patients in terms of improving lung function, exercise tolerance and health related quality of life (HRQL) of patient and carer, and reducing mortality and medical service utilisation.	Chronic obstructive pulmonary disease	Home visits by a respiratory healthcare provider vs. Routine care	Total: 9 (1427) Admissions data: 8 (1126)	No	9	Outreach nursing programmes for COPD improved disease-specific HRQL. However the effect on hospitalisations was heterogeneous, reducing admissions in one study, but increasing them in others, therefore we could not draw firm conclusions for this outcome.
Wu, 2015, 8914	Our goal was to assess the effects of fast-track programs on surgical outcomes compared with traditional surgical plans for liver surgery.	Open or laparoscopic liver surgery	Fast-track or enhanced recovery after surgery programs vs. Conventional surgery	Total: 9 (946) Admissions data: 3 (441)	Yes	7	Fast-track surgery programs are feasible and effective for liver surgery. Future studies should optimize fast-track surgery programs catering to liver surgery.
Xia, 2011, 8460	The primary objective was to assess the efficacy of psychoeducational interventions as means of helping severely mentally ill people when added to 'standard' care, compared to the efficacy of standard care alone. The secondary objective was to investigate whether there is evi- dence that a particular kind (individual/ family/group) or dura- tion (brief/other) of psychoeducational intervention is superior to others.	Schizophrenia	Psychoeducation vs. Standard care	Total: 44 (5142) Admissions data: 5 (483)	No	9	Psychoeducation does seem to reduce relapse, readmission and encourage medication compliance, as well as reduce the length of hospital stay in these hospital-based studies of limited quality. The true size of effect is likely to be less than demonstrated in this review - but, nevertheless, some sort of psychoeducation could be clinically effective and potentially cost beneficial. It is not difficult to justify better, more applicable, research in this area aimed at fully investigating the effects of this promising approach. Note: the 27 new citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.
Xie, 2016, 8916	Renin–angiotensin–aldosterone system(RAAS) blockers are effective therapies for heart failure and reduced ejection fraction (HFrEF) or left ventricular dysfunction (LVD). Weaimed to assess the efficacy and safety of RAAS blockers in these patients.	Heart failure with reduced ejection fraction or left ventricular dysfunction	Renin–angiotensin–aldosterone system blockade: Angiotensin converting enzyme inhibitor; Angiotensin II receptor blocker; Aldosterone antagonists ; Direct renin inhibitor vs. Angiotensin-converting enzyme inhibitor; angiotensin II receptor blockers	Total: 21 (69229) Admissions data: 20 (68976)	No	5	ARNI has the highest probability of being the most efficacious therapy for HFrEF in reducing death and hospitalization for heart failure. ARA has themost favorable benefit–risk profile as an adjunct to background ACEI and/or ARB therapy.
Xin, 2015, 8464	The primary aim of our meta-analysis was to evaluate the potential effects of B-type natriuretic peptide (BNP)-guided therapy on clinical outcomes in chronic heart failure (CHF) patients.	Chronic heart failure	BNP or NT-proBNP-guided heart failure medication therapy. vs. Usual care	Total: 14 (3223) Admissions data: 12 (2624)	No	6	BNP-guided therapy seemed to be safe and promising for CHF patients, and future studies with well- designed BNP-guided medication up-titration strategies are needed to confirm these results.
Yang, 2015, 8918	To assess the use of current prophylactic antibiotics in patients undergoing TRPB, we conducted a systematic review and meta-analysis to clarify which type, dose, route, and duration of antibiotics are the most appropriate and effective.	Prostate bopsy	Short course, single dose, or oral prophylactic antibiotics vs. Long course, multiple dose, systemically administered, or combined prophylactic antibiotics	Total: 22 (3846) Admissions data: 13 (2739)	No	8	Prophylactic antibiotics could be beneficial for the reduction of infective complications after TRPB. Single-dose or short-course oral administration with any type of antibiotic appears to be optimal. One additional type of antibiotic added to the basic antibiotic agent may contribute to the minimization of severe infection and drug resistance.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Yohannes, 2011, 8511	Therefore, we undertook a meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy of tiotropium on clinically relevant outcomes to patients with COPD, including health- related quality of life, dyspnea, adverse events, and clini- cal events (COPD exacerbations and related hospitaliza- tions) compared to placebo, ipratropium bromide, and long- acting b2 agonists (LABA).	Chronic obstructive pulmonary disease	Tiotropium vs. Placebo, ipratropium bromide, or long-acting beta agonists (LABA, salmeterol, or formoterol)	Total: 16 (16301) Admissions data: 9 (12379)	Yes	7	In stable COPD, tiotropium showed superior efficacy in improving quality of life and dyspnea, compared to placebo and ipratropium. However, tiotropium's differences with salmeterol were less clear.
Zhang, 2011, 8604	This study aimed to investigate the effect of statins on clinical outcomes of chronic systolic heart failure (CHF) by a meta- analysis based on randomized controlled trials (RCTs).	Chronic systolic heart failure	Statins vs. Placebo or blank in addition to contemporary standard therapy of CHF (no statin treatment).	Total: 13 (10447) Admissions data: 11 (10135)	No	6	Although statin has little impact on clinical outcomes in overall CHF patients, statin administration if needed is feasible to CHF patients, and the treatment might be effective when restricted to specific statins or populations.
Zhang, 2016, 8922	This meta-analysis was designed to assess the role of RAAS inhibitors on mortality, hospitalization, diastolic function, and exercise capacity in patients with HFpEF.	Heart failure with preserved ejection fraction (defined as signs or symptoms of heart failure with an EF > 40 %)	Renin–angiotensin–aldosterone system inhibitors vs. Placebo or diuretics	Total: 13 (12532) Admissions data: 11 (12308)	No	5	This meta-analysis shows that RAAS inhibitors could significantly reduce heart failure-related hospitalization and improve the E/e' index in patients with HFpEF. Further large-scale randomized controlled trials, especially on diastolic function, are needed to confirm the effects of RAAS inhibitors in patients with HFpEF.
Zhang, 2014, 9143	In this systematic review and meta-analysis, we weighed the relative effect size of montelukast for preventing asthma exacerbations under different standard teratment conditions and determined whether montelukast is effective in the treatment of acute asthma in adults	Chronic asthma or acute asthma	Montelukast and long acting beta 2 agonists vs. Long acting beta 2 agonists alone	Total: 26 (unclear) Admissions data: unclear (unclear)	No	6	Montelukast had low risk in hoarseness and insomnia. Our meta-analysis suggests that montelukast significantly reduces mild, moderate, and part of severe exacerbations in chronic mild to moderate asthma, but it has inferior efficacy to ICS or ICS plus LABA.
Zhao, 2016, 8924	Thus, we conducted a meta-analysis of published studies to evaluate the effect of laparoscopic colorectal surgery within fast track surgery.	Patients undergoing fast track surgery	Laparoscopic surgery vs. Open surgery	Total: 4 (683) Admissions data: 4 (394)	Yes	6	Within FTS, laparoscopic methods can significantly shorten postoperative hospital stay, accelerate postoperative recovery, and enhance safety in colorectal surgery. The FT elements "prevention of hypothermia", "no bowel preparation", and "no routine use of drains" may play important parts in the combined effect of these two methods.
Zhao, 2014, 8925	We performed this meta-analysis to compare the effects of FTS with those of traditional perioperative care in laparoscopic colorectal cancer surgery.	Laparoscopic colorectal cancer surgery	Fast-track surgery vs. Conventional perioperative care	Total: 5 (857) Admissions data: 5 (857)	No	6	Among patients undergoing laparoscopic colorectal cancer surgery, FTS is associated with a significantly shorter postoperative hospital stay, more rapid postoperative recovery, and, notably, greater safety than is expected from traditional care.
Zhi, 2013, 8627	The aim of the present study was to evaluate the risk of all-cause mortality, rehospitalization, renal function, weight change, and adverse events by conducting a meta-analysis of RCTs of diuretic versus ultrafiltration therapy in acute heart failure syndrome (AHFS).	Acute heart failure syndrome	Ultrafiltration therapy vs. Diuretic therapy	Total: 5 (494) Admissions data: 3 (434)	No	7	Compared with diuretic therapy, ultrafiltration produces greater weight loss and net fluid removal in a safe and effective manner.
Zhong, 2014, 8926	The aim of this systematic review was therefore to assess the influence of pharmacist care on health outcomes, humanistic outcomes [e.g., quality of life (QoL), medication compliance, and patient satisfaction], and healthcare utilization in patients with COPD.	Chronic obstructive pulmonary disease	Pharmacist directed care or pharmacist collaborative care vs. Usual care	Total: 8 (1603) Admissions data: 7 (1453)	No	8	Pharmacist care resulted in improvements in the medication compliance as well as reductions in hospital admissions and health-related costs. It is therefore a potent qstrategy for management of outpatients with COPD.

Table 6 continued. Information about included reviews

Author, Year, Review ID	Objective	Disease description	Intervention vs. comparison	No. of RCTs (patients)	Admissions were a primary outcome	AMSTAR score (/11)	Abstract conclusion
Zhou, 2015, 8927	To evaluate the long-term efficacy and safety of bronchial thermoplasty (BT) in the treatment of patients with moderate-to-severe persistent asthma.	Moderate-to-severe persistent asthma	Bronchial thermoplasty vs. Control	Total: 3 (443) Admissions data: 3 (249)	No	5	These data demonstrate long-term benefits of BT with regard to both asthma control and safety for moderate-to-severe asthmatic patients.
Zhou, 2014, 8928	We therefore performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the effects of TMZ treatment in CHF patients.	Chronic heart failure	Trimetazidine vs. Placebo	Total: 19 (1042) Admissions data: 4 (130)	No	4	TMZ treatment in CHF patients may improve clinical symptoms and cardiac function, reduce hospitalization for cardiac causes, and decrease serum levels of BNP and CRP.
Zhu, 2015, 8929	To compare the effectiveness of nurse-led early discharge planning programmes to standard care for inpatients with chronic disease or rehabilitation needs.	Hospitalised patients	Nurse-led early discharge planning programmes vs. Standard care	Total: 10 (3624) Admissions data: 10 (3624)	Yes	5	Compared to standard care, nurse-led early discharge planning programmes have a positive impact on several aspects of care for inpatients with chronic disease and rehabilitation requirements, including reducing readmission, readmission length of stay and mortality and improving quality of life. These findings should be taken into account in future health service policy development.
Zhuang, 2015, 8930	The purpose of this systemic review was to examine whether laparoscopic colorectal surgery still improved short-term postoperative outcomes in comparison with open surgery when both groups of patients received ERAS programs.	Patients receiving enhanced recovery after surgery programs	Laparoscopic surgery vs. Open surgery	Total: 5 (680) Admissions data: 5 (598)	Yes	8	Laparoscopic colorectal resection significantly reduced total hospital stay and number of complications when compared with open surgery in the setting of suboptimal ERAS programs, but the benefits of laparoscopic colorectal resection remain to be proved within optimal ERAS programs.
Ziff, 2015, 8931	To clarify the impact of digoxin on death and clinical outcomes across all observational and randomised controlled trials, accounting for study designs and methods.	Not specified (RCTs were all heart failure patients)	Digoxin vs. Placebo	Total: 7 (8406) Admissions data: 2 (7788)	No	7	Digoxin is associated with a neutral effect on mortality in randomised trials and a lower rate of admissions to hospital across all study types. Regardless of statistical analysis, prescription biases limit the value of observational data.
Zou, 2013, 8663	The purpose of this meta-analysis was to examine outcomes of self-management education interventions in persons with schizophrenia.	Schizophrenia	Self-management education interventions vs. Standard care or were on a wait list.	Total: 13 (1360) Admissions data: 7 (712)	No	6	The study concludes that self-management education intervention is a feasible and effective method for persons with schizophrenia and should be routinely offered to all persons with schizophrenia.
Zou, 2016, 8933	This meta-analysis assessed the efficacy of aclidinium bromide with respect to clinical events, health-related quality of life and symptom scales, pulmonary function, and safety among patients with stable COPD.	Moderate-to-severe chronic obstructive pulmonary disease	Aclidinium Bromide vs. Placebo	Total: 7 (7001) Admissions data: 7 (2601)	Yes	8	Aclidinium reduced the incidence of exacerbation-related hospitalizations and improved quality of life, COPD symptoms and pulmonary function. In addition, aclidinium did not increase the incidence of non-fatal serious adverse events, cardiac adverse events, or COPD exacerbations and was not associated with increased mortality.
Zwerink, 2014, 8672	1. To evaluate whether self management interventions in COPD lead to improved health outcomes. 2. To evaluate whether self management interventions in COPD lead to reduced healthcare utilisation.	Chronic obstructive pulmonary disease	Self-management vs. Control	Total: 27 (3642) Admissions data: 17 (3039)	Yes	11	Self management interventions in patients with COPD are associated with improved health-related quality of life as measured by the SGRQ, a reduction in respiratory-related and all cause hospital admissions, and improvement in dyspnoea as measured by the (m)MRC. No statistically significant differences were found in other outcome parameters. However, heterogeneity among interventions, study populations, follow-up time and outcome measures makes it difficult to formulate clear recommendations regarding the most effective form and content of self management in COPD.

Appendix 3.8 Distribution of review evidence by patient population and type of intervention

Table 7. Distribution of review evidence by patient population and type of intervention

Patient population[a] Subgroup[b]	Systematic reviews n=306 (%)[c]	Unique interventions investigated n=188 (%)[d]		
		Health systems interventions	Medications	Diagnostic, medical, and surgical interventions
Diseases of the circulatory system	90 (29%)	34 (18%)	32 (17%)	7 (4%)
Acute myocardial infarction	4 (1%)		2 (1%)	
Acute myocardial infarction; Angina pectoris	3 (1%)			1 (1%)
Acute myocardial infarction; Angina pectoris; Chronic ischaemic heart disease; or Heart failure	1 (<1%)	1 (1%)		
Acute myocardial infarction; Angina pectoris; or Other acute ischaemic heart diseases	1 (<1%)		1 (1%)	
Atrial fibrillation and flutter	7 (2%)		3 (2%)	3 (2%)
Chronic ischaemic heart disease	13 (4%)	3 (2%)	10 (5%)	
Chronic ischaemic heart disease or Heart failure	4 (1%)		2 (1%)	
Chronic ischaemic heart disease; Transient ischemic attack; Stroke; or Peripheral vascular disease	1 (<1%)	1 (1%)		
Essential (primary) hypertension	1 (<1%)		1 (1%)	
Heart failure	59 (19%)	34 (18%)	17 (9%)	4 (2%)
Other pulmonary heart diseases	2 (1%)		4 (2%)	
Patients at low risk of cardiovascular disease[f]	1 (<1%)		1 (1%)	
Diseases of the respiratory system	85 (28%)	16 (9%)	22 (12%)	3 (2%)
Asthma (chronic)	22 (7%)	6 (3%)	7 (4%)	1 (1%)
Asthma (acute - status asthmaticus)	20 (7%)	1 (1%)	10 (5%)	
Bronchiectasis	1 (<1%)		1 (1%)	
Influenza, virus not identified	3 (1%)		1 (1%)	
Other chronic obstructive pulmonary disease	37 (12%)	13 (7%)	9 (5%)	1 (1%)
Other chronic obstructive pulmonary disease; Simple and mucopurulent chronic bronchitis	1 (<1%)		1 (1%)	
Other interstitial pulmonary diseases	1 (<1%)		1 (1%)	
Pneumothorax	1 (<1%)			1 (1%)

Table 7 continued. Distribution of review evidence by patient population and type of intervention

Patient population[a] Subgroup[b]	Systematic reviews n=306 (%)[c]	Unique interventions investigated n=188 (%)[d]		
		Health systems interventions	Medications	Diagnostic, medical, and surgical interventions
Factors influencing health status and contact with health services	53 (17%)	13 (7%)	15 (8%)	7 (4%)
Hospitalised patients	8 (3%)	6 (3%)		
Need for immunization against other single viral diseases	2 (1%)		2 (1%)	
Patients on medication	3 (1%)	1 (1%)		
Patients presenting to primary care	2 (1%)	1 (1%)		
Patients receiving care involving dialysis	2 (1%)		1 (1%)	1 (1%)
Patients receiving other medical care	2 (1%)	1 (1%)	1 (1%)	
Patients receiving other orthopaedic follow-up care	1 (<1%)	2 (1%)		
Patients receiving special screening examination for neoplasms	1 (<1%)		4 (2%)	
Patients receiving surgery - cholecystectomy[f]	2 (1%)	1 (1%)		1 (1%)
Patients receiving surgery - colorectal[f]	8 (3%)	1 (1%)	2 (1%)	1 (1%)
Patients receiving surgery - day surgery	1 (<1%)		1 (1%)	
Patients receiving surgery – elective surgery	1 (<1%)	1 (1%)		
Patients receiving surgery - gastrointestinal[f]	5 (2%)	1 (1%)	2 (1%)	
Patients receiving surgery - gastrointestinal, liver and pancreatic[f]	1 (<1%)	1 (1%)		
Patients receiving surgery - gynaecological[f]	2 (1%)			2 (1%)
Patients receiving surgery - heart[f]	1 (<1%)	1 (1%)		
Patients receiving surgery - liver[f]	1 (<1%)	1 (1%)		
Patients receiving surgery - tonsil[f]	1 (<1%)		1 (1%)	
Patients requiring hospital admission for a medical condition	1 (<1%)	1 (1%)		
Patients with implantable cardioverter-defibrillators devices	1 (<1%)	1 (1%)		
Patients undergoing supervision of normal pregnancy	2 (1%)			2 (1%)
Patients undergoing supervision of high-risk pregnancy	1 (<1%)	1 (1%)		
Patients undergoing supervision of high-risk or normal pregnancy	1 (<1%)		1 (1%)	
Post-operative percutaneous coronary intervention care	1 (<1%)	1 (1%)		
Post-partum care and examination	1 (<1%)	1 (1%)		
Problems related to lifestyle	1 (<1%)	1 (1%)		

Table 7 continued. Distribution of review evidence by patient population and type of intervention

Patient population[a] Subgroup[b]	Systematic reviews n=306 (%)[c]	Unique interventions investigated n=188 (%)[d]		
		Health systems interventions	Medications	Diagnostic, medical, and surgical interventions
Mental and behavioural disorders	29 (9%)	17 (9%)	20 (11%)	
Bipolar affective disorder	3 (1%)	6 (3%)	1 (1%)	
Dementia in Alzheimer disease; Dementia in other diseases classified elsewhere; Unspecified dementia; Vascular dementia	1 (<1%)	1 (1%)		
Severe mental illness (Disorders of adult personality and behaviour; Mood [affective] disorders; Neurotic, stress-related and somatoform disorders; Schizophrenia, schizotypal and delusional disorders)	2	2 (1%)		
Schizophrenia	3 (1%)	2 (1%)	5 (3%)	
Schizophrenia and other types of schizophrenia-like psychoses (Acute and transient psychotic disorders; Bipolar affective disorder; Induced delusional disorder; Other nonorganic psychotic disorders; Persistent delusional disorders; Schizoaffective disorders; Schizophrenia; Schizotypal disorder; Unspecified nonorganic psychosis)	13	9 (5%)	16 (9%)	
Severe/chronic mental disorders/illnesses	5	4 (2%)		
Psychotic illness	3	5 (3%)		
Mixed patient populations[g]	16 (5%)	19 (10%)	3 (2%)	
Heart failure or Type 1 diabetes mellitus with renal complications	1 (<1%)		1 (1%)	
Patients indicated for treatment with non-steroidal anti-inflammatory drugs (Benign neoplasm of colon, rectum, anus and anal canal; Dimentia in Alzheimer disease; Inflammatory polyarthropathies (Rheumatoid arthritis); or Other arthrosis (Osteoarthritis)	1 (<1%)		1 (1%)	
Alcoholic liver diseases (alcoholic cirrhosis of the liver) or Other interstitial pulmonary diseases (idiopathic pulmonary fibrosis)	1 (<1%)		1 (1%)	
Elderly people	1 (<1%)	1 (1%)		
Elderly people in the community or being discharged from hospital	9 (3%)	16 (9%)		
Elderly in the acute illness or injury phase	1 (<1%)	1 (1%)		
Chronic disease	1 (<1%)	1 (1%)		
Frequent health care users	1 (<1%)	4 (2%)		
Type 1 diabetes mellitus with renal complications or High risk of cardiovascular disease	1 (<1%)		1 (1%)	

Table 7 continued. Distribution of review evidence by patient population and type of intervention

Patient population[a] Subgroup[b]	Systematic reviews n=306 (%)[c]	Unique interventions investigated n=188 (%)[d]		
		Health systems interventions	Medications	Diagnostic, medical, and surgical interventions
Multi-morbidity[h]	11 (4%)	1 (1%)	5 (3%)	2 (1%)
Acute myocardial infarction, Angina pectoris, Chronic kidney disease, or Other acute ischaemic heart diseases	1 (<1%)			1 (1%)
Acute myocardial infarction and Heart failure	1 (<1%)		1 (1%)	
Chronic ischaemic heart disease or Heart failure and Iron deficiency anaemia	1 (<1%)		1 (1%)	
Chronic ischaemic heart disease and Recurrent depressive disorder	2 (1%)		2 (1%)	
Chronic kidney disease and Iron deficiency anaemia	1 (<1%)		1 (1%)	
Heart failure and Acute renal failure	2 (1%)			1 (1%)
Heart failure and Iron deficiency anaemia	2 (1%)		2 (1%)	
Heart failure and a variety of co-morbid conditions	1 (<1%)	1 (1%)		
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	6 (2%)			3 (2%)
Abdominal and pelvic pain	1 (<1%)			1 (1%)
Abnormalities of breathing	2 (1%)			1 (1%)
Pain in throat and chest	3 (1%)			1 (1%)
Diseases of the digestive system	5 (2%)		3 (2%)	
Alcoholic liver disease	1 (<1%)		1 (1%)	
Crohn disease [regional enteritis]	2 (1%)		1 (1%)	
Crohn disease [regional enteritis] or Ulcerative colitis	1 (<1%)		1 (1%)	
Hepatic failure, not elsewhere classified	1 (<1%)		1 (1%)	
Ulcerative colitis	3 (1%)		1 (1%)	
Diseases of the genitourinary system	5 (2%)		4 (2%)	1 (1%)
Chronic kidney disease	3 (1%)		2 (1%)	1 (1%)
Calculus of kidney and ureter	1 (<1%)		1 (1%)	
Disorders resulting from impaired renal tubular function	1 (<1%)		1 (1%)	
Pregnancy, childbirth and the puerperium	5 (2%)		2 (1%)	1 (1%)
Excessive vomiting in pregnancy	1 (<1%)		1 (1%)	
Mild to moderate pre-eclampsia	2 (1%)		1 (1%)	
Premature rupture of membranes	2 (1%)			1 (1%)

Table 7 continued. Distribution of review evidence by patient population and type of intervention

Patient population[a] Subgroup[b]	Systematic reviews n=306 (%)[c]	Unique interventions investigated n=188 (%)[d]		
		Health systems interventions	Medications	Diagnostic, medical, and surgical interventions
Endocrine, nutritional, and metabolic diseases	5 (2%)		4 (2%)	
Diabetes mellitus	1 (<1%)		1 (1%)	
Malnourished (Kwashiorkor; Marasmic kwashiorkor; Nutritional marasmus; Retarded development following protein-energy malnutrition; Protein-energy malnutrition of moderate and mild degree; Unspecified protein-energy malnutrition; Unspecified severe protein-energy malnutrition)	3 (1%)		2 (1%)	
Non-insulin-dependent diabetes mellitus	1 (<1%)		1 (1%)	
Neoplasms	2 (<1%)	1 (1%)		1 (1%)
Cancer with febrile neutropenia[f]	1 (<1%)	1 (1%)		
Leiomyoma of uterus or Other benign neoplasms of uterus	1 (<1%)			1 (1%)
Diseases of the nervous system	2 (<1%)		2 (1%)	
Multiple sclerosis	2 (1%)		2 (1%)	
Diseases of the musculoskeletal system and connective tissue	1 (<1%)		1 (1%)	
Systemic lupus erythematosus	1 (<1%)		1 (1%)	
Infectious and parasitic diseases	1 (<1%)		1 (1%)	
Human immunodeficiency virus [HIV] disease	1 (<1%)		1 (1%)	

[a]Patient populations were classified using the World Health Organisations 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10). [b]These specific classifications represent the summary and 3-character coding level in the ICD 10. [c]Denominator for this column is the number of systematic reviews. [d]The numbers in the column do not add up to 188 as some of the interventions were used in multiple patient populations. [e]Chemical sub-group classification not possible because review reported limited detail of the medication. Therefore, this code represents the broader classification based on therapeutic or chemical characteristics. [f]Patient population(s) not captured in codes available in the ICD-10. [g]Mixed populations were defined as those with no defined disease group and those where two or more disease groups were included, as defined by the ICD-10 summary chapter level or three-character block level. [h]Multi-morbid populations were defined as those with two or more codes at the ICD-10 summary chapter level or two or more codes at the three-character block level.

Appendix 3.9 Full results for AMSTAR quality assessments

Table 8. Full results for AMSTAR quality assessments

Author	Year	Review ID	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Overall
			Was an a priori design provided?	Was there duplicate study selection and extraction?	Was a comprehensive literature search performed?	Was there a search for grey or unpublished literature?	Was a list of included and excluded studies provided?	Were the characteristics of included studies provided?	Was the scientific quality of included studies assessed and documented?	Was the scientific quality of included studies used appropriately in formulating conclusions?	Were the methods used to combine the results of included studies appropriate?	Was the likelihood of publication bias assessed?	Were conflicts of interest acknowledged?	Summary AMSTAR score
Abdelnoor	2017	9354	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Adams	2007	85	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Afilalo	2007	100	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	6
Aguinagalde	2010	119	No	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	5
Ahmed	2014	129	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	6
Akioyamen	2016	8711	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	7
Al-Majed	2011	212	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	9
Anderson	2015	8714	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Anderson	2016	8716	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Assasi	2009	378	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	9
Babalola	2014	432	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Badve	2011	446	No	No	Yes	Yes	No	Yes	No	Yes	Yes	No	No	5
Baigent	2013	1653	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	6
Baishnab	2012	472	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Barr	2006	548	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Baumeister	2011	593	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Beamish	2015	8724	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	6
Beck	2013	615	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	5
Berghella	2008	696	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Beswick	2008	725	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Bittencourt	2016	9221	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Blitz	2005	813	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	5
Bond-Smith	2016	8728	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Bonsu	2016	8729	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9
Bradley	2003	930	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9
Briasoulis	2015	8731	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Brophy	2001	1021	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	4
Brown	2011	1031	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Brown	2002	1039	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Buckley	2015	8733	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Burch	2009	1080	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8
Cammarano	2016	8735	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	4
Campschroer	2014	1164	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Cates	2013	1249	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Cawood	2012	1264	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7

Table 8 continued. Full results for AMSTAR quality assessments

Author	Year	Review ID	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Overall
			Was an a priori design provided?	Was there duplicate study selection and extraction?	Was a comprehensive literature search performed?	Was there a search for grey or unpublished literature?	Was a list of included and excluded studies provided?	Were the characteristics of included studies provided?	Was the scientific quality of included studies assessed and documented?	Was the scientific quality of included studies used appropriately in formulating conclusions?	Were the methods used to combine the results of included studies appropriate?	Was the likelihood of publication bias assessed?	Were conflicts of interest acknowledged?	Summary AMSTAR score
Ceron-Litvoc	2009	1281	No	No	Yes	Yes	Yes	No	Yes	No	Yes	No	No	5
Chapron	2002	1335	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	6
Charytan	2009	1340	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Chauhan	2012	1348	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Chauhan	2014	8681	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Chen	2013	1389	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Chen	2015	8739	No	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	6
Chen	2015	8740	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	7
Chen	2015	8742	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Cheng	2015	8743	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	5
Cheyne	2015	8744	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Chien	2008	1418	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7
Chong	2012	1438	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Choudhry	2005	1447	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Christensen	2016	8745	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Coeytaux	2014	8747	Yes	No	No	No	No	Yes	No	Yes	Yes	Yes	No	5
Conroy	2011	1575	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	6
Cordina	2005	1606	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Costa	2013	1629	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Danchin	2006	1752	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
De Waure	2013	1855	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Deshpande	2013	1921	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Dieterich	2017	9370	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
DiNicolantonio	2013	1991	No	No	Yes	No	Yes	Yes	Yes	No	Yes	No	No	5
Donald	2015	8759	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Doyle	2009	2055	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Dretzke	2015	8760	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Driscoll	2015	8761	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Ducharme	2010	2095	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Ebell	2013	2148	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	9
Echevarria	2016	8762	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Edmonds	2012	2158	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Edmonds	2012	2159	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	9
El-Hayek	2014	8763	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	6
Elkan	2001	2211	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7

Table 8 continued. Full results for AMSTAR quality assessments

Author	Year	Review ID	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Overall
			Was an a priori design provided?	Was there duplicate study selection and extraction?	Was a comprehensive literature search performed?	Was there a search for grey or unpublished literature?	Was a list of included and excluded studies provided?	Were the characteristics of included studies provided?	Was the scientific quality of included studies assessed and documented?	Was the scientific quality of included studies used appropriately in formulating conclusions?	Were the methods used to combine the results of included studies appropriate?	Was the likelihood of publication bias assessed?	Were conflicts of interest acknowledged?	Summary AMSTAR score
Ezekowitz	2009	2304	No	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	6
Fanning	2016	9247	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Farne	2015	8767	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Farrelly	2013	2335	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Feltner	2014	2359	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8
Filippini	2003	2402	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Fisher	2014	8769	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Fisher	2015	8770	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Fisher	2015	8771	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Fox	2011	2496	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	5
Fox	2012	2500	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Fredericks	2017	9375	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Fu	2012	2549	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	7
Gandhi	2014	2599	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Gandhi	2017	9376	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Gao	2014	8775	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Garside	2007	2640	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Gibson	2002	2715	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	7
Goffinet	1997	2780	No	No	Yes	No	Yes	Yes	Yes	Yes	No	No	No	5
Gonçalves-Bradley	2016	8776	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Gonseth	2004	2811	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Greco	2014	2894	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Griffiths	2007	2924	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Grimwade	2003	2933	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Grooten	2015	8780	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Gupta	2014	8688	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Gwadry-Sridhar	2004	3030	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Handoll	2009	3116	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Harrison	2015	8782	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	5
Hatah	2013	3183	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	5
Hemkens	2016	8784	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Heran	2012	3275	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Ho	2014	3350	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9
Hodnett	2010	3362	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9

Table 8 continued. Full results for AMSTAR quality assessments

Author	Year	Review ID	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Overall
			Was an a priori design provided?	Was there duplicate study selection and extraction?	Was a comprehensive literature search performed?	Was there a search for grey or unpublished literature?	Was a list of included and excluded studies provided?	Were the characteristics of included studies provided?	Was the scientific quality of included studies assessed and documented?	Was the scientific quality of included studies used appropriately in formulating conclusions?	Were the methods used to combine the results of included studies appropriate?	Was the likelihood of publication bias assessed?	Were conflicts of interest acknowledged?	Summary AMSTAR score
Holland	2005	3400	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	7
Holland	2007	3401	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Hood	2014	3415	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	7
Howcroft	2016	9261	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Hulten	2013	3492	Yes	No	No	Yes	No	No	Yes	No	Yes	Yes	No	5
Huntley	2013	3507	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8
Huntley	2016	9178	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Inglis	2015	8787	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Inglis	2015	8788	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8
Jaeschke	2008	3639	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	5
Jaeschke	2008	3640	No	Yes	No	Yes	No	Yes	No	No	Yes	No	No	4
James	2008	3657	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	7
Jankowska	2016	8790	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Jefferson	2014	3696	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Jeppesen	2012	3709	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Johnstone	1999	3761	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8
Jolly	2016	9198	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Jones	2012	3769	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Jong	2002	3781	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	6
Jonkman	2016	8795	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8
Jordan	2015	8796	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Kang	2007	3877	No	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	6
Kang	2008	3879	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	7
Kang	2015	8797	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Kang	2016	9271	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	6
Kansagara	2013	3885	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Karner	2011	3908	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Karner	2014	8692	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Kaur	2014	3937	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	7
Kew	2014	4002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Kew	2013	4003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Kew	2014	4004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Kew	2016	8802	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Kew	2015	8803	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Kew	2015	8805	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11

Table 8 continued. Full results for AMSTAR quality assessments

Author	Year	Review ID	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Overall
			Was an a priori design provided?	Was there duplicate study selection and extraction?	Was a comprehensive literature search performed?	Was there a search for grey or unpublished literature?	Was a list of included and excluded studies provided?	Were the characteristics of included studies provided?	Was the scientific quality of included studies assessed and documented?	Was the scientific quality of included studies used appropriately in formulating conclusions?	Were the methods used to combine the results of included studies appropriate?	Was the likelihood of publication bias assessed?	Were conflicts of interest acknowledged?	Summary AMSTAR score
Kim	2005	4041	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Kisely	2017	9387	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Kishimoto	2013	4065	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	6
Kishimoto	2014	4067	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Komossa	2010	4123	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Koshman	2008	4147	No	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	5
Kotb	2014	4154	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	5
Kruis	2013	4192	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Kuenzli	2010	4206	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Kul	2012	4210	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Kumar	2014	8815	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	6
Kuswardhani	2011	4239	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Kwong	2014	4254	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	5
Kwong	2012	4255	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
La Mantia	2010	4260	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Lam	2010	4296	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Lambrinou	2012	4305	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Lasserson	2011	4362	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Laurant	2005	9181	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	8
Le	2016	8817	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Lei	2015	8819	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Leppin	2014	4494	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Lethaby	2012	4502	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Leucht	2011	4505	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Leucht	2012	4508	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Levy	2010	4518	No	No	No	No	No	Yes	Yes	No	Yes	No	No	3
Li	2016	8822	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Liew	2014	4577	No	Yes	No	No	No	Yes	Yes	No	Yes	No	No	4
Lipinski	2009	4615	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	7
Liu	2014	4629	No	Yes	No	No	No	Yes	No	No	Yes	Yes	No	4
Liu	2014	8826	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	7
Liu	2014	8827	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Lopez	2015	8829	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8
Lowthian	2015	8830	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	6
Magee	2003	4812	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9

Table 8 continued. Full results for AMSTAR quality assessments

Author	Year	Review ID	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Overall
			Was an a priori design provided?	Was there duplicate study selection and extraction?	Was a comprehensive literature search performed?	Was there a search for grey or unpublished literature?	Was a list of included and excluded studies provided?	Were the characteristics of included studies provided?	Was the scientific quality of included studies assessed and documented?	Was the scientific quality of included studies used appropriately in formulating conclusions?	Were the methods used to combine the results of included studies appropriate?	Was the likelihood of publication bias assessed?	Were conflicts of interest acknowledged?	Summary AMSTAR score
Magee	2000	4815	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Maggio	2008	4817	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Majothi	2015	8833	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	8
Makani	2013	4838	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Makrides	2014	4844	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Malone	2007	4860	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Mannucci	2008	4889	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	5
Marshall	2011	4965	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Marshall	1998	4966	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	8
Marshall	1998	4968	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	8
Marshall	2011	4972	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Martínez-González	2014	4987	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Mayo-Wilson	2014	5047	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
McLean	2010	5145	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
McLean	2011	5147	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
McLellan	2016	9300	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Mead	2005	5161	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8
Meads	2007	5165	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8
Medic	2016	8842	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Mehta	2005	5183	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Mekonnen	2016	8844	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Mohammed	2007	5325	No	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	6
Møiniche	2003	5330	No	No	Yes	No	Yes	No	No	No	Yes	No	No	3
Moore	2006	5371	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Morriss	2007	5398	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Morriss	2013	5399	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Murphy	2015	8847	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Nair	2012	5515	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Nannini	2013	5533	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Nannini	2013	8694	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Ngo	2010	5606	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Ni	2009	5611	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Ni	2014	8850	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Ni	2015	9197	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	6

Table 8 continued. Full results for AMSTAR quality assessments

Author	Year	Review ID	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Overall
			Was an a priori design provided?	Was there duplicate study selection and extraction?	Was a comprehensive literature search performed?	Was there a search for grey or unpublished literature?	Was a list of included and excluded studies provided?	Were the characteristics of included studies provided?	Was the scientific quality of included studies assessed and documented?	Was the scientific quality of included studies used appropriately in formulating conclusions?	Were the methods used to combine the results of included studies appropriate?	Was the likelihood of publication bias assessed?	Were conflicts of interest acknowledged?	Summary AMSTAR score
Nicholson	2014	5620	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	10
Nistor	2015	8854	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Nyong	2016	9307	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Oud	2016	9309	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Parker	2002	5937	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Parthiban	2015	8859	No	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	5
Pharoah	2010	6091	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Phillips	2004	6099	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	5
Piccini	2009	6110	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Pizzi	2011	6161	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Poole	2015	8867	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Powell	2002	6220	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Powell	2015	8868	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Puhan	2016	9316	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Rabindranath	2007	6325	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Rajagopalan	2011	6347	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Ram	2004	6355	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Raman	2008	6360	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Randall	2015	8875	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Reilly	2015	8880	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Renner	2012	6442	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Roberts	2009	6536	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Roccaforte	2005	6552	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Rodrigo	1999	6564	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Rodrigo	2000	6566	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Rodrigo	2005	6568	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Rodrigo	2002	6576	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	6
Rodrigo	2003	6578	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7
Rowe	2000	6670	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8
Rowe	1992	6672	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Rowe	2001	6676	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Rowe	2007	6677	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8
Royal	2006	6681	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Saab	2015	8884	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	4
Saha	2007	6746	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	4

Table 8 continued. Full results for AMSTAR quality assessments

Author	Year	Review ID	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Overall
			Was an a priori design provided?	Was there duplicate study selection and extraction?	Was a comprehensive literature search performed?	Was there a search for grey or unpublished literature?	Was a list of included and excluded studies provided?	Were the characteristics of included studies provided?	Was the scientific quality of included studies assessed and documented?	Was the scientific quality of included studies used appropriately in formulating conclusions?	Were the methods used to combine the results of included studies appropriate?	Was the likelihood of publication bias assessed?	Were conflicts of interest acknowledged?	Summary AMSTAR score
Saha	2008	6747	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	4
Sajid	2012	6764	No	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	5
Salpeter	2006	6795	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	6
Salpeter	2006	6797	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	6
Sampson	2013	6806	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Shah	2015	8887	No	No	No	Yes	No	Yes	No	Yes	Yes	No	No	4
Shan	2013	7029	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	6
Shek	2009	7053	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Shepperd	2016	8888	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Shepperd	2016	9327	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Sin	2003	7186	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Smith	2005	7279	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Stavrakis	2012	7417	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	6
Stratton	2013	7484	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Su	2014	7504	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	6
Susantitaphong	2013	7543	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Takeda	2012	7600	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Tan	2012	7624	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Tan	2014	7626	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	5
Tapp	2007	7636	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Taylor	2001	7647	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Taylor	2014	7651	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Teuffel	2011	7687	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Thomas	2013	7723	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Thomas	2014	7724	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Toelle	2004	7778	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Tonelli	2008	7787	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Torloni	2009	7800	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Tran	2008	7820	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Tricco	2014	8899	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Trinquart	2011	7841	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	9
Vaughan	2013	8026	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Vedel	2015	8902	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	8
Villa-Roel	2016	9339	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Viswanathan	2015	8904	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Wallerstedt	2014	8176	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Walters	2014	8704	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10

Table 8 continued. Full results for AMSTAR quality assessments

Author	Year	Review ID	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Overall
			Was an a priori design provided?	Was there duplicate study selection and extraction?	Was a comprehensive literature search performed?	Was there a search for grey or unpublished literature?	Was a list of included and excluded studies provided?	Were the characteristics of included studies provided?	Was the scientific quality of included studies assessed and documented?	Was the scientific quality of included studies used appropriately in formulating conclusions?	Were the methods used to combine the results of included studies appropriate?	Was the likelihood of publication bias assessed?	Were conflicts of interest acknowledged?	Summary AMSTAR score
Wang	2015	8908	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	5
Wang	2014	8910	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Willcutts	2016	9138	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Wilt	2007	8367	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	8
Wong	2012	8404	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
Wu	2015	8914	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Xia	2011	8460	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Xie	2016	8916	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	5
Xin	2015	8464	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Yang	2015	8918	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8
Yohannes	2011	8511	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Zhang	2011	8604	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Zhang	2016	8922	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	5
Zhang	2014	9143	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	6
Zhao	2016	8924	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Zhao	2014	8925	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	6
Zhi	2013	8627	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7
Zhong	2014	8926	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Zhou	2015	8927	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	5
Zhou	2014	8928	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	4
Zhu	2015	8929	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	5
Zhuang	2015	8930	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Ziff	2015	8931	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	7
Zou	2013	8663	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	6
Zou	2016	8933	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Zwerink	2014	8672	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11

Appendix 3.10 Graded effect estimates for medications that reduce emergency hospital admissions

Table 9. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I^2%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Disease of the circulatory system											
Acute myocardial infarction											
Su, 2014, 7504	Undergoing percutaneous coronary intervention	Nitroprusside (10 per 100)	Placebo (22 per 100)	190 (2)	58 ±6	Readmission for cardiovascular issues (Unclear)	No	RR: 0.44 (0.21 to 0.91) NNT: 8 (6 to 51) 0%	Low	Summary estimate	(+) The results of the meta-analyses showed that intracoronary nitroprusside is beneficial in preventing no-reflow/slow-flow, in reducing corrected TIMI frame count, and in improving left ventricular ejection fraction. It also likely reduces adverse reactions in patients after PCI and rehospitalization due to cardiovascular events.
Chronic ischaemic heart disease											
Danchin, 2006, 1752a	Stable coronary heart disease and absence of heart failure or left ventricular systolic dysfunction	Angiotensin-Converting Enzyme Inhibitor [Ramipril, Perindopril, Trandolapril, or Enalapril] (2 per 100)	Placebo (3 per 100)	31750 (5)	62 ±3	Admission for heart failure (50 ±15 months)	Yes	OR: 0.76 (0.66 to 0.88) NNT: 146 (103 to 294) I^2: Unclear	Moderate	Summary estimate	(+) Angiotensin-converting enzyme inhibitors reduce total mortality and major cardiovascular end points in patients who have coronary artery disease and no left ventricular systolic dysfunction or heart failure.
Saha , 2007, 6746b	Patients with a prior cardiovascular event or at high risk for cardiovascular events with preserved left ventricular function	Tissue angiotensin converting enzyme Inhibitors [Ramipril, Perindopril, or Trandolapril] (2.5 per 100)	Placebo (3.2 per 100)	29805 (4)	63 ±3	Admission for heart failure (12 months)	Yes	RR: 0.78 (0.67 to 0.9) NNT: 140 (93 to 308) I^2: Unclear	High	Summary estimate	(+) Tissue angiotensin converting enzyme inhibitors have demonstrated benefit when used for secondary prevention of cardiovascular disease in patients with preserved left ventricular function in randomized placebo-controlled clinical trials.
Afilalo, 2007, 100c	Stable coronary heart disease	Intensive statin therapy [Atorvastatin or Simvastatin] (2 per 100)	Moderate statin therapy [Pravastatin, Atorvastatin or Simvastatin] (3 per 100)	27547 (4)	61 ±2	Admission for heart failure (41 ±20 months)	Yes	OR: 0.72 (0.62 to 0.83) NNT: 115 (84 to 189) I^2: 4%	Moderate	Summary estimate	(+) Compared with moderate statin therapy, intensive statin therapy reduces all-cause mortality in patients with recent acute coronary syndromes but not in patients with stable coronary heart disease.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Chronic ischaemic heart disease or Heart failure											
Le, 2016, 8817a	Heart failure with left ventricular dysfunction (New York Heart Association 1 to 4) and/or post-acute myocardial infarction with Killip scores between I and IV and indicated at least one assessment criteria	Aldosterone Antagonists [Canrenone, Spironolactone, Eplerenone, or Potassium Canrenoate] (20 per 100)	Placebo (21 per 100)	15786 (13)	63 ±6	Hospital admission (15 ±10 months)	No	RR: 0.93 (0.88 to 0.98) NNT: 67 (39 to 233) I²: 35%	Moderate	Summary estimate	(+) Aldosterone antagonists appear to be effective in reducing sudden cardiac death and other mortality events, compared with placebo or standard medication in patients with heart failure and/or after a myocardial infarction.
Le, 2016, 8817d	Heart failure with left ventricular dysfunction (New York Heart Association 1 to 4) and/or post-acute myocardial infarction with Killip scores between I and IV and indicated at least one assessment criteria	Aldosterone Antagonists [Canrenone, Spironolactone, Eplerenone, or Potassium Canrenoate] (12 per 100)	Control/placebo (15 per 100)	16730 (12)	64 ±4	Admission for cardiovascular issues (18 ±12 months)	No	RR: 0.82 (0.72 to 0.92) NNT: 37 (24 to 83) I²: 51%	Low	Summary estimate	(+) Aldosterone antagonists appear to be effective in reducing sudden cardiac death and other mortality events, compared with placebo or standard medication in patients with heart failure and/or after a myocardial infarction.
Chen, 2015, 8742a	Heart failure and/or previous myocardial infarction with preserved ejection fraction (>= 40%)	Aldosterone antagonists [Eplerenone or Spironolactone] (4.5 per 100)	Placebo or standard care (5.4 per 100)	4551 (3)	Unclear	Admission for heart failure (16 ±16 months)	Yes	RR: 0.83 (0.7 to 0.98) NNT: 108 (61 to 920) I²: 0%	Low	Summary estimate	(+) MRA treatment in PEF patients led to reduced hospitalization for heart failure, quantifiable improvements in quality of life and diastolic function, and reversal of cardiac remodeling, but did not provide any all-cause mortality benefit.
Fisher, 2014, 8769b	Heart failure and/or previous myocardial infarction	Bone marrow stem cells (4 per 100)	No cells (14 per 100)	198 (2)	58 ±4	Readmission for heart failure (36 ±34 months)	Yes	RR: 0.26 (0.07 to 0.94) NNT: 10 (8 to 122) I²: 0%	Low	Summary estimate	(?) This systematic review and meta-analysis found moderate quality evidence that BMSC treatment improves LVEF. Unlike in trials where BMSC were administered following acute myocardial infarction (AMI), we found some evidence for a potential beneficial clinical effect in terms of mortality and performance status in the long term (after at least one year) in people who suffer from chronic IHD and heart failure, although the quality of evidence was low.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Xie, 2016, 8916c	Heart failure with reduced ejection fraction or left ventricular dysfunction	Aldosterone antagonists [Canrenone, Eplerenone, or Spironolactone] (11 per 100)	Placebo (15 per 100)	11477 (4)	65 ±3	Admission for heart failure (18 ±5 months)	Yes	OR: 0.67 (0.53 to 0.86) NNT: 22 (15 to 54) I²: 74%	Moderate	Summary estimate	(+) Angiotensin Receptor-Neprilysin Inhibitors has the highest probability of being the most efficacious therapy for heart failure with reduced ejection fraction in reducing death and hospitalization for heart failure. Aldosterone receptor antagonists has the most favourable benefit–risk profile as an adjunct to background Angiotensin converting enzyme inhibitor and/or Angiotensin II receptor blocker therapy.
Le, 2016, 8817e	Heart failure with left ventricular dysfunction (New York Heart Association 1 to 4)	Aldosterone antagonists [Canrenone, Spironolactone, or Eplerenone] (11 per 100)	Control/placebo (14 per 100)	9040 (9)	66 ±3	Admission for cardiovascular issues (20 ±13 months)	No	RR: 0.79 (0.68 to 0.91) NNT: 33 (22 to 78) I²: 49%	Low	Sub-group by disease: Heart failure	(+) Aldosterone antagonists appear to be effective in reducing sudden cardiac death and other mortality events, compared with placebo or standard medication in patients with heart failure and/or after a myocardial infarction.
Xie, 2016, 8916a	Heart failure with reduced ejection fraction or left ventricular dysfunction	Angiotensin converting enzyme inhibitor [Ramipril, Captopril, Enalapril, or Trandolapril] (13 per 100)	Placebo (18 per 100)	12763 (5)	62 ±4	Admission for heart failure (32 ±12 months)	Yes	OR: 0.67 (0.61 to 0.74) NNT: 19 (16 to 25) I²: 0%	Moderate	Summary estimate	(+) Angiotensin Receptor-Neprilysin Inhibitors has the highest probability of being the most efficacious therapy for heart failure with reduced ejection fraction in reducing death and hospitalization for heart failure. Aldosterone receptor antagonists has the most favourable benefit–risk profile as an adjunct to background Angiotensin converting enzyme inhibitor and/or Angiotensin II receptor blocker therapy.
Xie, 2016, 8916b	Heart failure with reduced ejection fraction or left ventricular dysfunction	Angiotensin II receptor blocker [Candesartan or Valsartan] (18 per 100)	Placebo (23 per 100)	9878 (4)	65 ±2	Admission for heart failure (26 ±15 months)	Yes	OR: 0.72 (0.64 to 0.82) NNT: 19 (14 to 30) I²: 30%	Moderate	Summary estimate	(+) Angiotensin Receptor-Neprilysin Inhibitors has the highest probability of being the most efficacious therapy for heart failure with reduced ejection fraction in reducing death and hospitalization for heart failure. Aldosterone receptor antagonists has the most favourable benefit–risk profile as an adjunct to background Angiotensin converting enzyme inhibitor and/or Angiotensin II receptor blocker therapy.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Heran, 2012, 3275d	Heart failure with reduced left ventricular ejection fraction (<=40%)	Angiotensin II receptor blocker [Candesartan] (13 per 100)	Placebo (19 per 100)	2590 (3)	66 ±2	Admission for heart failure (14 ±17 months)	Yes	RR: 0.71 (0.61 to 0.82) NNT: 18 (14 to 30) I²: 0%	Low	Sub-group by disease severity: Patients with left ventricular ejection fractions less than or equal to 40%	(?) In patients with symptomatic HF and systolic dysfunction or with preserved ejection fraction, ARBs compared to placebo or ACEIs do not reduce total mortality or morbidity. Adding an ARB in combination with an ACEI does not reduce total mortality or total hospital admission but increases withdrawals due to adverse effects compared with ACEI alone.
Heran, 2012, 3275l	Heart failure, any ejection fraction	Angiotensin II receptor blocker and angiotensin converting enzyme inhibitor [ARB (Irbesartan or Candesartan) and ACE inhibitor (Enalapril or other)] (10 per 100)	Angiotensin converting enzyme inhibitors [Enalapril or other] (12 per 100)	8108 (4)	63 ±1	Admission for heart failure (18 ±15 months)	Yes	RR: 0.81 (0.74 to 0.89) NNT: 43 (31 to 74) I²: 35%	Very low	Summary estimate	(-) In patients with symptomatic HF and systolic dysfunction or with preserved ejection fraction, ARBs compared to placebo or ACEIs do not reduce total mortality or morbidity Adding an ARB in combination with an ACEI does not reduce total mortality or total hospital admission but increases withdrawals due to adverse effects compared with ACEI alone.
Kuenzli, 2010, 4206a	Congestive heart failure with left ventricular dysfunction	Angiotensin II receptor blocker and angiotensin converting enzyme inhibitor [ARB (Candesartan, Valsartan, Irbesartan, or other) and ACE inhibitor (Enalapril, Captopril, or other)] (19 per 100)	Angiotensin converting enzyme inhibitors [Enalapril, Captopril, or other] (24 per 100)	17895 (6)	64 ±2	Readmission for heart failure (23 ±12 months)	Yes	RR: 0.81 (0.72 to 0.91) NNT: 22 (15 to 47) I²: 57%	Moderate	Summary estimate	(-) Combination therapy with Angiotensin II receptor blocker and Angiotensin converting enzyme inhibitor inhibitors reduces admissions for heart failure in patients with congestive heart failure when compared to Angiotensin converting enzyme inhibitor therapy alone, but does not reduce overall mortality or all-cause hospitalization and is associated with more adverse events. Thus, based on current evidence, combination therapy with Angiotensin II receptor blockers and Angiotensin converting enzyme inhibitors may be reserved for patients who remain symptomatic on therapy with Angiotensin converting enzyme inhibitor inhibitors under strict monitoring for any signs of worsening renal function and/or symptomatic hypotension.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Jong, 2002, 3781d	New York Heart Association functional class 2 to 7	Angiotensin II receptor blocker and angiotensin converting enzyme inhibitor [ARB (Candesartan, Irbesartan, or Valsartan) and an ACE inhibitor] (4.8 per 100)	Angiotensin converting enzyme inhibitors (6.4 per 100)	5560 (3)	Unclear	Admission for heart failure (12 ±10 months)	Yes	OR: 0.74 (0.64 to 0.86) NNT: 63 (45 to 118) I²: p>0.1 heterogeneity	Moderate	Sub-group by intervention: Combination therapy of Angiotensin receptor blockers and angiotensin converting enzyme inhibitors vs. angiotensin converting enzyme inhibitors alone	(-) This meta-analysis cannot confirm that Angiotensin II receptor blockers are superior in reducing all-cause mortality or heart failure hospitalization in patients with symptomatic heart failure, particularly when compared with Angiotensin converting enzyme inhibitors. However, the use of Angiotensin II receptor blockers as monotherapy in the absence of Angiotensin converting enzyme inhibitors or as combination therapy with Angiotensin converting enzyme inhibitors appears promising.
Kuenzli, 2010, 4206c	Heart failure with left ventricular dysfunction	Angiotensin II receptor blocker and angiotensin converting enzyme inhibitor [ARB (Candesartan, Valsartan, or Irbesartan) and ACE inhibitor (Enalapril or other)] (19 per 100)	Angiotensin converting enzyme inhibitors [ACE inhibitor Enalapril or other] (23 per 100)	8049 (4)	64 ±2	Readmission for heart failure (22 ±14 months)	Yes	RR: 0.81 (0.72 to 0.91) NNT: 23 (15 to 48) I²: 23%	Moderate	Sub-group by disease: Excluding 2 trials with only acute myocardial infarction patients	(-) Combination therapy with Angiotensin II receptor blockers and angiotensin converting enzyme inhibitors reduces admissions for heart failure in patients with congestive heart failure when compared to angiotensin converting enzyme inhibitor therapy alone, but does not reduce overall mortality or all-cause hospitalization and is associated with more adverse events. Thus, based on current evidence, combination therapy with angiotensin II receptor blockers and angiotensin converting enzyme inhibitors may be reserved for patients who remain symptomatic on therapy with angiotensin converting enzyme inhibitors under strict monitoring for any signs of worsening renal function and/or symptomatic hypotension.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Makani, 2013, 4838b	Heart failure with reduced ejection fraction (less than or equal to 40%), New York Heart Association class II-IV, wth or without haemodialysis	Angiotensin II receptor blocker and angiotensin converting enzyme inhibitor [ARB (Candesartan, Telmisartan, or Valsartan) and an ACE inhibitor] (37 per 100)	Angiotensin converting enzyme inhibitors (48 per 100)	7890 (3)	63 ±1	Admission for heart failure (36 ±10 months)	Yes	RR: 0.77 (0.68 to 0.88) NNT: 9 (7 to 18) I²: 66%	Moderate	Sub-group by disease: Heart failure	(-) Although dual blockade of the renin-angiotensin system may have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy. The risk to benefit ratio argues against the use of dual therapy.
Lipinski, 2009, 4615e	Heart failure with reduced ejection fration (less than or equal to 45%) or heart failure hospitalisation in past year	Atorvastatin (10 per 100)	Placebo (28 per 100)	472 (6)	57 ±12	Admission for heart failure (13 ±10 months)	Yes	OR: 0.30 (0.18 to 0.49) NNT: 6 (5 to 6) I²: 0%	Very low	Summary estimate	(+) In conclusion, meta-analysis of randomized controlled trials demonstrated that statins are safe and improve LVEF and decrease hospitalization for worsening HF.
Zhang, 2011, 8604f	Chronic systolic cardiac insufficiency	Atorvastatin (9 per 100)	Placebo or nothing (19 per 100)	524 (8)	55 ±10	Readmission for heart failure (10 ±10 months)	Yes	RR: 0.51 (0.33 to 0.81) NNT: 11 (8 to 28) I²: 0%	Low	Sub-group by intervention: Atorvastatin	(?) Although statin has little impact on clinical outcomes in overall CHF patients, statin administration if needed is feasible to CHF patients, and the treatment might be effective when restricted to specific statins or populations.
Liu, 2014, 4629a	Heart failure with preserved ejection fraction (an EF greater than or equal to 40%)	Beta-blocker [Nebivolol or Carvedilol] (20 per 100)	No beta-blockers (28 per 100)	888 (2)	74 ±3	Hospital admission (30 ±12 months)	No	RR: 0.71 (0.55 to 0.93) NNT: 12 (8 to 51) I²: 7%	Moderate	Summary estimate	(?) The beta-blockers treatment for the patients with heart failure with preserved ejection fraction was associated with a lower risk of all-cause mortality, but not with a lower risk of hospitalization. These finding were mainly obtained from observational studies, and further investigations are needed to make an assertion.
Brophy, 2001, 1021	Heart failure with reduced ejection fraction	Beta-blocker [Metoprolol, Bucindolol, Bisoprolol, or Carvedilol] (7 per 100)	Placebo (12 per 100)	10076 (22)	57 ±6	Admission for heart failure (9 ±6 months)	Yes	OR: 0.64 (0.53 to 0.79) NNT: 24 (18 to 43) I²: Unclear	Moderate	Summary estimate	(+) b-Blocker therapy is associated with clinically meaningful reductions in mortality and morbidity in patients with stable congestive heart failure and should be routinely offered to all patients similar to those included in trials.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Fisher, 2015, 8770b	Heart failure secondary to ischemic and nonischemic cardiomyopathy	Bone marrow stem cells (4 per 100)	No cells (10 per 100)	173 (5)	Unclear	Readmission for heart failure (26 ±28 months)	Yes	RR: 0.39 (0.22 to 0.7) NNT: 16 (13 to 33) I²: 0%	Low	Summary estimate	(?) This study shows evidence that autologous cell therapy may be beneficial for patients having HF, but further evidence is required.
Hood, 2014, 3415	Normal sinus rhythm with reduced or preserved ejection fractions	Digoxin (9 per 100)	Placebo (12 per 100)	7262 (4)	61 ±3	Hospital admission (12 ±17 months)	No	OR: 0.68 (0.61 to 0.75) NNT: 28 (23 to 37) I²: 29%	High	Summary estimate	(?) The literature indicates that digitalis may have a useful role in the treatment of patients with heart failure who are in normal sinus rhythm. New trials are needed to elucidate the importance of the dosage of digitalis and its usefulness in the era of beta-blockers and other agents shown to be effective in treating heart failure
Ziff, 2015, 8931a	Heart failure, any ejection fraction	Digoxin (63 per 100)	Placebo (67 per 100)	7788 (2)	65 ±2	Hospital admission (37 months)	No	RR: 0.94 (0.9 to 0.99) NNT: 25 (15 to 150) I²: Unclear	Moderate	Summary estimate	(+) Digoxin is associated with a neutral effect on mortality in randomised trials and a lower rate of admissions to hospital across all study types. Regardless of statistical analysis, prescription biases limit the value of observational data.
Gandhi, 2014, 2599a	Acute decompensation	Hypertonic saline solution plus intravenous furosemide (19 per 100)	Furosemide alone, with or without dietary restriction of sodium (37 per 100)	2032 (4)	74 ±0.4	Readmission for heart failure (30 ±28 months)	Yes	RR: 0.50 (0.33 to 0.76) NNT: 5 (4 to 11) I²: 61%	Moderate	Summary estimate	(?) The results of this meta-analysis demonstrate that in patients with advanced congestive heart failure concomitant hypertonic saline administration improved weight loss, preserved renal function, and decreased length of hospitalization, mortality and heart failure rehospitalization. Pending further validation, there is promise for hypertonic saline as an advanced therapy for the management of acute advanced congestive heart failure.
Bonsu, 2016, 8729a	Heart failure with reduced ejection fraction (<40%)	Lipophilic statin [Atorvastatin, Simvastatin, Pitavastatin] (13 per 100)	Placebo (24 per 100)	1165 (9)	57 ±9	Admission for heart failure (13 ±12 months)	Yes	OR: 0.49 (0.36 to 0.67) NNT: 9 (7 to 15) I²: 38%	High	Summary estimate	(+) Lipophilic statin treatment shows significant decreases in all-cause mortality, cardiovascular mortality and hospitalization for worsening heart failure compared with rosuvastatin treatment. This meta-analysis provides preliminary evidence that lipophilic statins offer better clinical outcomes in heart failure till data from head to head comparisons are available.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Liu, 2014, 8826a	Heart failure with reduced ejection fraction (left ventricular ejection fraction less than or equal to 45%)	Lipophilic statin [Atorvastatin, or Simvastatin, Pitavastatin] (6 per 100)	Placebo or no statin (10 per 100)	1087 (9)	58 ±10	Admission for heart failure (13 ±12 months)	Yes	RR: 0.60 (0.45 to 0.80) NNT: 25 (18 to 50) I²: 11%	Moderate	Summary estimate	(?) It appears that further studies are needed to determine if lipophilic statins are beneficial for heart failure patients.
Zhang, 2016, 8922l	Heart failure with preserved ejection fraction (greater than or equal to 40%)	Renin–angiotensin–aldosterone system inhibitors [Perindopril, Eplerenone, Irbesartan, Spironolactone, Irbesartan + diuretics, Ramipril + diuretics, Candesartan, or Quinapril] (12 per 100)	Placebo (14 per 100)	11765 (8)	72 ±4	Admission for heart failure (20 ±17 months)	Yes	RR: 0.89 (0.82 to 0.97) NNT: 66 (41 to 244) I²: 0%	Low	Summary estimate	(?) This meta-analysis shows that RAAS inhibitors could significantly reduce heart failure-related hospitalization and improve the E/e' index in patients with HFpEF. Further large-scale randomized controlled trials, especially on diastolic function, are needed to confirm the effects of RAAS inhibitors in patients with HFpEF.
Lipinski, 2009, 4615d	Heart failure with reduced ejection fraction (less than or equal to 45%) or heart failure hospitalisation in past year	Statin [Atorvastatin, Rosuvastatin, or Simvastatin] (19 per 100)	Placebo (25 per 100)	10193 (10)	60 ±11	Admission for heart failure (17 ±15 months)	Yes	OR: 0.67 (0.50 to 0.90) NNT: 15 (9 to 51) I²: 64%	Low	Summary estimate	(+) In conclusion, meta-analysis of randomized controlled trials demonstrated that statins are safe and improve LVEF and decrease hospitalization for worsening HF.
Zhang, 2011, 8604b	Systolic insufficiency	Statin [Atorvastatin, Rosuvastatin, or Simvastatin] (12 per 100)	Placebo or nothing in addition to contemporary standard therapy of CHF (19 per 100)	5561 (10)	59 ±10	Readmission for heart failure (15 ±15 months)	Yes	RR: 0.66 (0.44 to 0.98) NNT: 16 (10 to 270) I²: 29%	Low	Sub-group for robustness to trial exclusion: GISSI-HF study excluded (highest weighted)	(?) Although statin has little impact on clinical outcomes in overall CHF patients, statin administration if needed is feasible to CHF patients, and the treatment might be effective when restricted to specific statins or populations.
Zhou, 2014, 8928	Left ventricular ejection fraction less than or equal to 50%	Trimetazidine (7 per 100)	Placebo (15 per 100)	156 (4)	67 ±8	Admission for cardiovascular issues (7 ±4 months)	No	RR: 0.43 (0.21 to 0.91) NNT: 11 (8 to 72) I²: 0%	Very low	Summary estimate	(+) TMZ treatment in CHF patients may improve clinical symptoms and cardiac function, reduce hospitalization for cardiac causes, and decrease serum levels of BNP and CRP.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Other pulmonary heart diseases											
Coeytaux, 2014, 8747a	Pulmonary arterial hypertension	Endothelin receptor antagonist (5 per 100)	Placebo (13 per 100)	606 (3)	Unclear	Hospital admission (Range 2 to 4 months)	No	OR: 0.34 (0.17 to 0.69) NNT: 12 (9 to 27) I²: 0%	Low	Summary estimate	(+) Although no studies were powered to detect a mortality reduction, monotherapy was associated with improved 6MWD and reduced hospitalization rates. Our findings also suggest an improvement in 6MWD when a second drug is added to monotherapy.
Coeytaux, 2014, 8747b	Pulmonary arterial hypertension	Phosphodiesterase inhibitors (5 per 100)	Placebo (9 per 100)	1011 (4)	Unclear	Hospital admission (Range 2 to 4 months)	No	OR: 0.48 (0.25 to 0.91) NNT: 22 (15 to 132) I²: 0%	Low	Summary estimate	(+) Although no studies were powered to detect a mortality reduction, monotherapy was associated with improved 6MWD and reduced hospitalization rates. Our findings also suggest an improvement in 6MWD when a second drug is added to monotherapy.
Diseases of the digestive system											
Crohn disease [regional enteritis] or Ulcerative colitis											
Costa, 2013, 1629a	Crohn disease or ulcerative colitis	Infliximab [Bosentan or Ambrisentan] (19 per 100)	Placebo (31 per 100)	1736 (2)	38 ±2	Hospital admission (17 ±13 months)	No	OR: 0.51 (0.4 to 0.65) NNT: 8 (6 to 12) I²: 0%	Moderate	Summary estimate	(+) The best evidence available points toward a reduction of the risk of hospitalization and major surgery requirement in patients with inflammatory bowel disease treated with infliximab. This impact is clinically and economically relevant because hospitalization and surgery are considered to be markers of disease severity and significantly contribute to the total direct costs associated with inflammatory bowel disease.
Hepatic failure											
Saab, 2015, 8884a	Hepatic encephalopathy	Probiotics [Lactobacilli, Bifidobacteria, or Streptococcus thermophiles] (18 per 100)	No treatment, placebo, or lactulose (30 per 100)	276 (4)	Range 16 or older	Hospital admission (7 ±4 months)	No	OR: 0.53 (0.33 to 0.86) NNT: 9 (6 to 33) I²: 0%	Moderate	Summary estimate	(+) Overall the use of probiotics was more effective in decreasing hospitalization rates, improving minimal hepatic encephalopathy and preventing progression to overt hepatic encephalopathy in patients with underlying minimal hepatic encephalopathy than placebo, but similar to that seen with lactulose. The use of probiotics did not affect mortality rates.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Ulcerative colitis											
Lopez, 2015, 8829a	Ulcerative colitis	Tumour necrosis factor antagonists (anti-TNF) (12 per 100)	Placebo (17 per 100)	1691 (2)	Unclear	Admissions for ulcerative colitis (Unclear)	No	RR: 0.71 (0.56 to 0.9) NNT: 20 (13 to 58) I²: 0%	Moderate	Summary estimate	(+) Anti-tumour necrosis factor therapy is more effective than placebo to induce and maintain clinical remission and mucosal healing. Both infliximab and adalimumab are associated with less hospitalisations. Infliximab reduces the need for colectomy. Anti-tumour necrosis factor therapy does not increase the risk of adverse events.
Calculus of kidney and ureter											
Campschroer, 2014, 1164	Ureteral stones	Alpha-blocker [Tamsulosin or Doxazosin] (13 per 100)	Standard therapy (38 per 100)	313 (4)	36 ±6	Hospital admission (23 ±7 days)	No	RR: 0.35 (0.13 to 0.97) NNT: 4 (3 to 88) I²: 64%	Very low	Summary estimate	(+) The use of alpha-blockers in patients with ureteral stones results in a higher stone-free rate and a shorter time to stone expulsion. Alpha blockers should therefore be offered as part of medical expulsive therapy as one of the primary treatment modalities.
Disorders resulting from impaired renal tubular function											
Garside, 2007, 2640b	Hyperparathyroidism secondary to end-stage renal disease in patients on dialysis	Cinacalcet (12 per 100)	Placebo (20 per 100)	1184 (4)	54	Admission for cardiovascular issues (8 ±3 months)	No	RR: 0.61 (0.43 to 0.86) NNT: 13 (9 to 36) I²: Unclear	Low	Summary estimate	(?) Cinacalcet in addition to standard care is more effective than placebo plus standard care at reducing PTH levels without compromising calcium levels. However, there is limited information about the impact of this reduction on patient-relevant clinical outcomes. Given the short follow-up in the trials, it is unclear how data should be extrapolated to the long term.
Systemic lupus erythematosus											
Moore, 2006, 5371	Systemic lupus erythematosus	Mycophenolate mofetil (2 per 100)	Cyclophosphamide and steroid (19 per 100)	220 (2)	35 ±4	Admission for drug-related adverse events (Range 3 to 84 months)	No	RR: 0.10 (0.04 to 0.50) NNT: 6 (6 to 11) I²: Unclear	Very low	Summary estimate	(?) The results form a basis on which to plan future studies and provide a guide for the use of MMF in lupus nephritis until results of larger studies are available. At least one such study is under way.
Multiple sclerosis											
La Mantia, 2010, 4260	Multiple sclerosis	Glatiramer acetate (12 per 100)	Placebo (21 per 100)	489 (2)	34 ±0.3	Hospital admission (23 ±19 months)	No	RR: 0.60 (0.40 to 0.91) NNT: 12 (8 to 54) I²: 0%	Moderate	Summary estimate	(?) Glatiramer acetate did show a partial efficacy in relapsing remitting multiple sclerosis in term of relapse - related clinical outcomes, without any significant effect on clinical progression of disease measured as sustained disability. The drug is not effective in progressive multiple sclerosis patients.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Diseases of the respiratory system											
Asthma / Status Asmaticus											
Rodrigo, 2005, 6568a	Acute asthma	Beta-2-agonists and anticholinergics [Glycopyrrolate, Ipratropium bromide or Oxitropium bromide] and B_2-agonists [Salbutamol] (19 per 100)	Beta-2-agonists [Salbutamol] (27 per 100)	1556 (9)	Range 18 to 55	Hospital admission (Length of emergency department stay)	No	RR: 0.68 (0.53 to 0.86) NNT: 11 (8 to 26) I²: 14%	Moderate	Summary estimate	(+) This review strongly suggests that the addition of multiple doses of inhaled ipratropium bromide to b2 agonists is indicated as the standard treatment in children, adolescents, and adults with moderate to severe exacerbations of asthma in the emergency setting.
Edmonds, 2012, 2159	Acute asthma	Early use of inhaled corticosteroids in the emergency department [Beclomethasone, Flunisolide, or Fluticasone] (11 per 100)	Placebo (26 per 100)	377 (5)	38 ±8	Hospital admission (Unclear)	No	OR: 0.35 (0.20 to 0.60) NNT: 7 (5 to 12) I²: 0%	Moderate	Summary estimate	(?) Inhaled corticosteroid therapy reduces hospital admissions in patients with acute asthma who are not treated with oral or intravenous corticosteroids. They may also reduce admissions when they are used in addition to systemic corticosteroids; however, the most recent evidence is conflicting. There is insufficient evidence that inhaled corticosteroid therapy results in clinically important changes in pulmonary function or clinical scores when used in acute asthma in addition to systemic corticosteroids. Also, there is insufficient evidence that inhaled corticosteroid therapy can be used in place of systemic corticosteroid therapy when treating acute asthma. Further research is needed to clarify the most appropriate drug dosage and delivery device, and to define which patients are most likely to benefit from inhaled corticosteroid therapy. Use of similar measures and reporting methods of lung function, and a common, validated, clinical score would be helpful in future versions of this meta-analysis.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Asthma / Status Asmaticus											
Rowe, 2000, 6670	Acute asthma	Intravenous magnesium sulfate (45 per 100)	Placebo (88 per 100)	422 (3)	Range 18 to 70	Hospital admission (Length of emergency department stay)	No	OR: 0.11 (0.03 to 0.34) NNT: 2 (1 to 6) I²: Unclear	Low	Summary estimate	(+) Current evidence does not clearly support routine use of intravenous magnesium sulfate in all patients with acute asthma presenting to the ED. However, magnesium sulfate appears to be safe and beneficial for patients who present with severe acute asthma. Practice guidelines need to be changed to reflect these results.
Kew, 2014, 4002h	Acute asthma	Intravenous magnesium sulfate (27 per 100)	Placebo (34 per 100)	1437 (8)	Unclear	Hospital admission (3 ±1 hours)	No	OR: 0.72 (0.57 to 0.91) NNT: 14 (9 to 48) I²: 35%	High	Sub-group by study quality: Removal of studies at high risk of bias for blinding	(+) This review provides evidence that a single infusion of 1.2 g or 2 g intravenous magnesium sulfate over 15 to 30 minutes reduces hospital admissions and improves lung function in adults with acute asthma who have not responded sufficiently to oxygen, nebulised short-acting beta2- agonists and inrtavenous corticosteroids. Differences in the ways the trials were conducted made it difficult for the review authors to assess whether severity of the exacerbation or additional co-medications altered the treatment effect of intravenous magnesium sulfate. Limited evidence was found for other measures of benefit and safety. Studies conducted in these populations should clearly define baseline severity parameters and systematically record adverse events. Studies recruiting participants with exacerbations of varying severity should consider subgrouping results on the basis of accepted severity classifications.
Jaeschke, 2008, 3639f	Chronic asthma using inhaled corticosteroids	Long acting beta agonists [Formoterol] with inhaled corticosteroids (0.3 per 100)	Inhaled corticosteroids [same dose as intervention] (0.7 per 100)	5371 (8)	41 ±4	Admission for asthma (Unclear)	Yes	OR: 0.49 (0.25 to 0.95) NNT: 289 (196 to 2960) I²: 0%	Low	Sub-group by intervention: Formoterol only and ICS dose same in both groups	(?) In patients with asthma using ICS, LABA did not increase the risk of asthma-related hospitalizations. There were very few asthma-related deaths and intubations, and events were too infrequent to establish LABA's relative effect on these outcomes.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Asthma / Status Asmaticus											
Jaeschke, 2008, 3640d	Chronic asthma using inhaled corticosteroids	Long acting beta agonists [Formoterol] with inhaled corticosteroids (0.47 per 100)	Inhaled corticosteroids [same dose as intervention] (1 per 100)	5334 (10)	Unclear	Admission for asthma (Unclear)	Yes	OR: 0.46 (0.23 to 0.93) NNT: 183 (128 to 1416) I²: Unclear	Low	Sub-group by intervention: Same dose of ICS in intervention and control groups	(?) In patients with asthma using inhaled corticosteroids formoterol decreased the risk of asthma‐related hospitalizations. There were too few asthma‐related deaths and intubations to establish formoterol's relative impact on these outcomes.
Jaeschke, 2008, 3640b	Chronic asthma using inhaled corticosteroids	Long acting beta agonists [Formoterol] with inhaled corticosteroids (0.6 per 100)	Inhaled corticosteroids alone [some same dose, some higher dose] (1 per 100)	1063 (16)	Unclear	Admission for asthma (Unclear)	Yes	OR: 0.59 (0.37 to 0.93) NNT: 228 (148 to 1338) I²: Unclear	Low	Summary estimate	(?) In patients with asthma using inhaled corticosteroids formoterol decreased the risk of asthma‐related hospitalizations. There were too few asthma‐related deaths and intubations to establish formoterol's relative impact on these outcomes.
Shan, 2013, 7029b	Acute asthma	Nebulized magnesium sulfate (12 per 100)	Control (18 per 100)	383 (6)	Range 18 to 65	Admission for asthma (Length of emergency department stay)	Yes	RR: 0.63 (0.43 to 0.92) NNT: 15 (10 to 68) I²: 0%	Moderate	Summary estimate	(+) The use of intravenous magnesium sulfate, in addition to b2-agonists and systemic steroids, in the treatment of acute asthma appears to produce benefits with respect to improve pulmonary function and reduce the number of hospital admissions for children, and only improve pulmonary function for adults. However, the use of nebulized magnesium sulfate just appears to produce benefits for adults.
Rowe, 2007, 6677	Acute asthma	Oral or Intramuscular corticosteroid (CS) [Methylprednisolone or Dexamethasone] (4 per 100)	Placebo (11 per 100)	184 (3)	Range 15 to 45	Hospital admission (9±3 days)	No	RR: 0.35 (0.12 to 0.95) NNT: 14 (11 to 185) I²: 0%	Low	Summary estimate	(+) A short course of corticosteroids following assessment for an asthma exacerbation significantly reduces the number of relapses to additional care, hospitalizations and use of short-acting beta2-agonist without an apparent increase in side effects. Intramuscular and oral corticosteroids are both effective.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Asthma / Status Asmaticus											
Rodrigo, 1999, 6564a	Acute asthma	Parenteral or inhaled corticosteroids [Methylprednisolone] (12 per 100)	Placebo in the emergency department (18 per 100)	480 (6)		Admission for asthma (Range of 2 to 6 hours in the emergency department)	Yes	RR: 0.68 (0.47 to 0.99) NNT: 17 (10 to 556) I²:	Low	Summary estimate	(?) This evidence-based evaluation suggests that the administration of parenteral CCSs to the patient on arrival at the emergency department (ED) neither improves airflow obstruction nor reduces the need for hospitalization. Parenteral CCSs probably require > 6 to 24 h to begin to act. Comprehensible conclusions about admission rates in the ED setting are difficult to make. At the 3-h assessment, only high doses of inhaled CCSs (in one study) significantly improved pulmonary function compared with placebo. IV and oral CCSs appear to have equivalent effects, and there is a tendency toward improvement in pulmonary function with medium or high doses.
Other chronic obstructive pulmonary disease											
Ni, 2014, 8850a	Moderate to severe chronic obstructive pulmonary disease	Aclidinium bromide (2 per 100)	Placebo (3 per 100)	5624 (10)	64 ±3	Admission for chronic obstructive pulmonary disease (14 ±8 months)	Yes	OR: 0.64 (0.46 to 0.88) NNT: 106 (70 to 321) I²: 0%	High	Summary estimate	(+) Aclidinium is associated with improved quality of life and reduced hospitalisations due to severe exacerbations in patients with moderate to severe stable chronic obstructive pulmonary disease compared to placebo. Overall, aclidinium did not significantly reduce mortality, serious adverse event or exacerbations requiring oral steroids or antibiotics, or both. Currently, the available data are insufficient and of very low quality in comparisons of the efficacy of aclidinium versus tiotropium. The efficacy of aclidinium versus long acting beta agonists cannot be assessed due to inaccurate data. Thus additional trials are recommended to assess the efficacy and safety of aclidinium compared to other long acting muscarinic antagonists or long acting beta agonists.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Other chronic obstructive pulmonary disease											
Zou, 2016, 8933a	Moderate to severe chronic obstructive pulmonary disease	Aclidinium Bromide (2 per 100)	Placebo (3 per 100)	4788 (5)	63 ±1	Admission for chronic obstructive pulmonary disease (7 ±4 months)	Yes	OR: 0.64 (0.47 to 0.89) NNT: 103 (7 to 339) I²: 17%	Moderate	Summary estimate	(+) Aclidinium reduced the incidence of exacerbation-related hospitalizations and improved quality of life, chronic obstructive pulmonary disease symptoms and pulmonary function. In addition, aclidinium did not increase the incidence of non-fatal serious adverse events, cardiac adverse events, or chronic obstructive pulmonary disease exacerbations and was not associated with increased mortality.
Nannini, 2013, 5533g	Moderate to severe chronic obstructive pulmonary disease	Combined inhalers with Mometasone Furoate and Formoterol (2 per 100)	Placbeo (4 per 100)	894 (2)	61 ±3	Admission for chronic obstructive pulmonary disease (12 months)	Yes	OR: 0.36 (0.15 to 0.86) NNT: 38 (28 to 177) I²: 0%	Low	Sub-group by intervention: Mometasone/formoterol 200/10 mcg	(?) Combined inhaler therapy led to around a quarter fewer COPD exacerbations than were seen with placebo. A significant reduction in all-cause mortality was noted, but this outcome was dominated by one trial (TORCH), emphasising the need for further trials of longer duration. Increased risk of pneumonia is a concern; however, this did not translate into increased exacerbations, hospitalisations or deaths.
Kew, 2013, 4003e	Moderate to severe chronic obstructive pulmonary disease	Formoterol (3 per 100)	Placebo (4 per 100)	2614 (6)	63 ±2	Admission for chronic obstructive pulmonary disease (14 ±12 months)	Yes	OR: 0.73 (0.54 to 0.99) NNT: 91 (53 to 2488) I²: 0%	Low	Summary estimate	(+) Moderate-quality evidence from 26 studies showed that inhaled long-acting beta2-agonists are effective over the medium and long term for patients with moderate to severe chronic obstructive pulmonary disease. Their use is associated with improved quality of life and reduced exacerbations, including those requiring hospitalisation. Overall, findings showed that inhaled long-acting beta2-agonists did not significantly reduce mortality or serious adverse events.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Other chronic obstructive pulmonary disease											
Kew, 2013, 4003a	Moderate to severe chronic obstructive pulmonary disease	Long-acting beta2-agonists [Formoterol or Salmeterol] (4 per 100)	Placebo (5 per 100)	3804 (7)	62 ±2	Admission for chronic obstructive pulmonary disease (9 ±3 months)	Yes	OR: 0.73 (0.56 to 0.95) NNT: 77 (47 to 420) I²: 10%	Moderate	Summary estimate	(+) Moderate-quality evidence from 26 studies showed that inhaled long-acting beta2-agonists are effective over the medium and long term for patients with moderate to severe chronic obstructive pulmonary disease. Their use is associated with improved quality of life and reduced exacerbations, including those requiring hospitalisation. Overall, findings showed that inhaled long-acting beta2-agonists did not significantly reduce mortality or serious adverse events.
Cheyne, 2015, 8744d	Moderate to severe chronic obstructive pulmonary disease	Tiotropium (1 per 100)	Ipratropium bromide (2 per 100)	1073 (2)	64 ±0.2	Admission for chronic obstructive pulmonary disease (6 ±5 months)	Yes	OR: 0.56 (0.31 to 0.99) NNT: 102 (65 to 4551) I²: 0%	Moderate	Summary estimate	(+) This review shows that tiotropium treatment, when compared with ipratropium bromide, was associated with improved lung function, fewer hospital admissions (including those for exacerbations of chronic obstructive pulmonary disease), fewer exacerbations of chronic obstructive pulmonary disease and improved quality of life. There were both fewer serious adverse events and disease specific events in the tiotropium group, but no significant difference in deaths with ipratropium bromide when compared to tiotropium. Thus, tiotropium appears to be a reasonable choice (instead of ipratropium bromide) for patients with stable chronic obstructive pulmonary disease, as proposed in guidelines. A recent large double-blind trial of the two delivery devices found no substantial difference in mortality using 2.5 µg or 5 µg of tiotropium via Respimat in comparison to 18 µg via Handihaler.
Yohannes, 2011, 8511a	Moderate to severe chronic obstructive pulmonary disease	Tiotropium (7 per 100)	Placebo (8 per 100)	11844 (9)	65 ±2	Admission for chronic obstructive pulmonary disease (15 ±15 months)	Yes	OR: 0.89 (0.80 to 0.98) NNT: 120 (65 to 663) I²: 18%	Low	Summary estimate	(+) In stable COPD, tiotropium showed superior efficacy in improving quality of life and dyspnea, compared to placebo and ipratropium. However, tiotropium's differences with salmeterol were less clear.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Other chronic obstructive pulmonary disease											
Chong, 2012, 1438a	Moderate to severe chronic obstructive pulmonary disease	Tiotropium (3.8 per 100)	Long acting beta-2-agonist (4.8 per 100)	9267 (4)	63 ±1	Admission for chronic obstructive pulmonary disease (7 ±4 months)	Yes	OR: 0.87 (0.77 to 0.99) NNT: 183 (103 to 2390) I²: 0%	Moderate	Summary estimate	(?) In people with chronic obstructive pulmonary disease, the evidence is equivocal as to whether or not tiotropium offers greater benefit than long acting beta-2-agonists in improving quality of life; however, this is complicated by differences in effect among the long acting beta-2-agonist types. Tiotropium was more effective than long acting beta-2-agonists as a group in preventing chronic obstructive pulmonary disease exacerbations and disease-related hospitalisations, although there were no statistical differences between groups in overall hospitalisation rates or mortality during the study periods. There were fewer serious adverse events and study withdrawals recorded with tiotropium compared with long acting beta-2-agonists. Symptom improvement and changes in lung function were similar between the treatment groups. Given the small number of studies to date, with high levels of heterogeneity among them, one approach may be to give a chronic obstructive pulmonary disease patient a substantial trial of tiotropium, followed by a long acting beta-2-agonist (or vice versa), then to continue prescribing the long-acting bronchodilator that the patient prefers. Further studies are needed to compare tiotropium with different long acting beta-2-agonists, which are currently ongoing. The available economic evidence indicates that tiotropium may be cost-effective compared with salmeterol in several specific settings, but there is considerable uncertainty around this finding.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Other chronic obstructive pulmonary disease											
Karner, 2014, 8692e	Moderate to severe chronic obstructive pulmonary disease	Tiotropium with soft mist inhaler (6 per 100)	Placebo (7 per 100)	6522 (3)	65 ±1	Admission for chronic obstructive pulmonary disease (9 ±5 months)	Yes	OR: 0.82 (0.68 to 0.99) NNT: 87 (49 to 1590) I²: 0%	Moderate	Sub-group by intervention: Soft mist inhaler	(+) This review shows that tiotropium treatment was associated with a significant improvement in patients' quality of life and it reduced the risk of exacerbations, with a number needed to treat to benefit (NNTB) of 16 to prevent one exacerbation. Tiotropium also reduced exacerbations leading to hospitalisation but no significant difference was found for hospitalisation of any cause or mortality. Thus, tiotropium appears to be a reasonable choice for the management of patients with stable chronic obstructive pulmonary disease, as proposed in guidelines. The trials included in this review showed a difference in the risk of mortality when compared with placebo depending on the type of tiotropium delivery device used. However, these results have not been confirmed in a recent trial when 2.5mcg or 5mcg of tiotropium via Respimat was used in a direct comparison to the 18 mcg Handihaler.
Other chronic obstructive pulmonary disease; Simple and mucopurulent chronic bronchitis											
Poole, 2015, 8867	Chronic obstructive pulmonary disease or Chronic bronchitis	Mucolytic [N-acetylcysteine, Erdosteine, or Carbocysteine] (19 per 100)	Placebo (25 per 100)	1788 (4)	66 ±12	Hospital admission (17 ±13 months)	No	OR: 0.68 (0.52 to 0.89) NNT: 15 (10 to 47) I²: 58%	Moderate	Summary estimate	(+) In participants with chronic bronchitis or chronic obstructive pulmonary disease, we are moderately confident that treatment with mucolytics may produce a small reduction in acute exacerbations and a small effect on overall quality of life. Our confidence in the results is reduced by the fact that effects on exacerbations shown in early trials were larger than those reported by more recent studies, possibly because the earlier smaller trials were at greater risk of selection or publication bias, thus benefits of treatment may not be as great as was suggested by previous evidence.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Endocrine, nutritional and metabolic diseases											
Malnourishment											
Stratton, 2013, 7484a	Malnourished patients being discharged from the hospital to the community	Oral nutritional supplements [Nova source liquid, Clinutren Soup and Clinutren, Fortisip, Fresubin, or Fortifresh] (21 per 100)	Usual care or dietary counselling (31 per 100)	852 (6)	Range 51 to 92	Readmission (13 ±4 months)	No	OR: 0.59 (0.43 to 0.8) NNT: 10 (7 to 22) I²: Unclear	Moderate	Summary estimate.	(+) This systematic review shows that oral nutritional supplements significantly reduce hospital (re)admissions, particularly in older patient groups, with economic implications for health care.
Cawood, 2012, 1264	Malnourished patients or patients at-risk of disease-related malnutrition in hospital or community settings	High protein oral nutritional supplements (31 per 100)	Placebo or usual care (44 per 100)	546 (2)	65 ±17	Readmission (5 ±2 months)	No	OR: 0.59 (0.41 to 0.84) NNT: 8 (5 to 24) I²: 0%	Low	Summary estimate.	(+) The systematic review and meta-analysis provides evidence that high protein supplements produce clinical benefits, with economic implications.
Factors influencing health status and contact with health services											
Care involving dialysis											
James, 2008, 3657	Patients on long term hemodialysis with a central venous catheter	Topical prophylactic antibiotics [Mupirocin or Polysporin triple-antibiotic ointment] (1 per 100)	No antibiotic therapy (22 per 100)	305 (2)	57 ±13	Admission for infection (3 ±3 months)	Yes	rR: 0.06 (0.03 to 0.12) NNT: 6 (5 to 8) I²: Unclear	Moderate	Summary estimate	(+) Both topical and intraluminal antibiotics reduced the rate of bacteremia as well as the need for catheter removal secondary to complications. Whether these strategies will lead to antimicrobial resistance and loss of efficacy over longer periods remains unclear.
Other medical care											
Renner, 2012, 6442a	Breast cancer patients receiving chemotherapy	Primary prophylactic colony-stimulating factors [Granulocyte colony-stimulating factors or Granulocyte-macrophage colony-stimulating factors] (1 per 100)	Placebo or no treatment (10 per 100)	1149 (4)	Range 21 to 88	Admission for febrile neutropenia with antibiotics (19 ±4 months)	No	RR: 0.13 (0.06 to 0.3) NNT: 12 (11 to 15) I²: 0%	Low	Summary estimate	(?) In patients with breast cancer receiving chemotherapy, CSFs have shown evidence of benefit in the prevention of FN. There is evidence, though less reliable, of a decrease of all-cause mortality during chemotherapy and a reduced need for hospital care. No reliable evidence was found for a reduction of infection-related mortality, a higher dose intensity of chemotherapy with CSFs or diminished rates of severe neutropenia and infections. The majority of adverse events reported from CSF use were bone pain and injection-site reactions but no conclusions could be drawn regarding late-term side effects.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Patients receiving surgery											
Kumar, 2014, 8815a	Patients receiving day surgery	Total intravenous anaesthesia using propofol (0.3 per 100)	Inhalational agents sevoflurane or desflurane (0.8 per 100)	556 (5)	37 ±4	Hospital admission (Unclear)	No	OR: 0.35 (0.14 to 0.91) NNT: 214 (162 to 1555) I²: 0%	Low	Summary estimate	(-) Therefore, based on the published evidence to date, maintenance of anaesthesia using propofol appeared to have no bearing on the incidence of unplanned admission to hospital and was more expensive, but was associated with a decreased incidence of early postoperative nausea and vomiting compared with sevoflurane or desflurane in patients undergoing ambulatory surgery.
Special screening examination for neoplasms											
Yang, 2015, 8918a	Patients undergoing prostate biopsy	Antibiotics [Ofloxacin, Trimethoprim, Sulfonamide methoxazole, or Ciprofloxacin] (2 per 100)	Placebo or no treatment (13 per 100)	650 (3)	Unclear	Hospital admission (Unclear)	No	RR: 0.13 (0.03 to 0.55) NNT: 9 (8 to 17) I²: 0%	Moderate	Summary estimate	(+) Prophylactic antibiotics could be beneficial for the reduction of infective complications after trans-renal prostate biopsy. Single-dose or short-course oral administration with any type of antibiotic appears to be optimal. One additional type of antibiotic added to the basic antibiotic agent may contribute to the minimization of severe infection and drug resistance.
Supervision of high-risk pregnancy; Supervision of normal pregnancy											
Makrides, 2014, 4844	Normal or high-risk pregnancy	Magnesium supplementation (8 per 100)	Placebo (12 per 100)	1158 (3)	Unclear	Hospital admission (Unclear)	No	RR: 0.65 (0.48 to 0.86) NNT: 24 (16 to 60) I²: 0%	Moderate	Summary estimate	(?) There is not enough high-quality evidence to show that dietary magnesium supplementation during pregnancy is beneficial.
Certain infectious and parasitic diseases											
Human immunodeficiency virus											
Grimwade, 2009, 2933a	Human Immunodeficieny Virus	Cotrimoxazole (11 per 100)	Placebo (17 per 100)	764 (3)	34 ±2	Hospital admission (Unclear)	No	RR: 0.66 (0.48 to 0.92) NNT: 17 (11 to 74) I²: 91%	Moderate	Summary estimate	(?) In the trials included in the review, cotrimoxazole prophylaxis had a beneficial effect in preventing death and illness episodes in adults with both early and advanced Human Immunodeficieny Virus disease. However, the wider applicability of these findings is unclear, in particular to areas with higher background bacterial resistance to cotrimoxazole. Further trials would be required in differing settings to widen applicability.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Mental and behavioural disorders											
Schizophrenia and other types of schizophrenia-like psychoses (Acute and transient psychotic disorders; Bipolar affective disorder; Induced delusional disorder; Other nonorganic psychotic disorders; Persistent delusional disorders; Schizoaffective disorders; Schizophrenia; Schizotypal disorder; Unspecified nonorganic psychosis)											
Kishimoto, 2014, 4067b	Schizophrenia and other types of schizophrenia-like psychoses	Fluphenazine depot [Fulphenazine Decanoate or Fulphenazine Enanthate] (23 per 100)	Oral antipsychotic drugs [Pimozide, Trifluoperazine, or Fulphenazine] (28 per 100)	197 (4)	44 ±7	Hospital admission (12 ±3 months)	No	RR: 0.82 (0.67 to 0.99) NNT: 20 (11 to 358) I²: 0%	Low	Sub-group by intervention: Fluphenazine depot.	(?) In RCTs, which are less representative of real-world patients than naturalistic studies, pooled long acting injections did not reduce relapse compared with oral acting antipsychotics in schizophrenia patients. The exceptions were FGA-LAIs, mostly consisting of fluphenazine-LAI studies, which were all conducted through 1991. Because this finding is vulnerable to a cohort bias, studies comparing FGA-LAI vs second-generation antipsychotics-LAI and LAI vs OAP RCTs in real-world patients are needed.
Leucht, 2012, 4508a	Schizophrenia and other types of schizophrenia-like psychoses	Maintenance/continuous treatment with antipsychotic drugs [Fluphenazine decanoate, Prochlorpromazine, Perphenazine, Chlorpromazine, Promazine Trifluoperazine, Haloperidol, Olanzapine, Quetiapine, Paliperidone palmitate, Pimozide, Risperidone, Zuclopenthixol] (12 per 100)	Placebo or no treatment (33 per 100)	2090 (16)	38 ±9	Readmission (11 ±7 months)	No	RR: 0.38 (0.27 to 0.55) NNT: 5 (4 to 7) I²: 45%	High	Summary estimate. Kishimoto 2014 showed no effect of second-generation antipsychotic depot injections, but the comparator was oral medication whereas Leucht comparator was placebo.	(+) The results clearly demonstrate the superiority of antipsychotic drugs compared to placebo in preventing relapse. This effect must be weighed against the side effects of antipsychotic drugs. Future studies should focus on outcomes of social participation and clarify the long-term morbidity and mortality associated with these drugs.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Schizophrenia and other types of schizophrenia-like psychoses (Acute and transient psychotic disorders; Bipolar affective disorder; Induced delusional disorder; Other nonorganic psychotic disorders; Persistent delusional disorders; Schizoaffective disorders; Schizophrenia; Schizotypal disorder; Unspecified nonorganic psychosis)											
Komossa, 2013, 4123i	Schizophrenia and other types of schizophrenia-like psychoses	Olanzapine (11 per 100)	Ziprasidon (17 per 100)	766 (2)	41 ±0.1	Readmission (13 ±9 months)	No	RD: -0.06 (-0.01 to -0.11) NNT: 17 (9 to 100) I²: 0%	Moderate	Summary estimate	(?) Olanzapine may be a somewhat more efficacious drug than some other second generation antipsychotic drugs. This small superiority in efficacy needs to be weighed against a larger weight gain and associated metabolic problems than most other second generation antipsychotic drugs, except clozapine. These conclusions are tentative due to the large number of people leaving the studies early which possibly limits the validity of the findings. Further large, well-designed trials are necessary to establish the relative effects of different second generation antipsychotic drugs.
Komossa, 2013, 4123b	Schizophrenia and other types of schizophrenia-like psychoses	Olanzapine (11 per 100)	Quetiapin (20 per 100)	876 (2)	40 ±0.4	Readmission (13 ±9 months)	No	RR: 0.56 (0.41 to 0.77) NNT: 11 (8 to 22) I²: 0%	Moderate	Summary estimate	(?) Olanzapine may be a somewhat more efficacious drug than some other second generation antipsychotic drugs. This small superiority in efficacy needs to be weighed against a larger weight gain and associated metabolic problems than most other second generation antipsychotic drugs, except clozapine. These conclusions are tentative due to the large number of people leaving the studies early which possibly limits the validity of the findings. Further large, well-designed trials are necessary to establish the relative effects of different second generation antipsychotic drugs.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Schizophrenia and other types of schizophrenia-like psychoses (Acute and transient psychotic disorders; Bipolar affective disorder; Induced delusional disorder; Other nonorganic psychotic disorders; Persistent delusional disorders; Schizoaffective disorders; Schizophrenia; Schizotypal disorder; Unspecified nonorganic psychosis)											
Kishimoto, 2013, 4065a	Schizophrenia	Second generation antipsychotics [Amisulpride, Clozapine, Iloperidone, Olanzapine, Quetiapine, Risperidone, Sertindole, or Ziprasidone] (15 per 100)	First generation antipsychotics [Haloperidol] (21 per 100)	2869 (12)	33 ±6	Hospital admission (13 ±4 months)	No	RR: 0.72 (0.58 to 0.9) NNT: 17 (11 to 48) I²: 18%	Moderate	Summary estimate	(+) In conclusion, results from this meta-analysis suggest that, whereas individually second generation antipsychotics were not consistently superior to first generation antipsychotics, as a group, second generation antipsychotics were associated with less study-defined relapse, overall treatment failure and hospitalization than first generation antipsychotics, having a modest but clinically relevant effect size. Future relapse prevention studies should carefully assess extra-pyramidal side effects and adherence. Moreover, additional studies with a variety of second generation antipsychotics using non-haloperidol first generation antipsychotic comparators at low-medium doses that do not produce significantly greater extra-pyramidal side effects than second generation antipsychotic are needed to extend these findings. In particular, sufficiently large data sets are needed to allow examination of the relative merits of individual second generation antipsychotics, and to guide an individualized and evidence-based maintenance treatment selection in schizophrenia.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Mixed population											
Hemkens, 2016, 8784a	Preventing cardiovascular events in patients with alcoholic cirrhosis or idiopathic pulmonary fibrosis	Colchicine (41 per 100)	Control (47 per 100)	599 (2)	61 ±8	Hospital admission (49 ±33 months)	No	RR: 0.87 (0.77 to 0.99) NNT: 16 (9 to 212) I²: 0%	Low	Summary estimate	(?) Overall, we found that further research would probably change our assessment of the benefits and harms of colchicine. Our findings should therefore be interpreted with caution. However, new treatments in heart diseases are urgently needed. Although there is much uncertainty around the benefits and harms of colchicine treatment, it may be associated with cardiovascular benefits, especially on myocardial infarction. We therefore think that large high-quality clinical trials should be conducted to further investigate colchicine in heart disease.
Makani, 2013, 4838a	Heart failure; heart failure and haemodialysis; diabetic nephropathy; high risk cardiovascular disease	Dual renin-angiotensin blockade [Angiotensin II receptor blocker (Candesartan, Telmisartan, Valsartan, or other), angiotensin converting enzyme inhibitor (any), direct renin inhibitor (Aliskiren)] (23 per 100)	Single renin-angiotensin blockade [Angiotensin II receptor blocker (Telmisartan), angiotensin converting enzyme inhibitor inhibitor (Any), or direct renin inhibitor (Aliskiren)] (28 per 100)	42071 (5)	64 ±2	Admission for heart failure (38 ±12 months)	Yes	RR: 0.82 (0.74 to 0.92) NNT: 20 (14 to 45) I²: 68%	Low	Summary estimate	(-) Although dual blockade of the renin-angiotensin system may have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy. The risk to benefit ratio argues against the use of dual therapy.
Multi-morbidity											
Ngo, 2010, 5606	Heart failure with reduced left ejection fraction (less than or equal to 40%) and anemia	Erythropoiesis stimulating agent [Darbepoetin-alpha, Beta-erythropoietin, or Erythropoietin] (16 per 100)	Placebo or no treatment (25 per 100)	734 (9)	72 ±3	Admission for heart failure (7 ±5 months)	Yes	RR: 0.62 (0.44 to 0.87) NNT: 11 (7 to 31) I²: 0%	Moderate	Summary estimate	(+) Meta-analysis of small randomised controlled trials suggests that erythropoiesis stimulating agent treatment in patients with symptomatic congestive heart failure and mild anaemia (haemoglobin more than 10g/dL) can improve anaemia and exercise tolerance, reduce symptoms and have benefits on clinical outcomes. Confirmation requires well-designed studies with careful attention to dose, haemoglobin treatment target and associated iron therapy.

Table 9 continued. Graded effect estimates for medications that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes on estimates	Abstract conclusion and summary categorisation of overall balance of benefit to harm (+ - ?)[g]
Multi-morbidity											
Jankowska, 2016, 8790a	Heart failure with reduced left ventricular ejection fraction and Iron deficiency	Intravenous iron [Iron sucrose or Ferric carboxymaltose] (6 per 100)	Placebo (20 per 100)	835 (4)	69 ±5	Admission for heart failure (7 ±5 months)	Yes	OR: 0.28 (0.16 to 0.5) NNT: 8 (6 to 11) I²: 0%	Moderate	Summary estimate	(+) The evidence indicates that intravenous iron therapy in iron-deficient patients with systolic heart failure improves outcomes, exercise capacity, and quality of life, and alleviates heart failure symptoms.
Baumeister , 2011 593	Depression in patients with recent acute coronary syndromes	Atypical antidepressant or selective serotonin reuptake inhibitor [Mirtazapine; Sertraline; Fluoxetine] (15 per 100)	Placebo (23 per 100)	514 (3)	57 ±0.1	Hospital admission (6 ±0.5 months)	No	OR: 0.58 (0.39 to 0.85) NNT: 12 (8 to 37) I²: 0%	Very low	Summary estimate	(?) Psychological interventions and pharmacological interventions with SSRIs may have a small yet clinically meaningful effect on depression outcomes in CAD patients. No beneficial effects on the reduction of mortality rates and cardiac events were found. Overall, however, the evidence is sparse due to the low number of high quality trials per outcome and the heterogeneity of examined populations and interventions.
Pregnancy, childbirth and the puerperium"											
Magee, 2012, 4812a	Mild to moderate, late-onset pre-eclampsia	Beta-blocker [Oxprenolol, Labetalol, or Metoprolol] (56 per 100)	Placebo or no treatment (73 per 100)	291 (3)	Unclear	Hospital admission (Range from first week to babies birth)	No	RR: 0.77 (0.64 to 0.93) NNT: 6 (4 to 20) I²: 85%	Low	Summary estimate	(?) Improvement in control of maternal blood pressure with use of beta-blockers would be worthwhile only if it were reflected in substantive benefits for mother and/or baby, and none have been clearly demonstrated. The effect of beta-blockers on perinatal outcome is uncertain; the worrying trend to an increase in SGA infants is partly dependent on one small outlying trial. Large randomised trials are needed to determine whether antihypertensive therapy in general (rather than beta-blocker therapy specifically) results in greater benefit than risk, for treatment of mild-moderate pregnancy hypertension. If so, then it would be appropriate to consider which antihypertensive is best, and beta-blockers should be evaluated.

[a]Median hospitalisation event rate observed across the trials contributing to the pooled estimate. [b]Means and standard deviations for patient ages in years, unless otherwise specified. Mean of means and median ages in trials contributing to the pooled estimate. Not all included trials reported age in a form that could be averaged. [c]Means and standard deviations for length of follow-up across trials, unless otherwise specified. Mean of means, medians, and total study durations reported in trials contributing to the pooled estimate. Not all included trials reported follow-up in a form that could be averaged. [d]RR= risk ratio; OR=odds ratio; rR= rate ratio; HR= hazard ratio; RD= risk difference. [e]CI=confidence interval. [f]NNT= Number needed to treat to benefit by avoiding one hospital admission. gAs indicated in Table 2 : the symbol (+) denotes when review conclusions indicated an favourable overall balance of benefit to harm or the authors recommend use of intervention; the symbol (-) denotes when review conclusions indicated that there was not a favourable overall balance of benefit to harm or the authors recommended not to use the intervention; and the symbol (?) denotes when review conclusions indicated that the overall balance of benefit to harm was unclear, the authors did not comment on the overall balance of benefit to harm, or the authors indicated that more research was required before a recommendation regarding use of the intervention could be made.

Appendix 3.11 Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Table 10. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I^2%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Disease of the circulatory system											
Angina pectoris; Acute myocardial infarction; Chronic ischaemic heart disease; or Heart failure											
Kang, 2016, 9271a	Heart failure with left ventricular dysfunction, coronary artery disease, or acute coronary syndrome	Pharmacist-involved care (41 per 100)	Usual care (48 per 100)	4240 (13)	Unclear	Hospital admission (9 ±5 months)	No	OR: 0.74 (0.58 to 0.94) NNT: 13 (8 to 65) I^2: 61%	Moderate	Summary estimate	(?) All-cause hospitalization showed improvement in the pharmaceutical care group. However, the strength of evidence for the majority of outcomes with pharmaceutical care, except direct performance measures such as prescription rates, was either insufficient or low. This could be explained by the presence of imprecision and inconsistency derived from the diversity of pharmaceutical care, the heterogeneity of patient populations or clinical settings. Moreover, it may indicate the necessity for homogeneous applicable criteria for assessment. A standardized consensus of the guidelines for pharmaceutical care service should be considered to improve homogeneity.
Heart failure											
Takeda, 2012, 7600c	Heart failure	Case management (26 per 100)	Usual care (36 per 100)	655 (3)	69 ±5	Readmission for heart failure (8 ±2 months)	Yes	OR: 0.64 (0.46 to 0.88) NNT: 11 (7 to 35) I^2: 0%	Moderate	Sub-group by intervention and follow-up length: Case management, Follow-up at 6 months	(+) Amongst CHF patients who have previously been admitted to hospital for this condition there is now good evidence that case management type interventions led by a heart failure specialist nurse reduces CHF related readmissions after 12 months follow up, all cause readmissions and all-cause mortality. It is not possible to say what the optimal components of these case management type interventions are, however telephone follow up by the nurse specialist was a common component. Multidisciplinary interventions may be effective in reducing both CHF and all cause readmissions. There is currently limited evidence to support interventions whose major component is follow up in a CHF clinic.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Takeda, 2012, 7600e	Heart failure	Case management (19 per 100)	Usual care (36 per 100)	604 (3)	71 ±7	Readmission for heart failure (10 ±3 months)	Yes	OR: 0.42 (0.29 to 0.62) NNT: 6 (5 to 10) I²: 9%	High	Sub-group by intervention and study quality: Case management, Allocation concealment confirmed	(+) Amongst CHF patients who have previously been admitted to hospital for this condition there is now good evidence that case management type interventions led by a heart failure specialist nurse reduces CHF related readmissions after 12 months follow up, all cause readmissions and all cause mortality. It is not possible to say what the optimal components of these case management type interventions are, however telephone follow up by the nurse specialist was a common component. Multidisciplinary interventions may be effective in reducing both CHF and all cause readmissions. There is currently limited evidence to support interventions whose major component is follow up in a CHF clinic.
Huntley, 2016, 9178a	Heart failure	Case management (hospital initiated) (28 per 100)	Usual care (38 per 100)	3066 (12)	75 ±3	Readmission (Range 3 to 18 months)	No	rR: 0.74 (0.6 to 0.92) NNT: 10 (7 to 33) I²: 69%	Moderate	Summary estimate	(+) Hospital-initiated CM can be successful in reducing unplanned hospital readmissions for HF and length of hospital stay for people with HF. 9 trials described cost data; no clear difference emerged between CM and usual care. There was limited evidence for community initiated CM which suggested it does not reduce admission.
Huntley, 2016, 9178e	Heart failure	Case management (hospital initiated) (34 per 100)	Usual care (41 per 100)	2032 (6)	75 ±2	Readmission (Range 12 to 18 months)	No	rR: 0.83 (0.7 to 0.98) NNT: 14 (8 to 123) I²: 35%	Moderate	Sub-group by follow-up length: 12-18 month follow-up	(+) Hospital-initiated CM can be successful in reducing unplanned hospital readmissions for HF and length of hospital stay for people with HF. 9 trials described cost data; no clear difference emerged between CM and usual care. There was limited evidence for community initiated CM which suggested it does not reduce admission.
Huntley, 2016, 9178c	Heart failure	Case management (hospital initiated) (15 per 100)	Usual care (23 per 100)	848 (5)	75 ±4	Readmission (3 months)	No	rR: 0.67 (0.51 to 0.9) NNT: 13 (9 to 44) I²: 19%	Moderate	Sub-group by follow-up length: 3 month follow-up	(+) Hospital-initiated CM can be successful in reducing unplanned hospital readmissions for HF and length of hospital stay for people with HF. 9 trials described cost data; no clear difference emerged between CM and usual care. There was limited evidence for community initiated CM which suggested it does not reduce admission.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Huntley, 2016, 9178h	Heart failure	Case management (hospital initiated) with medication review (Review and adjustment of medication by experienced case manager (nurse), pharmacist, GP or consultant often using a combination of these health professionals) (33 per 100)	Usual care (45 per 100)	748 (5)	77 ±2	Readmission (Range 3 to 18 months)	No	rR: 0.73 (0.59 to 0.91) NNT: 8 (5 to 25) I²: 28%	Moderate	Sub-group by intervention: Medication review	(+) Hospital-initiated CM can be successful in reducing unplanned hospital readmissions for HF and length of hospital stay for people with HF. 9 trials described cost data; no clear difference emerged between CM and usual care. There was limited evidence for community initiated CM which suggested it does not reduce admission.
Takeda, 2012, 7600a	Heart failure	Clinical service organisation interventions (26 per 100)	Usual care (39 per 100)	3135 (12)	70 ±6	Readmission for heart failure (9 ±4 months)	Yes	OR: 0.57 (0.43 to 0.75) NNT: 8 (6 to 15) I²: 62%	Low	Summary estimate	(+) Amongst CHF patients who have previously been admitted to hospital for this condition there is now good evidence that case management type interventions led by a heart failure specialist nurse reduces CHF related readmissions after 12 months follow up, all cause readmissions and all cause mortality. It is not possible to say what the optimal components of these case management type interventions are, however telephone follow up by the nurse specialist was a common component. Multidisciplinary interventions may be effective in reducing both CHF and all cause readmissions. There is currently limited evidence to support interventions whose major component is follow up in a CHF clinic.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Takeda, 2012, 7600n	Heart failure	Clinical service organisation interventions (Low intensity) (37 per 100)	Usual care (51 per 100)	489 (3)	71 ±1	Readmission for heart failure (9 ±4 months)	Yes	OR: 0.56 (0.39 to 0.81) NNT: 7 (5 to 19) I²: 0%	Moderate	Sub-group by intervention: Low intensity intervention	(+) Amongst CHF patients who have peviously been admitted to hospital for this condition there is now good evidence that case management type interventions led by a heart failure specialist nurse reduces CHF related readmissions after 12 months follow up, all cause readmissions and all cause mortality. It is not possible to say what the optimal components of these case management type interventions are, however telephone follow up by the nurse specialist was a common component. Multidisciplinary interventions may be effective in reducing both CHF and all cause readmissions. There is currently limited evidence to support interventions whose major component is follow up in a CHF clinic.
Raman, 2008, 6360b	Heart failure	Clinic visits post-discharge (44 per 100)	Usual care (57 per 100)	1155 (5)	69 ±5	Readmission (4 ±3 months)	No	RR: 0.78 (0.64 to 0.95) NNT: 4 (5 to 35) I²: 57%	Low	Summary estimate	(+) Interventions that utilized increased clinic visits, home visits, and multidisciplinary care reduced the risk of readmissions. Studies with intermediate- to long-term follow-up, interventions initiated in the inpatient setting, and patient ages greater than 75 years were associated with significant reduction of all cause readmissions in the intervention group. These interventions often utilized a combination of components. There was no distinct combination of intervention components that was associated with improved clinical outcomes. The evidence was sparse for interventions beginning in the outpatient clinics.
Roccaforte, 2005, 6552i	Heart failure	Comprehensive disease management programmes (41 per 100)	Usual care (48 per 100)	2071 (10)	Range 35 to 91	Readmission (11 ±9 months)	No	OR: 0.75 (0.63 to 0.8) NNT: 14 (9 to 18) I²: p>0.1 heterogeneity	High	Sub-group by study quality: High quality studies only	(+) Disease management programmes reduce mortality and hospitalisations in heart failure patients. Because various types of disease management programmes appear to be similarly effective, the choice of a specific programme depends on local health services characteristics, patient population, and resources available.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Roccaforte, 2005, 6552p	Heart failure	Comprehensive disease management programmes (23 per 100)	Usual care (34 per 100)	1539 (8)	Range 59 to 75	Readmission for heart failure (10 ±7 months)	Yes	OR: 0.58 (0.45 to 0.75) NNT: 9 (7 to 16) I²: p>0.1 heterogeneity	High	Sub-group by study quality: High quality studies only	(+) Disease management programmes reduce mortality and hospitalisations in heart failure patients. Because various types of disease management programmes appear to be similarly effective, the choice of a specific programme depends on local health services characteristics, patient population, and resources available.
Roccaforte, 2005, 6552m	Heart failure	Comprehensive disease management programmes (35 per 100)	Usual care (46 per 100)	1999 (13)	Range 35 to 91	Readmission (10 ±10 months)	No	OR: 0.61 (0.51 to 0.74) NNT: 8 (6 to 14) I²: p>0.1 heterogeneity	Moderate	Sub-group by follow-up length: Short intervention (0-3) months	(+) Disease management programmes reduce mortality and hospitalisations in heart failure patients. Because various types of disease management programmes appear to be similarly effective, the choice of a specific programme depends on local health services characteristics, patient population, and resources available.
Phillips, 2004, 6099a	Heart failure in elderly patients	Comprehensive discharge planning with post discharge support (35 per 100)	Usual care (46 per 100)	3304 (18)	73 ±5	Readmission (11 ±6 months)	No	RR: 0.75 (0.64 to 0.88) NNT: 9 (6 to 18) I²: p<0.1 heterogeneity	Low	Summary estimate	(+) Comprehensive discharge planning plus post-discharge support for older patients with CHF significantly reduced readmission rates and may improve health outcomes such as survival and QOL without increasing costs.
Phillips, 2004, 6099h	Heart failure in elderly patients	Comprehensive discharge planning with home visit and/or frequent telephone contact (40 per 100)	Usual care (50 per 100)	970 (6)	75 ±3	Readmission (8 ±3 months)	No	RR: 0.79 (0.69 to 0.91) NNT: 10 (6 to 22) I²: p>0.1 heterogeneity	Moderate	Sub-group by intervention: Home visit and/or frequent telephone contact	(+) Comprehensive discharge planning plus post-discharge support for older patients with CHF significantly reduced readmission rates and may improve health outcomes such as survival and QOL without increasing costs.
Phillips, 2004, 6099f	Heart failure in elderly patients	Comprehensive discharge planning with single home visit (39 per 100)	Usual care (51 per 100)	476 (3)	74 ±1	Readmission (10 ±9 months)	No	RR: 0.76 (0.63 to 0.93) NNT: 8 (5 to 28) I²: p>0.1 heterogeneity	Moderate	Sub-group by intervention: Single home visit	(+) Comprehensive discharge planning plus post-discharge support for older patients with CHF significantly reduced readmission rates and may improve health outcomes such as survival and QOL without increasing costs.
Phillips, 2004, 6099e	Heart failure in elderly patients	Comprehensive discharge planning with post discharge support (33 per 100)	Usual care (50 per 100)	1153 (6)	72 ±1	Cardiovascular readmission (25 ±19 months)	No	RR: 0.65 (0.54 to 0.79) NNT: 6 (4 to 10) I²: 12%	Moderate	Sub-group by outcome type: Congestive heart failure or cardiovascular readmission	(+) Comprehensive discharge planning plus post-discharge support for older patients with CHF significantly reduced readmission rates and may improve health outcomes such as survival and QOL without increasing costs.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Lambrinou, 2012, 4305a	Heart failure	Disease management programme with nurse-led discharge planning (22 per 100)	Usual care (32 per 100)	2898 (13)	71 ±4	Readmission for heart failure (94 ±36 months)	Yes	RR: 0.68 (0.53 to 0.86) NNT: 10 (7 to 22) I²: 64%	Moderate	Summary estimate	(?) The results of the current meta-analysis highlight the potential of HF-MPs with nurse-driven pre-discharge interventions to reduce hospital re-admissions. Essential characteristics or components of a successful HF-MP are still to be determined; thus more studies are required to solve this issue.
Lambrinou, 2012, 4305f	Heart failure	Disease management programme with nurse-led discharge planning (45 per 100)	Usual care (53 per 100)	3713 (17)	72 ±4	Readmission (18 ±9 months)	No	RR: 0.85 (0.76 to 0.94) NNT: 13 (8 to 31) I²: 50%	Moderate	Summary estimate	(?) The results of the current meta-analysis highlight the potential of HF-MPs with nurse-driven pre-discharge interventions to reduce hospital re-admissions. Essential characteristics or components of a successful HF-MP are still to be determined; thus more studies are required to solve this issue.
Gonseth, 2004, 2811a	Heart failure and age 65 and older	Disease management programs (22 per 100)	Control (32 per 100)	3160 (11)	72 ±4	Readmission for heart failure (8 ±6 months)	Yes	RR: 0.70 (0.62 to 0.79) NNT: 10 (8 to 15) I²: 27%	Low	Summary estimate	(+) DMPs are effective at reducing re-admissions among elderly patients with HF. Their effectiveness is close to that observed in clinical trials evaluating drugs for HF, such as angiotensin-converting enzyme inhibitors, beta-blockers or digoxin. However, since none of the DMP studies compared different interventions directly, we do not know the relative effectiveness of types of healthcare delivery within the DMP.
Gonseth, 2004, 2811g	Heart failure and age 65 and older	Disease management programs (44 per 100)	Control (50 per 100)	4440 (16)	75 ±4	Readmission (8 ±4 months)	No	RR: 0.88 (0.79 to 0.97) NNT: 17 (10 to 67) I²: 49%	Very low	Summary estimate	(+) DMPs are effective at reducing re-admissions among elderly patients with HF. Their effectiveness is close to that observed in clinical trials evaluating drugs for HF, such as angiotensin-converting enzyme inhibitors, beta-blockers or digoxin. However, since none of the DMP studies compared different interventions directly, we do not know the relative effectiveness of types of healthcare delivery within the DMP.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Lambrinou, 2012, 4305d	Heart failure	Disease management programme with nurse-led discharge planning (18 per 100)	Usual care (36 per 100)	535 (4)	76 ±2	Readmission for heart failure (22 ±8 months)	Yes	RR: 0.51 (0.33 to 0.79) NNT: 6 (4 to 13) I²: 45%	Low	Sub-group by intervention: Home follow up	(?) The results of the current meta-analysis highlight the potential of HF-MPs with nurse-driven pre-discharge interventions to reduce hospital re-admissions. Essential characteristics or components of a successful HF-MP are still to be determined; thus more studies are required to solve this issue.
Lambrinou, 2012, 4305i	Heart failure	Disease management programme with nurse-led discharge planning (43 per 100)	Usual care (54 per 100)	1052 (6)	76 ±2	Readmission (18 ±6 months)	No	RR: 0.80 (0.70 to 0.91) NNT: 9 (6 to 21) I²: 0%	High	Sub-group by intervention: Home follow up	(?) The results of the current meta-analysis highlight the potential of HF-MPs with nurse-driven pre-discharge interventions to reduce hospital re-admissions. Essential characteristics or components of a successful HF-MP are still to be determined; thus more studies are required to solve this issue.
Taylor, 2014, 7651a	Heart failure with preserved or reduced ejection fraction	Exercise-based rehabilitation (13 per 100)	Usual care or active intervention but no exercise training (17 per 100)	1278 (14)	65 ±10	Hospital admission (Range 0.1 to 12 months)	No	RR: 0.75 (0.62 to 0.92) NNT: 24 (16 to 75) I²: 0%	Low	Summary estimate	(+) This updated Cochrane review supports the conclusions of the previous version of this review that, compared with no exercise control, exercise-based rehabilitation does not increase or decrease the risk of all-cause mortality in the short term (up to 12-months' follow-up) but reduces the risk of hospital admissions and confers important improvements in health-related quality of life. This update provides further evidence that exercise training may reduce mortality in the longer term and that the benefits of exercise training on appear to be consistent across participant characteristics including age, gender and HF severity. Further randomised controlled trials are needed to confirm the small body of evidence seen in this review for the benefit of exercise in HFPEF and when exercise rehabilitation is exclusively delivered in a home-based setting.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Taylor, 2014, 7651b	Heart failure with preserved or reduced ejection fraction	Exercise-based rehabilitation (7 per 100)	Usual care or active intervention but no exercise training (12 per 100)	1036 (12)	61 ±8	Admission for heart failure (27 ±35 months)	Yes	RR: 0.61 (0.46 to 0.8) NNT: 22 (16 to 43) I²: 34%	Low	Summary estimate	(+) This updated Cochrane review supports the conclusions of the previous version of this review that, compared with no exercise control, exercise-based rehabilitation does not increase or decrease the risk of all-cause mortality in the short term (up to 12-months' follow-up) but reduces the risk of hospital admissions and confers important improvements in health-related quality of life. This update provides further evidence that exercise training may reduce mortality in the longer term and that the benefits of exercise training on appear to be consistent across participant characteristics including age, gender and HF severity. Further randomised controlled trials are needed to confirm the small body of evidence seen in this review for the benefit of exercise in HFPEF and when exercise rehabilitation is exclusively delivered in a home-based setting.
Thomas, 2014, 7724i	Heart failure	Hospital-based pharmacist intervention (37 per 100)	Usual care (49 per 100)	314 (3)	76 ±0.4	Hospital admission (38 ±34 months)	No	RR: 0.75 (0.59 to 0.95) NNT: 8 (5 to 41) I²: Unclear	Low	Summary estimate	(+) Evidence from three randomised controlled trials suggests that interventions led by hospital pharmacists reduce unplanned hospital admissions in older patients with heart failure, although these trials were heterogeneous. Data from trials do not support the concept that interventions led by hospital or community pharmacists for the general older population reduces unplanned admissions.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Tran, 2008, 7820a	Heart failure	Home telemonitoring (34 per 100)	Usual care (42 per 100)	787 (3)	67 ±11	Readmission (18 ±9 months)	No	RR: 0.80 (0.68 to 0.95) NNT: 12 (7 to 48) I²: 0%	Low	Summary estimate	(+) Despite the limited evidence, this assessment indicates that, overall, home telehealth is effective and that it can reduce health resource use. The economic studies were highly heterogeneous. More studies of a higher methodological quality are needed to give greater insights into the potential cost-effectiveness of home telehealth interventions. A framework for such studies is suggested. Home telehealth is a useful addition to Canadian health care delivery. It has been applied in the management of several chronic diseases. Many ethical, legal, anf psychosocial issues that may arise can be solved using existing models. Some issues regarding the criteria for identifying suitable patients, liability, reimbursement, and unique patient identifiers, which are crucial to home telehealth implementation, require further discussion.
Holland, 2005, 3400b	Heart failure	Home visits, home physiological monitoring, or televideo link (41 per 100)	Usual care (51 per 100)	1519 (10)	74 ±7	Hospital admission (9 ±4 months)	No	RR: 0.80 (0.71 to 0.89) NNT: 10 (7 to 18) I²: 0%	Moderate	Sub-group by intervention: Home visits, home physiological monitoring, or televideo link	(+) Multidisciplinary interventions for heart failure reduce both hospital admission and all-cause mortality. The most effective interventions were delivered at least partly in the home.
Feltner, 2014, 2359c	Heart failure	Home-visiting programs (32 per 100)	Usual care (43 per 100)	1563 (9)	76 ±2	Readmission (6 ±3 months)	No	RR: 0.75 (0.68 to 0.86) NNT: 4 (7 to 17) I²: 0%	High	Summary estimate	(+) Home-visiting programs and MDS-HF clinics reduced all-cause readmission and mortality; STS reduced HF-specific readmission and mortality. These interventions should receive the greatest consideration by systems or providers seeking to implement transitional care interventions for persons with HF.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Raman, 2008, 6360d	Heart failure	Home visits post-discharge (49 per 100)	Usual care (60 per 100)	633 (4)	75 ±2	Readmission (10 ±5 months)	No	RR: 0.82 (0.69 to 0.97) NNT: 9 (5 to 56) I²: 0%	Low	Summary estimate	(+) Interventions that utilized increased clinic visits, home visits, and multidisciplinary care reduced the risk of readmissions. Studies with intermediate- to long-term followup, interventions initiated in the inpatient setting, and patient ages greater than 75 years were associated with significant reduction of all cause readmissions in the intervention group. These interventions often utilized a combination of components. There was no distinct combination of intervention components that was associated with improved clinical outcomes. The evidence was sparse for interventions beginning in the outpatient clinics.
Inglis, 2015, 8787d	Heart failure	Mobile/person digital assistant (23 per 100)	Usual post-discharge care (31 per 100)	560 (2)	56 ±1	Hospital admission (17 ±10 months)	No	RR: 0.76 (0.60 to 0.97) NNT: 14 (8 to 108) I²: 70%	Very low	Sub-group by intervention: Mobile/person digital assistant	(+) For people with heart failure, structured telephone support and non-invasive home telemonitoring reduce the risk of all-cause mortality and heart failure-related hospitalisations; these interventions also demonstrated improvements in health-related quality of life and heart failure knowledge and self-care behaviours. Studies also demonstrated participant satisfaction with the majority of the interventions which assessed this outcome.
Takeda, 2012, 7600k	Heart failure	Multidisciplinary interventions (47 per 100)	Usual care (66 per 100)	403 (2)	77	Readmission (7 ±5 months)	No	OR: 0.46 (0.30 to 0.69) NNT: 5 (3 to 11) I²: 0%	Low	Sub-group by intervention: Multidisciplinary interventions	(?) Amongst CHF patients who have previously been admitted to hospital for this condition there is now good evidence that case management type interventions led by a heart failure specialist nurse reduces CHF related readmissions after 12 months follow up, all cause readmissions and all cause mortality. It is not possible to say what the optimal components of these case management type interventions are, however telephone follow up by the nurse specialist was a common component. Multidisciplinary interventions may be effective in reducing both CHF and all cause readmissions. There is currently limited evidence to support interventions whose major component is follow up in a CHF clinic.

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Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I^2%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Raman, 2008, 6360f	Heart failure	Multidisciplinary care post-discharge (28 per 100)	Usual care (44 per 100)	1279 (4)	73 ±11	Readmission (14 ±4 months)	No	RR: 0.63 (0.44 to 0.90) NNT: 6 (4 to 23) I^2: 69%	Moderate	Summary estimate	(+) Interventions that utilized increased clinic visits, home visits, and multidisciplinary care reduced the risk of readmissions. Studies with intermediate- to long-term followup, interventions initiated in the inpatient setting, and patient ages greater than 75 years were associated with significant reduction of all cause readmissions in the intervention group. These interventions often utilized a combination of components. There was no distinct combination of intervention components that was associated with improved clinical outcomes. The evidence was sparse for interventions beginning in the outpatient clinics.
Feltner, 2014, 2359l	Heart failure	Multidisciplinary-heart failure clinic (34 per 100)	Usual care (49 per 100)	336 (2)	65 ±6	Readmission (6 months)	No	RR: 0.70 (0.55 to 0.89) NNT: 7 (5 to 19) I^2: 0%	High	Summary estimate	(+) Home-visiting programs and multi-disciplinary heart failure clinics reduced all-cause readmission and mortality; structured telephone support reduced heart failure-specific readmission and mortality. These interventions should receive the greatest consideration by systems or providers seeking to implement transitional care interventions for persons with heart failure..
Takeda, 2012, 7600j	Heart failure	Multidisciplinary interventions (20 per 100)	Usual care (36 per 100)	403 (2)	77	Readmission for heart failure (6 ±5 months)	Yes	OR: 0.45 (0.28 to 0.72) NNT: 6 (4 to 14) I^2: 0%	Low	Sub-group by intervention: Multidisciplinary interventions	(?) Amongst CHF patients who have previously been admitted to hospital for this condition there is now good evidence that case management type interventions led by a heart failure specialist nurse reduces CHF related readmissions after 12 months follow up, all cause readmissions and all cause mortality. It is not possible to say what the optimal components of these case management type interventions are, however telephone follow up by the nurse specialist was a common component. Multidisciplinary interventions may be effective in reducing both CHF and all cause readmissions. There is currently limited evidence to support interventions whose major component is follow up in a CHF clinic.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Holland, 2005, 3400a	Heart failure	Multidisciplinary interventions: multidisciplinary team; provision of home visits; home physiological monitoring or televideo link; telephone follow up but no home visits; and hospital or clinic interventions alone (individual and group hopsital-based and outpatient-based education sessions with self-monitoring and a home-based care pathway; broad quality improvement intervention with standardised admission orders, health professional education). (43 per 100)	Usual care (49 per 100)	6569 (21)	74 ±7	Hospital admission (13 ±2 months)	No	RR: 0.87 (0.79 to 0.95) NNT: 16 (10 to 40) I²: 54%	Low	Summary estimate	(+) Multidisciplinary interventions for heart failure reduce both hospital admission and all cause mortality. The most effective interventions were delivered at least partly in the home.
Inglis, 2015, 8787h	Heart failure	Non-invasive telemonitoring with office hours (56 per 100)	Usual post-discharge care (66 per 100)	1140 (6)	72 ±7	Hospital admission (8 ±3 months)	No	RR: 0.85 (0.76 to 0.94) NNT: 10 (6 to 25) I²: 76%	Very low	Sub-group by intervention: Non-invasive telemonitoring with office hours	(+) For people with heart failure, structured telephone support and non-invasive home telemonitoring reduce the risk of all-cause mortality and heart failure-related hospitalisations; these interventions also demonstrated improvements in health-related quality of life and heart failure knowledge and self-care behaviours. Studies also demonstrated participant satisfaction with the majority of the interventions which assessed this outcome.
Inglis, 2015, 8787p	Heart failure	Non-invasive telemonitoring (68 per 100)	Usual post-discharge care (75 per 100)	1147 (6)	75 ±2	Hospital admission (9 ±4 months)	No	RR: 0.90 (0.82 to 0.99) NNT: 13 (7 to 133) I²: 80%	Very low	Sub-group by patient age: Age 70 years or older	(+) For people with heart failure, structured telephone support and non-invasive home telemonitoring reduce the risk of all-cause mortality and heart failure-related hospitalisations; these interventions also demonstrated improvements in health-related quality of life and heart failure knowledge and self-care behaviours. Studies also demonstrated participant satisfaction with the majority of the interventions which assessed this outcome.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Inglis, 2015, 8787w	Heart failure	Non-invasive telemonitoring (21 per 100)	Usual post-discharge care (30 per 100)	2148 (8)	Range 18 to 80	Admission for heart failure (23 ±33 months)	Yes	RR: 0.71 (0.6 to 0.83) NNT: 12 (8 to 20) I²: 20%	Moderate	Summary estimate	(+) For people with heart failure, structured telephone support and non-invasive home telemonitoring reduce the risk of all-cause mortality and heart failure-related hospitalisations; these interventions also demonstrated improvements in health-related quality of life and heart failure knowledge and self-care behaviours. Studies also demonstrated participant satisfaction with the majority of the interventions which assessed this outcome.
Driscoll, 2015, 8761a	Heart failure with reduced ejection fraction and prescribed beta-adrenergic blocking agents, angiotensin converting enzyme inhibitor, and/or Angiotensin II receptor blocker	Nurse-led titration of medication (35 per 100)	Usual care (44 per 100)	560 (4)	Unclear	Hospital admission (7 ±4 months)	No	RR: 0.80 (0.72 to 0.88) NNT: 11 (8 to 19) I²: 0%	High	Summary estimate	(+) Participants in the nurse led titration group experienced fewer hospital admissions for any cause and an increase in survival and number of participants reaching target dose within a shorter time period. However, the quality of evidence regarding the proportion of participants reaching target dose was low and should be interpreted with caution. We found high-quality evidence supporting NLT as one strategy that may improve the optimisation of beta-adrenergic blocking agents resulting in a reduction in hospital admissions. Despite evidence of a dose dependent relationship of beta-adrenergic blocking agents, ACEIs, and ARBs with improving outcomes in patients with HFrEF, the translation of this evidence into clinical practice is poor. NLT is one strategy that facilitates the implementation of this evidence into practice.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Driscoll, 2015, 8761b	Reduced ejection fraction and prescribed beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, and/or Angiotensin II receptor blocker	Nurse-led titration of medication (14 per 100)	Usual care (27 per 100)	617 (3)	Unclear	Admission for heart failure (11 ±4 months)	Yes	RR: 0.51 (0.36 to 0.72) NNT: 7 (6 to 13) I²: 0%	Moderate	Summary estimate	(+) Participants in the NLT group experienced fewer hospital admissions for any cause and an increase in survival and number of participants reaching target dose within a shorter time period. However, the quality of evidence regarding the proportion of participants reaching target dose was low and should be interpreted with caution. We found high-quality evidence supporting NLT as one strategy that may improve the optimisation of beta-adrenergic blocking agents resulting in a reduction in hospital admissions. Despite evidence of a dosedependent relationship of beta-adrenergic blocking agents, ACEIs, and ARBs with improving outcomes in patients with HFrEF, the translation of this evidence into clinical practice is poor. NLT is one strategy that facilitates the implementation of this evidence into practice.
Koshman, 2008, 4147a	Heart failure	Pharmacist directed care or pharmacist collaborative care (40 per 100)	No pharmacist care (48 per 100)	2026 (11)	71 ±7	Hospital admission (9 ±5 months)	No	OR: 0.71 (0.54 to 0.94) NNT: 12 (7 to 65) I²: 50%	Low	Summary estimate	(+) Pharmacist care in the treatment of patients with HF greatly reduces the risk of all-cause and HF hospitalizations. Since hospitalizations associated with HF are a major public health problem, the incorporation of pharmacists into HF care teams should be strongly considered.
Gwadry-Sridhar, 2004, 3030a	Heart failure	Pre-discharge multidisciplinary patient education program (39 per 100)	Usual care (50 per 100)	1246 (8)	75 ±5	Readmission (10 ±4 months)	No	RR: 0.79 (0.68 to 0.91) NNT: 10 (6 to 22) I²: p>0.1 heterogeneity	Moderate	Summary estimate	(+) This systematic review suggests that specific heart failure–targeted interventions significantly decrease hospital readmissions but do not affect mortality rates.
Jonkman, 2016, 795b	Heart failure	Self-management (28 per 100)	Usual ca(35 per 100)re	3461 (10)	Unclear	Admission for heart failure (10 ±5 months)	Yes	HR: 0.80 (0.69 to 0.92) NNT: 17 (11 to 44) I²: 61%	Low	Summary estimate	(+) This study shows that self-management interventions had a beneficial effect on time to HF-related hospitalization or all-cause death and HF-related hospitalization alone and elicited a small increase in HF-related quality of life. The findings do not endorse limiting self-management interventions to subgroups of patients with HF, but increased mortality in depressed patients warrants caution in applying self-management strategies in these patients.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Thomas, 2013, 7723c	Heart failure	Specialist heart-failure clinics (15 per 100)	Usual care (30 per 100)	1173 (6)	69 ±8	Hospital admission (9 ±5 months)	No	RR: 0.51 (0.41 to 0.63) NNT: 7 (6 to 9) I²: 50%	High	Summary estimate	(+) Specialist clinics for patients with heart failure can reduce the risk of unplanned admissions; these were most effective when there was a high intensity of clinic appointments close to the time of discharge which then reduced over the follow-up period.
Thomas, 2013, 7723i	Heart failure	Specialist heart-failure clinics with decreasing intensity of follow-up (11 per 100)	Usual care (26 per 100)	475 (3)	72 ±3	Hospital admission (18 ±8 months)	No	RR: 0.42 (0.27 to 0.65) NNT: 7 (5 to 11) I²: 4%	Moderate	Summary estimate	(+) Specialist clinics for patients with heart failure can reduce the risk of unplanned admissions; these were most effective when there was a high intensity of clinic appointments close to the time of discharge which then reduced over the follow-up period.
Thomas, 2013, 7723m	Heart failure	Specialist heart-failure clinics with inpatient interventions (9 per 100)	Usual care (35 per 100)	408 (2)	69 ±1	Hospital admission (7 ±4 months)	No	RR: 0.26 (0.07 to 0.92) NNT: 4 (3 to 36) I²: 45%	Moderate	Sub-group by study quality: Study with contamination bias removed	(+) Specialist clinics for patients with heart failure can reduce the risk of unplanned admissions; these were most effective when there was a high intensity of clinic appointments close to the time of discharge which then reduced over the follow-up period.
Inglis, 2015, 8787v	Heart failure	Structured telephone support (15 per 100)	Usual post-discharge care (18 per 100)	6996 (15)	66 ±9	Admission for heart failure (19 ±7 months)	Yes	RR: 0.85 (0.77 to 0.93) NNT: 37 (24 to 80) I²: 27%	Moderate	Summary estimate	(+) For people with heart failure, structured telephone support and non-invasive home telemonitoring reduce the risk of all-cause mortality and heart failure-related hospitalisations; these interventions also demonstrated improvements in health-related quality of life and heart failure knowledge and self-care behaviours. Studies also demonstrated participant satisfaction with the majority of the interventions which assessed this outcome.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Inglis, 2015, 8788c	Heart failure	Structured telephone support (23 per 100)	Usual care (28 per 100)	1556 (6)	72 ±1	Admission for heart failure (Unclear)	Yes	RR: 0.81 (0.67 to 0.99) NNT: 19 (11 to 360) I²: 0%	Low	Summary estimate	(+) Despite a systematic bias towards recruitment of individuals younger than the epidemiological average into the randomized controlled trials, older people with heart failure did benefit from structured telephone support and telemonitoring. These post-hoc sub-analysis results were similar to overall effects observed in the main metaanalysis. While further research is required to confirm these observational findings, the evidence at hand indicates that discrimination by age alone may be not be appropriate when inviting participation in a remote monitoring service for heart failure.
Inglis, 2015, 8787t	Heart failure	Structured telephone support (45 per 100)	Usual post-discharge care (50 per 100)	3451 (7)	66 ±5	Hospital admission (13 ±2 months)	No	RR: 0.89 (0.82 to 0.96) NNT: 18 (11 to 50) I²: 37%	Moderate	Sub-group by follow-up length: Follow-up more than 6 months	(+) For people with heart failure, structured telephone support and non-invasive home telemonitoring reduce the risk of all-cause mortality and heart failure-related hospitalisations; these interventions also demonstrated improvements in health-related quality of life and heart failure knowledge and self-care behaviours. Studies also demonstrated participant satisfaction with the majority of the interventions which assessed this outcome.
Inglis, 2015, 8787c	Heart failure	Structured telephone support (36 per 100)	Usual post-discharge care (38 per 100)	4756 (12)	67 ±5	Hospital admission (7 ±6 months)	No	RR: 0.93 (0.86 to 0.99) NNT: 37 (19 to 261) I²: 51%	Very low	Sub-group by study quality: Only trials where type of technology was reported	(+) For people with heart failure, structured telephone support and non-invasive home telemonitoring reduce the risk of all-cause mortality and heart failure-related hospitalisations; these interventions also demonstrated improvements in health-related quality of life and heart failure knowledge and self-care behaviours. Studies also demonstrated participant satisfaction with the majority of the interventions which assessed this outcome.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I^2%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Feltner, 2014, 2359h	Heart failure	Structured telephone support: Monitoring, education, or self-care management (or various combinations) using simple telephone technology after discharge in a structured format (e.g., series of scheduled calls with a specific goal, structured questioning, or use of decision-support software). (20 per 100)	Usual care (28 per 100)	1790 (7)	69 ±3	Readmission for heart failure (8 ±6 months)	Yes	RR: 0.74 (0.61 to 0.9) NNT: 5 (9 to 36) I^2: 0%	High	Summary estimate	(+) Home-visiting programs and MDS-HF clinics reduced all-cause readmission and mortality; STS reduced HF-specific readmission and mortality. These interventions should receive the greatest consideration by systems or providers seeking to implement transitional care interventions for persons with HF.
Tran, 2008, 7820b	Heart failure	Telephone support (47 per 100)	Usual (52 per 100)care	3076 (8)	70 ±3	Readmission (12 ±12 months)	No	RR: 0.91 (0.83 to 0.99) NNT: 21 (11 to 192) I^2: 21%	Low	Summary estimate	(+) Despite the limited evidence, this assessment indicates that, overall, home telehealth is effective and that it can reduce health resource use. The economic studies were highly heterogeneous. More studies of a higher methodological quality are needed to give greater insights into the potential cost-effectiveness of home telehealth interventions. A framework for such studies is suggested. Home telehealth is a useful addition to Canadian health care delivery. It has been applied in the management of several chronic diseases. Many ethical, legal, and psychosocial issues that may arise can be solved using existing models. Some issues regarding the criteria for identifying suitable patients, liability, reimbursement, and unique patient identifiers, which are crucial to home telehealth implementation, require further discussion.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Tran, 2008, 7820c	Heart failure	Telephone support (24 per 100)	Usual care (31 per 100)	2167 (5)	70 ±3	Readmission for heart failure (8 ±8 months)	Yes	RR: 0.77 (0.66 to 0.89) NNT: 14 (10 to 29) I²: 0%	Low	Summary estimate	(+) Despite the limited evidence, this assessment indicates that, overall, home telehealth is effective and that it can reduce health resource use. The economic studies were highly heterogeneous. More studies of a higher methodological quality are needed to give greater insights into the potential cost-effectiveness of home telehealth interventions. A framework for such studies is suggested. Home telehealth is a useful addition to Canadian health care delivery. It has been applied in the management of several chronic diseases. Many ethical, legal, and psychosocial issues that may arise can be solved using existing models. Some issues regarding the criteria for identifying suitable patients, liability, reimbursement, and unique patient identifiers, which are crucial to home telehealth implementation, require further discussion.
Tran, 2008, 7820f	Heart failure	Telephone support (26 per 100)	Usual care (34 per 100)	1517 (8)	72 ±1	Admission for heart failure (20 ±12 months)	Yes	rR: 0.78 (0.63 to 0.96) NNT: 13 (8 to 74) I²: 39%	Very low	Summary estimate	(+) Despite the limited evidence, this assessment indicates that, overall, home telehealth is effective and that it can reduce health resource use. The economic studies were highly heterogeneous. More studies of a higher methodological quality are needed to give greater insights into the potential cost-effectiveness of home telehealth interventions. A framework for such studies is suggested. Home telehealth is a useful addition to Canadian health care delivery. It has been applied in the management of several chronic diseases. Many ethical, legal, and psychosocial issues that may arise can be solved using existing models. Some issues regarding the criteria for identifying suitable patients, liability, reimbursement, and unique patient identifiers, which are crucial to home telehealth implementation, require further discussion.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I^2%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Vedel, 2015, 8902i	Heart failure	Transitional care intervention (45 per 100)	Usual care (54 per 100)	1951 (13)	77 ±2	Readmission (31 ±42 months)	No	RR: 0.83 (0.76 to 0.92) NNT: 11 (8 to 23) I^2: 7%	Moderate	Sub-group by patient age: Mean age 75 years and older	(+) Clinicians and managers who implement TCIs in primary care can incorporate these results with their own health care context to determine the optimal balance between intensity and duration of TCIs. High-intensity interventions seem to be the best option. Moderate-intensity interventions implemented for 6 months or longer may be another option.
Vedel, 2015, 8902m	Heart failure	Transitional care intervention (45 per 100)	Usual care (50 per 100)	10392 (35)	71 ±6	Readmission (15 ±10 months)	No	RR: 0.91 (0.86 to 0.97) NNT: 22 (14 to 67) I^2: 52%	Low	Sub-group by study quality: Low quality trials removed	(+) Clinicians and managers who implement TCIs in primary care can incorporate these results with their own health care context to determine the optimal balance between intensity and duration of TCIs. High-intensity interventions seem to be the best option. Moderate-intensity interventions implemented for 6 months or longer may be another option.
Vedel, 2015, 8902d	Heart failure	Transitional care intervention: A combination of home visits with other types of follow-up (telephone and/or clinic follow-up) or Telecare combined with prearranged direct contact with patients (eg, home visits, telephone follow-up, video visits) (38 per 100)	Usual care (45 per 100)	3339 (16)	72 ±7	Readmission (9 ±10 months)	No	RR: 0.86 (0.78 to 0.94) NNT: 16 (10 to 37) I^2: 31%	Moderate	Sub-group by intervention: High intensity intervention	(+) Clinicians and managers who implement TCIs in primary care can incorporate these results with their own health care context to determine the optimal balance between intensity and duration of TCIs. High-intensity interventions seem to be the best option. Moderate-intensity interventions implemented for 6 months or longer may be another option.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I^2%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Diseases of the respiratory system											
Asthma / Status Asmaticus											
Tapp, 2007, 7636c	Acute asthma	Education interventions (12 per 100)	Usual care (19 per 100)	386 (2)	Unclear	Hospital admission (7 ±8 months)	No	RR: 0.63 (0.40 to 0.97) NNT: 14 (9 to 178) I^2: 0%	Moderate	Sub-group by study quality: Studies at low risk of selection bias	(+) Our findings support educational interventions applied in the emergency department as a means of reducing subsequent asthma admissions to hospital. Whilst the direction of the effect on ED presentations was consistent with the reduction in risk of admission, the results were not definitive. Outcomes were measured on average at 6 months after index ED presentation. The impact of educational intervention in this context on longer term outcomes relating to asthma morbidity is unclear. Priorities for additional research in this area include assessment of health-related quality of life, lung function assessment, exploration of the relationship between socioeconomic status and asthma morbidity, and better description of the intervention assessed.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Asthma / Status Asmaticus											
Smith, 2005, 7279b	Chronic difficult asthma	Psycho-educational interventions (27 per 100)	Other psycho-educational interventions (15 per 100)	1073 (5)	Range 2 to 72	Hospital admission (Unclear)	No	RR: 0.57 (0.34 to 0.93) NNT: 9 (6 to 53) I²: p<0.1 heterogeneity	Low	Summary estimate	(?) There was some evidence of overall positive effects of psycho-educational interventions on hospital admissions in adults and children, and on symptoms in children, but limited evidence of effects on other outcomes. The majority of research and greatest effects, especially in adults, were confined to patients with severe disease but who lacked other characteristics indicative of difficult asthma or likely to put them at risk. A lack of good-quality research limited conclusions about cost-effectiveness. Although psycho-educational interventions may be of some benefit to patients with severe disease, there is currently a lack of evidence to warrant significant changes in clinical practice with regard to the care of patients with more difficult asthma. Further research is needed to: (1) standardise reporting of complex interventions; (2) extend and update this review; (3) improve identification of patients at risk from their asthma; (4) develop and test appropriate outcome measures for this group; and (5) design and evaluate, via the conduct of high-quality pragmatic RCTs, more powerful psycho-educational interventions that are conceptualised in terms of the ways in which psychosocial factors and asthma interact.
McLean, 2010, 5145a	Chronic asthma	Telehealthcare (5 per 100)	Usual care or any other control intervention (27 per 100)	126 (2)	Range 18 to 55	Hospital admission (Unclear)	No	OR: 0.14 (0.04 to 0.49) NNT: 5 (4 to 9) I²: 0%	Very low	Summary estimate	(?) Telehealthcare interventions are unlikely to result in clinically relevant improvements in health outcomes in those with relatively mild asthma, but they may have a role in those with more severe disease who are at high risk of hospital admission. Further trials evaluating the effectiveness and cost-effectiveness of a range of telehealthcare interventions are needed.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Other chronic obstructive pulmonary disease											
Echevarria, 2016, 8762a	Acute exacerbation of chronic obstructive pulmonary disease	Early supported discharge or hospital at home (27 per 100)	Traditional in-patient care (36 per 100)	688 (8)	43 ±19	Readmission (8 ±4 months)	No	RR: 0.74 (0.6 to 0.9) NNT: 4 (7 to 28) I²: 26%	Moderate	Summary estimate	(+) ESD/HAH is safe in selected patients with an AECOPD. Further research is required to define optimal criteria to guide patient selection and models of care.
Jordan, 2015, 8796m	Moderate to severe chronic obstructive pulmonary disease	Enhanced support in addition to informational approaches,: regular telephone contact to reinforce information or behaviour change techniques, provided encouragement or included scheduled home visits for assessment with reinforcement or encouragement. (39 per 100)	Usual care (51 per 100)	2122 (10)	68 ±3	Hospital admission (11 ±7 months)	No	HR: 0.78 (0.62 to 0.99) NNT: 12 (7 to 286) I²: 55%	Low	Sub-group by intervention and follow-up length: Enhanced support in addition to informational approaches, Follow-up over 6 months	(-) Self-management support delivered shortly after an acute exacerbation may have some benefit in terms of HRQoL and possibly admissions but the evidence is thin and unconvincing. Exercise may play an important role but there are not enough data to explore this. Any future trials should address issues of bias, particularly loss to follow-up, but this may be inherent in the nature of the intervention and the fact that patients are still trying to recover from an exacerbation. The evidence is not in support of SM interventions to be put into practice for patients with COPD at, or recently after, hospital discharge.
Jeppesen, 2012, 3709a	Acute exacerbation of chronic obstructive pulmonary disease	Hospital at home (26 per 100)	In-hospital care (34 per 100)	870 (8)	71 ±4	Readmission (9 ±4 months)	No	RR: 0.76 (0.59 to 0.99) NNT: 12 (7 to 295) I²: 34%	Moderate	Summary estimate	(+) Selected patients presenting to hospital emergency departments with acute exacerbations of COPDcan be safely and successfully treated at home with support from respiratory nurses.We found evidence of moderate quality that hospital at home may be advantageous with respect to readmission rates in these patients. Treatment of acute exacerbation of COPD in hospital at home also show a trend towards reduced mortality rate when compared with conventional inpatient treatment, but these results did not reach statistical significance (moderate quality evidence). For other outcomes than readmission and mortality rate, we assessed the evidence to be of low or very low quality.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Other chronic obstructive pulmonary disease											
Zhong, 2014, 8926a	Chronic obstructive pulmonary disease	Pharmacist directed care or pharmacist collaborative care (8 per 100)	Usual care (15 per 100)	684 (6)	64 ±5	Hospital admission (19 ±9 months)	No	RR: 0.50 (0.39 to 0.64) NNT: 13 (11 to 18) I²: 47%	High	Summary estimate	(+) Pharmacist care resulted in improvements in the medication compliance as well as reductions in hospital admissions and health-related costs. It is therefore a potent strategy for management of outpatients with COPD.
Puhan, 2016, 9316a	Recent acute exacerbation of chronic obstructive pulmonary disease	Pulmonary rehabilitation programmes (30 per 100)	Conventional community care (49 per 100)	810 (8)	70 ±3	Readmission (3 ±2 months)	No	OR: 0.44 (0.21 to 0.91) NNT: 5 (3 to 42) I²: 77%	Moderate	Summary estimate	(?) Overall, evidence of high quality shows moderate to large effects of rehabilitation on health-related quality of life and exercise capacity in patients with COPD after an exacerbation. Some recent studies showed no benefit of rehabilitation on hospital readmissions and mortality and introduced heterogeneity as compared with the last update of this review. Such heterogeneity of effects on hospital readmissions and mortality may be explained to some extent by the extensiveness of rehabilitation programmes and by the methodological quality of the included studies. Future researchers must investigate how the extent of rehabilitation programmes in terms of exercise sessions, self-management education and other components affects the outcomes, and how the organisation of such programmes within specific healthcare systems determines their effects after COPD exacerbations on hospital readmissions and mortality.
Zwerink, 2014, 8672a	Chronic obstructive pulmonary disease	Self-management (28 per 100)	Control (39 per 100)	1365 (7)	68 ±3	Hospital admission (11 ±6 months)	No	OR: 0.60 (0.40 to 0.89) NNT: 9 (5 to 37) I²: 47%	Moderate	Summary estimate	(+) Self-management interventions in patients with COPD are associated with improved health-related quality of life as measured by the SGRQ, a reduction in respiratory-related and all cause hospital admissions, and improvement in dyspnoea as measured by the (m)MRC. No statistically significant differences were found in other outcome parameters. However, heterogeneity among interventions, study populations, follow-up time and outcome measures makes it difficult to formulate clear recommendations regarding the most effective form and content of self-management in COPD.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Factors influencing health status and contact with health services											
Hospitalised patients											
Gonçalves-Bradley, 2016, 8776a	Hospitalised patients	Discharge planning from hospital (23 per 100)	Standard care with no individualised discharge plan (26 per 100)	4853 (17)	71 ±12	Readmission (9 ±5 months)	No	RR: 0.88 (0.79 to 0.97) NNT: 32 (18 to 128) I²: 22%	Moderate	Summary estimate	(+) A discharge plan tailored to the individual patient probably brings about a small reduction in hospital length of stay and reduces the risk of readmission to hospital at three months follow-up for older people with a medical condition. Discharge planning may lead to increased satisfaction with healthcare for patients and professionals. There is little evidence that discharge planning reduces costs to the health service.
Leppin, 2014, 4494a	Hospitalised patients	Peridischarge interventions: any of discharge planning; case management; telephone follow-up; telemonitoring; patient education; self-management; medication review; home visits; scheduled follow-up; patient-centered discharge instructions; clinician continuity; timely follow-up; timely primary care provider communication; patient hotline; rehabilitation; streamlining services. (13 per 100)	Any comparator (16 per 100)	17273 (42)	72 ±6	Readmission (33 ±12 months)	No	RR: 0.82 (0.73 to 0.91) NNT: 35 (24 to 71) I²: 31%	Moderate	Summary estimate	(+) Tested interventions are effective at reducing readmissions, but more effective interventions are complex and support patient capacity for self-care. Interventions tested more recently are less effective.
Zhu, 2015, 8929a	Hospitalised patients with chronic disease or rehabilitation needs	Nurse-led early discharge planning programmes (15 per 100)	Standard care (20 per 100)	3376 (10)	67 ±14	Readmission (25 ±10 months)	No	RR: 0.72 (0.58 to 0.89) NNT: 18 (12 to 45) I²: 66%	Moderate	Summary estimate	(+) Compared to standard care, nurse-led early discharge planning programmes have a positive impact on several aspects of care for inpatients with chronic disease and rehabilitation requirements, including reducing readmission, readmission length of stay and mortality and improving quality of life. These findings should be taken into account in future health service policy development.
Zhu, 2015, 8929f	Hospitalised patients with chronic disease or rehabilitation needs	Nurse-led early discharge planning programmes (30 per 100)	Standard care (62 per 100)	393 (2)	56 ±27	Readmission (14 ±3 months)	No	RR: 0.48 (0.37 to 0.63) NNT: 4 (3 to 4) I²: 0%	Moderate	Sub-group by follow-up: Follow-up six months	(+) Compared to standard care, nurse-led early discharge planning programmes have a positive impact on several aspects of care for inpatients with chronic disease and rehabilitation requirements, including reducing readmission, readmission length of stay and mortality and improving quality of life. These findings should be taken into account in future health service policy development.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Hospitalised patients											
Zhu, 2015, 8929g	Hospitalised patients with chronic disease or rehabilitation needs	Nurse-led early discharge planning programmes (44 per 100)	Standard care (58 per 100)	1042 (3)	53 ±22	Readmission (16 ±6 months)	No	RR: 0.76 (0.65 to 0.88) NNT: 7 (5 to 14) I²: 0%	High	Sub-group by follow-up: Twelve months follow-up	(+) Compared to standard care, nurse-led early discharge planning programmes have a positive impact on several aspects of care for inpatients with chronic disease and rehabilitation requirements, including reducing readmission, readmission length of stay and mortality and improving quality of life. These findings should be taken into account in future health service policy development.
Zhu, 2015, 8929i	Hospitalised patients with chronic disease or rehabilitation needs	Nurse-led early discharge planning programmes (30 per 100)	Standard care (44 per 100)	768 (2)	44 ±9	Readmission (13 ±12 months)	No	RR: 0.69 (0.51 to 0.92) NNT: 7 (5 to 29) I²: 0%	High	Sub-group by patient age: Patients under 65 years	(+) Compared to standard care, nurse-led early discharge planning programmes have a positive impact on several aspects of care for inpatients with chronic disease and rehabilitation requirements, including reducing readmission, readmission length of stay and mortality and improving quality of life. These findings should be taken into account in future health service policy development.
Zhu, 2015, 8929c	Hospitalised patients with chronic disease or rehabilitation needs	Nurse-led early discharge planning programmes (16 per 100)	Standard care (21 per 100)	1638 (7)	63 ±16	Readmission (17 ±9 months)	No	RR: 0.78 (0.68 to 0.89) NNT: 22 (15 to 44) I²: 0%	High	Sub-group for robustness to trial exclusion: Three studies generating significant heterogeneity excluded	(+) Compared to standard care, nurse-led early discharge planning programmes have a positive impact on several aspects of care for inpatients with chronic disease and rehabilitation requirements, including reducing readmission, readmission length of stay and mortality and improving quality of life. These findings should be taken into account in future health service policy development.
Patients presenting to primary care											
Martínez-González, 2014, 4987a	Patients presenting to primary care	Nurse-led primary care (7 per 100)	Physician-led care (10 per 100)	3890 (5)	50 ±18	Hospital admission (11 ±2 months)	No	RR: 0.76 (0.64 to 0.91) NNT: 42 (28 to 113) I²: 7%	Moderate	Summary estimate	(?) The available evidence continues to be limited by the quality of the research considered. Nurse-led care seems to have a positive effect on patient satisfaction, hospital admission and mortality. This important finding should be confirmed and the determinants of this effect should be assessed in further, larger and more methodically rigorous research.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Supervision of high-risk pregnancy											
Hodnett, 2010, 3362a	At risk of having preterm or growth restricted babies, or both	Family or psychosocial support (44 per 100)	Usual care (56 per 100)	737 (3)	Unclear	Hospital admission (11 ±8 months)	No	RR: 0.79 (0.68 to 0.92) NNT: 9 (6 to 22) I²: 0%	Low	Summary estimate	(+) Pregnant women need the support of caring family members, friends, and health professionals. While programs which offer additional support during pregnancy are unlikely to prevent the pregnancy from resulting in a low birthweight or preterm baby, they may be helpful in reducing the likelihood of antenatal hospital admission and caesarean birth.
Mental and behavioural disorders											
Bipolar											
Oud, 2016, 9309c	Bipolar disorder	Collaborative care (37 per 100)	Treatment as usual (55 per 100)	572 (2)	40 ±6	Hospital admission (8 ±4 months)	No	RR: 0.68 (0.49 to 0.94) NNT: 6 (4 to 31) I²: 0%	Moderate	Summary estimate	(?) There is evidence that psychological interventions are effective for people with bipolar disorder. Much of the evidence was of low or very low quality thereby limiting our conclusions. Further research should identify the most effective (and cost-effective) interventions for each phase of this disorder.
Morriss, 2007, 5398a	Bipolar disorder	Interventions to recognise early warning signs of bipolar recurrence (24 per 100)	Treatment as usual (36 per 100)	679 (4)	41 ±6	Hospital admission (27 ±35 months)	No	RR: 0.67 (0.47 to 0.95) NNT: 9 (5 to 56) I²: 1%	Low	Summary estimate	(+) This review shows a beneficial effect of EWS in time to recurrence, percentage of people hospitalised and functioning in people with bipolar disorder. However, the absence of data on the primary outcome measure in so many included studies is a source of concern and a potential source of bias. Mental health services should consider routinely providing EWS interventions to adults with bipolar disorder, as they appear to reduce hospitalisation and therefore may be cost-effective.
Schizophrenia and other types of schizophrenia-like psychoses (Acute and transient psychotic disorders; Bipolar affective disorder; Induced delusional disorder; Other nonorganic psychotic disorders; Persistent delusional disorders; Schizoaffective disorders; Schizophrenia; Schizotypal disorder; Unspecified nonorganic psychosis)											
Marshall, 1998, 4968a	Schizophrenia and schizophrenia-like disorders, bipolar disorder or depression with psychotic features	Assertive community treatment (45 per 100)	Standard care (58 per 100)	1047 (6)	30 ±9	Hospital admission (8 ±2 months)	No	OR: 0.59 (0.45 to 0.78) NNT: 8 (5 to 16) I²: 73%	Low	Summary estimate	(+) ACT is a clinically effective approach to managing the care of severely mentally ill people in the community. ACT, if correctly targeted on high users of in-patient care, can substantially reduce the costs of hospital care whilst improving outcome and patient satisfaction. Policy makers, clinicians, and consumers should support the setting up of ACT teams.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Schizophrenia and other types of schizophrenia-like psychoses (Acute and transient psychotic disorders; Bipolar affective disorder; Induced delusional disorder; Other nonorganic psychotic disorders; Persistent delusional disorders; Schizoaffective disorders; Schizophrenia; Schizotypal disorder; Unspecified nonorganic psychosis)											
Dieterich, 2017, 9370b	Non-acutely ill with schizophrenia, schizophrenia-like disorders, bipolar disorder, depression with psychotic features or/and personality disorder	Case management (intensive) (51 per 100)	Standard care (60 per 100)	1303 (5)	33 ±5	Hospital admission (7 ±2 months)	No	RR: 0.85 (0.77 to 0.93) NNT: 11 (7 to 24) I²: 0%	Moderate	Summary estimate	(+) Based on very low- to moderate-quality evidence, ICMis effective in ameliorating many outcomes relevant to people with severe mental illness. Compared to standard care, ICM may reduce hospitalisation and increase retention in care. It also globally improved social functioning, although ICM's effect on mental state and quality of life remains unclear. Intensive Case Management is at least valuable to people with severe mental illnesses in the subgroup of those with a high level of hospitalisation (about four days per month in past two years). Intensive Case Management models with high fidelity to the original team organisation of ACT model were more effective at reducing time in hospital. However, it is unclear what overall gain ICM provides on top of a less formal non-ICM approach. We do not think that more trials comparing current ICM with standard care or non-ICM are justified, however we currently know of no review comparing non-ICM with standard care, and this should be undertaken.
Jones, 2012, 3769e	Schizophrenia	Cognitive behavioural therapy adjunct to standard care (5 per 100)	Active therapies (17 per 100)	136 (2)	Range 18 to 65	Readmission (12 ±8 months)	No	RR: 0.31 (0.1 to 0.97) NNT: 9 (7 to 198) I²: 0%	Low	Summary estimate	(-) Trial-based evidence suggests no clear and convincing advantage for cognitive behavioural therapy over other - and sometime much less sophisticated - therapies for people with schizophrenia.
Xia, 2011, 8460b	Schizophrenia and other types of schizophrenia-like psychoses	Psychoeducation (any form) (51 per 100)	Standard care (72 per 100)	206 (2)	31 ±2	Readmission (27 ±13 months)	No	RR: 0.71 (0.56 to 0.89) NNT: 5 (3 to 13) I²: 68%	Low	Summary estimate	(+) Psychoeducation does seem to reduce relapse, readmission and encourage medication compliance, as well as reduce the length of hospital stay in these hospital-based studies of limited quality. The true size of effect is likely to be less than demonstrated in this review - but, nevertheless, some sort of psychoeducation could be clinically effective and potentially cost beneficial. It is not difficult to justify better, more applicable, research in this area aimed at fully investigating the effects of this promising approach.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Schizophrenia and other types of schizophrenia-like psychoses (Acute and transient psychotic disorders; Bipolar affective disorder; Induced delusional disorder; Other nonorganic psychotic disorders; Persistent delusional disorders; Schizoaffective disorders; Schizophrenia; Schizotypal disorder; Unspecified nonorganic psychosis)											
Pharoah, 2010, 6091b	Schizophrenia and other types of schizophrenia-like psychoses	Psychosocial intervention with relatives (Any family-based intervention) (39 per 100)	Standard care (50 per 100)	532 (9)	29 ±2	Hospital admission (15 ±8 months)	No	RR: 0.78 (0.63 to 0.98) NNT: 9 (5 to 100) I²: 31%	Low	Summary estimate	(?) Family intervention may reduce the number of relapse events and hospitalisations and would therefore be of interest to people with schizophrenia, clinicians and policy makers. However, the treatment effects of these trials may be overestimated due to the poor methodological quality. Further data from trials that describe the methods of randomisation, test the blindness of the study evaluators and implement the CONSORT guidelines would enable greater confidence in these findings.
Pharoah, 2010, 6091c	Schizophrenia and other types of schizophrenia-like psychoses	Psychosocial intervention with relatives (Any family-based intervention) (18 per 100)	Standard care (39 per 100)	228 (3)	28 ±4	Hospital admission (10 ±3 months)	No	RR: 0.46 (0.3 to 0.69) NNT: 5 (4 to 8) I²: 0%	Very low	Summary estimate	(?) Family intervention may reduce the number of relapse events and hospitalisations and would therefore be of interest to people with schizophrenia, clinicians and policy makers. However, the treatment effects of these trials may be overestimated due to the poor methodological quality. Further data from trials that describe the methods of randomisation, test the blindness of the study evaluators and implement the CONSORT guidelines would enable greater confidence in these findings.
Zou, 2013, 8663a	Schizophrenia	Self-management education interventions (6 per 100)	Standard care or were on a wait list. (10 per 100)	771 (7)	34 ±3	Readmission (10 ±3 months)	No	OR: 0.55 (0.39 to 0.77) NNT: 24 (17 to 47) I²: 0%	Low	Summary estimate	(+) The study concludes that self-management education intervention is a feasible and effective method for persons with schizophrenia and should be routinely offered to all persons with schizophrenia.
Severe/chronic mental disorders/illnesses											
Malone, 2007, 4860a	Severe mental illnesses and disordered personality	Community Mental Health Teams (25 per 100)	Standard or usual care (31 per 100)	587 (3)	Range 16 to 65	Hospital admission (30 ±10 months)	No	RR: 0.81 (0.67 to 0.97) NNT: 17 (10 to 108) I²: 28%	Low	Summary estimate	(?) Community mental health team management is not inferior to non-team standard care in any important respects and is superior in promoting greater acceptance of treatment. It may also be superior in reducing hospital admission and avoiding death by suicide. The evidence for CMHT based care is insubstantial considering the massive impact the drive toward community care has on patients, carers, clinicians and the community at large.

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Severe/chronic mental disorders/illnesses											
Morriss, 2013, 5399d	Schizophrenia or a nonaffective, non-organic serious or chronic mental illness based on standardised psychiatric criteria	Education/self-management (23 per 100)	Usual care (36 per 100)	625 (7)	32 ±4	Readmission (8 ±5 months)	No	RR: 0.64 (0.51 to 0.79) NNT: 8 (6 to 13) I²: 0%	Moderate	Sub-group by intervention: Training delivered to both patient and carer/health professional	(?) This review indicates that early warning signs interventions may have a positive effect on the proportions of people re-hospitalised and on rates of relapse, but not on time to recurrence. However, the overall quality of the evidence was very low, indicating that we do not know if early warning signs interventions will have similar effects outside trials and that it is very likely that further research will alter these estimates. Moreover, the early warning signs interventions were used alongside other psychological interventions, and we do not know if they would be effective on their own. They may be cost-effective due to reduced hospitalisation and relapse rates, but before mental health services consider routinely providing psychological interventions involving the early recognition and prompt management of early warning signs to adults with schizophrenia, further research is required to provide evidence of high or moderate quality regarding the efficacy of early warning signs interventions added to usual care without additional psychological interventions, or to clarify the kinds of additional psychological interventions that might aid its efficacy. Future RCTs should be adequately-powered, and designed to minimise the risk of bias and be transparently reported. They should also systematically evaluate resource costs and resource use, alongside efficacy outcomes and other outcomes that are important to people with serious mental illness and their carers.
Morriss, 2013, 5399j	Schizophrenia or a nonaffective, non-organic serious or chronic mental illness based on standardised psychiatric criteria	Education/self-management (30 per 100)	Usual care (49 per 100)	740 (3)	34 ±6	Time to readmission (10 ±4 months)	No	HR: 0.62 (0.46 to 0.83) NNT: 7 (5 to 16) I²: 0%	Moderate	Sub-group by intervention: Training delivered to both patient and carer/health professional	
Morriss, 2013, 5399a	Schizophrenia or a nonaffective, non-organic serious or chronic mental illness based on standardised psychiatric criteria	Education/self-management (17 per 100)	Usual care (36 per 100)	1457 (15)	33 ±3	Readmission (10 ±3 months)	No	RR: 0.48 (0.35 to 0.66) NNT: 4 (4 to 8) I²: 62%	Very low	Summary estimate	

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Mixed population											
Beswick, 2008 725a	Elderly in the community or being discharged from hospital	Community-based multifactorial intervention: geriatric assessment; community-based care; fall prevention; group education and counselling (35 per 100)	Usual care or minimum intervention (37 per 100)	20047 (41)	78 ±3	Hospital admission (7 ±4 months)	No	RR: 0.94 (0.91 to 0.97) NNT: 45 (30 to 90) I²: 43%	Moderate	Summary estimate	(+) Complex interventions can help elderly people to live safely and independently, and could be tailored to meet individuals' needs and preferences.
Tricco, 2014, 8899g	Frequent health care users	Coordination of care quality improvement strategies: Self- management (37 per 100)	Usual care, no intervention or other quality improvement strategies (46 per 100)	2475 (12)	20 ±20	Hospital admission (10 ±7 months)	No	RR: 0.80 (0.71 to 0.90) NNT: 11 (7 to 22) I²: 0%	Moderate	Sub-group by intervention: Self-management	(+) We found that quality improvement strategies for coordination of care reduced hospital admissions among patients with chronic conditions other than mental illness and reduced emergency department visits among older patients. Our results may help clinicians and policy-makers reduce utilization through the use of strategies that target the system (team changes, case management) and the patient (promotion of self-management).
Tricco, 2014, 8899e	Frequent health care users	Coordination of care quality improvement strategies: Team changes (changes to the primary health care team and how it functions, including routine patient visits with personnel other than the primary care physician, use of multidisciplinary teams and the expansion or revision of team members' professional roles) (36 per 100)	Usual care, no intervention or other quality improvement strategies (46 per 100)	2334 (12)	61 ±21	Hospital admission (10 ±10 months)	No	RR: 0.77 (0.67 to 0.87) NNT: 9 (7 to 17) I²: 46%	Low	Sub-group by intervention: Team changes	(+) We found that quality improvement strategies for coordination of care reduced hospital admissions among patients with chronic conditions other than mental illness and reduced emergency department visits among older patients. Our results may help clinicians and policy-makers reduce utilization through the use of strategies that target the system (team changes, case management) and the patient (promotion of self-management).
Tricco, 2014, 8899a	Frequent health care users	Coordination of care quality improvement strategies: Case management; Team changes; Promotion of self-management; Decision support; Clinical information system (37 per 100)	Usual care, no intervention or other quality improvement strategies (46 per 100)	4162 (18)	55 ±21	Hospital admission (11 ±9 months)	No	RR: 0.81 (0.72 to 0.91) NNT: 11 (8 to 24) I²: 58%	Low	Summary estimate	(+) We found that quality improvement strategies for coordination of care reduced hospital admissions among patients with chronic conditions other than mental illness and reduced emergency department visits among older patients. Our results may help clinicians and policy-makers reduce utilization through the use of strategies that target the system (team changes, case management) and the patient (promotion of self-management).

Table 10 continued. Graded effect estimates for health systems interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[e,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Mixed population											
Parker, 2002, 5937a	Elderly being discharged from hospital	Discharge arrangements: Discharge planning; Comprehensive geriatric assessment; Discharge support; Educational interventions (29 per 100)	Usual care (34 per 100)	8920 (35)	76 ±6	Readmission (27 ±13 months)	No	RR: 0.85 (0.76 to 0.95) NNT: 20 (12 to 60) I²: Unclear	Low	Summary estimate	(?) The evidence from these trials does not suggest that discharge arrangements have effects on mortality or length of hospital stay. This review supports the concept that arrangements for discharging older people from hospital can have beneficial effects on subsequent readmission rates. Interventions provided across the hospital-- community interface, both in hospital and in the patient's home, showed the largest effect. Evidence from RCTs is not available to support the general adoption of discharge planning protocols, geriatric assessment processes or discharge support schemes as means of improving discharge outcomes.

[a]Median hospitalisation event rate observed across the trials contributing to the pooled estimate. [b]Means and standard deviations for patient ages in years, unless otherwise specified. Mean of means and median ages in trials contributing to the pooled estimate. Not all included trials reported age in a form that could be averaged. [c]Means and standard deviations for length of follow-up across trials, unless otherwise specified. Mean of means, medians, and total study durations reported in trials contributing to the pooled estimate. Not all included trials reported follow-up in a form that could be averaged. [d]RR= risk ratio; OR=odds ratio; rR= rate ratio; HR= hazard ratio; RD= risk difference. [e]CI=confidence interval. [f]NNT= Number needed to treat to benefit by avoiding one hospital admission. gAs indicated in Table 2 : the symbol (+) denotes when review conclusions indicated an favourable overall balance of benefit to harm or the authors recommend use of intervention; the symbol (-) denotes when review conclusions indicated that there was not a favourable overall balance of benefit to harm or the authors recommended not to use the intervention; and the symbol (?) denotes when review conclusions indicated that the overall balance of benefit to harm was unclear, the authors did not comment on the overall balance of benefit to harm, or the authors indicated that more research was required before a recommendation regarding use of the intervention could be made.

Appendix 3.12 Graded effect estimates for diagnostic, medical, and surgical interventions that reduce emergency hospital admissions

Table 11. Graded effect estimates for diagnostic, medical, and surgical interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a,b]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[c]	Outcome (follow-up)[d]	ACSC	Effect (95% CI)[e,f] NNT (95% CI)[f,g] I^2%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Disease of the circulatory system											
Atrial fibrillation											
Stavrakis, 2012, 7417a	Persistent or permanent atrial fibrillation receiving atrioventricular junction ablation	Cardiac resynchronization therapy (5 per 100)	Right ventricular pacing (13 per 100)	325 (3)	69 ±4	Admission for heart failure (9 ±6 months)	Yes	RR: 0.38 (0.17 to 0.85) NNT: 12 (9 to 49) I^2: 15%	Moderate	Summary estimate	(?) Cardiac resynchronization therapy may be superior to RV pacing in patients undergoing AVJ ablation for AF. Further studies, adequately powered to detect clinical outcomes, are required.
Piccini, 2009, 6110a	Atrial fibrillation	Radiofrequency catheter ablation (8 per 100)	Control or antiarrhythmic drug therapy (54 per 100)	405 (3)	57 ±4	Admission for cardiovascular issues (12 months)	No	rR: 0.15 (0.1 to 0.23) NNT: 2 (2 to 2) I^2: Unclear	Low	Summary estimate	(+) Compared with a nonablation treatment strategy, PVI results in dramatically increased freedom from AF at 1 year. Although the procedure can be associated with major complications, the risk of these complications is comparable to other interventional procedures.
Nyong, 2016, 9307a	Persistent atrial fibrillation or long-standing persistent atrial fibrillation	Radiofrequency catheter ablation (5 per 100)	Antiarrhythmic drugs (20 per 100)	216 (2)	60 ±6	Admission for cardiovascular issues (10 ±4 months)	No	RR: 0.27 (0.1 to 0.72) NNT: 6 (5 to 18) I^2: 0%	Low	Summary estimate	(+) In people with non-paroxysmal atrial fibrillation, evidence suggests a superiority of RFCA to antiarrhythmic drugs in achieving freedom from atrial arrhythmias, reducing the need for cardioversion, and reducing cardiac-related hospitalisations. There was uncertainty surrounding the effect of RFCA with significant bradycardia (or need for a pacemaker), periprocedural complications, and other safety outcomes. Evidence should be interpreted with caution, as event rates were low and quality of evidence ranged from moderate to very low.
Angina pectoris or Acute myocardial infarction											
Choudhry, 2005, 1447a	Unstable angina or non-ST-segment elevation myocardial infarction	Early/routine coronary angiography (16 per 100)	Selective coronary angiography (symptom/stress test–driven angiography) (22 per 100)	6482 (5)	62 ±4	Readmission (7 ±4 months)	No	OR: 0.67 (0.48 to 0.94) NNT: 16 (10 to 95) I^2: p<0.1 heterogeneity	Low	Summary estimate	(+) For patients with unstable angina/non-ST-segment elevation MI, an invasive strategy reduces rates of fatal or nonfatal re-infarction and hospital readmission, but not all-cause mortality, when compared with a noninvasive strategy. These results suggest that an invasive management strategy should be considered for all patients with unstable angina/non-ST-segment elevation MI and perhaps in particular those with ST-segment depression.

Table 11 continued. Graded effect estimates for diagnostic, medical, and surgical interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a,b]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[c]	Outcome (follow-up)[d]	ACSC	Effect (95% CI)[e,f] NNT (95% CI)[f,g] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Angina pectoris or Acute myocardial infarction											
Fanning, 2016, 9247a	Unstable angina or non–ST-segment elevation myocardial infarction	Early/routine coronary angiography (9 per 100)	Selective coronary angiography (symptom/stress test–driven angiography) (12 per 100)	6921 (6)	Unclear	Readmission (8 ±5 months)	No	RR: 0.77 (0.63 to 0.94) NNT: 36 (22 to 137) I²: 54%	Moderate	Summary estimate	(-) In the all-study analysis, the evidence failed to show appreciable benefit with routine invasive strategies for unstable angina and non- ST elevation MI compared to conservative strategies in all-cause mortality and death or non-fatal MI at six to 12 months. There was evidence of risk reduction in MI, refractory angina and re-hospitalisation with routine invasive strategies compared to conservative (selective invasive) strategies at six to 12 months follow-up. However, routine invasive strategies were associated with a relatively high risk (almost double the risk) of procedure-related MI, and increased risk of bleeding complications. This systematic analysis of published RCTs supports the conclusion that, in patients with UA/NSTEMI, a selectively invasive (conservative) strategy based on clinical risk for recurrent events is the preferred management strategy.
Fanning, 2016, 9247c	Unstable angina or non–ST-segment elevation myocardial infarction	Early/routine coronary angiography (12 per 100)	Selective coronary angiography (symptom/stress test–driven angiography) (17 per 100)	2901 (3)	Unclear	Readmission (8 ±5 months)	No	RR: 0.71 (0.54 to 0.94) NNT: 7 (13 to 98) I²: 30%	Moderate	Sub-group by intervention: No routine glycoprotein IIb/IIIa receptor antagonist use	(-) In the all-study analysis, the evidence failed to show appreciable benefit with routine invasive strategies for unstable angina and non- ST elevation MI compared to conservative strategies in all-cause mortality and death or non-fatal MI at six to 12 months. There was evidence of risk reduction in MI, refractory angina and re-hospitalisation with routine invasive strategies compared to conservative (selective invasive) strategies at six to 12 months follow-up. However, routine invasive strategies were associated with a relatively high risk (almost double the risk) of procedure-relatedMI, and increased risk of bleeding complications. This systematic analysis of published RCTs supports the conclusion that, in patients with UA/NSTEMI, a selectively invasive (conservative) strategy based on clinical risk for recurrent events is the preferred management strategy.

Table 11 continued. Graded effect estimates for diagnostic, medical, and surgical interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a,b]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[c]	Outcome (follow-up)[d]	ACSC	Effect (95% CI)[e,f] NNT (95% CI)[f,g] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Angina pectoris or Acute myocardial infarction											
Mehta, 2005, 5183a	Unstable angina or non–ST-segment elevation myocardial infarction	Early/routine coronary angiography (28 per 100)	Selective coronary angiography (symptom/stress test–driven angiography) (37 per 100)	9147 (7)	62 ±3	Readmission (13 ±15 months)	No	OR: 0.66 (0.6 to 0.72) NNT: 11 (9 to 14) I²: p<0.1 heterogeneity	Low	Summary estimate	(?) A routine invasive strategy exceeded a selective invasive strategy in reducing MI, severe angina, and rehospitalization over a mean follow-up of 17 months. But routine intervention was associated with a higher early mortality hazard and a trend toward a mortality reduction at follow-up. Future strategies should explore ways to minimize the early hazard and enhance later benefits by focusing on higher-risk patients and optimizing timing of intervention and use of proven therapies.
Heart failure											
Bradely, 2003 930a	Heart failure	Cardiac resynchronization therapy (12 per 100)	Resynchronization off (16 per 100)	1497 (3)	65 ±1	Admission for heart failure (9 ±3 months)	Yes	OR: 0.71 (0.53 to 0.96) NNT: 25 (15 to 186) I²: p>0.1 heterogeneity	Moderate	Summary estimate	(+) Cardiac resynchronization reduces mortality from progressive heart failure in patients with symptomatic left ventricular dysfunction. This finding suggests that cardiac resynchronization may have a substantial impact on the most common mechanism of death among patients with advanced heart failure. Cardiac resynchronization also reduces heart failure hospitalization and shows a trend toward reducing all-cause mortality.
Kang, 2015, 8797a	Heart failure with reduced left ventricular ejection fraction (<= 40%)	Cardiac resynchronization therapy (14 per 100)	Left ventricular pacing (22 per 100)	7511 (16)	64 ±3	Admission for heart failure (9 ±5 months)	Yes	OR: 0.59 (0.47 to 0.74) NNT: 13 (10 to 21) I²: 54%	Moderate	Summary estimate	(+) This meta-regression analysis implies that patients with a QRS duration ≥ 150 ms would most benefit from CRT, and in those with a QRS duration < 130 ms CRT implantation may be potentially harmful.
Al-Majed, 2011, 212a	Heart failure with reduced left ventricular ejection fraction (<=40%)	Cardiac resynchronization therapy (13 per 100)	Inactive pacing, right ventricular pacing alone, left ventricular pacing alone, implantable cardioverter-defibrillator alone, or usual care (19 per 100)	3393 (15)	66 ±4	Admission for heart failure (12 ±12 months)	Yes	RR: 0.69 (0.58 to 0.82) NNT: 7 (13 to 29) I²: 50%	Very low	Summary estimate	(+) Cardiac resynchronization therapy is beneficial for patients with reduced left ventricular ejection fraction, symptoms of heart failure, and prolonged QRS, regardless of NYHA class.

Table 11 continued. Graded effect estimates for diagnostic, medical, and surgical interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a,b]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[c]	Outcome (follow-up)[d]	ACSC	Effect (95% CI)[e,f] NNT (95% CI)[f,g] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Heart failure											
Al-Majed, 2011, 212d	Heart failure with reduce left ventricular ejection fration (<35%) and only patients with New York Heart Association class I or II symptoms	Cardiac resynchronization therapy (9 per 100)	Inactive pacing, right ventricular pacing alone, left ventricular pacing alone, implantable cardioverter-defibrillator alone, or usual care (14 per 100)	3863 (2)	64 ±1	Admission for heart failure (7 ±4 months)	Yes	RR: 0.69 (0.59 to 0.8) NNT: 23 (18 to 37) I²: 0%	Low	Sub-group by disease severity: Exclusively patients with New York Heart Association class I or II symptoms	(+) Cardiac resynchronization therapy is beneficial for patients with reduced left ventricular ejection fraction, symptoms of heart failure, and prolonged QRS, regardless of NYHA class.
Al-Majed, 2011, 212b	Heart failure with reduce left ventricular ejection fration (<35%) and predominantly New York Heart Association class III or IV symptoms	Cardiac resynchronization therapy (12 per 100)	Inactive pacing, right ventricular pacing alone, left ventricular pacing alone, implantable cardioverter-defibrillator alone, or usual care (19 per 100)	593 (11)	66 ±4	Admission for heart failure (9 ±4 months)	Yes	RR: 0.65 (0.50 to 0.86) NNT: 7 (11 to 38) I²: 57%	Very low	Sub-group by disease severity: Predominantly New York Heart Association class III or IV symptoms	(+) Cardiac resynchronization therapy is beneficial for patients with reduced left ventricular ejection fraction, symptoms of heart failure, and prolonged QRS, regardless of NYHA class.
Xin, 2015, 8464b	Heart failure	Natriuretic peptide (BNP or NT-proBNP) guided therapy (29 per 100)	Clinically guided therapy (36 per 100)	2572 (11)	72 ±5	Admission for heart failure (20 ±8 months)	Yes	RR: 0.79 (0.63 to 0.98) NNT: 13 (7 to 139) I²: 67%	Low	Summary estimate	(?) BNP-guided therapy seemed to be safe and promising for CHF patients, and future studies with well- designed BNP-guided medication up-titration strategies are needed to confirm these results.
McLellan, 2016, 9300i	Heart failure	Natriuretic peptide (BNP or NT-proBNP) guided therapy (23 per 100)	Clinically guided therapy (36 per 100)	814 (5)	68 ±4	Admission for heart failure (9 ±3 months)	Yes	RR: 0.63 (0.49 to 0.81) NNT: 8 (5 to 15) I²: 68%	Low	Sub-group by study quality: Studies with low risk of bias for attrition	(?) In patients with heart failure low-quality evidence showed a reduction in heart failure admission with NP-guided treatment while lowquality evidence showed uncertainty in the effect of NP-guided treatment for all-cause mortality, heart failure mortality, and all-cause admission. Uncertainty in the effect was further shown by very low-quality evidence for patient's quality of life. The evidence for adverse events and cost of treatment was low quality and we were unable to pool results.
McLellan, 2016, 9300g	Heart failure	Natriuretic peptide (BNP or NT-proBNP) guided therapy (33 per 100)	Clinically guided therapy (40 per 100)	1318 (6)	73 ±2	Admission for heart failure (15 ±13 months)	Yes	RR: 0.83 (0.71 to 0.98) NNT: 15 (9 to 125) I²: 38%	Moderate	Sub-group by study quality: Studies with low risk of bias for blinding of outcome assessment	
McLellan, 2016, 9300c	Heart failure	Natriuretic peptide (BNP or NT-proBNP) guided therapy (28 per 100)	Clinically guided therapy (40 per 100)	1609 (10)	71 ±7	Admission for heart failure (15 ±13 months)	Yes	RR: 0.70 (0.60 to 0.81) NNT: 8 (6 to 13) I²: 57%	Low	Sub-group by intervention: Clinical assessment	

Table 11 continued. Graded effect estimates for diagnostic, medical, and surgical interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a,b]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[c]	Outcome (follow-up)[d]	ACSC	Effect (95% CI)[e,f] NNT (95% CI)[f,g] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Diseases of the respiratory system											
Pneumothorax											
Aguinagalde, 2010, 119a	Idiopathic spontaneous pneumothorax	Percutaneous aspiration of plural cavity (11 per 100)	Chest tube drainage of the plural cavity (29 per 100)	197 (2)	26 ±3	Hospital readmission (5 ±2 months)	No	RR: 0.37 (0.18 to 0.75) NNT: 6 (4 to 14) I²: Unclear	Moderate	Summary estimate	(+) As has been observed in this review, it seems that in terms of immediate results, the drainage tube may be more effective, but that this effect disappears after 1 week and does not persist in the long term. In addition, it should be pointed out that the percutaneous aspiration strategy requires less material and human resources and that the number of hospital admissions is much lower. For this reason, it would appear reasonable to begin with aspiration and to consider chest tube drainage as a backup technique.
Factors influencing health status and contact with health services											
Patients receiving surgery											
Wang, 2014, 8910d	Gastrointestinal surgery for cancer	Laparoscopic surgery with fast track rehabilitation (7 per 100)	Open surgery with fast track rehabilitation (15 per 100)	671 (6)	67 ±6	Readmission (1 month)	No	RR: 0.45 (0.29 to 0.71) NNT: 12 (10 to 23) I²: 14%	Moderate	Summary estimate	(?) Fast-tracks are safe after gastrointestinal surgery. Additional large, prospective RCTs should be conducted to establish further the safety of this approach.
Sajid, 2012, 6764a	Cholecystectomy: laparoscopic, laparoscopic converted to open, and open	Routine on-table cholangiography (0.4 per 100)	No on-table cholangiography (4 per 100)	465 (2)	Unclear	Readmission secondary to retained common bile duct stones (8 ±4 months)	No	OR: 0.01 (0.01 to 0.78) NNT: 29 (26 to 122) I²: 0%	Low	Summary estimate	(?) N-OTC is associated with shorter operative time and fewer peri-operative complications, and it is comparable to R-OTC in terms of CBD injury risk during cholecystectomy. R-OTC is helpful for peri-operative CBD stone detection and there is therefore reduced readmission for retained CBD stones. The N-OTC approach may be adopted routinely for patients undergoing laparoscopic cholecystectomy providing there are no clinical, biochemical or radiological features suggestive of CBD stones. However, a major multicentre randomised controlled trial is required to validate this conclusion.

Table 11 continued. Graded effect estimates for diagnostic, medical, and surgical interventions that reduce emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a,b]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[c]	Outcome (follow-up)[d]	ACSC	Effect (95% CI)[e,f] NNT (95% CI)[f,g] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Multi-morbidity											
Charytan, 2009, 1340a	Acute coronary syndromes with non-ST segment, Stages 3 to 5 chronic kidney disease	Early/routine coronary angiography (10 per 100)	Selective coronary angiography (symptom/stress test–driven angiography) (14 per 100)	7481 (5)	63 ±3	Readmission (7 ±4 months)	No	RR: 0.76 (0.66 to 0.87) NNT: 31 (22 to 56) I²: 0%	Moderate	Summary estimate	(+) This collaborative study suggests that the benefits of an early invasive strategy are preserved in patients with CKD and that an early invasive approach reduces the risk for rehospitalization and is associated with trends of reduction in the risk for death and nonfatal re-infarction in patients with CKD. Coronary angiography should be considered for patients who have CKD and are admitted with non–ST elevation acute coronary syndromes.

[a]Median hospitalisation event rate observed across the trials contributing to the pooled estimate. [b]Intervention, comparison, and outcome abbreviations: BNP=b-type natriuretic peptide; NT-proBNP=N-terminal pro b-type Natriuretic Peptide. [c]Means and standard deviations for patient ages in years, unless otherwise specified. Mean of means and median ages in trials contributing to the pooled estimate. Not all included trials reported age in a form that could be averaged. [d]Means and standard deviations for length of follow-up across trials, unless otherwise specified. Mean of means, medians, and total study durations reported in trials contributing to the pooled estimate. Not all included trials reported follow-up in a form that could be averaged. [e]RR= risk ratio; OR=odds ratio; rR= rate ratio; HR= hazard ratio; RD= risk difference. [f]CI=confidence interval. [g]NNT= Number needed to treat to benefit by avoiding one hospital admission. gAs indicated in Table 2 : the symbol (+) denotes when review conclusions indicated an favourable overall balance of benefit to harm or the authors recommend use of intervention; the symbol (-) denotes when review conclusions indicated that there was not a favourable overall balance of benefit to harm or the authors recommended not to use the intervention; and the symbol (?) denotes when review conclusions indicated that the overall balance of benefit to harm was unclear, the authors did not comment on the overall balance of benefit to harm, or the authors indicated that more research was required before a recommendation regarding use of the intervention could be made.

Appendix 3.13 Graded effect estimates for interventions that increase emergency hospital admissions

Table 12. Graded effect estimates for interventions that increase emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[d,f] I^2%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Disease of the circulatory system											
Atrial fibrillation											
Cordina, 2005, 1606a	Paroxysmal, sustained, or permanent atrial fibrillation or atrial flutter	Rhythm medications (antiarrhythmic drugs) (49 per 100)	Rate control medications (rate control drugs) (42 per 100)	4312 (2)	65 ±6	Hospital admission (27 ±21 months)	No	RR: 1.16 (1.11 to 1.22) NNT: 15 (11 to 22) I^2: 97%	Low	Summary estimate	(-) There is no evidence that pharmacological cardioversion of atrial fibrillation to sinus rhythmis superior to rate control. Rhythm control is associated with more adverse effects and increased hospitalisation. It does not reduce the risk of stroke. The conclusions cannot be generalised to all people with atrial fibrillation. Most of the patients included in these studies were relatively older (>60 years) with significant cardiovascular risk factors.
Heart Failure											
Heran, 2012, 3275e	Heart failure, any ejection fraction	Angiotensin II receptor blocker (39 per 100)	Placebo (37 per 100)	9449 (4)	68 ±3	Hospital admission (31 ±20 months)	No	RR: 1.06 (1.01 to 1.12) NNT: 45 (23 to 272) I^2: 0%	Very low	Summary estimate	(-) In patients with symptomatic HF and systolic dysfunction or with preserved ejection fraction, ARBs compared to placebo or ACEIs do not reduce total mortality or morbidity. Adding an ARB in combination with an ACEI does not reduce total mortality or total hospital admission but increases withdrawals due to adverse effects compared with ACEI alone.

Table 12 continued. Graded effect estimates for interventions that increase emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[d,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Diseases of the respiratory system											
Other chronic obstructive pulmonary disease											
Kew, 2014, 4004o	Moderate to severe chronic obstructive pulmonary disease	Budesonide (4.5 per 100)	Placebo (1.3 per 100)	867 (3)	63 ±0.2	Admission for pneumonia (Range 6 to 48 months)	Yes	OR: 3.47 (1.11 to 10.83) NNT: 31 (9 to 685) I²: 0%	Low	Sub-group by comparison: Placebo	(?) Budesonide and fluticasone, delivered alone or in combination with a LABA, are associated with increased risk of serious adverse pneumonia events, but neither significantly affected mortality compared with controls. The safety concerns highlighted in this review should be balanced with recent cohort data and established randomised evidence of efficacy regarding exacerbations and quality of life. Comparison of the two drugs revealed no statistically significant difference in serious pneumonias, mortality or serious adverse events. Fluticasone was associated with higher risk of any pneumonia when compared with budesonide (i.e. less serious cases dealt with in the community), but variation in the definitions used by the respective manufacturers is a potential confounding factor in their comparison. Primary research should accurately measure pneumonia outcomes and should clarify both the definition and the method of diagnosis used, especially for new formulations and combinations for which little evidence of the associated pneumonia risk is currently available. Similarly, systematic reviews and cohorts should address the reliability of assigning 'pneumonia' as an adverse event or cause of death and should determine how this affects the applicability of findings.
Kew, 2014, 4004r	Moderate to severe chronic obstructive pulmonary disease	Budesonide (with or without formoterol) (1.4 per 100)	Controls (placebo or formoterol) (0.7 per 100)	4659 (6)	64 ±1	Admission for pneumonia (8 ±4 months)	Yes	OR: 2.02 (1.15 to 3.57) NNT: 141 (57 to 954) I²: 4%	Low	Sub-group by intervention: Budesonide 640 mcg (320 mcg bid)	
Kew, 2014, 4004y	Moderate to severe chronic obstructive pulmonary disease	Budesonide (with or without formoterol) (1 per 100)	Controls (placebo or formoterol) (0.3 per 100)	3515 (4)	65 ±2	Admission for pneumonia (7 ±3 months)	Yes	OR: 3.28 (1.22 to 8.81) NNT: 133 (40 to 1369) I²: 0%	Low	Sub-group by study quality: Trials at high risk of bias removed	
Kew, 2014, 4004z	Moderate to severe chronic obstructive pulmonary disease	Fluticasone (with or without long acting beta2-agonist) (1.4 per 100)	Controls (placebo or long acting beta2-agonist) (0.8 per 100)	16338 (15)	64 ±1	Admission for pneumonia (12 ±11 months)	Yes	OR: 1.82 (1.52 to 2.19) NNT: 164 (114 to 259) I²: 0%	High	Sub-group by study quality: Trials at high risk of bias removed	
Factors influencing health status and contact with health services											
Patients presenting to primary care											
Laurant, 2005, 9181a	Patients presenting to primary care	Nurse-led primary care (12 per 100)	Physician-led primary care (11 per 100)	15860 (3)	45	Hospital admission (6 ±4 months)	No	RR: 1.17 (1.04 to 1.31) NNT: 56 (31 to 238) I²: 40%	Moderate	Summary estimate	(+) The findings suggest that appropriately trained nurses can produce as high-quality care as primary care doctors and achieve as good health outcomes for patients. However, this conclusion should be viewed with caution given that only one study was powered to assess equivalence of care, many studies had methodological limitations, and patient follow-up was generally 12 months or less. While doctor-nurse substitution has the potential to reduce doctors' workload and direct healthcare costs, achieving such reductions depends on the particular context of care. Doctors' workload may remain unchanged either because nurses are deployed to meet previously unmet patient need or because nurses generate demand for care where previously there was none. Savings in cost depend on the magnitude of the salary differential between doctors and nurses, and may be offset by the lower productivity of nurses compared to doctors.

Table 12 continued. Graded effect estimates for interventions that increase emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[d,f] I^2%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Special screening examination for neoplasms											
Yang, 2015, 8918n	Patients undergoing prostate biopsy	Single drug (3 per 100)	Combined drugs (0.5 per 100)	659 (3)	Unclear	Hospital admission (0.55 ± 0.66 months)	No	RR: 5.91 (2.2 to 15.87) NNT: 38 (13 to 157) I^2: 0%	Low	Summary estimate	(+) Prophylactic antibiotics could be beneficial for the reduction of infective complications after TRPB. Single-dose or short-course oral administration with any type of antibiotic appears to be optimal. One additional type of antibiotic added to the basic antibiotic agent may contribute to the minimization of severe infection and drug resistance.
Mental and behavioural disorders											
Schizophrenia and other types of schizophrenia-like psychoses (Acute and transient psychotic disorders; Bipolar affective disorder; Induced delusional disorder; Other nonorganic psychotic disorders; Persistent delusional disorders; Schizoaffective disorders; Schizophrenia; Schizotypal disorder; Unspecified nonorganic psychosis)											
Marshall, 1998, 4966a	Schizophrenia and schizophrenia-like disorders, bipolar disorder or depression with psychotic features	Case management (34 per 100)	Standard care (22 per 100)	1300 (6)	45 ±5	Hospital admission (13 ±5 months)	No	OR: 1.84 (1.43 to 2.37) NNT: 8 (6 to 15) I^2: 61%	Low	Summary estimate	(?) Case management ensures that more people remain in contact with psychiatric services (one extra person remains in contact for every 15 people who receive case management), but it also increases hospital admission rates. Present evidence suggests that case management also increases duration of hospital admissions, but this is not certain. Whilst there is some evidence that case management improves compliance, it does not produce clinically significant improvement in mental state, social functioning, or quality of life. There is no evidence that case management improves outcome on any other clinical or social variables. Present evidence suggests that case management increases health care costs, perhaps substantially, although this is not certain. In summary, therefore, case management is an intervention of questionable value, to the extent that it is doubtful whether it should be offered by community psychiatric services. It is hard to see how policymakers who subscribe to an evidence-based approach can justify retaining case management as 'the cornerstone' of community mental health care. Case management is compared to the main alternative approach (ACT) in a forthcoming Cochrane review.
Sampson, 2013, 6806f	Schizophrenia and other types of schizophrenia-like psychoses	Intermittent drug technique (specific drug) (38 per 100)	Maintenance therapy (24 per 100)	661 (6)	35 ±5	Hospital admission (21 ±7 months)	No	RR: 1.58 (1.28 to 1.97) NNT: 7 (4 to 15) I^2: 19%	Low	Summary estimate	(-) Results of this review support the existing evidence that intermittent antipsychotic treatment is not as effective as continuous, maintained antipsychotic therapy in preventing relapse in people with schizophrenia. More research is needed to assess any potential benefits or harm of intermittent treatment regarding adverse effects typically associated with maintained antipsychotic treatment, as well as any cost-effectiveness of this experimental treatment.

Table 12 continued. Graded effect estimates for interventions that increase emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[d,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Severe mental illnesses and disordered personality											
Buckley, 2015, 8733c	Schizophrenia and other types of schizophrenia-like psychoses	Supportive therapy: interventions provided by a single person with the main purpose of maintaining current functioning or assisting pre-existing coping abilities. A number of common therapies were excluded as they are designed to teach new skills or change pre-existing skills: cognitive behavioural therapy, social skills training, psycho-education, compliance therapy and problem-solving therapy. (21 per 100)	Any other psychological or psychosocial treatment (12 per 100)	306 (4)	Range 18 to 65	Hospital admission (34 ±50 months)	No	RR: 1.82 (1.11 to 2.99) NNT: 11 (79 to 4) I²: 13%	Very low	Summary estimate	(?) There are insufficient data to identify a difference in outcome between supportive therapy and standard care. There are several outcomes, including hospitalisation and general mental state, indicating advantages for other psychological therapies over supportive therapy but these findings are based on a few small studies where we graded the evidence as very low quality. Future research would benefit from larger trials that use supportive therapy as the main treatment arm rather than the comparator.
Mixed population											
Baigent, 2013, 1653a	Patients indicated for treatment with non-steroidal anti-inflammatory drugs: Rheumatoid arthritis; Osteoarthritis; Colorectal adenomata; Alzheimer's disease	Cox-2-inhibitors (59 per 100)	Placebo (26 per 100)	88367 (184)	Unclear	Admission for heart failure (Unclear)	Yes	rR: 2.28 (1.62 to 3.2) NNT: 3 (2 to 6) I²: Unclear	Moderate	Summary estimate	(?) The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs. Although NSAIDs increase vascular and gastrointestinal risks, the size of these risks can be predicted, which could help guide clinical decision making.

Table 12 continued. Graded effect estimates for interventions that increase emergency hospital admissions

Author, Year, Estimate ID	Population description	Intervention (Event rate)[a]	Comparison (Event rate)[a]	Patients (RCTs)	Patient age[b]	Outcome (follow-up)[c]	ACSC	Effect (95% CI)[d,e] NNT (95% CI)[d,f] I²%	Quality of evidence (GRADE)	Notes	Abstract conclusion and categorisation of overall balance of benefit to harm (+ - ?)[g]
Neoplasms											
Gupta, 2014, 8688a	Symptomatic uterine fibroids	Uterine artery embolization (27 per 100)	Myomectomy (13 per 100)	278 (2)	39 ±9	Readmission (9 ±4 months)	No	RD: 0.14 (0.05 to 0.22) NNT: 7 (5 to 20) I²: 86%	Low	Summary estimate	(?) When we compared patient satisfaction rates at up to two years following UAE versus surgery (myomectomy or hysterectomy) our findings are that there is no evidence of a difference between the interventions. Findings at five year follow-up were similarly inconclusive. There was very low quality evidence to suggest that myomectomy may be associated with better fertility outcomes than UAE, but this information was only available from a selected subgroup in one small trial. We found no clear evidence of a difference between UAE and surgery in the risk of major complications, but UAE was associated with a higher rate of minor complications and an increased likelihood of requiring surgical intervention within two to five years of the initial procedure. If we assume that 7% of women will require further surgery within two years of hysterectomy or myomectomy, between 15% and 32% will require further surgery within two years of UAE. This increase in the surgical re-intervention rate may balance out any initial cost advantage of UAE. Thus although UAE is a safe, minimally invasive alternative to surgery, patient selection and counselling are paramount due to the much higher risk of requiring further surgical intervention.

[a]Median hospitalisation event rate observed across the trials contributing to the pooled estimate. [b]Means and standard deviations for patient ages in years, unless otherwise specified. Mean of means and median ages in trials contributing to the pooled estimate. Not all included trials reported age in a form that could be averaged. [c]Means and standard deviations for length of follow-up across trials, unless otherwise specified. Mean of means, medians, and total study durations reported in trials contributing to the pooled estimate. Not all included trials reported follow-up in a form that could be averaged. [d]RR= risk ratio; OR=odds ratio. [e]CI=confidence interval. [f]NNT= Number needed to treat to benefit by avoiding one hospital admission. gAs indicated in Table 2 : the symbol (+) denotes when review conclusions indicated an favourable overall balance of benefit to harm or the authors recommend use of intervention; the symbol (-) denotes when review conclusions indicated that there was not a favourable overall balance of benefit to harm or the authors recommended not to use the intervention; and the symbol (?) denotes when review conclusions indicated that the overall balance of benefit to harm was unclear, the authors did not comment on the overall balance of benefit to harm, or the authors indicated that more research was required before a recommendation regarding use of the intervention could be made.

Appendix 3.14 Summary details of GRADE ratings

Table 13. Summary details of GRADE ratings

Estimate ID	GRADE provided in review	GRADE rating	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias
85a	No	Very low	-1	0	0	-1	-1
100c	No	Moderate	0	0	0	0	0
119a	No	Moderate	0	0	0	0	-1
212a	No	Very low	-1	-1	0	0	-1
212b	No	Very low	-1	-1	0	0	-1
212d	No	Low	-1	0	0	0	-1
593	Yes	Very low	0	0	0	0	0
725a	No	Moderate	-1	0	0	0	0
930a	No	Moderate	-1	0	0	0	0
1021	No	Moderate	0	-1	0	0	0
1164	Yes	Very low	0	0	0	0	0
1264	No	Low	0	0	0	0	0
1340a	No	Moderate	-1	0	0	0	0
1438a	Yes	Moderate	0	0	0	0	0
1447a	No	Low	-1	-1	0	0	0
1606a	No	Low	0	0	0	0	0
1629a	No	Moderate	0	0	0	0	0
1653a	No	Moderate	0	0	0	0	0
1752a	No	Moderate	0	0	0	0	0
2159	Yes	Moderate	0	0	0	0	0
2359c	Yes	High	0	0	0	0	0
2359h	Yes	High	0	0	0	0	0
2359l	Yes	High	0	0	0	0	0
2599a	No	Moderate	0	0	0	0	0
2640b	No	Low	0	0	0	0	0
2811a	No	Low	-1	0	0	0	-1
2811g	No	Very low	-1	-1	0	0	-1
2933a	Yes	Moderate	0	0	0	0	0
3030a	No	Moderate	-1	0	0	0	0
3275d	Yes	Low	0	0	0	0	0
3275e	Yes	Very low	0	0	0	0	0
3275l	Yes	Very low	0	0	0	0	0
3362a	No	Low	-1	0	0	0	-1
3400a	No	Low	-1	-1	0	0	0
3400b	No	Moderate	-1	0	0	0	0
3415	No	High	0	0	0	0	0
3639f	No	Low	0	0	0	0	0
3640b	No	Low	0	0	0	0	0
3640d	No	Low	0	0	0	0	0
3657	No	Moderate	0	0	0	0	0
3709a	Yes	Moderate	0	0	0	0	0
3769e	No	Low	0	0	0	-1	-1
3781d	No	Moderate	0	0	0	0	0
4002h	No	High	0	0	0	0	0
4003a	Yes	Moderate	0	0	0	0	0
4003e	No	Low	0	0	0	0	0
4004o	No	Low	0	0	0	0	0
4004r	No	Low	0	0	0	0	0
4004y	No	Low	0	0	0	0	0
4004z	No	High	0	0	0	0	0
4065a	No	Moderate	0	0	0	0	0
4067b	No	Low	0	0	0	0	0
4123b	No	Moderate	0	0	0	0	0
4123i	No	Moderate	0	0	0	0	0
4147a	No	Low	-1	-1	0	0	0
4154a	No	Moderate	-1	0	0	0	0
4192c	Yes	High	0	0	0	0	0
4206a	No	Moderate	0	0	0	0	0
4206c	No	Moderate	0	0	0	0	0
4260	No	Moderate	0	0	0	0	0
4305a	No	Moderate	0	-1	0	0	0
4305d	No	Low	-1	0	0	-1	0
4305f	No	Moderate	0	-1	0	0	0
4305i	No	High	0	0	0	0	0
4494a	No	Moderate	0	0	0	0	-1
4508a	Yes	High	0	0	0	0	0
4615d	No	Low	0	0	0	0	0
4615e	No	Very Low	0	0	0	0	0
4629a	No	Moderate	0	0	0	0	0
4812a	No	Low	0	0	0	0	0
4838a	No	Low	0	0	0	0	0
4838b	No	Moderate	0	0	0	0	0
4844	No	Moderate	0	0	0	0	0

Table 13 continued. Summary details of GRADE ratings

Estimate ID	GRADE provided in review	GRADE rating	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias
4860a	No	Low	-1	0	0	-1	0
4966a	No	Low	-1	-1	0	0	0
4968a	No	Low	-1	-1	0	0	0
4987a	No	Moderate	-1	0	0	0	0
5145a	No	Very low	-1	0	0	-1	-1
5147a	No	Low	-1	0	0	0	-1
5183a	No	Low	-1	-1	0	0	0
5371	No	Very Low	0	0	0	0	0
5398a	No	Low	-1	0	0	-1	0
5399a	Yes	Very low	0	0	0	0	0
5399d	No	Moderate	-1	0	0	0	0
5399j	No	Moderate	0	0	0	-1	0
5533g	No	Low	0	0	0	0	0
5606	No	Moderate	0	0	0	0	0
5937a	No	Low	-1	-1	0	0	0
6091b	Yes	Low	0	0	0	0	0
6091c	No	Very low	-1	0	-1	-1	-1
6099a	No	Low	-1	-1	0	0	0
6099e	No	Moderate	-1	0	0	0	0
6099f	No	Moderate	-1	0	0	0	0
6099h	No	Moderate	-1	0	0	0	0
6110a	No	Low	-1	0	0	0	-1
6360b	No	Low	-1	-1	0	0	0
6360d	No	Low	-1	-1	0	0	0
6360f	No	Moderate	-1	0	0	0	0
6442a	Yes	Low	0	0	0	0	0
6552i	No	High	0	0	0	0	0
6552m	No	Moderate	-1	0	0	0	0
6552p	No	High	0	0	0	0	0
6564a	No	Low	0	0	0	0	0
6568a	No	Moderate	0	0	0	0	0
6670	No	Low	0	0	0	0	0
6677	No	Low	0	0	0	0	0
6746b	No	High	0	0	0	0	0
6764a	No	Low	-1	0	0	-1	0
6797a	No	Low	0	0	0	0	0
6797b	No	Low	0	0	0	0	0
6797d	No	Low	0	0	0	0	0
6806f	No	Low	0	0	0	0	0
7029b	No	Moderate	0	0	0	0	0
7279b	No	Low	-1	-1	0	0	0
7417a	No	Moderate	0	0	0	-1	0
7484a	No	Moderate	0	0	0	0	0
7504	No	Low	0	0	0	0	0
7600a	No	Low	-1	-1	0	0	0
7600c	No	Moderate	-1	0	0	0	0
7600e	No	High	0	0	0	0	0
7600j	No	Low	-2	0	0	0	0
7600k	No	Low	-2	0	0	0	0
7600n	No	Moderate	-1	0	0	0	0
7624a	No	High	0	0	0	0	0
7636c	No	Moderate	0	0	0	-1	0
7651a	No	Low	-1	0	0	-1	0
7651b	No	Low	-1	0	0	-1	0
7723c	No	High	0	0	0	0	0
7723i	No	Moderate	0	0	0	-1	0
7723m	No	Moderate	-1	0	0	0	0
7724i	No	Low	-1	0	0	-1	0
7820a	No	Low	-1	0	0	-1	0
7820b	No	Low	-1	0	0	-1	0
7820c	No	Low	-1	0	0	0	-1
7820f	No	Very low	-1	0	0	-1	-1
8460b	Yes	Low	0	0	0	0	0
8464b	No	Low	-1	-1	0	0	-1
8511a	No	Low	0	0	0	0	0
8604b	No	Low	0	0	0	0	0
8604f	No	Low	0	0	0	0	0
8663a	No	Low	-1	0	0	-1	0
8672a	Yes	Moderate	0	0	0	0	0
8672b	Yes	Moderate	0	0	0	0	0
8688a	No	Low	0	-1	0	-1	0
8692e	No	Low	0	0	-1	0	0
8716a	Yes	Low	0	0	0	0	0
8729a	No	High	0	0	0	0	0
8733c	Yes	Very low	0	0	0	0	0
8742a	No	Low	0	0	0	0	0
8744d	No	Moderate	0	0	0	0	0

Table 13 continued. Summary details of GRADE ratings

Estimate ID	GRADE provided in review	GRADE rating	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias
8747a	No	Low	0	0	0	0	0
8747b	No	Low	0	0	0	0	0
8761a	Yes	High	0	0	0	0	0
8761b	Yes	Moderate	0	0	0	0	0
8762a	No	Moderate	0	0	0	-1	0
8769b	Yes	Low	0	0	0	0	0
8770b	No	Low	0	0	0	0	0
8776a	No	Moderate	-1	0	0	0	0
8784a	No	Low	0	0	0	0	0
8787c	No	Very low	0	-1	0	-1	-1
8787d	No	Very low	-1	-1	0	-1	-1
8787h	No	Very low	-1	-1	0	0	-1
8787p	No	Very low	-1	-1	0	0	-1
8787t	No	Moderate	0	0	0	0	-1
8787v	Yes	Moderate	0	0	0	0	0
8787w	Yes	Moderate	0	0	0	0	0
8788c	No	Low	-1	0	0	-1	0
8790a	No	Moderate	0	0	0	0	0
8795b	No	Low	-1	-1	0	0	0
8796m	No	Low	-1	-1	0	0	0
8797a	No	Moderate	0	-1	0	0	0
8815a	No	Low	0	0	0	0	0
8817a	No	Moderate	0	0	0	0	0
8817d	No	Low	0	0	0	0	0
8817e	No	Low	0	0	0	0	0
8826a	No	Moderate	0	0	0	0	0
8829a	No	Moderate	0	0	0	0	0
8850a	Yes	High	0	0	0	0	0
8867	Yes	Moderate	0	0	0	0	0
8884a	No	Low	0	0	-1	0	0
8899a	No	Low	-1	-1	0	0	0
8899e	No	Low	-1	-1	0	0	0
8899g	No	Moderate	-1	0	0	0	0
8902d	No	Moderate	-1	0	0	0	0
8902i	No	Moderate	-1	0	0	0	0
8902m	No	Low	-1	-1	0	0	0
8910d	No	Moderate	0	0	0	-1	0
8916a	No	Moderate	0	0	0	0	0
8916b	No	Moderate	0	0	0	0	0
8916c	No	Moderate	0	0	0	0	0
8918a	No	Moderate	0	0	0	0	0
8918n	No	Low	0	0	0	0	0
8922l	No	Low	0	0	0	0	0
8926a	Yes	High	0	0	0	0	0
8928	No	Very Low	0	0	0	0	0
8929a	No	Moderate	0	-1	0	0	0
8929c	No	High	0	0	0	0	0
8929f	No	Moderate	0	0	0	-1	0
8929g	No	High	0	0	0	0	0
8929i	No	High	0	0	0	0	0
8931a	No	High	0	0	0	-1	0
8933a	No	Moderate	0	0	0	0	0
9178a	No	Moderate	0	-1	0	0	0
9178c	No	Moderate	0	0	0	0	-1
9178e	No	Moderate	0	0	0	-1	0
9178h	No	Moderate	0	0	0	0	-1
9181a	No	Moderate	-1	0	0	0	0
9247a	Yes	Moderate	0	0	0	0	0
9247c	No	Moderate	-1	0	0	0	0
9261b	Yes	Moderate	0	0	0	0	0
9271a	No	Moderate	0	-1	0	0	0
9300c	No	Low	-1	-1	0	0	0
9300g	No	Moderate	0	0	0	-1	0
9300i	No	Low	-1	-1	0	0	0
9300k	No	Moderate	-1	0	0	0	0
9300l	No	Low	0	-1	0	0	-1
9307a	Yes	Low	0	0	0	0	0
9309c	Yes	Moderate	0	0	0	0	0
9316a	Yes	Moderate	0	0	0	0	0
9370b	No	Moderate	-1	0	0	0	0

Appendix 3.15 GRADE risk of bias domain

Table 14. GRADE risk of bias domain

Estimate ID	Risk of bias	Justification for rating	**Decision:** *not serious, serious, very serious*	Risk of bias notes
85a	Unclear	Allocation concealment unclear in all studies.	Serious	
100c	unclear	Information on sequence generation and allocation concealment not reported but 75% of trials double blind, all were intention treat, and follow-up was near 100% for all trials.	serious	
119a	Low	Despite high risk allocation concealment, baseline groups were equal in the Ayed study.	Not serious	
212a	Unclear	3 trials at high risk of bias but contributed small sample sizes, 6 trials were unclear	Serious	
212b	Unclear	3 trials at high risk of bias but contributed small sample sizes, 3 trials were unclear	Serious	
212d	Unclear	Both trials at unclear risk of bias	Serious	
593	unclear	Random sequence unclear 66%; allocation conealment unclear 100%; selective reporting unclear 66%, high risk 33%; high risk other bias 100%	serious	
725a	Unclear		Serious	Insufficient information to assess risk of bias for the majority of trials.
930a	Unclear	Sequence generation and concealment unclear in all trials.	Serious	
1021	unclear	The authors stated that "The overall quality of the trials was high; each followed a double-blinded protocol, and only one study had possible irregularities in the randomization process. Follow-up of randomly assigned patients was almost complete. The only minor methodologic flaw was lack of description of the randomization process in 18 of the 22 trials."	Not serious	
1164	high	Unclear risk for random sequence 3/4; allocation concealment 4/4; blinding 2/4; other bias 1/4. High risk blinding 2/4	very serious	
1264	unclear	Sequence generation, allocation concealment, completeness of reporting, and selective reporting unclear in all trials.	serious	
1340a	Unclear	No information presented to assess the majority of domains for all trials.	Serious	
1438a	low	Unclear risk incomplete outcome data 2/4; High risk blinding participants/personnel 1/4	not serious	
1447a	Unclear	Information to assess the majority of domains was not provided.	Serious	
1606a	low	No blinded outcome assessment in one of the two included trials but this is less important for the outcome of hospitalisatiosn and the trial carried little weight in the meta-analysis.	not serious	
1629a	unclear	All elements unclear for all trials.	serious	
1653a	unclear	The authors reported that studies were only eligible if they used a randomisation method with robust allocation concealment. They also report that "most events occurred in a small number of recent trials that used secure randomisation methods and treatment blinding, sensitivity analyses (available on request) indicated that our results were not materially influenced by uncertainties about the quality of older trials. However, they provide little to no actual information on the risk of bias in included studies.	not serious	
1752a	low	Authors assessed "trials for the adequacy of allocation concealment, blindness of patients and physicians to the treatment, and blind assessment of the outcome of interest". All included studies received 5/5. Authors used completeness of follow-up as an inclusion criteria although "adequate" follow-up not defined.	not serious	
2159	unclear	High risk: random sequence 1/5, blinding (ALL) 1/5; Unclear risk: random sequence 1/5, incomplete outcome data 5/5; selective reporting 5/5	not serious	
2359c				
2359h				
2359l				
2599a	unclear	Newcastle Ottawa scale used but only summary scores were provided as opposed to individual criteria attainment by trial. Only blinding information was available to assess risk of bias. Other source for potential bias is that all included studies came from the same research group, within eight years, and all showed significant reductions in admissions.	serious	
2640b	low	Detailed information relevant for risk of bias assessment were provided.	not serious	
2811a	Unclear	Insufficient information to assess majority of domains.	Serious	
2811g	Unclear	Insufficient information to assess majority of domains.	Serious	
2933a	low	Three studies all described in detail central randomisation with adequate allocation concealment. Only one study (Wiktor 1999) had a small number of exclusions following randomisation (7participants out of a total of 771).	not serious	
3030a	Unclear	No information about losses to follow-up	Not serious	

Table 14 continued. GRADE risk of bias domain

Estimate ID	Risk of bias	Justification for rating	Decision: *not serious, serious, very serious*	Risk of bias notes
3275d	unclear	unclear risk: for random sequence 3/3, allocation concealment 2/3 and high risk for other biases 3/3; however CHARM-Alternative 2003 contribute 90% = unclear risk for random sequence only but high risk for other biases	serious	
3275e	unclear	unclear risk: for random sequence 3/4, allocation concealment 1/4; and high risk for other biases 4/4. Selection bias identified by review authors	serious	
3275l	unclear	All studies unclear risk for random sequence; 3/4 for allocatin concealment; 1/4 unclear for blinding; 1/4 high risk incomplete outcome data and 4/4 high risk other bias	serious	
3362a	Unclear	Allocation concealment unclear in 66% of trials.	Serious	
3400a	Unclear	Insufficient information to assess majority of domains.	Serious	
3400b	Unclear	Insufficient information to assess majority of domains.	Serious	
3415	low	Sequence generation unclear in all trials but groups were even at baseline and all other domains were low risk of bias.	not serious	
3639f	unclear	Sequence generation, follow-up completeness, and selective reporting unclear in 100% of trials.	serious	
3640b	low	Inclusion criteria ensured all included trials had double-blinding or patients and care-givers; adequate follow-up completion and outcome reporting. Authors report that all studies had adeaqaute allocation concealment, outcome assessment was blinded, and all were sponsored by pharma.	not serious	
3640d	low	Inclusion criteria ensured all included trials had double-blinding or patients and care-givers; adequate follow-up completion and outcome reporting. Authors report that all studies had adeaqaute allocation concealment, outcome assessment was blinded, and all were sponsored by pharma.	not serious	
3657	unclear	No blinding in 1 of the 2 included trials although low risk of bias otherwise.	serious	
3709a				
3769e	Low		Not serious	
3781d	unclear	Sequence generation, concealment, and selective reporting unclear in all trials.	serious	
4002h	low		not serious	
4003a				
4003e	unclear	Allocation concealment unclear in 83% of trials.	serious	
4004o	high	Allocation concealment unclear in both studies. High risk of bias for incomplete outcome reporting in one trial: high rate of drop outs. Both industry funded.	serious	
4004r	high	43% of trials had high drop out rates relative to event rates. All industry funded. 71% of trials had unclear allocation concealment methods.	serious	
4004y	unclear	Allocation concealment unclear in 80% of trials.	serious	
4004z	high	All trials industry funded. Allocation concealment unclear in 62% of trials although these trials received little weight in the meta-analysis.	not serious	Not downgraded because bias that may affect the outcome occurred in studies that represent a small weight in the overall analysis and the effect estimates span both directions (reductions/increases in admissions).
4065a	unclear	Sequence generation, allocation concealment, incomplete outcome assessment, and selective reporting unclear in all trials. 50% of trials were unblinded. Funding unclear for all studies.	serious	
4067b	unclear	Sequence generation, allocation concealment, completeness of outcome assessement, and reporting bias unclear in all trials.	serious	
4123b	high	Very high attrition in both trials (greater than 75%)	serious	
4123i	high	Very high attrition in both trials (greater than 75%)	serious	
4147a	Unclear	Insufficient information to assess majority of domains.	Serious	
4154a	Unclear	Sequence generation and allocation concealment unclear in half of the trials.	Serious	
4192c				
4206a	unclear	No blinding in 33% of studies. Sequence generation unclear in all trials.	serious	
4206c	unclear	Sequence generation unclear in all trials. Selective reporting unclear in all trials.	serious	
4260	low		not serious	
4305a	Low		Not serious	
4305d	Unclear	Attrition bias unclear in all trials	Serious	
4305f	Low		Not serious	
4305i	Low		Not serious	
4494a	Low		Not serious	
4508a				
4615d	high	Sequence generation unclear in 50% of trials. Allocation concealment inadequate in 40% of trials. No blinding in 50% of trials. Completeness of outcome data and selective reporting unclear in all trials.	serious	

Table 14 continued. GRADE risk of bias domain

Estimate ID	Risk of bias	Justification for rating	Decision: *not serious, serious, very serious*	Risk of bias notes
4615e	high	Sequence generation unclear in 50% of trials. Allocation concealment high risk of bias in 50% of trials. No blinding in 67% of trials. Completeness of outcome data and selective reporting unclear in all trials.	very serious	
4629a	unclear	Allocation concealment and selective reporting unclear in all trials. All other elements unclearin 50% of the trials.	serious	
4812a	unclear	Allocation concealment unclear in 33% of studies. Blinding unclear in 66% of studies.	serious	
4838a	low	Authors used Cochrane criteria to asses risk of bias. All included trials had adequate sequence generation, allocation concealment, and had blinding of patients, providers, and outcome assessors. Incomplete outcome data and selective reporting results not reported although all trials deemed low risk by the authors.	not serious	"The criteria used for quality assessment were sequence generation of allocation; allocation concealment; masking of participants, staff, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias, as recommended by the Cochrane Collaboration. We classed studies with high or unclear risk of bias for any of the first three components to be of low quality."
4838b	low	Authors used Cochrane criteria to asses risk of bias. All included trials had adequate sequence generation, allocation concealment, and had blinding of patients, providers, and outcome assessors. Incomplete outcome data and selective reporting results not reported although all trials deemed low risk by the authors.	not serious	"The criteria used for quality assessment were sequence generation of allocation; allocation concealment; masking of participants, staff, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias, as recommended by the Cochrane Collaboration. We classed studies with high or unclear risk of bias for any of the first three components to be of low quality."
4844	high	No blinding in 33% of trials. One trial used date of birth for "randomisation". Allocation concealment in the other 66% of trials.	serious	
4860a	Unclear	The majority of domains could not be assessed due to lack of information	Serious	
4966a	Unclear	The majority of domains could not be assessed due to lack of information	Serious	
4968a	Unclear	The majority of domains could not be assessed due to lack of information	Serious	
4987a	High	High rate of attrition in the majority of trials. Allocation concealment unclear or high risk of bias for most trials.	Serious	
5145a	Unclear	Sequence generation and allocation concealment could not be assessed due to lack of information	Serious	
5147a	High	Allocation concealment and complete outcome assessment at high risk of bias in 25% of trials. All trials were high risk for additional sources of bias.	Serious	
5183a	Unclear	Information to assess the majority of domains was not provided.	Serious	
5371	unclear	JADAD score used. Neither trial was double blinded (unclear if single blinded) and allocation concealment unclear in both. All other criteria relevant for risk of bias unclear.	serious	
5398a	Unclear	The majority of domains could not be assessed due to lack of information	Serious	

Table 14 continued. GRADE risk of bias domain

Estimate ID	Risk of bias	Justification for rating	Decision: *not serious, serious, very serious*	Risk of bias notes
5399a				Three studies had an unclear risk of bias for random sequence generation and all studies had an unclear risk for allocation concealment. In one study the assessors were not blinded and in another the risk of bias for blinding was unclear. In three studies there was an unclear risk of bias for attrition.
5399d	Unclear	Sequence generation unclear in 3 trials. Allocation concealment unclear in 5 trials. Attrition bias unclear in 5 trials.	Serious	
5399j	Low		Not serious	
5533g	high	Large drop out rates in 50% of trials. Sequence generation, concealment, completeness of follow-up, and selective reporting unclear in 50% of trials	serious	
5606	low	Sequence generation and allocation concealment unclear in 44% of studies. No blinding in 33% of studies. Selective reporting bias in 33% of studies. However, studies with low risk of bias had the majority of weighting in meta-analysis.	not serious	
5937a	Unclear	Assessments for all domains not possible due to lack of information	Serious	
6091b				Randomisation not well described.
6091c	High	Loss to follow-up not reportd in 66% of included trials	Serious	
6099a	Unclear	Sequence generation and allocation concealment unclear for all trials.	Serious	
6099e	Unclear	Sequence generation and allocation concealment unclear for all trials.	Serious	
6099f	Unclear	Sequence generation and allocation concealment unclear for all trials.	Serious	
6099h	Unclear	Sequence generation and allocation concealment unclear for all trials.	Serious	
6110a	Unclear	Information to assess the majority of domains was not provided.	Serious	
6360b	Unclear	Insufficient information to assess majority of domains.	Serious	
6360d	Unclear	Insufficient information to assess majority of domains.	Serious	
6360f	Unclear	Insufficient information to assess majority of domains.	Serious	
6442a				
6552i	Low		Not serious	
6552m	Unclear	Sequence generation and allocation concealment unclear for most trials.	Serious	
6552p	Low		Not serious	
6564a	unclear	Quality scores given but no descriptive information on criteria to assess risk of bias.	serious	
6568a	unclear	Allocation concealment and selective reporting unclear for all trials. Sequence generation and completeness of follow-up unclear in 80% of trials.	serious	
6670	unclear	Allocation concealment and selective reporting unclear in all trials.	serious	
6677	unclear	Allocation concealment, completeness of follow-up, and selective reporting unclear in all trials.	serious	
6746b	low		not serious	
6764a	Unclear	Information to assess the majority of domains was not provided.	Serious	
6797a	unclear	Sequence generation, allocation concealment, and selective reporting unclear in all trials.	serious	
6797b	unclear	Sequence generation, allocation concealment, and selective reporting unclear in all trials.	serious	
6797d	unclear	Sequence generation, allocation concealment, and selective reporting unclear in all trials.	serious	
6806f	high	High risk of selective reporting bias in 83% of trials. Allocation concealment unclear in 83% of trials and high risk of bias in remaining 17% of trials. High risk of bias regarding blinding in 50% of trials.	very serious	
7029b	unclear	Allocation concealment and selective reporting unclear in all trials.	serious	
7279b	Unclear	Sequence generation and allocation concealment unclear in 4/5 trials.	Serious	
7417a	Low		Not serious	
7484a	high	No blinding in 83% of studies. Information on selective reporting unclear in all trials.	serious	
7504	unclear	Allocation concealment, completeness of follow-up, and selective reporting unclear in 100% of trials	serious	
7600a	Unclear	Allocation concealment unclear in 8/13 trials.	Serious	
7600c	Unclear		Serious	
7600e	Low		Not serious	
7600j	High	Allocation concealment at high risk of bias in 1/2 trials. "Eligible patients were randomised and informed consent was given on the basis of information relevant to the allocated study group"	Very serious	

Table 14 continued. GRADE risk of bias domain

Estimate ID	Risk of bias	Justification for rating	**Decision:** *not serious, serious, very serious*	Risk of bias notes
7600k	High	Allocation concealment at high risk of bias in 1/2 trials. "Eligible patients were randomised and informed consent was given on the basis of information relevant to the allocated study group"	Very serious	
7600n	Unclear	Allocation concealment unclear in all trials.	Serious	
7624a	Low		Not serious	
7636c	Low		Not serious	
7651a	Unclear	Sequence generation and allocation concealment unclear in the majority of trials	Serious	
7651b	Unclear	Sequence generation and allocation concealment unclear for majority of trials.	Serious	
7723c	Low		Not serious	
7723i	Low		Not serious	
7723m	Unclear	Sequence generation and allocation concealment unclear in half the trials.	Serious	
7724i	High	One trial at high risk of bias.	Serious	
7820a	Unclear	No assessments could be made given the lack of information.	Serious	
7820b	Unclear	No assessments could be made given the lack of information.	Serious	
7820c	Unclear	No assessments could be made given the lack of information.	Serious	
7820f	Unclear	No assessments could be made given the lack of information.	Serious	
8460b				Randomisation poorly described.
8464b	Unclear	Unclear sequence generation and allocation concealment for more than half of the trials	Serious	
8511a	unclear	Risk of bias for sequence generation, allocation concealment, completeness of follow-up, selective reporting unclear in all but one study.	serious	

Appendix 3.16 GRADE inconsistency domain

Table 15. GRADE inconsistency domain

Estimate ID	**Large variations in the size of effect**	**Overlap of confidence intervals**	**Statistical significance of heterogeneity (p<0.1)**	**I-squared:** small (0-39%) medium (40-74%) large (≥75%)	**Decision:** *not serious, serious, very serious*	**Inconsistency notes**
85a	No	Yes	Unclear	Small	Not serious	
100c	no	yes	no	small	not serious	
119a	No	Yes	Unclear	Unclear	Not serious	
212a	No	No	Yes	Medium	Serious	
212b	No	No	Yes	Medium	Serious	
212d	Unclear	Unclear	Unclear	Small	Not serious	
593	yes	yes	no	small	not serious	
725a	Yes	No	Unclear	Medium	Not serious	
930a	No	Yes	Unclear	Unclear	Not serious	
1021	yes	no	unclear	unclear	serious	
1164	yes	no	yes	medium	serious	
1264	no	unclear	no	small	not serious	
1340a	No	Yes	Unclear	Small	Not serious	
1438a	yes	yes	no	small	not serious	
1447a	Unclear	Unclear	Yes	Unclear	Serious	
1606a	yes	no	yes	large	serious	
1629a	no	yes	no	small	not serious	
1653a	unclear	unclear (forrest plot not provided)	unclear	unclear	serious	
1752a	no	yes	no	unclear	not serious	
2159	no	yes	no	small	not serious	
2359c						
2359h						
2359l						
2599a	yes	yes	no	medium	not serious	
2640b	unclear	unclear	unclear	unclear	serious	
2811a	No	Yes	No	Small	Not serious	
2811g	No	No	Yes	Medium	Serious	
2933a	yes	yes	no	small	not serious	
3030a	No	Yes	No	Unclear	Not serious	
3275d	no	yes	no	small	not serious	
3275e	yes	yes	no	small	not serious	
3275l	yes	yes	no	small	not serious	
3362a	No	Yes	No	Small	Not Serious	
3400a	No	No	Yes	Medium	Serious	
3400b	No	Yes	No	Small	Not serious	
3415	no	yes	no	small	not serious	
3639f	no	yes	no	small	not serious	
3640b	unclear	unclear	no	unclear	not serious	
3640d	unclear	unclear	no	unclear	not serious	
3657	unclear	unclear	no	unclear	not serious	
3709a						
3769e	No	Yes	No	Small	Not serious	
3781d	no	yes	no	unclear	not serious	
4002h	no	yes	no	small	not serious	
4003a						
4003e	no	yes	no	small	not serious	
4004o	no	yes	no	small	not serious	
4004r	yes	yes	no	small	not serious	
4004y	yes	yes	no	small	not serious	
4004z	yes	yes	no	small	not serious	
4065a	no	yes	no	small	not serious	
4067b	no	yes	no	small	not serious	
4123b	no	yes	no	small	not serious	
4123i	no	yes	no	small	not serious	
4147a	Yes	No	Yes	Small	Serious	
4154a	Yes	Yes	No	Small	Not serious	
4192c						
4206a	no	yes	yes	medium	not serious	
4206c	unclear	0	no	small	not serious	
4260	no	yes	no	small	not serious	
4305a	Yes	No	Yes	Medium	Serious	
4305d	No	Yes	No	Medium	Not serious	
4305f	No	No	Yes	Medium	Serious	
4305i	No	Yes	No	Small	Not serious	
4494a	No	No	Unclear	Small	Not serious	
4508a						

Table 15 continued. GRADE inconsistency domain

Estimate ID	Large variations in the size of effect	Overlap of confidence intervals	Statistical significance of heterogeneity (p<0.1)	I-squared: small (0-39%) medium (40-74%) large (≥75%)	Decision: *not serious, serious, very serious*	Inconsistency notes
4615d	yes	no	yes	medium	serious	
4615e	no	yes	no	small	not serious	
4629a	no	yes	no	small	not serious	
4812a	no	no	yes	large	serious	
4838a	no	yes	yes	medium	serious	
4838b	no	yes	yes	medium	serious	
4844	no	no	no	small	not serious	
4860a	No	Yes	No	Small	Not serious	
4966a	Yes	No	Yes	Medium	Serious	
4968a	Yes	No	Yes	Medium	Serious	
4987a	Yes	Yes	No	Small	Not serious	
5145a	No	Yes	No	Small	Not serious	
5147a	No	Yes	No	Small	Not serious	
5183a	No	No	Yes	Unclear	Serious	
5371	unclear	unclear	unclear	unclear	serious	
5398a	No	Yes	No	Small	Not serious	
5399a						
5399d	Yes	Yes	No	Small	Not serious	
5399j	No	Yes	No	Small	Not serious	
5533g	no	yes	no	small	not serious	
5606	yes	yes	no	small	not serious	
5937a	Yes	No	Unclear	Unclear	Serious	
6091b						
6091c	No	Yes	No	Small	Not serious	
6099a	No	No	Yes	Unclear	Serious	
6099e	No	Yes	No	Unclear	Not serious	
6099f	No	Yes	No	Unclear	Not serious	
6099h	No	Yes	No	Unclear	Not serious	
6110a	No	Yes	Unclear	Unclear	Not serious	
6360b	No	Yes	Yes	Small	Serious	
6360d	No	Yes	Yes	Small	Serious	
6360f	No	Yes	No	Small	Not serious	
6442a						
6552i	Yes	No	No	Unclear	Not serious	
6552m	Unclear	Unclear	No	Unclear	Not serious	
6552p	Unclear	Unclear	No	Unclear	Not serious	
6564a	yes	yes	no	unclear	not serious	
6568a	yes	yes	no	small	not serious	
6670	unclear	unclear	unclear	unclear	serious	
6677	no	yes	no	small	not serious	
6746b	unclear	unclear	no	unclear	not serious	
6764a	No	Yes	No	No	Not serious	
6797a	no	yes	no	small	not serious	
6797b	unclear	unclear	unclear	unclear	serious	
6797d	no	yes	no	small	not serious	
6806f	yes	yes	no	small	not serious	
7029b	unclear	unclear	no	small	not serious	
7279b	Yes	Yes	Yes	Unclear	Serious	
7417a	Yes	Yes	No	Small	Not serious	
7484a	no	yes	unclear	unclear	not serious	
7504	no	yes	no	small	not serious	
7600a	Yes	No	Yes	Medium	Serious	
7600c	No	Yes	No	Small	Not serious	
7600e	No	Yes	No	Small	Not serious	
7600j	No	Yes	No	Small	Not serious	
7600k	No	Yes	No	Small	Not serious	
7600n	No	Yes	No	Small	Not serious	
7624a	No	Yes	No	Small	Not serious	
7636c	No	Yes	No	Small	Not serious	
7651a	Yes	No	No	Small	Not serious	
7651b	Yes	Yes	No	Small	Not serious	
7723c	No	Yes	Yes	Small	Not serious	Despite borderline significant heterogeneity the effect estimates are all in the same direction and fairly tightly clustered.

Table 15 continued. GRADE inconsistency domain

Estimate ID	**Large variations in the size of effect**	**Overlap of confidence intervals**	**Statistical significance of heterogeneity (p<0.1)**	**I-squared:** small (0-39%) medium (40-74%) large (≥75%)	**Decision:** *not serious, serious, very serious*	**Inconsistency notes**
7723i	No	Yes	No	Small	Not serious	
7723m	No	Yes	No	Small	Not serious	
7724i	Yes	Yes	Unclear	Unclear	Not serious	All the confidence intervals overlapped.
7820a	Unclear	Unclear	No	Small	Not serious	
7820b	No	Yes	Unclear	Small	Not serious	
7820c	No	Yes	Unclear	Small	Not serious	
7820f	Yes	Yes	Unclear	Small	Not serious	
8460b						
8464b	Yes	No	Yes	Medium	Serious	
8511a	yes	yes	yes	small	not serious	
8604b	yes	no	no	small	not serious	
8604f	unclear	unclear	no	small	not serious	
8663a	Unclear	Unclear	No	Small	Not serious	
8672a						
8672b						
8688a	No	No	Yes	Large	Serious	
8692e	no	no	no	small	not serious	
8716a						
8729a	yes	yes	no	small	not serious	
8733c						
8742a	no	yes	no	small	not serious	
8744d	no	yes	no	small	not serious	
8747a	yes	yes	no	small	not serious	
8747b	no	yes	no	small	not serious	
8761a						
8761b						
8762a	No	Yes	No	Small	Not serious	
8769b						
8770b	yes	yes	no	small	not serious	
8776a	Yes	No	No	Small	Not serious	
8784a	no	yes	no	small	not serious	
8787c	No	No	Yes	Small	Serious	
8787d	Yes	Yes	Yes	Medium	Serious	
8787h	Yes	No	Yes	Large	Serious	
8787p	Yes	No	Yes	Large	Serious	
8787t	No	Yes	No	Small	Not serious	
8787v						
8787w						
8788c	No	Yes	No	Small	Not serious	
8790a	no	yes	no	small	not serious	
8795b	Yes	No	Unclear	Medium	Serious	
8796m	Yes	Yes	Yes	Medium	Serious	
8797a	No	Yes	Yes	Medium	Serious	
8815a	no	yes	no	small	not serious	
8817a	yes	yes	no	small	not serious	
8817d	yes	no	yes	medium	serious	
8817e	yes	no	yes	medium	serious	
8826a	yes	yes	no	small	not serious	
8829a	no	yes	no	small	not serious	
8850a						
8867						
8884a	no	yes	no	small	not serious	
8899a	Yes	No	Yes	Medium	Serious	
8899e	Yes	No	Yes	Medium	Serious	
8899g	Unclear	Unclear	Unclear	Small	Not serious	
8902d	Yes	No	Unclear	Small	Not serious	
8902i	No	Yes	Unclear	Small	Not serious	
8902m	Yes	No	Unclear	Medium	Serious	
8910d	Yes	Yes	No	Small	Not serious	
8916a	no	yes	no	small	not serious	
8916b	no	yes	no	small	not serious	
8916c	no	yes	no	small	not serious	
8918a	no	yes	no	small	not serious	
8918n	unclear	unclear	no	small	not serious	
8922l	unclear	unclear	no	small	not serious	
8926a						
8928	no	yes	no	small	not serious	
8929a	Yes	No	Yes	Medium	Serious	
8929c	No	Yes	Unclear	Small	Not serious	
8929f	Yes	Yes	Unclear	Small	Not serious	

Table 15 continued. GRADE inconsistency domain

Estimate ID	**Large variations in the size of effect**	**Overlap of confidence intervals**	**Statistical significance of heterogeneity (p<0.1)**	**I-squared:** small (0-39%) medium (40-74%) large (≥75%)	**Decision:** *not serious, serious, very serious*	**Inconsistency notes**
8929g	No	Yes	Unclear	Small	Not serious	
8929i	No	Yes	Unclear	Small	Not serious	
8931a	no	yes	unclear	unclear	not serious	
8933a	yes	yes	no	small	not serious	
9178a	Yes	No	Yes	Medium	Serious	
9178c	No	Yes	No	Small	Not serious	
9178e	No	Yes	No	Small	Not serious	
9178h	No	Yes	No	Small	Not serious	
9181a	Yes	Yes	No	Small	Not serious	
9247a						
9247c	No	Yes	No	Small	Not serious	
9261b						
9271a	Yes	No	Unclear	Medium	Serious	
9300c	No	Yes	Yes	Medium	Serious	
9300g	No	Yes	No	Small	Not serious	
9300i	No	Yes	Yes	Medium	Serious	
9300k	No	Yes	No	Small	Not serious	
9300l	No	Yes	Yes	Medium	Serious	
9307a						
9309c						
9316a						
9370b	No	Yes	No	Small	Not serious	

Appendix 3.17 GRADE indirectness domain

Table 16. GRADE indirectness domain

Estimate ID	Direct comparison (A vs. B, not network analysis)	Patients	Interventions	Comparator	Outcome	Majority OECD countries	**Decision:** *no indirectness, serious indirectness, very serious indirections*	Indirectness notes
85a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
100c	yes	no (previous use of statins varied from 0% to 76% between trials)	yes	yes	yes	Yes	no indirectness	
119a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
212a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
212b	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
212d	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
593	yes	yes	No, different interventions drugs	yes	yes	Yes	no indirectness	
725a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
930a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
1021	yes	yes	yes	yes	yes	Yes	no indirectness	
1164	yes	yes	No, different drugs/doses/number of interventions used across studies	No, different comparators/ doses used	yes	Yes	no indirectness	
1264	yes	yes	yes	yes	Yes	Yes	no indirectness	
1340a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
1438a	yes	yes	yes	No, different comparator drugs/doses	yes	Yes	no indirectness	
1447a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
1606a	yes	yes	no (one rhythm control drug used in one study and a variety of drugs used in the other trial)	yes	no (one rate control drug used in one trial and a variety of drugs used in the other trial)	Yes	serious indirectness	
1629a	yes	yes	yes	yes	yes	Yes	no indirectness	
1653a	yes	yes	yes	yes	yes	Yes	no indirectness	
1752a	yes	yes	yes	yes	yes	Yes	no indirectness	
2159	yes	yes	no, different interventions across studies	no, different comparators across studies	yes	Yes	no indirectness	
2359c								
2359h								
2359l								
2599a	yes	yes	yes	yes	yes	Yes	no indirectness	
2640b	yes	yes	yes	yes	yes	Yes	no indirectness	
2811a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
2811g	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
2933a	yes	yes	No, 2/3 same dose, 1/3 half-dose	yes	yes	Yes	no indirectness	
3030a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
3275d	yes	no, different severties of CHF	no, different doses used	yes	no, review does not state outcome was assessed (SPICE 2000). However, only contributes 4.6%% to overall pooled estimate	Yes	no indirectness	

Table 16 continued. GRADE indirectness domain

Estimate ID	Direct comparison (A vs. B, not network analysis)	Patients	Interventions	Comparator	Outcome	Majority OECD countries	**Decision:** *no indirectness, serious indirectness, very serious indirections*	Indirectness notes
3275e	yes	no, different severties of CHF	no, different doses used	yes	no, review does not state outcome was assessed (SPICE 2000). However, only contributes 0.4% to overall pooled estimate	Yes	no indirectness	
3275l	yes	no, different severties of CHF	no, different doses in all 3 arms	unclear: insufficient info on ACEI therapy regimen or placebo used. Placebo used alongside ACEi in some studies but not others	yes	Yes	serious indirectness	
3362a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
3400a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
3400b	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
3415	yes	yes	yes	yes	yes	Yes	no indirectness	
3639f	yes	yes	yes	yes	yes	Yes	no indirectness	
3640b	yes	yes	yes	yes	yes	Yes	no indirectness	
3640d	yes	yes	yes	yes	yes	Yes	no indirectness	
3657	yes	yes	yes	yes	yes	Yes	no indirectness	
3709a								
3769e	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
3781d	yes	yes	yes	yes	yes	Yes	no indirectness	
4002h	yes	yes	yes	yes	yes	Yes	no indirectness	
4003a								
4003e	yes	yes	yes	yes	yes	Yes	no indirectness	
4004o	yes	yes	yes	yes	yes	Yes	no indirectness	
4004r	yes	yes	yes	yes	yes	Yes	no indirectness	
4004y	yes	yes	yes	yes	yes	Yes	no indirectness	
4004z	yes	yes	yes	yes	yes	Yes	no indirectness	
4065a	yes	yes	yes	yes	yes	Yes	no indirectness	
4067b	yes	yes	yes	yes	yes	Yes	no indirectness	
4123b	yes	yes	yes	yes	yes	Yes	no indirectness	
4123i	yes	yes	yes	yes	yes	Yes	no indirectness	
4147a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
4154a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
4192c								
4206a	yes	yes	yes	yes	yes	Yes	no indirectness	
4206c	yes	yes	yse	yes	yes	Yes	no indirectness	
4260	yes	yes	yes	yes	yes	Yes	no indirectness	
4305a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
4305d	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
4305f	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
4305i	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
4494a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
4508a								
4615d	yes	yes	yes	yes	yes	Yes	no indirectness	
4615e	yes	yes	yes	yes	yes	Yes	no indirectness	
4629a	yes	yes	yes	yes	yes	Yes	no indirectness	
4812a	yes	yes	yes	yes	yes	Yes	no indirectness	
4838a	yes	yes	yes	yes	yes	Yes	no indirectness	
4838b	yes	yes	yes	yes	yes	Yes	no indirectness	
4844	yes	yes	yes	yes	yes	Yes	no indirectness	
4860a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
4966a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
4968a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
4987a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
5145a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
5147a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
5183a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
5371	yes	yes	yes	yes	yes	Yes	no indirectness	
5398a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	

Table 16 continued. GRADE indirectness domain

Estimate ID	Direct comparison (A vs. B, not network analysis)	Patients	Interventions	Comparator	Outcome	Majority OECD countries	**Decision:** *no indirectness, serious indirectness, very serious indirections*	Indirectness notes
5399a								The data were not provided for most studies and had to be imputed.
5399d	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
5399j	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
5533g	yes	yes	yes	yes	yes	Yes	no indirectness	
5606	yes	yes	yes	yes	yes	Yes	no indirectness	
5937a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6091b								
6091c	Yes	Yes	Yes	Yes	Yes	No	Serious indirectness	
6099a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6099e	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6099f	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6099h	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6110a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6360b	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6360d	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6360f	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6442a								
6552i	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6552m	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6552p	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6564a	yes	yes	yes	yes	yes	Yes	no indirectness	
6568a	yes	yes	yes	yes	yes	Yes	no indirectness	
6670	yes	yes	yes	yes	yes	Yes	no indirectness	
6677	yes	yes	yes	yes	yes	Yes	no indirectness	
6746b	yes	yes	yes	yes	yes	Yes	no indirectness	
6764a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
6797a	yes	yes	yes	yes	yes	Yes	no indirectness	
6797b	yes	yes	yes	yes	yes	Yes	no indirectness	
6797d	yes	yes	yes	yes	yes	Yes	no indirectness	
6806f	yes	yes	yes	yes	yes	Yes	no indirectness	
7029b	yes	yes	yes	yes	yes	Yes	no indirectness	
7279b	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7417a	Yes	Yes	No	No	Yes	Yes	No indirectness	Different pacing systems implanted in some trials, while all received CRT implants in other trials
7484a	yes	yes	yes	yes	yes	Yes	no indirectness	
7504	yes	yes	yes	yes	yes	Yes	no indirectness	
7600a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7600c	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7600e	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7600j	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7600k	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7600n	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7624a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7636c	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7651a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7651b	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7723c	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7723i	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7723m	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7724i	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7820a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7820b	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7820c	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
7820f	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8460b								
8464b	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8511a	yes	yes	yes	yes	yes	Yes	no indirectness	
8604b	yes	yes	yes	yes	yes	Yes	no indirectness	
8604f	yes	yes	yes	yes	yes	Yes	no indirectness	
8663a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8672a								

Table 16 continued. GRADE indirectness domain

Estimate ID	Direct comparison (A vs. B, not network analysis)	Patients	Interventions	Comparator	Outcome	Majority OECD countries	**Decision:** *no indirectness, serious indirectness, very serious indirections*	Indirectness notes
8672b								
8688a	Yes	Yes	No	No	Yes	Yes	No indirectness	
8692e	yes	yes	yes	yes	yes	No	Serious indirectness	
8716a								
8729a	yes	yes	yes	yes	yes	Yes	no indirectness	
8733c								
8742a	yes	yes	yes	yes	yes	Yes	no indirectness	
8744d	yes	yes	yes	yes	yes	Yes	no indirectness	
8747a	yes	yes	yes	yes	yes	Yes	no indirectness	
8747b	yes	yes	yes	yes	yes	Yes	no indirectness	
8761a								
8761b								
8762a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8769b								
8770b	yes	yes	yes	yes	yes	Yes	no indirectness	
8776a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8784a	yes	yes	yes	yes	yes	Yes	no indirectness	
8787c	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8787d	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8787h	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8787p	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8787t	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8787v								
8787w								
8788c	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8790a	yes	yes	yes	yes	yes	Yes	no indirectness	
8795b	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8796m	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8797a	Yes	Yes	No	Yes	Yes	Yes	No indirectness	
8815a	yes	yes	yes	yes	yes	Yes	no indirectness	
8817a	yes	yes	yes	yes	yes	Yes	no indirectness	
8817d	yes	yes	yes	yes	yes	Yes	no indirectness	
8817e	yes	yes	yes	yes	yes	Yes	no indirectness	
8826a	yes	yes	yes	yes	yes	Yes	no indirectness	
8829a	yes	yes	yes	yes	yes	Yes	no indirectness	
8850a								
8867								
8884a	yes	yes	yes	yes	yes	No	Serious indirectness	
8899a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8899e	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8899g	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8902d	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8902i	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8902m	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8910d	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8916a	yes	yes	yes	yes	yes	Yes	no indirectness	
8916b	yes	yes	yes	yes	yes	Yes	no indirectness	
8916c	yes	yes	yes	yes	yes	Yes	no indirectness	
8918a	yes	yes	yes	yes	yes	Yes	no indirectness	
8918n	yes	yes	yes	yes	yes	Yes	no indirectness	
8922l	yes	yes	yes	yes	yes	Yes	no indirectness	
8926a								
8928	yes	yes	yes	yes	yes	Yes	no indirectness	
8929a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8929c	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8929f	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8929g	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8929i	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
8931a	yes	yes	yes	yes	yes	Yes	no indirectness	
8933a	yes	yes	yes	yes	yes	Yes	no indirectness	
9178a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
9178c	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
9178e	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
9178h	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
9181a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
9247a								
9247c	Yes	Yes	No	Yes	Yes	Yes	No indirectness	
9261b								
9271a	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	

Table 16 continued. GRADE indirectness domain

Estimate ID	Direct comparison (A vs. B, not network analysis)	Patients	Interventions	Comparator	Outcome	Majority OECD countries	**Decision:** *no indirectness, serious indirectness, very serious indirections*	Indirectness notes
9300c	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
9300g	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
9300i	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
9300k	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
9300l	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	
9307a								
9309c								
9316a								
9370b	Yes	Yes	Yes	Yes	Yes	Yes	No indirectness	

Appendix 3.18 GRADE imprecision domain

Table 17. GRADE imprecision domain

Estimate ID	Does the 95% CI include the null effect and appreciable benefit/harm?	Does the 95% CI include a trivial effect and appreciable benefit/harm?	Meets the optimal information size	Decision: *not serious, serious, very serious*	Imprecision notes
85a	No	No	No	Serious	
100c	no	no	yes	not serious	
119a	No	No	Yes	Not serious	
212a	No	No	Yes	Not serious	
212b	No	No	Yes	Not serious	
212d	No	No	Yes	Not serious	
593	no	no	yes	not serious	
725a	No	No	Yes	Not serious	
930a	No	Yes	Yes	Not serious	
1021	no	no	yes	not serious	
1164	no	yes	yes	serious	
1264	no	no	no	serious	
1340a	No	No	Yes	Not serious	
1438a	no	yes	yes	serious	
1447a	No	No	Yes	Not serious	
1606a	no	no	yes	not serious	
1629a	no	no	yes	not serious	
1653a	no	no	yes	not serious	
1752a	no	no	no	serious	
2159	no	no	yes	not serious	
2359c					
2359h					
2359l					
2599a	no	no	yes	not serious	
2640b	no	no	yes	not serious	
2811a	No	No	Yes	Not serious	
2811g	No	No	Yes	Not serious	
2933a	no	no	yes	not serious	
3030a	No	No	Yes	Not serious	
3275d	no	no	yes	not serious	
3275e	no	yes	yes	serious	
3275l	no	no	yes	not serious	
3362a	No	No	Yes	Not serious	
3400a	No	No	Yes	Not serious	
3400b	No	No	Yes	Not serious	
3415	no	no	yes	not serious	
3639f	no	no	no	serious	
3640b	no	no	no	serious	
3640d	no	no	no	serious	
3657	no	no	yes	not serious	
3709a					We downgraded one for a wide confidence interval
3769e	No	No	No	Serious	Downgraded by 2 due to very small number of events
3781d	no	no	yes	not serious	
4002h	no	no	yes	not serious	
4003a					
4003e	no	yes	yes	serious	
4004o	no	no	no	serious	
4004r	no	no	no	serious	
4004y	no	no	no	serious	
4004z	no	no	yes	not serious	
4065a	no	no	yes	not serious	
4067b	no	yes	no	serious	
4123b	no	no	yes	not serious	
4123i	no	no	yes	not serious	
4147a	No	No	Yes	Not serious	
4154a	No	No	Yes	Not serious	
4192c					
4206a	no	no	yes	not serious	
4206c	no	no	yes	not serious	
4260	no	no	no	serious	
4305a	No	No	Yes	Not serious	
4305d	No	No	No	Serious	
4305f	No	No	Yes	Not serious	
4305i	No	No	Yes	Not serious	
4494a	No	No	Yes	Not serious	
4508a					
4615d	no	no	yes	not serious	
4615e	no	no	no	serious	
4629a	no	no	yes	not serious	

Table 17 continued. GRADE imprecision domain

Estimate ID	Does the 95% CI include the null effect and appreciable benefit/harm?	Does the 95% CI include a trivial effect and appreciable benefit/harm?	Meets the optimal information size	Decision: *not serious, serious, very serious*	Imprecision notes
4812a	no	no	yes	not serious	
4838a	no	no	no	serious	
4838b	no	no	yes	not serious	
4844	no	no	yes	not serious	
4860a	No	No	No	Serious	
4966a	No	No	Yes	Not serious	
4968a	No	No	Yes	Not serious	
4987a	No	No	Yes	Not serious	
5145a	No	No	No	Serious	
5147a	No	No	Yes	Not serious	
5183a	No	No	Yes	Not serious	
5371	no	no	no	serious	
5398a	No	No	No	Serious	
5399a					There was high heterogeneity in the pooled results. The 95% confidence intervals are wide and include both significant benefit and harm of the intervention.
5399d	No	No	Yes	Not serious	
5399j	No	No	No	Serious	
5533g	no	no	no	serious	
5606	no	no	yes	not serious	
5937a	No	No	Yes	Not serious	
6091b					
6091c	No	No	No	Serious	
6099a	No	No	Yes	Not serious	
6099e	No	No	Yes	Not serious	
6099f	No	No	Yes	Not serious	
6099h	No	No	Yes	Not serious	
6110a	No	No	Yes	Not serious	
6360b	No	No	Yes	Not serious	
6360d	No	No	No	Serious	
6360f	No	No	Yes	Not serious	
6442a					
6552i	No	No	Yes	Not serious	
6552m	No	No	Yes	Not serious	
6552p	No	No	Yes	Not serious	
6564a	no	yes	no	serious	
6568a	no	no	yes	not serious	
6670	no	no	yes	not serious	
6677	no	no	no	not serious	
6746b	no	no	yes	not serious	
6764a	No	No	No	Serious	
6797a	no	no	no	serious	
6797b	no	no	yes	not serious	
6797d	no	no	no	serious	
6806f	no	no	yes	not serious	
7029b	no	no	yes	not serious	
7279b	No	No	Yes	Not serious	
7417a	No	No	No	Serious	
7484a	no	no	yes	not serious	
7504	no	no	no	serious	
7600a	No	No	Yes	Not serious	
7600c	No	No	Yes	Not serious	
7600e	No	No	Yes	Not serious	
7600j	No	No	Yes	Not serious	
7600k	No	No	Yes	Not serious	
7600n	No	No	Yes	Not serious	
7624a	No	No	Yes	Not serious	
7636c	No	No	No	Serious	
7651a	No	No	No	Serious	
7651b	No	No	No	Serious	
7723c	No	No	Yes	Not serious	
7723i	No	No	No	Serious	
7723m	No	No	Yes	Not serious	
7724i	No	No	No	Serious	
7820a	No	No	No	Serious	
7820b	No	Yes	Yes	Serious	
7820c	No	No	Yes	Not serious	
7820f	No	No	Unclear	Serious	Proportion of patients with heart failure admissions unclear for four of the trials.

Table 17 continued. GRADE imprecision domain

Estimate ID	Does the 95% CI include the null effect and appreciable benefit/harm?	Does the 95% CI include a trivial effect and appreciable benefit/harm?	Meets the optimal information size	Decision: *not serious, serious, very serious*	Imprecision notes
8460b					Small sample size - confidence interval around best estimate of effect include both no effect and appreciable benefit/harm
8464b	No	Yes	Yes	Not serious	
8511a	no	yes	no	serious	
8604b	no	yes	yes	serious	
8604f	no	no	yes	no serious	
8663a	No	No	No	Serious	
8672a					Confidence intervals of several included studies were wide, and several studies showed low event rates (-1 imprecision).
8672b					Confidence intervals of several included studies were wide, and several studies showed low event rates (-1 imprecision).
8688a	No	No	No	Serious	
8692e	no	yes	no	serious	
8716a					
8729a	no	no	yes	not serious	
8733c					
8742a	no	yes	no	serious	
8744d	no	yes	no	serious	
8747a	no	no	no	serious	
8747b	no	no	no	serious	
8761a					
8761b					
8762a	No	No	No	Serious	
8769b					
8770b	no	no	no	serious	
8776a	No	No	Yes	Not serious	
8784a	no	yes	yes	serious	
8787c	No	Yes	Yes	Serious	
8787d	No	No	No	Serious	
8787h	No	No	Yes	Not serious	
8787p	No	Yes	Yes	Not serious	
8787t	No	No	Yes	Not serious	
8787v					
8787w					
8788c	No	Yes	No	Serious	
8790a	no	no	no	serious	
8795b	No	No	Yes	Not serious	
8796m	No	Yes	Yes	Not serious	
8797a	No	No	Yes	Not serious	
8815a	no	no	no	serious	
8817a	no	yes	yes	not serious	
8817d	no	no	yes	not serious	
8817e	no	no	yes	not serious	
8826a	no	no	yes	not serious	
8829a	no	no	yes	not serious	
8850a					
8867					
8884a	no	no	yes	not serious	
8899a	No	No	Yes	Not serious	
8899e	No	No	Yes	Not serious	
8899g	No	No	Yes	Not serious	
8902d	No	No	Yes	Not serious	
8902i	No	No	Yes	Not serious	
8902m	No	No	Yes	Not serious	
8910d	No	No	No	Serious	
8916a	no	no	yes	not serious	
8916b	no	no	yes	not serious	
8916c	no	no	yes	not serious	
8918a	no	no	no	serious	
8918n	no	no	no	serious	
8922l	no	yes	no	serious	
8926a					
8928	no	no	no	serious	
8929a	No	No	Yes	Not serious	
8929c	No	No	Yes	Not serious	
8929f	No	No	No	Serious	
8929g	No	No	Yes	Not serious	
8929i	No	No	Yes	Not serious	
8931a	no	yes	yes	serious	
8933a	no	no	no	serious	
9178a	No	No	Yes	Not serious	

Table 17 continued. GRADE imprecision domain

Estimate ID	Does the 95% CI include the null effect and appreciable benefit/harm?	Does the 95% CI include a trivial effect and appreciable benefit/harm?	Meets the optimal information size	Decision: *not serious, serious, very serious*	Imprecision notes
9178c	No	No	Yes	Not serious	
9178e	No	Yes	Yes	Serious	
9178h	No	No	Yes	Not serious	
9181a	No	No	Yes	Not serious	
9247a					
9247c	No	No	Yes	Not serious	
9261b					
9271a	No	No	Yes	Not serious	
9300c	No	No	Yes	Not serious	
9300g	No	Yes	Yes	Serious	
9300i	No	No	Yes	Not serious	
9300k	No	No	Yes	Not serious	
9300l	No	No	Yes	Not serious	
9307a					Very serious imprecision due to low event rates; downgraded two.
9309c					Imprecision
9316a					
9370b	No	No	Yes	Not serious	

Appendix 3.19 GRADE publication bias domain

Table 18. GRADE publication bias domain

Estimate ID	High number of small studies	Percentage of included trials with conflicts of interest	Funnel plot reported	Visual evidence of public-ation bias	Statistical evidence of publication bias	RCTs of new therapy and unrobust search	The review searched for and presents findings from unpublished studies that showed different results	Decision: *undetected, strongly suspected, very strongly suspected*	Publication bias notes
85a	Yes	Unclear	No	Unclear	Unclear	No	No	Strongly suspected	
100c	no	unclear	no	NR	NR	no	no	undetected	
119a	Yes	Unclear	No	Unclear	Unclear	No	No	Strongly suspected	
212a	No	73%	Yes	Yes	No	No	No	Strongly suspected	
212b	No	73%	Yes	Yes	No	No	No	Strongly suspected	
212d	No	100%	Yes	Yes	No	No	No	Strongly suspected	
593	yes	100%	no	NR	NR	no	no	strongly suspected	
725a	No	Unclear	Yes	No	Unclear	No	No	Undetected	
930a	No	100%	No	Unclear	Unclear	No	No	Undetected	
1021	yes	unclear	no	no	NR	no	no	undetected	
1164	yes	unclear	no	NR	NR	no	no	undetected	
1264	yes	unclear	no	NR	NR	no	no	undetected	
1340a	No	Unclear	No	Unclear	No	No	No	Undetected	
1438a	no	100%	no	NR	NR	no	no	undetected	
1447a	No	Unclear	Yes	No	No	No	No	Undetected	
1606a	no	unclear	no (only two studies so formal analysis not possible)	NR	NR	no	no	undetected	
1629a	no	unclear	no	NR	NR	no	no	undetected	
1653a	unclear	unclear	no	NR	NR	no	no (included some unpublished data however, it is unclear if more unpublished data were witheld by participating drug companies)	undetected	
1752a	no	unclear	yes	no	no	no	no	undetected	
2159	yes	unclear	no	NR	NR	no	no	undetected	
2359c									
2359h									
2359l									
2599a	yes	unclear	yes	no	NR	no	no	undetected	asymetrical appearance to the funnel plot but only 4 studies included so difficult to make a judgement
2640b	no	100%	no	NR	NR	no	no	strongly suspected	FDA trial reports utilised
2811a	No	Unclear	Yes	Yes	Yes	No	No	Strongly suspected	
2811g	No	Unclear	Yes	Yes	Yes	No	No	Strongly suspected	
2933a	no	unclear	no	NR	NR	no	no	undetected	
3030a	Yes	Unclear	Yes	No	Unclear	No	No	Undetected	
3275d	no	100%	no	NR	NR	no	no	strongly suspected	
3275e	no	100%	no	NR	NR	no	no	undetected	
3275l	no	100%	no	NR	NR	no	no	undetected	
3362a	Yes	Unclear	No	Unclear	Unclear	No	No	Strongly suspected	

Table 18 continued. GRADE publication bias domain

Estimate ID	High number of small studies	Percentage of included trials with conflicts of interest	Funnel plot reported	Visual evidence of public-ation bias	Statistical evidence of publication bias	RCTs of new therapy and unrobust search	The review searched for and presents findings from unpublished studies that showed different results	Decision: *undetected, strongly suspected, very strongly suspected*	Publication bias notes
3400a	No	Unclear	Yes	No	No	No	No	Undetected	
3400b	No	Unclear	Yes	No	No	No	No	Undetected	
3415	no	unclear	no	NR	NR	no	no	undetected	
3639f	no	100%	no	NR	NR	no	no	undetected	
3640b	no	100%	no	NR	NR	no	no	strongly suspected	In addition to all trials being industry funded, the review authors had potential conflicts of interest with companies that funded some of the studies.
3640d	no	100%	no	NR	NR	no	no	strongly suspected	In addition to all trials being industry funded, the review authors had potential conflicts of interest with companies that funded some of the studies.
3657	no	0%	no	NR	NR	no	no	undetected	
3709a									
3769e	Yes	Unclear	No	Unclear	Unclear	No	No	Strongly suspected	
3781d	no	unclear	no	no	no	no	no	undetected	
4002h	yes	0	no	NR	NR	no	no	undetected	
4003a									
4003e	no	100%	no	NR	NR	no	no	undetected	
4004o	no	100%	no	NR	NR	no	no	undetected	
4004r	no	100%	no	NR	NR	no	no	undetected	
4004y	no	80%	no	NR	NR	no	no	undetected	Outcome under-reported across studies of Budesonide vs. control.
4004z	no	100%	no	NR	NR	no	no	undetected	
4065a	yes	unclear	no	NR	NR	no	no	undetected	
4067b	yes	unclear	no	NR	NR	no	no	undetected	
4123b	no	0	no	NR	NR	no	no	undetected	
4123i	no	0	no	NR	NR	no	no	undetected	
4147a	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
4154a	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
4192c									
4206a	no		no	NR	NR	no	no	undetected	
4206c	no		no	NR	NR	no	no	undetected	
4260	no	0	no	NR	NR	no	no	undetected	
4305a	Yes	Unclear	No	No	No	No	No	Undetected	
4305d	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
4305f	Yes	Unclear	No	No	No	No	No	Undetected	
4305i	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
4494a	Yes	Unclear	Yes	Yes	Yes	No	No	Strongly suspected	
4508a									
4615d	yes	unclear	no	NR	no	no	no	undetected	
4615e	yes	unclear	no	NR	no	no	no	undetected	
4629a	no	unclear	yes	no	no	no	no	undetected	
4812a	yes	unclear	no	NR	NR	no	no	undetected	
4838a	no	unclear	no	no	no	no	no	undetected	
4838b	no	unclear	no	no	no	no	no	undetected	
4844	yes	unclear	no	NR	NR	no	no	undetected	
4860a	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
4966a	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
4968a	No	Unclear	No	Unclear	Unclear	No	No	Undetected	

Table 18 continued. GRADE publication bias domain

Estimate ID	High number of small studies	Percentage of included trials with conflicts of interest	Funnel plot reported	Visual evidence of public-ation bias	Statistical evidence of publication bias	RCTs of new therapy and unrobust search	The review searched for and presents findings from unpublished studies that showed different results	Decision: *undetected, strongly suspected, very strongly suspected*	Publication bias notes
4987a	No	0	No	Unclear	Unclear	No	No	Undetected	
5145a	Yes	Unclear	No	Unclear	Unclear	No	No	Strongly suspected	
5147a	Yes	Unclear	No	Unclear	Unclear	No	No	Strongly suspected	
5183a	No	Unclear	Unclear	Unclear	Unclear	No	No	Undetected	
5371	yes	unclear	no	NR	NR	no	no	undetected	
5398a	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
5399a									
5399d	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	Funnel plot of the summary estimate showed some evidence of publication bias, but no plot was provided for the sub-group estimate. The sub-group estimate did not include the trials with the highest standard errors or those with the most postive results.
5399j	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
5533g	no	100%	no	NR	NR	no	no	undetected	
5606	yes	44%	no	NR	NR	no	no	strongly suspected	
5937a	No	Unclear	No	No	No	No	No	Undetected	
6091b									Best quality funnel plot of review suggests small negative studies not identified.
6091c	Yes	Unclear	No	Unclear	Unclear	No	No	Strongly suspected	Funnel plot for summary estimate showed evidence of publication bias.
6099a	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Strongly suspected	Reanalysis excluding results of studies with sample sizes less than 100 to assess the effect of publication bias did not significantly alter the results.
6099e	Yes	Unclear	No	Unclear	No	No	No	Undetected	
6099f	Yes	Unclear	No	Unclear	No	No	No	Undetected	
6099h	Yes	Unclear	No	Unclear	No	No	No	Undetected	
6110a	Yes	66%	No	Unclear	Unclear	Yes	No	Strongly suspected	
6360b	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
6360d	Yes	Unclear	No	Unclear	Unclear	yes	No	Undetected	
6360f	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
6442a									
6552i	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
6552m	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
6552p	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
6564a	yes	unclear	no	NR	no	no	no	undetected	
6568a	yes	unclear	no	NR	no	no	no	undetected	

Table 18 continued. GRADE publication bias domain

Estimate ID	High number of small studies	Percentage of included trials with conflicts of interest	Funnel plot reported	Visual evidence of public-ation bias	Statistical evidence of publication bias	RCTs of new therapy and unrobust search	The review searched for and presents findings from unpublished studies that showed different results	Decision: *undetected, strongly suspected, very strongly suspected*	Publication bias notes
6670	no	unclear	no	NR	NR	no	no	undetected	
6677	yes	unclear	no	NR	NR	no	no	strongly suspected	
6746b	no	unclear	no	NR	NR	no	no	undetected	
6764a	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
6797a	no	unclear	no	NR	NR	no	no	undetected	
6797b	no	unclear	no	NR	NR	no	no	undetected	
6797d	no	unclear	no	NR	NR	no	no	undetected	
6806f	no	unclear	no	no (but there was a funnel plot with evidence of publication bias for relapse)	no	no	no	undetected	
7029b	yes	unclear	yes	no	NR	no	no	undetected	
7279b	Yes	Unclear	Yes	Unclear	Unclear	No	No	Undetected	
7417a	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7484a	yes	unclear	no	NR	NR	no	no	undetected	
7504	no	unclear	no	NR	NR	no	no	undetected	
7600a	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
7600c	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
7600e	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
7600j	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7600k	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7600n	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7624a	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7636c	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7651a	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7651b	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7723c	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7723i	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7723m	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7724i	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
7820a	No	33%	No	Unclear	Unclear	No	No	Undetected	
7820b	No	50%	No	Unclear	Unclear	No	No	Undetected	
7820c	Yes	60%	No	Unclear	Unclear	No	No	Strongly suspected	
7820f	Yes	38%	No	Unclear	Unclear	No	No	Strongly suspected	
8460b									
8464b	No	Unclear	Yes	Yes	Yes	No	No	Strongly suspected	
8511a	no	unclear	no	NR	NR	no	no	undetected	
8604b	yes	unclear	no	NR	NR	no	no	undetected	
8604f	yes	unclear	no	NR	NR	no	no	undetected	
8663a	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
8672a									
8672b									
8688a	Yes	0	No	No	Unclear	Yes	No	Undetected	
8692e	no	100%	no	NR	NR	no	no	undetected	
8716a									Funnel Plots and / or Egger test suggest evidence of asymmetry, therefore quality of evidence downgraded by one level.
8729a	yes	unclear	no	NR	no	no	no	undetected	
8733c									
8742a	no	unclear	yes	no	no	no	no	undetected	
8744d	no	100%	no	NR	NR	no	no	undetected	
8747a	no	unclear	no	NR	NR	no	no	undetected	
8747b	no	unclear	no	NR	NR	no	no	undetected	
8761a									

Table 18 continued. GRADE publication bias domain

Estimate ID	High number of small studies	Percentage of included trials with conflicts of interest	Funnel plot reported	Visual evidence of public-ation bias	Statistical evidence of publication bias	RCTs of new therapy and unrobust search	The review searched for and presents findings from unpublished studies that showed different results	Decision: *undetected, strongly suspected, very strongly suspected*	Publication bias notes
8761b									
8762a	Yes	Unclear	No	Unclear	Yes	No	No	Undetected	
8769b									
8770b	yes	14%	no	NR	NR	no	no	undetected	
8776a	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
8784a	yes	0	no	NR	NR	no	no	undetected	
8787c	No	42%	Yes	Yes	Yes	No	No	Strongly suspected	
8787d	No	0	Yes	Yes	Yes	No	No	Strongly suspected	
8787h	No	33%	Yes	Yes	Yes	No	No	Strongly suspected	
8787p	Yes	17%	Yes	Yes	Yes	No	No	Strongly suspected	
8787t	No	29%	Yes	Yes	Yes	No	No	Strongly suspected	
8787v									Publication bias strongly suspected.
8787w									Publication bias strongly suspected.
8788c	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
8790a	no	unclear	no	NR	NR	no	no	undetected	
8795b	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
8796m	No	Unclear	Yes	No	No	No	No	Undetected	
8797a	No	Unclear	No	No	No	No	No	Undetected	
8815a	yes	unclear	no	NR	NR	no	no	undetected	
8817a	no	unclear	yes	yes	yes	no	no	strongly suspected	
8817d	no	unclear	yes	yes	yes	no	no	strongly suspected	
8817e	no	unclear	yes	yes	yes	no	no	strongly suspected	
8826a	yes	unclear	no	NR	NR	no	no	undetected	
8829a	no	unclear	no	NR	NR	no	no	undetected	
8850a									
8867									
8884a	yes	unclear	no	NR	NR	no	no	undetected	
8899a	No	Unclear	No	No	Unclear	No	No	Undetected	
8899e	No	Unclear	No	No	Unclear	No	No	Undetected	
8899g	No	Unclear	No	No	Unclear	No	No	Undetected	
8902d	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
8902i	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
8902m	No	Unclear	Yes	No	Unclear	No	No	Undetected	
8910d	Yes	Unclear	Yes	No	No	No	No	Undetected	
8916a	no	unclear	no	NR	NR	no	no	undetected	
8916b	no	unclear	no	NR	NR	no	no	undetected	
8916c	no	unclear	no	NR	NR	no	no	undetected	
8918a	yes	unclear	no	NR	NR	no	no	undetected	
8918n	yes	unclear	no	NR	NR	no	no	undetected	
8922l	yes	unclear	no	NR	NR	no	no	undetected	
8926a									
8928	yes	unclear	no	NR	NR	no	no	strongly suspected	
8929a	No	Unclear	Yes	No	Unclear	No	No	Undetected	
8929c	No	Unclear	Yes	No	Unclear	No	No	Undetected	
8929f	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
8929g	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
8929i	Yes	Unclear	No	Unclear	Unclear	No	No	Undetected	
8931a	no	unclear	no	NR	no	no	no	undetected	
8933a	no	unclear	no	NR	NR	no	no	undetected	
9178a	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
9178c	Yes	Unclear	No	Unclear	Unclear	No	No	Strongly suspected	
9178e	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
9178h	Yes	Unclear	No	Unclear	Unclear	No	No	Strongly suspected	
9181a	No	Unclear	No	Unclear	Unclear	No	No	Undetected	
9247a									

Table 18 continued. GRADE publication bias domain

Estimate ID	High number of small studies	Percentage of included trials with conflicts of interest	Funnel plot reported	Visual evidence of public-ation bias	Statistical evidence of publication bias	RCTs of new therapy and unrobust search	The review searched for and presents findings from unpublished studies that showed different results	Decision: *undetected, strongly suspected, very strongly suspected*	Publication bias notes
9247c	No	33%	No	Unclear	Unclear	No	No	Undetected	
9261b									
9271a	Yes	Unclear	No	No	No	No	No	Undetected	
9300c	No	50%	No	Unclear	Unclear	No	No	Undetected	
9300g	No	50%	No	Unclear	Unclear	No	No	Undetected	
9300i	No	40%	No	Unclear	Unclear	No	No	Undetected	
9300k	Yes	33%	No	Unclear	Unclear	No	No	Undetected	
9300l	No	67%	No	Unclear	Unclear	No	No	Strongly suspected	
9307a									
9309c									
9316a									
9370b	No	0	No	Unclear	Unclear	No	No	Undetected	

Chapter 4. Mapping national efforts to promote use of evidence-based interventions that reduce emergency hospital admissions: a content analysis of NICE resources in England

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4.0 Chapter overview

This chapter describes a content analysis of national guidelines, quality standards, quality indicators, and audits in England. The aim was to map national efforts to promote use of the effective evidence-based interventions that reduce emergency hospital admissions. The results showed that many interventions to reduce admissions have been recommended in national guidelines however, few have been incorporated into quality standards, quality indicators, and national audits. The chapter ends with a discussion about opportunities to further promote use of interventions that reduce emergency hospital admissions, which may help to alleviate the emergency care crisis.

4.1 Publication statement

Elements of this chapter published in BMC Medicine[1] and on the websites of the School for Primary Care Research[2,3], Oxford University Medical Sciences Division[4], Nuffield Department of Primary Care Health Sciences[5], and Oxford Centre for Evidence-Based Medicine.[6]

4.2 Introduction

4.2.1 Building on findings of previous chapters

Chapter 3 systematically identified 56 interventions that reduce emergency hospital admissions and are supported by high or moderate quality evidence. It was recommended that stakeholders consider implementing these interventions in practice and optimise their use.

This chapter builds on the previous chapter in order to refine and strengthen recommendations for policy and practice in England, which has experienced the largest and most sustained increases in emergency hospital admissions among UK countries. Specifically, this chapter examines which of the 56 prioritised interventions have been incorporated in national clinical guidelines and quality measurement and improvement efforts, and which may be considered for future such initiatives.

4.2.2 How are evidence-based interventions promoted in England?

The National Institute for Health and Care Excellence (NICE) is the main organisation responsible for promoting evidence-based health care interventions in England. NICE became a legal entity in 1999 with the aim of creating consistent guidelines and ending rationing of treatment by geographic area. In 2012 NICE became a non-departmental government body established by the Health and Social Care Act. Their legislated role is to provide guidance and support for practitioners and commissioners to help improve outcomes for people using the NHS, public health services, and social care services. To fulfil this role they produce evidence-based guidance and develop quality measurement and improvement tools that cover all types of interventions and patients.[78]

NICE is the only non-governmental organisation whose health recommendations have legal status and, although not all of their recommendations have legal obligations, health professionals are encouraged to follow NICE guidance. Furthermore, the NHS Constitution states that patients have the right to drugs and treatments that have been recommended by NICE for use in the NHS, if the doctor responsible for the patient's care judges them to be clinically appropriate. As such,

NICE guidelines and quality measurement and improvement tools serve as important frameworks to inform medical decision making and quality improvement initiatives in the English health system.

4.2.3 Mapping national efforts in England to promote use of evidence-based interventions that reduce emergency hospital admissions

The 56 prioritised interventions identified in chapter 3 were supported by strong evidence from multiple RCTs. As a result, it was anticipated that some of the interventions would be well-known in existing clinical practice and may be the subject of ongoing efforts to optimise care. For example, the use of ACE-inhibitors in heart failure patients is supported by NICE clinical guidelines and has been operationalised as a quality indicator in the Quality and Outcomes framework, a general practice pay for performance initiative in England.[9] However, it was unclear which of the interventions had been promoted in this manner which could be considered for future such initiatives. Therefore, to map national efforts to promote evidence-based interventions that reduce EHA a content analysis of NICE resources and national audits using NICE resources was conducted.

4.3 Aim and objectives

4.3.1 Aim

The aim of this chapter was to map national efforts to promote use of evidence-based interventions that reduce emergency hospital admissions in England.

4.3.2 Objectives

To achieve the aim, the objectives of this chapter were:

1. To identify which evidence-based interventions that reduce EHA have been formally recommended in NICE guidelines
2. To identify which evidence-based interventions that reduce EHA have been incorporated into NICE quality of care standards and quality of care indicators
3. To describe the extent to which NICE guideline recommendations, quality of care standards, and quality of care indicators for evidence-based interventions that reduce EHA have been incorporated into national audits and to describe the results of the audits

4.4 Methods

4.4.1 Study design

This study was a content analysis of clinical guidelines, quality standards, quality indicators, and national initiatives to measure and improve the quality of care. Content analysis is a hybrid qualitative/quantitative method that allows one to systematically analyse text in order to describe its contents.[10] There are three types of content analysis: conventional, directed, and summative. All aim to interpret meaning from the content of text data but differ with regard to coding schemes and derivation of codes. Conventional analysis involves deriving all coding categories from the text. Directed analysis uses theory or previous research to guide the development of initial codes. Summative analysis involves counting and comparisons of keywords or content, followed by interpretation of the underlying context.

In this study, a summative content analysis was used. This approach can be used to explore usage of words, phrases, and content, specified *a priori*, and to examine the context within which they are used.[10] Therefore, this summative approach was well-suited to this study as it offered a simple, systematic method to analyse NICE guidance, NICE quality of care standards and indicators, and reports of audit initiatives in England to determine if they contain the evidence-based interventions which were identified in chapter 3.

4.4.2 The six steps of content analysis

The six steps of content analysis are summarised here and described in detail in the next six sections[10]:

1. select data sources to be analysed (section 4.4.3)
2. define the coding framework to be applied (section 4.4.4)
3. outline the coding process (section 4.4.5)
4. implement the coding process (section 4.4.6)
5. determine trustworthiness of coding (section 4.4.7)
6. analyse the results of the coding process (section 4.4.8)

4.4.3 Selecting data sources to be analysed

Twelve sources of data were used in this study to determine which evidence-based interventions that reduce emergency hospital admissions have been formally recommended by NICE, operationalised as quality of care standards and indicators, and subjected to national audit in England. Other than the list of interventions obtained from chapter 3 of this thesis, all data was obtained from the NICE website and its online databases. Table 1 provides a summary of the twelve data sources. Detailed descriptions of the data sources are located in Appendix 4.1.

To be eligible for analysis, the data had to meet the following inclusion criteria:

1. The data included an explicit recommendation about provision of an intervention for a defined patient population or clinical indication;
2. The recommendation had to be developed or endorsed by NICE;
3. Audit initiatives targeting NICE recommendations had to describe the setting of the initiative, the NICE recommendation examined, and the results of the initiative, including the percentage of cases/patients for which the NICE recommendation was followed.

NICE provides several information services which critically appraise and summarise evidence in the form of 'NICE advice', but these do not include formal recommendations about use. Although these services may inform decision making, only formal NICE recommendations have legal status or are translated into quality standards and indicators. Therefore, NICE advice was not included in this content analysis.

Table 1. Summary of data sources

Name of data • Source of data	Description	Corresponding objective and purpose
1. Interventions that reduce emergency admissions • Review in chapter 3	73 intervention-clinical indication combinations found to reduce hospital admissions.	Used to create the coding framework for the content analysis.
NICE guidance: **2. Clinical guidelines** **3. Technology appraisal** **4. Medical technologies** **5. Diagnostics** **6. Interventional procedures** • NICE guidance and quality standards database[11–15]	NICE uses the best-available evidence to provide guidance across all clinical disciplines. Guidance documents contain recommendations about use of interventions.	**Objective 1:** Content analysis conducted to identify NICE recommendations about use of interventions that reduce emergency admissions for clinical indications of interest.
7. Quality standards • NICE guidance and quality standards database[16]	Quality standards are a set of aspirational statements (targets) designed to drive priority quality measurement and improvement within a particular area of care for example, "People with hip fracture have surgery on the day of admission".	**Objective 2:** Content analysis conducted to determine which recommendations about interventions that reduce hospital admissions had been operationalised as quality of care standards and indicators.
8. Quality indicators menu • NICE published menu of quality indicators[17]	Quality indicators measure outcomes that reflect the quality of care, or processes linked by evidence to improved outcomes. While quality standards provide a focus for quality improvement, quality indicators serve as specific, measurable elements of care for example: "The proportion of people with hip fracture who receive surgery on the day of admission." Local and national organisations select indicators from the menu to help them measure and improve the quality of care.	
9. Quality and Outcomes Framework (QOF) • NICE published menu of quality indicators and NHS QOF website[16–18]	A pay-for-performance scheme which measures and incentives a selection of quality indicators (developed by NICE) in English general practice.	**Objectives 3:** Content analysis conducted to describe the extent to which NICE guideline recommendations, quality of care standards, and quality of care indicators for evidence-based interventions that reduce emergency hospital admissions have been incorporated into national audits
10. Clinical Commissioning Group Outcomes Indicator Set (CCG OIS) • NICE published menu of quality indicators and NHS CCG OIS website [16,19]	Indicators (developed by NICE) for measuring health outcomes and the quality of care at the regional level. CCGs use these indicators to identify local priorities for quality improvement, compare their performance to other CCGs, and to demonstrate progress towards improving outcomes.	
11. Clinical Commissioning Group Improvement and Assessment Framework (CCG IAF) • NICE published menu of quality indicators and NHS CCG IAF website[17,20]	Indicators (developed by NICE) for measuring health outcomes and the quality of care at the regional level. CCG IAF targets elements of care that require coordination by multiple stakeholders (i.e., CCGs, NHS England, and local authorities).	
12. Impact reports • NICE database on uptake of its resources[21]	NICE publishes impact reports about the uptake of their guidance, quality standards, and quality indicators by audits; reports; surveys; academic studies; and indicator frameworks. The reports include performance results from real-world clinical practice.	

4.4.4 Defining the coding framework to be applied

A pre-defined coding framework was developed by the thesis author using words and phrases to represent the content of interest (i.e., the prioritised interventions from chapter 3). The 56 prioritised interventions were intended for use in 31 patient populations (hence forth known in this chapter as clinical indications). This corresponded to 73 unique intervention-clinical indication combinations (e.g., ACE-inhibitors for patients with chronic heart failure, ACE-inhibitors for patients with chronic ischaemic heart disease). Descriptions of these 73 combinations (Appendix 4.2) were used to create the pre-defined coding framework.

Disease synonyms were obtained using the ICD 10 coding manual and scout searching of the NICE website.[22] Synonyms for medication names were derived from the BNF Medicines Complete website.[22] The coding framework was reviewed for accuracy and completeness by a health researcher (DC) and a qualified general practitioner (JL). The coding framework is included in Appendix 4.2.

4.4.5 Outlining the coding process

The coding process involved three steps which are described below.

Step 1. Identifying relevant guidelines, quality standards, and quality indicators using keyword searches

Keywords from the coding framework were used to search the NICE database of guidelines, the database of quality standards, and the quality indicators menu. The number of documents in which the codes occurred was recorded. These documents were considered relevant and were then subjected to additional screening in step 2.

Step 2. Identifying recommendations about use of the interventions of interest in relevant guidelines, quality standards, and quality indicators

Documents containing keywords were then screened in-depth using codes and phrases for the interventions of interest. Text referring to the interventions was compared to full descriptions for the interventions and clinical indications listed in Tables 3 to 5. The number of documents containing recommendations about use of the interventions for the clinical indications of interest were recorded, with the source document identified (i.e., Clinical Guideline 108: Chronic Heart Failure).

Step 3. Identifying national audits of NICE recommendations for the interventions of interest

NICE reports which of its quality indicators have been adopted by national NHS-related audit frameworks, including the Quality and Outcomes Framework (QOF), Clinical Commissioning Group Outcomes Indicator Set (CCG OIS), and Clinical Commissioning Group Improvement and Assessment Framework (CCG IAF). Therefore, after having identified relevant quality indicators in step 2, information on the uptake of the indicators by national audit frameworks was recorded.

NICE also provides links to impact summaries on the webpages of individual guidelines, quality standards, and quality indicators. These impact summaries include results for NHS-driven and non-NHS-driven national audits that have targeted NICE recommendations in the form of adherence to guidelines, quality standards, or quality indicators. These links were used to access audit information for the guidelines, quality standards, or quality indicators identified in step 2. The coding framework was applied to identify relevant audits. The number of audits with relevant codes was recorded. Relevant text was then reviewed in-depth and compared to full descriptions of the interventions and clinical indications in Tables 3 to 5. The number of audits targeting NICE recommendations for the interventions and clinical indications of interest were recorded. The specific elements of care that were audited, the settings of the audits, and results of the audits were also recorded.

4.4.6 Implementing the coding process

Systematic searches and analysis of NICE resources using the coding framework were originally conducted in October 2017 and updated in September 2018.

4.4.7 Determining the trustworthiness of coding

Two reviewers (NB and DC) conducted the coding independently and in duplicate. Discrepancies in the number of documents with relevant codes or in the interpretation of relevant text were discussed and resolved by consensus, with arbitration by a third author (JL) when needed.

4.4.8 Analysing results of the coding process

Based on the results of the coding process, the following values were calculated:

- the proportion of intervention-clinical indication combinations that were formally recommended in NICE guidance
- the proportion of intervention-clinical indication combinations that were operationalised in quality standards and quality indicators
- the proportion of intervention-clinical indication combinations that have been featured in national audit initiatives in England

Results from relevant national audits are presented. These results include quality indicators that measured use of the interventions of interest. The results are presented as proportions in which the denominators represent the number of patients eligible for the interventions and the numerators represent the number of eligible patients that received the interventions. Medians with interquartile ranges are presented to summarise results across audits. Microsoft Excel was used for data management and analysis.

4.5 Results

4.5.1 Broad search results

Seventy-two sets of searches were conducted – one for each intervention and its associated clinical indication. These searches yielded a total of 4,080 resources including 2,228 guidelines, quality standards, and quality indicators; 1,849 audit summaries; and reports for three national audit frameworks. The mean number of resources yielded for each search was 56 (SD 47). Figure 1 shows a summary of the search and screening process.

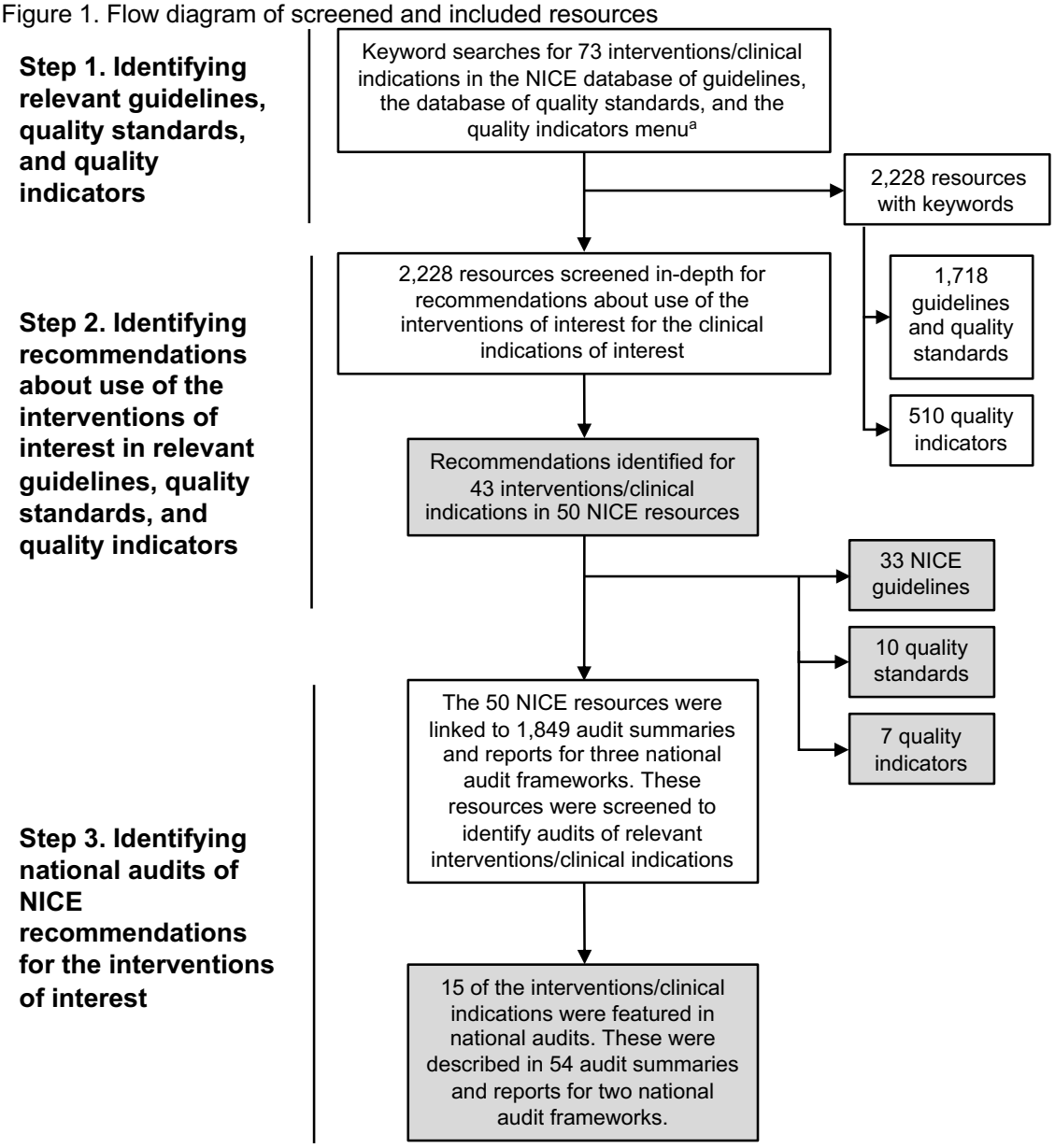
Details of the keyword searches and screened items are presented in Appendix 4.2. Among these search results were guidelines, quality standards, and quality indicators addressing management for the majority of the clinical indications of interest (Appendix 4.3). There were NICE resources addressing diagnosis or management of 84% (n=26/31) of the specific patient clinical indications of interest (Appendix 4.3).

4.5.2 Interventions recommended in NICE guidelines, quality standards, and quality indicators

Table 2 shows the proportion of the interventions of interest that were recommended in NICE resources. Overall, 60% (n=44/73) of the interventions were recommended in NICE guidelines, 19% (n=14/73) had been featured in a quality of care standard, and 11% (n=8/73) had been operationalised as a quality indicator.

Results for medications are shown in Table 3, health systems interventions in Table 4, and diagnostic, medical, and surgical interventions in Table 5. Full annotated results, including names of guidelines, quality standards, and quality indicators are located in Appendices 4.4 to 4.6. A summary list of the NICE guidelines, quality standards, and quality indicators that contained relevant recommendations is provided in Appendix 4.7.

Figure 1. Flow diagram of screened and included resources



[a]56 unique interventions for 31 clinical indications

Table 2. Results of content analysis examining inclusion of interventions that reduce emergency admissions in NICE resources and national audits

Characteristic	Interventions that reduce emergency hospital admissions			
	Medications % (n=35)	**Health systems % (n=32)**	**Diagnostic, medical, and surgical % (n=6)**	**Total % (n=73)**
Recommended in NICE resources				
NICE guidelines	57% (20)	66% (21)	50% (3)	60% (44)
Quality standards	20% (7)	22% (7)	0	19% (14)
Quality indicators	14% (5)	9% (3)	0	11% (8)
Recommended in NICE resources and featured in a national audit	23% (8)	22% (7)	0	21% (15)

4.5.3 NICE recommended interventions featured in national audits

Table 2 shows the proportion of interventions that were recommended by NICE and featured in national audits in England. Overall, 21% (n=15/73) of the interventions had been audited nationally using 34 quality indicators informed by NICE resources. The quality indicators used in national audits are listed in Appendix 4.8, along with details about the initiatives and achievement of the indicators.

4.5.4 Results of national audits of NICE recommended interventions that reduce emergency hospital admissions

The results for the most recent year of the national audits are shown in Figure 2. Information on achievement solely in England was available for 29% (10/34) of the indicators; 71% (24/34) of the indicators were measured across multiple countries within the UK and the results were aggregated. The median achievement in national audits in England was 79% (IQR 56% to 84%) while achievement measured across the UK (including England) was 62% (IQR 43% to 85%).

Audit results for medications are shown in Table 3, health systems are shown in Table 4, and diagnostic, medical, and surgical interventions are shown in Table 5. Full details of these results are located in Appendix 4.8.

Table 3. Results of content analysis examining inclusion of medications that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes ✓ Under-Review -- No X Reviewed and Rejected [X]						
ID No.	**Broad indication:** specific indication[a]	**Intervention that reduces emergency hospital admissions**	**Promoted in NICE resources**			**Featured in a national audit initiative[b]**
			NICE guidelines	Quality standards	Quality indicators menu	
Reduces hospital admissions from the emergency department						
1	**Asthma**: patients in the emergency department for an acute asthma exacerbation	Combination of anticholinergics and beta-2-agonists in the emergency department	X	X	X	X
2		Early use of inhaled corticosteroids in the emergency department	X	X	X	X
3		Intravenous magnesium sulfate in the emergency department	X	X	X	X
4		Nebulised magnesium sulfate in the emergency department	X	X	X	X
Reduces hospital admissions from out-patient, day procedure, or community settings						
5	**Chronic obstructive pulmonary disease**: moderate to severe stable chronic obstructive pulmonary disease	Aclidinium bromide	✓	X	X	X
6		Long-acting beta-2 agonists	✓	X	X	X
7		Mucolytics	✓	X	X	X
8		Tiotropium	✓	X	X	X
9	**Chronic ischaemic heart disease:** stable coronary heart disease	Intensive statin therapy	✓	✓	✓	X
10	**Chronic ischaemic heart disease or heart failure with left ventricular dysfunction:** heart failure with left ventricular dysfunction and/or post-acute myocardial infarction	Aldosterone antagonists	✓	X	X	X
11	**Chronic ischaemic heart disease without heart failure or left ventricular systolic dysfunction:** stable coronary heart disease and absence of heart failure or left ventricular systolic dysfunction; patients with a prior cardiovascular event or at high risk for cardiovascular events with preserved left ventricular function	Angiotensin-converting enzyme (ACE) inhibitors	✓	X	✓	✓
12	**Heart failure:** heart failure with reduced ejection fraction or left ventricular dysfunction	Angiotensin converting enzyme (ACE) inhibitors	✓	✓	✓	✓
13		Angiotensin-II receptor blockers (ARBs)	✓	X	✓	✓
14		Dual therapy with ACE-inhibitors and ARBs	✓	X	X	X
15		Aldosterone antagonists	✓	X	X	X

Table 3 continued. Results of content analysis examining inclusion of medications that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes ✓ Under-Review -- No X Reviewed and Rejected [X]

ID No.	Broad indication: specific indication[a]	Intervention that reduces emergency hospital admissions	Promoted in NICE resources			Featured in a national audit initiative[b]
			NICE guidelines	Quality standards	Quality indicators menu	
Reduces hospital admissions from out-patient, day procedure, or community settings						
16	**Heart failure:** heart failure with reduced ejection fraction or left ventricular dysfunction	Beta-blockers	✓	✓	✓	✓
17		Lipophilic statins	X	X	X	X
18		Digoxin	✓	X	X	X
19	**Heart failure:** heart failure with reduced ejection fraction and iron deficiency/anemia	Erythropoiesis-stimulating agent	X	X	X	X
20		Intravenous iron	[X]	X	X	X
21	**Heart failure:** heart failure with preserved ejection fraction	Beta-blockers	[X]	X	X	X
22	**Heart failure:** heart failure with any ejection fraction	Digoxin	[X]	X	X	X
23	**Inflammatory bowel disease:** crohn's disease or ulcerative colitis	Infliximab	✓	X	X	✓
24	**Inflammatory bowel disease:** ulcerative colitis	Tumor necrosis factor antagonists	✓	X	X	✓
25	**Hepatic encephalopathy**	Probiotics	X	X	X	X
26	**Human immunodeficiency virus**	Cotrimoxazole	X	X	X	X
27	**Dialysis**: long term hemodialysis with a central venous catheter	Topical prophylactic antibiotics	X	X	X	X
28	**Multiple sclerosis**	Glatiramer acetate	✓	✓	X	X
29	**Pregnancy:** normal or high-risk pregnancy	Magnesium supplementation	[X]	X	X	X
30	**Cancer:** prostate biopsy	Antibiotics	✓	X	X	✓
31	**Schizophrenia**	Second generation antipsychotics	✓	✓	X	✓
Reduces readmissions after an index hospital admission						
32	**Hospitalised:** discharged from hospital malnourished (under 65)	Oral nutritional supplements	✓	✓	X	X
33	**Heart failure:** acute decompensation	Hypertonic saline and furosemide	[X]	X	X	X
34	**Schizophrenia**	Antipsychotic maintenance or continuous therapy	✓	✓	X	X
35	**Schizophrenia**	Olanzapine	X	X	X	X

[a]Organisation and categories informed by the World Health Organisation's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding. The broad categories correspond to the second and third level of the ICD-10 hierarchical coding scheme. [b]Quality measurement and improvement frameworks, audits, evaluations, or surveys. National initiatives include the Quality Outcomes Framework, Clinical Commission Group Outcomes Indicator Set, Clinical Commissioning Group Improvement Action Framework, and other initiatives by professional medical organisations and researchers. Abbreviations: ID No.= identifying number; NICE=national institute for health and care excellence; GP= general practitioner; CCG=clinical commissioning group.

Table 4. Results of content analysis examining inclusion of health systems interventions that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes ✓ Under-Review -- No X Reviewed and Rejected [X]

ID No.	**Broad indication:** specific indication[a]	**Description of intervention that reduces emergency hospital admissions**	**Promoted in NICE resources**			**Featured in a national audit initiative[b]**
			NICE guidelines	Quality standards	Quality indicators menu	
Reduces hospital admissions from out-patient, day procedure, or community settings						
36	**Asthma:** patients in the emergency department for an acute asthma exacerbation	Education interventions after an emergency department visit for asthma exacerbation	X	X	X	X
37	**Acute coronary syndrome:** unstable angina; acute myocardial infarction; or **Coronary artery disease:** chronic ischaemic heart disease; stable angina; or **Heart Failure:** chronic heart failure with left ventricular dysfunction	Pharmacist-involved care	✓	X	X	X
38	**Bipolar disorder**	Collaborative care	✓	✓	✓	✓
39	**Chronic obstructive pulmonary disease**	Self-management	✓	X	X	X
40	**Chronic obstructive pulmonary disease**: acute exacerbation of chronic obstructive pulmonary disease	Pharmacist-directed care or pharmacist collaborative care	X	X	X	X
41	**Elderly patients:** elderly in the community or being discharged from hospital	Community-based multifactorial interventions	✓	✓	X	✓
42	**Frequent health care users**	Self-management	X	X	X	X
43	**Heart failure:** chronic heart failure, ejection fraction unspecified	Multidisciplinary care	✓	X	X	X
44		Non-invasive telemonitoring	[X]	X	X	X
45		Specialist heart-failure clinics	✓	✓	X	X
46	**Heart failure:** chronic heart failure with reduced ejection fraction on medication	Nurse-led titration of medication	✓	X	X	X
47	**Schizophrenia:** schizophrenia and other types of schizophrenia-like psychoses	Case management (intensive)	✓	X	X	X
48	**Patients presenting to primary care**	Nurse-led primary care	X	X	X	X
Reduces readmissions after an index hospital admission						
49	**Chronic obstructive pulmonary disease**	Pulmonary rehabilitation programs	✓	✓	✓	✓
50	**Chronic obstructive pulmonary disease**: acute exacerbation of chronic obstructive pulmonary disease	Early supported discharge	✓	X	X	X
51		Hospital at home	✓	X	X	X

Table 4 continue. Results of content analysis examining inclusion of health systems interventions that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes ✓ Under-Review -- No X Reviewed and Rejected [X]

ID No.	Broad indication: specific indication[a]	Description of intervention that reduces emergency hospital admissions	Promoted in NICE resources			Featured in a national audit initiative[b]
			NICE guidelines	Quality standards	Quality indicators menu	
Reduces readmissions after an index hospital admission						
52	**Heart failure:** chronic heart failure, ejection fraction unspecified	Case management (hospital initiated)	✓	[X]	X	X
53		Clinical service organisation interventions (analysis of case management, specialist clinic care, multi-disciplinary care)	✓	✓	✓	✓
54		Disease management programs with multi-disciplinary teams	✓	[X]	X	X
55		Disease management programs with nurse-led discharge planning	X	X	X	X
56		Discharge planning with post-discharge support	✓	[X]	X	X
57		Home-visiting programs	✓	✓	X	X
58		Multidisciplinary care post-discharge	✓	[X]	X	✓
59		Pre-discharge multidisciplinary patient education programs	✓	[X]	X	X
60		Structured telephone support: monitoring; education; or self-care management	[X]	X	X	X
61		Specialist heart failure clinics (multi-disciplinary)	✓	[X]	X	✓
62		Transitional care interventions: telecare and pre-arranged direct patient contact	✓	[X]	X	X
63	**Hospitalised patients**	Discharge planning from hospital	X	X	X	X
64		Nurse-led early discharge planning programs	X	X	X	X
65		Peri-discharge interventions (analysis of 17 types of interventions)	X	X	X	X
66	**Cancer:** patients receiving gastrointestinal cancer surgery	Fast-track rehabilitation after laparoscopic gastrointestinal cancer surgery	X	X	X	X
67	**Mental illness:** severe or chronic mental disorder or illness	Education/self-management	✓	✓	X	✓

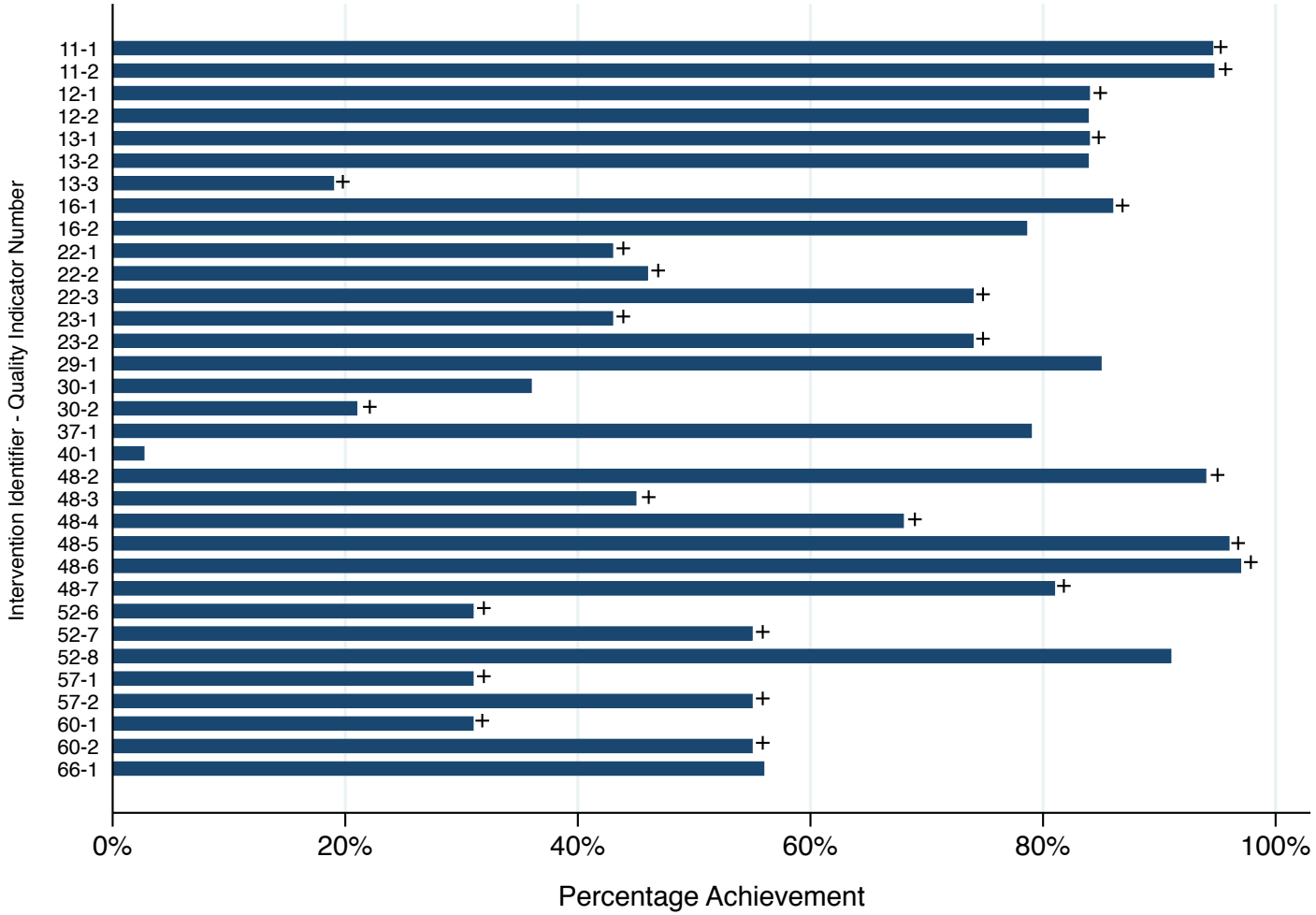
[a]Organisation and categories informed by the World Health Organisation's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding. The broad categories correspond to the second and third level of the ICD-10 hierarchical coding scheme. [b]Quality measurement and improvement frameworks, audits, studies, evaluations, or surveys. National initiatives include the Quality and Outcomes Framework, Clinical Commission Group Outcomes Indicator Set, Clinical Commissioning Group Improvement Action Framework, and other initiatives by professional medical organisations and researchers. Abbreviations: ID No.= identifying number; NICE=national institute for health and care excellence; GP= general practitioner; CCG=clinical commissioning group.

Table 5. Results of content analysis examining inclusion of diagnostic, medical, and surgical interventions that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes ✓ Under-Review -- No X Reviewed and Rejected [X]						
ID No.	**Broad indication:** specific indication[a]	**Description of intervention that reduces emergency hospital admissions**	**Promoted in NICE resources**			**Featured in a national audit initiative[b]**
			NICE guidelines	Quality standards	Quality indicators menu	
Reduces hospital admissions from out-patient, day procedure, or community settings						
68	**Atrial fibrillation:** persistent or permanent atrial fibrillation receiving atrioventricular junction ablation	Cardiac resynchronization therapy	✓	X	X	X
69	**Heart failure:** Heart failure with reduced ejection fraction or left ventricular dysfunction	Cardiac resynchronization therapy	✓	X	X	X
70	**Heart failure:** Heart failure with reduced ejection fraction or left ventricular dysfunction	Natriuretic peptide (B-type and N-terminal Pro B-type) guided therapy	✓	X	X	X
Reduces readmissions after an index hospital admission						
71	**Acute coronary syndrome:** unstable angina or non–ST-segment elevation myocardial infarction	Early/routine coronary angiography	--[c]	X	X	X
72	**Acute coronary syndrome:** acute coronary syndromes with non-ST segment elevation and stages 3 to 5 chronic kidney disease	Early/routine coronary angiography	--[c]	X	X	X
73	**Pneumothorax**: idiopathic spontaneous pneumothorax	Percutaneous aspiration of plural cavity	X	X	X	X

[a]Based on the 3-character coding level using the World Health Organisation's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10). [b]Quality measurement and improvement frameworks, audits, studies, evaluations, or surveys. National initiatives include the Quality Outcomes Framework, Clinical Commission Group Outcomes Indicator Set, Clinical Commissioning Group Improvement Action Framework, and other initiatives by professional medical organisations and researchers. [c]These interventions had previously been reviewed and rejected due to evidence of increased morality. Abbreviations: ID No.= identifying number; NICE=national institute for health and care excellence; GP= general practitioner; CCG=clinical commissioning group.

Figure 2. National achievement of quality indicators measuring the use of NICE recommended interventions that reduce emergency hospital admissions.



Results are for the most recent year the indicator was measured and reported.
+ shows aggregate achievement for quality indicators measured across multiple countries in the UK, not just England.

4.6 Discussion

4.6.1 Summary of findings

This was a content analysis of NICE guidelines, quality standards, quality indicators, and national audits that have used these resources. The purpose of the analysis was to map national efforts in England to promote evidence-based interventions that reduce emergency hospital admissions. The analysis showed that, of the 73 intervention/clinical indications of interest, 44 (60%) were recommended in NICE guidelines, 14 (19%) had informed a quality standard, and 8 (11%) had been operationalised in a quality indicator. National audits have investigated use of 15 (21%) of these interventions using 34 quality indicators based on NICE resources. The results of these audits showed some gaps in use of the interventions. Median achievement in use of the interventions among eligible patients was 79% (IQR 56% to 84%) in England, and 62% (IQR 43% to 85%) in initiatives involving England and other countries in the UK.

4.6.2 Findings in the context of existing research

This study builds on the research reported in chapter 3. A key limitation of the previous chapter was that the overall balance of benefit to harm for interventions was categorised by the thesis author and a second reviewer based on conclusions in included studies. This represents an incomplete assessment given the lack of key stakeholder involvement (i.e., patients, policy-makers, etc.). This study fills that gap by cross-referencing the results with the judgments of NICE guideline committees. These committees engage in a robust review process to determine clinical appropriateness (i.e. balance of benefit to harm) that includes input from patients, practitioners, managers, economists, policy-makers, NHS England, the Care Quality Commission, Public Health England, NHS Improvement, and Health Education England. Therefore, taken together, the results in this chapter and the previous chapter provide a robust list of 43 evidence- and guideline-based interventions that reduce emergency hospital admissions and are clinically appropriate for use in practice.

The results of this study somewhat conflict with research and discourse on reducing emergency hospital admissions. Many stakeholders, including health researchers, health care decision makers, and members of the government, have claimed that there are few evidence-based interventions that reduce emergency admissions and that novel interventions and new models of care are needed to alleviate the admission crisis.[23–27] The review in the previous chapter contradicted these claims by showing that there are a variety of evidence-based interventions that reduce admissions. The results of this chapter further contradict the prevailing literature by showing that many evidence-based interventions that reduce admissions are established elements of clinical practice. These findings suggest that focusing on optimising existing high-value clinical practices may serve to reduce emergency admission rates.

The results of this study suggest that the small pool of UK literature on optimising care for reducing hospital admissions may be incomplete. Researchers have shown that variations in emergency admission rates in England may be partially attributed to variations in the quality of care[23,28–30], yet analyses over time have shown that efforts to optimise quality of care have had little impact on emergency admission rates.[29] As a result, some researchers believe there is little capacity to reduce admissions by further improving the quality of care. However, many of these studies have measured quality of care using metrics in the Quality and Outcomes Frameworks. The results of this chapter have shown that few interventions that reduce hospital admissions are measured as part of the QOF or any other national audit initiative using NICE resources. Therefore, many of the most valuable elements of care for reducing admissions have not been assessed. This may explain why literature on optimising care to reduce hospital admissions has not shown more promise and suggests that more research is needed.

The audit results reported in study showed gaps in use of evidence- and guideline-based interventions for patients with major chronic diseases including chronic ischaemic heart disease, heart failure, inflammatory bowel disease, cancer, schizophrenia, bipolar disorder, serious mental illness, and chronic obstructive pulmonary disease. Although these findings may not be representative of all national audits in England the results match research on gaps in chronic disease care from

other countries.[31–37] For example, a systematic review of U.S. and European studies on heart failure prescribing showed that only 79.8% of patients with reduced left ventricular ejection fractions whom are eligible for treatment receive ACE-inhibitors and ARBs.[28] This chapter found a similar treatment gap for the same medications in the same patient population (84%).

4.6.3 Strengths

This study had three strengths.

Firstly, it was systematic. Two authors (NB, DC) followed an established six-step process to content analysis. The pre-defined coding framework was developed by both authors and the framework was then applied to the data sources independently and in-duplicate.

Secondly, it was comprehensive. Keyword searches led to screening of 4,080 NICE resources. All guidelines, quality standards, quality indicators, and audit reports were carefully reviewed, and key details of these resources were extracted and reported in Appendices 4.4 to 4.8.

Thirdly, this study was minimally invasive and represents a creative use of publicly available resources to answer an important question.

4.6.4 Limitations

This study had limitations. Firstly, it is possible that relevant resources were missed. Although content analysis is a flexible method, the need to search using keywords matching the clinical indications of interest may have led to exclusion of relevant data. For example, there were no guidelines for management of in-patients and, therefore, the use of discharge planning interventions was not recommended for “hospitalised patients”. However, there were sections of disease-specific guidelines focused on in-patient care after a disease-exacerbation and some of these did include recommendations for use of discharge planning interventions. This was a limitation of the systematic nature of the analysis however, such a process was required to ensure reproducibility.

Secondly, the results may have limited generalisability. The study focused on England because it has experienced the most radical and persistent increases in emergency admission rates among UK countries, and because a systematic and comprehensive content analysis of resources in England was feasible. The NICE platform is user-friendly and includes a high-quality search function, similar to that of an electronic database such as Pubmed. Resources of similar organisations in Scotland, Wales, and Northern Ireland were considered for inclusion in this study but their online platforms did not include a high-quality search option necessary for systematic searching. Therefore, ensuring an equally systematic and robust search of resources across the UK would not have been feasible. That being said, the results are relevant to the 55 million people in England that are served by the health system and whose care may be influenced by NICE recommendations. Furthermore, some of the findings in this study likely do have some generalisability across the UK. Health care stakeholders in Scotland, Wales, and Northern Ireland are often involved in the development of NICE guidelines and, ultimately, adopt a large portion of them.[40] Therefore, the results in this study regarding guideline recommended interventions are likely similar across the UK. However, the same cannot be said of quality standards and indicators, the development of which is largely driven by national health priorities and improvement goals, which vary between UK nations.

Thirdly, NICE is not the only organisation responsible for promoting evidence-based interventions in England. Therefore, it is possible that additional interventions that reduce admissions have been promoted by other means including guidelines of professional societies and organisations, enhanced service contracts, and regulatory requirements enacted by organisations such as the Care Quality Commission. All of these mechanisms may serve to promote use of evidence-based interventions. Therefore, this study likely underestimated the extent to which evidence-based interventions that reduce admissions have been promoted in clinical practice in England. However, NICE is the only legally empowered organisation in England whose primary responsibility is promoting evidence-base care and whose resources extend across all health care disciplines. Analysis of all professional society guidelines, enhanced service contracts, and regulatory frameworks would not have been feasible as part of this thesis and likely would have

resulted in similar conclusions given the stature of NICE recommendations and their ubiquity in the policies of other organisations.

Fourthly, the audit data examined in this study likely represents only a portion of all national audits of the English health system and, therefore, this study may have underestimated the number of interventions that have been audited. NICE only reports on audits of partner organisations that measure adherence to their recommendations and use their resources. There have likely been other national audits which have not target NICE recommendations but that have assessed utilisation of some of the interventions in this study. However, the results of this chapter provide insights into which types of interventions have been assessed in national audits and provide some real-world data on gaps in utilisation that match research from other countries.

4.6.5 Implications for policy and practice

The results of this study have implications for clinical policy and practice in England.

Firstly, NICE may consider developing quality standards and indicators for all of the 43 evidence-based interventions which they recommend in their guidelines. Currently, only 16 of these interventions had quality standards or quality indicators however, all 43 interventions meet the criteria for quality standard and indicator development: they are evidence-based; they are supported by NICE guidelines; they address an important patient outcome; they address a national health priority (reducing admissions); and they are related to a significant burden of care (rising admission rates). Development of these resources would facilitate future quality measurement and improvements activities for interventions that reduce admissions.

Secondly, NICE may consider reviewing some of the 20 interventions in this study that had not yet been assessed by their guideline committees. A list of these interventions and their supporting evidence from chapter 3 has been submitted to NICE for consideration.

Thirdly, NICE may consider creating a package of quality standards and indicators that target emergency hospital admissions. This study found no such cluster of quality measurement and improvement tools among NICE resources. The existing standards and indicators are bundled according to patient population, for example, five quality statements/indicators were combined to form “Quality Standard 21: improving diagnosis and management of stable angina in adults”. Therefore, such a package would be unique in that it would target a health care problem that cuts across clinical disciplines and patient populations. This package could then be used to inform audits and drive quality improvements in health care services.

Fourthly, policy-makers and commissioners may use the results to prioritise future audits and quality improvement initiatives. This study contains a list of 43 evidence-based interventions that reduce hospital admissions and are recommended in national guidance. Only 15 of these interventions had been nationally audited. Policymakers, commissioners, and practitioners should consider auditing the remaining 28 interventions in an effort to optimise best-practices and reduce emergency admissions.

Fifthly, national quality measurement frameworks informed by NICE (i.e., Quality and Outcomes Framework and Clinical Commissioning Group Improvement Action Framework) may consider adding more process of care indicators to their audits. These national frameworks have recently undergone reform to include new indicators focused on emergency admissions. However, the results of this study show that these new indicators are mostly outcome measures (i.e., rates of admissions). While tracking outcomes is important and necessary, it may also be valuable to track processes of care that may lead to reductions in admissions (i.e., utilisation of specific interventions).

Sixthly, this study identified gaps in utilisation of interventions that should be closed. For some of the interventions in this study, bridging treatment gaps and improving utilisation may only rely on a small number of stakeholders. For example, a 2015 audit by the National Institute for Cardiovascular Outcomes Research found that only 19% of patients with heart failure were prescribed an Angiotensin II receptor antagonists on discharge for left ventricular systolic dysfunction.[41] Optimal utilisation

of this intervention could be achieved through direct efforts by hospital cardiologists and pharmacists. However, many of the interventions in this study form part of ongoing chronic disease management and improving utilisation would require coordination of multiple stakeholders over time, including physicians in different specialties, home care or case management nurses, pharmacists, social care workers, patients, and family members.

The above recommendations ought to be considered in the light of challenges in translating evidence and guidelines into practice. It would be an over-simplification to suggest that utilisation of an intervention can be increased simply by producing an evidence-based guideline, quality standard, or quality indicator that recommends its use. There are many factors that affect the adoption of clinical guidance and clinical practices.[42–44] Furthermore, guidelines and quality improvement resources are intended to act as frameworks for decision making rather than overriding directives about how to act. There are justifiable gaps in the use of evidence- and guideline-based practices and, ultimately, the decision to utilise an intervention or diagnostic test rests with the patient, their family, and their practitioner. However, surveys show that, despite some concerns about the practicalities of using guidelines, most health practitioners view guidelines positively and believe that they help to improve the quality of care.[42] There is also evidence that uptake of evidence- and guideline-based recommendations is associated with improved patient outcomes and achievement of national health priorities.[42,45–48]

4.6.6 Future research

The results of this research highlight three areas of important future investigation.

Firstly, the 28 evidence- and guideline-based interventions that have not been nationally audited should be investigated to identify potential gaps in care. These results could be used by stakeholders to estimate potential reductions in admissions through improved utilisation and, thereby, prioritise quality improvement efforts. For example, an audit in this study found that 15% of heart failure patients with reduced left ventricular ejection fractions do not receive first line therapy (ACE-inhibitors or Angiotensin-II receptor blockers). It has been estimated that 1.5% of people in

developed countries have heart failure, of whom 40% have reduced ejection fractions.[49–52] Therefore, about 49,311 patients with heart failure and reduced ejection fractions in England are eligible for first-line therapy, but are not receiving it.[53] Combining this data on gaps in care with the results reported in chapter 3 allows estimation of potential reductions in admissions through improved utilisation. As reported in chapter 3, the relative risk reduction in admissions from first line heart failure therapy was 23% (95% CI: 14% to 30%) and the baseline hospitalisation event rate was 21 per 100. Therefore, closing these treatment gaps could help to avoid approximately 2,381 (95% CI: 1,450 to 3,106) emergency admissions in England per year. If estimates of this type were calculated for all the evidence- and guideline-based interventions identified in this thesis, a clear quality improvement agenda would emerge.

Secondly, researchers should explore how the evidence- and guideline-based interventions identified in this chapter are being used, as opposed to simply whether or not they are used. Nearly all of the relevant quality standards and quality indicators in this study assessed whether or not an intervention had been administered, without specifying additional metrics about its use. Studies should explore additional details about implementation that may be relevant to the effect of the interventions for reducing emergency admissions including the frequency, duration, dose, and intensity of the interventions. This information would be relevant for determine whether or not an intervention was being optimally utilised and to gauge capacity for improvement. This research is addressed in chapter 6.

Thirdly, researchers need to identify strategies to optimise use of the evidence- and guideline-based interventions in this chapter. The strategies required will likely vary based on the intervention being targeted and the nature of the gaps in care. However, there is a large behavioural science literature on improving use of medical interventions.[54–58] Review of this literature and contact with experts would be of value once specific shortfalls in care have been adequately mapped.

4.7 Conclusion

This content analysis mapped national efforts in England to promote evidence-based interventions that reduce emergency hospital admissions. The results showed that many interventions to reduce admissions have been promoted in national guidelines, although few have informed quality of care standards and indicators and few have been audited nationally. Of those interventions that have been audited, gaps in utilisation have been demonstrated. Therefore, there may be opportunities to further promote and utilise evidence-based interventions in England, which may lead to reductions in emergency hospital admissions.

4.8 Chapter summary

- This chapter mapped national efforts in England to promote use of evidence-based interventions that reduce emergency hospital admissions
- A content analysis was conducted on NICE resources and national audits that have featured NICE resources
- 4,080 NICE resources were screened using keywords from 73 intervention-clinical indications of interest
- 43 intervention-clinical indications were recommended in guidelines
- 16 intervention-clinical indications had been incorporated into a quality standard or quality indicator
- 15 of the intervention-clinical indications had been featured in a national audit, and these audits showed some gaps in utilisation
- This study provides an agenda for action in policy, practice, and research to reduce emergency hospital admission including a list of 20 intervention-clinical indications that could be considered for inclusion in NICE guidelines, 27 intervention-clinical indications that could be operationalised as quality standards and indicators, and 28 intervention-clinical indications that could be audited in clinical practice

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Chapter 4. Appendix

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Appendix 4.1 Detailed description of data sources

Data source 1. List of evidence-based interventions that reduce emergency hospital admissions

References for the resources below are provided at the end of this section.

1. Evidence-based interventions that reduce emergency hospital admissions

Chapter 3 of this thesis identified 56 prioritised interventions that reduce emergency hospital admissions for 31 clinical indications, amounting to 73 unique intervention-clinical indication combinations. Descriptions of the 73 intervention-indication combinations (Appendix 7.2) were used to create the coding framework for use in the content analysis.

Data sources 2 to 6. NICE guidance documents with recommendations about interventions.

NICE recommendations are published in five types of guidance. Content analysis of these guidance documents was conducted to identify if, and under what circumstances, NICE recommends use of the interventions that reduce emergency hospital admissions.

2. NICE clinical guidelines[1]

NICE uses the best-available evidence to provide guidance across all clinical disciplines. They set out the care and services suitable for most people with a specific condition or need, and people in particular circumstances or settings.[1] NICE recommends interventions based on their clinical appropriateness (overall balance of benefit to harm), safety, cost-effectiveness, and feasibility as judged by clinical experts, health economists, administrators, regulators, and patients.[2] The NICE websites includes lists of its published guidelines, guidelines in consultation, guidelines in development, and proposed guidelines.[3] All of these categories were included in the analysis study. Published guidelines also include details about interventions that were considered for inclusion and rejected by the guideline committee.

3. Technology appraisal guidance[4]

NICE assesses the clinical and cost effectiveness of health technologies and provides recommendations on their use in their technology appraisal guidance. Technologies include new and existing medications, procedures, devices, and diagnostic agents. The NHS is legally obligated to fund technologies recommended in NICE appraisals.

4. Medical technologies[5]

This guidance provides evaluations of novel medical devices and diagnostics that sponsors elect to have assessed by NICE. Recommendations for adoption are based on the advantages of introducing the technology compared with current care.

5. Diagnostic guidance[6]

This guidance provides evaluations of novel diagnostic technologies that sponsors elect to have assessed by NICE, including all types of measurements and tests that are used to evaluate a patient's condition.

6. Interventional procedure guidance[7]

This guidance examines whether interventional procedures are effective and safe enough for wider use in the health system.

Data sources 7 and 8. NICE quality standards and indicators based on recommendations about evidence-based interventions that reduce emergency hospital admissions

NICE develops quality measurement and improvement resources based on their recommendations and guidance. Content analysis of these resources was conducted to determine which recommendations about interventions that reduce hospital admissions had been operationalised as quality of care standards and indicators.

7. Quality standards[8]

NICE develops and publishes quality of care standards to help improve the quality of care delivered in the NHS.[3] A quality standard is a concise set of aspirational

statements designed to drive and measure priority quality improvements within a particular area of care. For example, a quality standard for hip fracture may be "People with hip fracture have surgery on the day of, or the day after, admission". NICE publishes these statements along with information about measuring progress towards the standard. A quality indicator developed to accompany this quality standard may be "The proportion of people with hip fracture who receive surgery on the day of, or the day after, admission."

These standards set out priority areas for quality improvement in health and social care and cover areas where there is variation in care. They are not a mandatory component of health care delivery in the NHS but can be used to identify gaps and areas for improvement; measure the quality of care; understand how to improve care; demonstrate that quality care is being delivered; and to commission high-quality services. Quality standards are based on NICE guidance and other NICE-accredited sources.

8. Quality indicators menu for general practice and clinical commissioning groups[9]

NICE quality indicators measure outcomes that reflect the quality of care or processes linked by evidence to improved outcomes. While quality standards provide a focus for quality improvement, quality indicators serve as specific, measurable elements of care that may be implemented as are. Achievement of certain levels of the indicator may be incentivised. Each indicator includes a denominator describing the target population and a numerator describing the number of people in the denominator who should have the specified intervention.

Local and national organisations select indicators from the indicators menu to help them measure and improve the quality of care across the health system. NICE General Practice indicators are candidates for the national general practice pay-for-performance framework (i.e., Quality and Outcomes Framework) and their Clinical Commissioning Group indicators are candidates for NHS England's CCG Outcomes Indicator Set (CCG OIS) and the CCG Improvement and Assessment Framework (CCG IAF).

Data sources 9 to 12. National audits of NICE guideline recommendations, quality of care standards, and quality of care indicators for evidence-based interventions that reduce emergency hospital admissions

NICE guidance, quality standards, and quality indicators inform local and national initiatives in England to measure and improve the quality of care. Content analysis of these initiatives was conducted to identify national audits that have assessed use of evidence-based interventions that reduce emergency hospital admissions.

9. Quality Outcomes Framework (QOF)[8–10]

The QOF is a pay-for-performance scheme which measures and incentives a selection of quality indicators in English general practice. NICE directly supports this initiative as it develops indicators for the QOF in collaboration with key stakeholders.

10. Clinical Commissioning Group Outcome Indicator Set (CCG OIS)[8,11]

The CCG OIS consists of indicators for measuring health outcomes and the quality of care at the regional level. CCGs use these indicators to identify local priorities for quality improvement, compare their performance to other CCGs, and to demonstrate progress towards improving outcomes. NICE directly supports this initiative as it develops indicators for the CCG OIS in collaboration with key stakeholders.

11. CCG Improvement and Assessment Framework (CCG IAF)[9,12]

The CCG IAF is another set of indicators for measuring health outcomes and the quality of care at the regional level. The CCG IAF was introduced to measure progress towards health system reform as outlined in NHS's 'Five Year Forward View' transformation plan. Specifically, it intends to evaluate elements of care requiring joint effort by multiple stakeholders (i.e., CCGs, NHS England, and local authorities) and not just those elements fully in control of the CCGs. NICE directly supports this initiative as it develops indicators for the CCG OIS in collaboration with key stakeholders.

12. Impact reports tracking use of NICE recommendations in audits, surveys, and quality indicator frameworks[13]

NICE publishes impact reports about the uptake of their guidance, quality standards, and quality indicators from audits; surveys; academic studies; and indicator frameworks. The reports include performance results from real-world clinical practice. Content analysis on the impact reports was conducted to identify the extent to which NICE recommendations on interventions that reduce emergency hospital admissions have been audited in real practice and to quantity variation in real-world adherence to the recommendations.

The methodology used by NICE to collect this information is not publicly available. Therefore, a NICE representative was contacted via email. The representative provided an infographic (Figure 1: next page) and indicated that information for impact reports are systematically collected each month from partner organisations. Their information services team also carries out monthly literature searches to look for information about the uptake, impact, or implementation of NICE recommendations.

Figure 1. Infographic provided by NICE representative

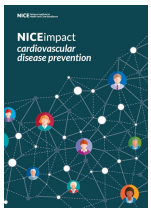
NICE National Institute for Health and Care Excellence

Communicating the impact of NICE guidance

Jennifer Beveridge, Leighton Coombs, Dominick Moran, Xavier Vaz, Cheryl Pace, Paul Chrisp, Professor Gillian Leng

Background

NICE guidance needs to be put into practice to have an impact on the health and wellbeing of the population, and on quality of care. We aimed to develop a process for reviewing the uptake and impact of NICE's recommendations, and communicating our findings in an accessible format.



Objectives

To describe:
- our process for identifying published data that measure the uptake of NICE guidance and standards
- how an accessible format for presenting these data was developed.

Methods

Since 2014, we have carried out a monthly review of publically available sources and a search of relevant databases to identify data that measure the percentage uptake of NICE recommendations or quality statements at a national or local level. We have uploaded these data to an uptake database, which is available to browse via the Into Practice pages of the NICE website.

To make these data more accessible and bring our findings to wider attention, we developed a topic-based reporting format. The first **NICE**impact report, on cancer, was published in January 2018 and a process to publish 6 reports each year was established. The broad topic areas covered by the reports were selected by the NICE senior management team to align with current health and care system priorities in England.

The reports aim to highlight areas where NICE guidance and standards appear to be making a difference to the care given in health and care services in England. They also draw attention to areas where there is still room for improvement.

Regularly reviewed sources include:

- publications from the National Clinical Audit and Patient Outcomes Programme
- routinely collected data published by NHS Digital, NHS England, Public Health England and the Office for National Statistics
- data releases from national indicator sets such as the Quality and Outcomes Framework
- national patient and service user surveys published by the Care Quality Commission and NHS England
- audits, reports and surveys published by Medical Royal Colleges, All-Party Parliamentary Groups and third sector organisations
- monthly searches of Embase, Medline in Progress and Health Management Information Consortium (HMIC).

From broad topic area to focused NICEimpact report

1. **IDENTIFY** all NICE guidance and quality standards relevant to a broad topic area and extract uptake data from the NICE uptake database
2. **PRIORITISE** the data by engaging with topic experts, including NHS England's National Clinical Directors and policy leads from Public Health England, NHS RightCare and third sector organisations, to align report themes with current health and care system priorities in England
3. **SEARCH** for additional data to inform the agreed themes, including prevalence, incidence, prescribing and outcomes data
4. **COLLABORATE** with NICE colleagues to source relevant examples of wider impact such as national partnership working and NICE guidance being implemented in practice
5. **CONNECT** with patients and service users through NICE's Public Involvement Programme to understand how our guidance has affected them
6. **ENGAGE** with an expert commentator to contextualise the data, highlight key findings and identify barriers to implementation

Results and impact

Presenting routinely collected data in accessible, visually appealing, topic-focused reports has widened the audience for such information. The reports are now an embedded part of NICE's strategic approach to external communications.

The **NICE**impact cardiovascular disease (CVD) prevention report, published in June 2018, was shared over the NICE Twitter, Facebook, Instagram and LinkedIn pages, with supporting graphics to highlight the changes in childhood smoking rates and statin prescriptions. Tweets promoting this report by @NICEcomms had nearly 18,000 impressions and more than 200 people accessed the report via Twitter links.

Partners in the health and social care system engaged with the **NICE**impact CVD prevention report; Public Health England, the Care Quality Commission, Heart UK, Blood Pressure UK and the Faculty of Public Health are among those who retweeted or otherwise promoted the report through their own communications and social media channels.

Conclusions

By bringing together uptake data with information about the wider impact of NICE, our **NICE**impact reports highlight areas where NICE guidance and standards appear to be making a difference, and bring to attention areas for improvement. Presenting this information in a visually appealing, accessible format has helped make it available to a wide audience.

Key design features of the reports

Working with a designer, we developed a reporting format that is accessible, easy to navigate and visually appealing. **NICE**impact reports have a strong visual identity aligned with NICE's corporate branding.



Key findings are repeated in the report index and chapter introductions to help users navigate and find content of interest



Design elements such as pull-text, data headlines and marginal boxes are used to highlight key findings



Charts have a clean, simple design and need no written interpretation in the main body of the text



Patient and service user quotes are presented so that they stand out



Examples of local implementation and partnership working are highlighted in feature boxes



Bespoke infographics are used to summarise complex data

Contact: Jennifer Beveridge
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Search for **NICE**impact at www.nice.org.uk

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Appendix 4.2 Details of keyword searches and search results screened

Table 1. Detailed search strategy and results

ID	Population/clinical indication keywords searched	Intervention synonyms considered during the review of resources	Total number of items screened	Breakdown of number of search results identified and screened
1	asthma	anticholinergic, antimuscarinic, muscarinic antagonist, bronchodilator, glycopyrrolate, ipratropium bromide, oxitropium bromide, beta-2-agonist, b2-adrenergic agonists, salbutamol	17	Guidance and quality standards: 14 Quality indicators menu: 3 National audits, reports, or surveys: 0
2	asthma	inhaled corticosteroid, beclomethasone, flunisolide, fluticasone	17	Guidance and quality standards: 14 Quality indicators menu: 3 National audits, reports, or surveys: 0
3	asthma	magnesium sulfate, intravenous	17	Guidance and quality standards: 14 Quality indicators menu: 3 National audits, reports, or surveys: 0
4	asthma	magnesium sulfate, nebulised	17	Guidance and quality standards: 14 Quality indicators menu: 3 National audits, reports, or surveys: 0
5	chronic obstructive pulmonary disease	aclidinium bromide, antimuscarinic, muscarinic antagonist	59	Guidance and quality standards: 6 Quality indicators menu: 13 National audits, reports, or surveys: 40
6	chronic obstructive pulmonary disease	long-acting beta-2 agonist, beta-2 agonist	59	Guidance and quality standards: 6 Quality indicators menu: 13 National audits, reports, or surveys: 40
7	chronic obstructive pulmonary disease	mucolytic	59	Guidance and quality standards: 6 Quality indicators menu: 13 National audits, reports, or surveys: 40
8	chronic obstructive pulmonary disease	tiotropium, antimuscarinic, muscarinic antagonist	59	Guidance and quality standards: 6 Quality indicators menu: 13 National audits, reports, or surveys: 40
9	heart disease, angina, coronary, chest pain, cardiovascular, atherosclerotic, atherosclerosis, myocardial infarction, cardiomyopathy	intensive statin therapy, lipid regulating drugs	81	Guidance and quality standards: 49 Quality indicators menu: 9 National audits, reports, or surveys: 23
10	heart disease, angina, coronary, chest pain, cardiovascular, atherosclerotic, atherosclerosis, myocardial infarction, cardiomyopathy, heart failure	aldosterone antagonists, potassium-sparing diuretics	139	Guidance and quality standards: 65 Quality indicators menu: 15 National audits, reports, or surveys: 59
11	heart disease, angina, coronary, chest pain, cardiovascular, atherosclerotic, atherosclerosis, myocardial infarction, cardiomyopathy	angiotensin-converting enzyme inhibitors	75	Guidance and quality standards: 49 Quality indicators menu: 9 National audits, reports, or surveys: 17
12	heart failure	angiotensin-converting enzyme inhibitors	75	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 52
13	heart failure	angiotensin-II receptor blockers	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
14	heart failure	dual therapy with angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
15	heart failure	aldosterone antagonists	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
16	heart failure	beta-blockers	32	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 9

Table 1 continued. Detailed search strategy and results

ID	Population/clinical indication keywords searched	Intervention synonyms considered during the review of resources	Total number of items screened	Breakdown of number of search results identified and screened
17	heart failure	lipophilic statins	23	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 0
18	heart failure	erythropoiesis stimulating agent, epoetin, darbepoetin	23	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 0
19	heart failure	intravenous iron, iron supplementation	23	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 0
20	heart failure	beta-blockers	23	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 0
21	heart failure (any ejection fraction	digoxin, cardiac glycoside	23	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 0
22	heart failure (reduced ejection fraction)	digoxin, cardiac glycoside	23	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 0
23	crohn, ulcerative, colitis, inflammatory	infliximab, bosentan, ambrisentan, TNF inhibitors, anti-TNF	60	Guidance and quality standards: 29 Quality indicators menu: 0 National audits, reports, or surveys: 31
24	ulcerative, colitis, inflammatory	tumour necrosis factor antagonists, TNF inhibitors, anti-TNF, tumour necrosis factor antagonists	42	Guidance and quality standards: 19 Quality indicators menu: 0 National audits, reports, or surveys: 23
25	hepatic, encephalopathy	prrobiotics, lactobacilli, bifidobacteria, streptococcus thermophiles	8	Guidance and quality standards: 8 Quality indicators menu: 0 National audits, reports, or surveys: 0
26	human immunodeficiency virus, HIV	cotrimoxazole	3	Guidance and quality standards: 3 Quality indicators menu: 0 National audits, reports, or surveys: 0
27	hemodialysis, dialysis, central venous, catheter	topical prophylactic antibiotics, mupirocin, polysporin triple-antibiotic ointment	29	Guidance and quality standards: 29 Quality indicators menu: 0 National audits, reports, or surveys: 0
28	multiple sclerosis	glatiramer acetate, copaxone	21	Guidance and quality standards: 21 Quality indicators menu: 0 National audits, reports, or surveys: 0
29	pregnant, pregnancy, labour, maternal	magnesium supplementation	50	Guidance and quality standards: 33 Quality indicators menu: 17 National audits, reports, or surveys: 0
30	cancer, biopsy, prostate	antibiotic, ofloxacin, trimethoprim, sulfonamide methoxazole, or ciprofloxacin	332	Guidance and quality standards: 285 Quality indicators menu: 9 National audits, reports, or surveys: 38
31	schizophrenia, mental illness, mental health	second generation antipsychotics, amisulpride, clozapine, iloperidone, olanzapine, quetiapine, risperidone, sertindole, or ziprasidone	122	Guidance and quality standards: 6 Quality indicators menu: 11 National audits, reports, or surveys: 105
32	malnourished, nutrition, discharge, transition, nutritional, supplement	supplement, nutrition, hova source liquid, clinutren soup and clinutren, fortisip, fresubin, fortifresh	24	Guidance and quality standards: 16 Quality indicators menu: 0 National audits, reports, or surveys: 8
33	heart failure, decompensation, furosemide	hypertonic saline solution plus intravenous furosemide	24	Guidance and quality standards: 17 Quality indicators menu: 7 National audits, reports, or surveys: 0
34	schizophrenia	maintenance, depot, injectable	122	Guidance and quality standards: 6 Quality indicators menu: 11 National audits, reports, or surveys: 105
35	schizophrenia	olanzapine	17	Guidance and quality standards: 6 Quality indicators menu: 11 National audits, reports, or surveys: 0
36	asthma	education interventions	20	Guidance and quality standards: 14 Quality indicators menu: 3 National audits, reports, or surveys: 3

Table 1 continued. Detailed search strategy and results

ID	Population/clinical indication keywords searched	Intervention synonyms considered during the review of resources	Total number of items screened	Breakdown of number of search results identified and screened
37	coronary, artery, heart, angina, chronic ischaemic, myocardial infarction, heart failure	pharmacist-led care, pharmacist-directed, pharmacists involved, pharmacy care, multi-disciplinary team with a pharmacist	162	Guidance and quality standards: 102 Quality indicators menu: 17 National audits, reports, or surveys: 43
38	bipolar	collaborative care, multiple stakeholders working together to provide support and care for the patient	37	Guidance and quality standards: 7 Quality indicators menu: 11 National audits, reports, or surveys: 19
39	chronic obstructive pulmonary disease	self-management	59	Guidance and quality standards: 6 Quality indicators menu: 13 National audits, reports, or surveys: 40
40	chronic obstructive pulmonary disease	pharmacist-led care, pharmacist-directed, pharmacists involved, pharmacy care, multi-disciplinary team with a pharmacist	19	Guidance and quality standards: 6 Quality indicators menu: 13 National audits, reports, or surveys: 0
41	elderly, older, senior, senile, geriatric, hospitalised, discharge, transition	community-based, multifactorial interventions, multi-component interventions	91	Guidance and quality standards: 19 Quality indicators menu: 0 National audits, reports, or surveys: 72
42	Due to the broadly defined population, the intervention was also included in the search strategy: frequent, high-flyer, common, high-risk, high risk, utilisation, repeat, readmission, self-management	self-management	12	Guidance and quality standards: 12 Quality indicators menu: 0 National audits, reports, or surveys: 0
43	heart failure	multidisciplinary care	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
44	heart failure	non-invasive telemonitoring	23	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 0
45	heart failure	specialist heart-failure clinics, assessments at clinics with specialist in heart failure	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
46	heart failure	nurse-led titration of medication	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
47	schizophrenia, psychosis	intensive case management	93	Guidance and quality standards: 13 Quality indicators menu: 11 National audits, reports, or surveys: 69
48	Due to the broadly defined population, the intervention was also included in the search strategy: primary, community, nurse-led, nurse led, nursing, staff, workforce	nurse-led primary care	29	Guidance and quality standards: 29 Quality indicators menu: 0 National audits, reports, or surveys: 0
49	chronic obstructive pulmonary disease	pulmonary rehabilitation programs	85	Guidance and quality standards: 6 Quality indicators menu: 13 National audits, reports, or surveys: 66
50	chronic obstructive pulmonary disease	early supported discharge	85	Guidance and quality standards: 6 Quality indicators menu: 13 National audits, reports, or surveys: 66
51	chronic obstructive pulmonary disease	hospital at home	85	Guidance and quality standards: 6 Quality indicators menu: 13 National audits, reports, or surveys: 66
52	heart failure	case management (hospital initiated)	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43

Table 1 continued. Detailed search strategy and results

ID	Population/clinical indication keywords searched	Intervention synonyms considered during the review of resources	Total number of items screened	Breakdown of number of search results identified and screened
53	heart failure	clinical service organisation interventions including case management, specialist clinic care, or multi-disciplinary care	72	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 49
54	heart failure	disease management programs with multi-disciplinary teams	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
55	heart failure	disease management programs with nurse-led discharge planning	23	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 0
56	heart failure	discharge planning with post-discharge support	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
57	heart failure	home-visiting programs	72	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 49
58	heart failure	multidisciplinary care post-discharge	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
59	heart failure	pre-discharge multidisciplinary patient education programs	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
60	heart failure	structured telephone support: monitoring; education; or self-care management	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
61	heart failure	specialist heart failure clinics that include a multi-disciplinary set of providers	66	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 43
62	heart failure	transitional care interventions: telecare and pre-arranged direct patient contact	23	Guidance and quality standards: 16 Quality indicators menu: 7 National audits, reports, or surveys: 0
63	inpatient, hospital, discharge, transition	in-hospital discharge planning	22	Guidance and quality standards: 22 Quality indicators menu: 0 National audits, reports, or surveys: 0
64	inpatient, hospital, discharge, transition	nurse-led early discharge planning programs	22	Guidance and quality standards: 22 Quality indicators menu: 0 National audits, reports, or surveys: 0
65	inpatient, hospital, discharge, transition	peri-discharge interventions, readmission avoidance, in-hospital discharge planning, follow-up post-discharge	22	Guidance and quality standards: 22 Quality indicators menu: 0 National audits, reports, or surveys: 0
66	gastrointestinal, gastrectomy, surgical, surgery, laparoscopic	fast-track rehabilitation after laparoscopic surgery	96	Guidance and quality standards: 96 Quality indicators menu: 0 National audits, reports, or surveys: 0
67	mental	education or self-management	107	Guidance and quality standards: 30 Quality indicators menu: 4 National audits, reports, or surveys: 73
68	atrial fibrillation, arrhythmia, ablation	cardiac resynchronization, implantable cardioverter defibrillator, biventricular pacemaker, pacing	79	Guidance and quality standards: 69 Quality indicators menu: 8 National audits, reports, or surveys: 2
69	heart failure, ventricular	cardiac resynchronization therapy	80	Guidance and quality standards: 27 Quality indicators menu: 10 National audits, reports, or surveys: 43
70	heart failure, ventricular	natriuretic peptide (B-typeN-terminal Pro B-type) guided therapy	37	Guidance and quality standards: 27 Quality indicators menu: 10 National audits, reports, or surveys: 0
71	acute coronary, angina, nstemi, myocardial infarction	early/routine coronary angiography	30	Guidance and quality standards: 17 Quality indicators menu: 13 National audits, reports, or surveys: 0
72	acute coronary, angina, nstemi, myocardial infarction, chronic kidney disease	early/routine coronary angiography	36	Guidance and quality standards: 23 Quality indicators menu: 13 National audits, reports, or surveys: 0
73	pneumothorax	percutaneous aspiration of plural cavity	0	Guidance and quality standards: 0 Quality indicators menu: 0 National audits, reports, or surveys: 0

Appendix 4.3 Coverage of relevant clinical indications in NICE guidance, quality standards, and quality indicators

Table 2. Coverage of relevant clinical indications in NICE guidance, quality standards, and quality indicators

Broad clinical indication	Are there NICE clinical resources addressing the broad clinical indication?		Specific clinical indication	Are there NICE clinical resources addressing the specific clinical indication?	
	Clinical guidance	Quality standards and indicators		Clinical guidance	Quality standards and indicators
Acute coronary syndromes	Yes	Yes	Unstable angina or non–ST-segment elevation myocardial infarction	Yes	No
			Acute coronary syndromes with non-ST segment elevation and stages 3 to 5 chronic kidney disease	No	No
Asthma	Yes	Yes	Patients in the emergency department for an acute asthma exacerbation	No	Yes
Atrial fibrillation	Yes	Yes	Persistent or permanent atrial fibrillation receiving atrioventricular junction ablation	Yes	Yes
Mood disorders	No	No	Bipolar disorder	Yes	Yes
Cancer	Yes	Yes	Prostate biopsy	Yes	No
			Patients receiving laparoscopic gastrointestinal cancer surgery	Yes	No
Chronic ischaemic heart disease	Yes	Yes	Post-acute myocardial infarction with Killip scores between I and IV and indicated at least one assessment criteria	Yes	Yes
			Stable coronary heart disease, patients with a prior cardiovascular event, or patients at high risk for cardiovascular events with preserved left ventricular function	Yes	Yes
Heart failure	Yes	Yes	Acute decompensated heart failure	Yes	Yes
			Chronic heart failure with reduced ejection fraction or left ventricular dysfunction	Yes	Yes
			Chronic heart failure with reduced ejection fraction and iron deficiency/anemia	Yes	No
			Chronic heart failure with preserved ejection fraction	Yes	Yes
			Chronic heart failure with any ejection fraction	Yes	Yes

Table 2 continued. Coverage of relevant clinical indications in NICE guidance, quality standards, and quality indicators

Broad clinical indication	Are there NICE clinical resources addressing the broad clinical indication?		Specific clinical indication	Are there NICE clinical resources addressing the specific clinical indication?	
	Clinical guidance	Quality standards and indicators		Clinical guidance	Quality standards and indicators
Chronic obstructive pulmonary disease	Yes	Yes	Moderate to severe stable chronic obstructive pulmonary disease	Yes	Yes
			Acute exacerbation of chronic obstructive pulmonary disease	Yes	Yes
Dialysis[b]	Yes	No	Long term hemodialysis with a central venous catheter	Yes	No
Elderly people[b]	Yes	Yes	Elderly people in the community or being discharged from hospital	Yes	Yes
Hepatic failure	Yes	No	Hepatic encephalopathy	Yes	No
Human immunodeficiency virus	Yes	Yes	Human immunodeficiency virus	Yes	Yes
Inflammatory bowel disease	Yes	Yes	Crohn's disease	Yes	Yes
			Ulcerative colitis	Yes	Yes
Chronic ischaemic heart disease	Yes	Yes			
Malnourishment	Yes	Yes	Discharged from hospital malnourished	Yes	Yes
Mental illness	Yes	Yes	Severe or chronic mental disorder or illness	Yes	Yes
Multiple sclerosis	Yes	Yes	Multiple sclerosis	Yes	Yes
Patients using health care services[c]	Yes	Yes	Hospitalised patients	No	No
			Patients presenting to primary care	No	No
			Frequent health care users	No	No
Pneumothorax	No	No	Idiopathic spontaneous pneumothorax	No	No
Pregnancy[c]	Yes	Yes	Normal or high-risk pregnancy	Yes	Yes
Schizophrenia	Yes	Yes	Schizophrenia and other types of schizophrenia-like psychoses	Yes	Yes

[a]Organisation and categories informed by the World Health Organisation's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding. The broad categories correspond to the second and third level of the ICD-10 hierarchical coding scheme. [b]Not an ICD coding category. [c]ICD level one code.

Appendix 4.4 Medications that reduce emergency hospital admissions recommended in NICE resources and featured in national audits

Table 3. Medications that reduce emergency hospital admissions recommended in NICE resources and featured in national audits

Legend: Yes Under-Review No Reviewed and Rejected

ID	Broad indication: specific indication[a]	Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]	Promoted in NICE resources			Featured in a national audit[c] (% achievement)
			NICE guidance	Quality standards	Quality indicators menu	
Reduces hospital admissions from the emergency department						
1	**Asthma**: patients in the emergency department for an acute asthma exacerbation	Combination of anticholinergics and beta-2-agonists in the emergency department (Rodrigo 2005: 6568a)	No	No	No	No
2		Early use of inhaled corticosteroids in the emergency department (Edmonds 2012: 2159)	No	No	No	No
3		Intravenous magnesium sulfate in the emergency department (Kew 2014: 4002h)	No	No	No	No
4		Nebulised magnesium sulfate in the emergency department (Shan 2013: 7029b)	No	No	No	No
Reduces hospital admissions from out-patient, day procedure, or community settings						
5	**Chronic obstructive pulmonary disease**: moderate to severe stable chronic obstructive pulmonary disease	Aclidinium bromide (Ni 2014: 8850a) (Zou 2016: 8933a)	Yes: CG101	No	No	No
6		Long-acting beta-2 agonists (Kew 2013: 4003a)	Yes: CG101	No	No	No
7		Mucolytics (Poole 2015: 8867)	Yes: CG101 (but not for routine prevention of exacerbations)[d]	No	No	No
8		Tiotropium (Karner 2014: 8692e) (Cheyne 2015: 8744d) (Chong 2012: 1438a)	Yes: CG101	No	No	No
9	**Chronic ischaemic heart disease:** stable coronary heart disease	Intensive statin therapy (Afilalo 2007: 100c)	Yes: CG181, CG126, CG172	Yes: QS100	Yes: NM79, NM80	No

Table 3 continued. Medications that reduce emergency hospital admissions recommended in NICE resources and featured in national audits

Legend: Yes Under-Review No Reviewed and Rejected

ID	**Broad indication:** specific indication[a]	**Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]**	**Promoted in NICE resources**			**Featured in a national audit[c] (% achievement)**
			NICE guidance	Quality standards	Quality indicators menu	
Reduces hospital admissions from out-patient, day procedure, or community settings						
10	**Chronic ischaemic heart disease or heart failure with left ventricular dysfunction:** heart failure with left ventricular dysfunction (New York Heart Association 1 to 4) and/or post-acute myocardial infarction with Killip scores between I and IV and indicated at least one assessment criteria	Aldosterone antagonists (Le 2016: 8817a)	Yes: NG106, CG172, CG108	No	No	No
11	**Chronic ischaemic heart disease without heart failure or left ventricular systolic dysfunction:** stable coronary heart disease and absence of heart failure or left ventricular systolic dysfunction; patients with a prior cardiovascular event or at high risk for cardiovascular events with preserved left ventricular function	Angiotensin-converting enzyme inhibitors (Danchin 2006: 1752a) (Saha 2007: 6746b)	Yes: CG126, CG172	No	Yes: NM79, NM80	Yes: 2015, 2016 Myocardial Ischaemia National Audit Project by the National Institute for Cardiovascular Outcomes Research (94.6%, 94.7%)
12	**Heart failure:** heart failure with reduced ejection fraction or left ventricular dysfunction	Angiotensin converting enzyme (ACE) inhibitors (Xie 2016: 8916a)	Yes: NG106, CG108	Yes: QS9	Yes: NM89	Yes: 2014, 2015 National Heart Failure Audit by the National Institute for Cardiovascular Outcomes Research (85%, 84%) 2016, 2017 QOF indicator HF003 by the Health and Social Care Information Centre (84.7%, 83.9%)
13		Angiotensin-II receptor blockers (ARBs) (Xie 2016: 8916b)	Yes: NG106, CG108, TA388	No	Yes: NM89	Yes: 2014x2, 2015x2 National Heart Failure Audit by the National Institute for Cardiovascular Outcomes Research (85%, 19%, 84%, 19%) 2016, 2017 QOF indicator HF003 by the Health and Social Care Information Centre (84.7%, 83.9%)

Table 3 continued. Medications that reduce emergency hospital admissions recommended in NICE resources and featured in national audits

Legend: Yes Under-Review No Reviewed and Rejected

ID	Broad indication: specific indication[a]	Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]	Promoted in NICE resources			Featured in a national audit[c] (% achievement)
			NICE guidance	Quality standards	Quality indicators menu	
Reduces hospital admissions from out-patient, day procedure, or community settings						
14	**Heart failure:** heart failure with reduced ejection fraction or left ventricular dysfunction	Dual therapy with ACE-inhibitors and ARBs (Kuenzli 2010: 4206a) (Kuenzli 2010: 4206c) (Jong 2002: 3781d) (Makani 2013: 4838b)	Yes: NG106 (in select patients), CG108	No	No	No
15		Aldosterone antagonists (Xie 2016: 8916c)	Yes: NG106, CG108	No	No	No
16		Beta-blockers (Brophy 2001: 1021)	Yes: NG106, CG108	Yes: QS9	Yes: NM90	Yes: 2014, 2015 National Heart Failure Audit by the National Institute for Cardiovascular Outcomes Research (85%, 86%) 2015, 2016, 2017 QOF indicator HF004 by the Health and Social Care Information Centre (76.4%, 77.7%, 78.8%)
17		Lipophilic statins (Bonsu 2016: 8729a) (Liu 2014: 8826a)	No	No	No	No
18		Digoxin (Hood 2014: 3415)	Yes: NG106, CG108	No	No	No
19	**Heart failure:** heart failure with reduced ejection fraction and iron deficiency/anemia	Erythropoiesis-stimulating agent (Ngo 2010: 5606)	No	No	No	No
20		Intravenous iron (Jankowska 2016: 8790a)	No: reviewed and rejected	No	No	No
21	**Heart failure:** heart failure with preserved ejection fraction	Beta-blockers (Liu 2014: 4629a)	No: NG106 and CG108 only recommends beta-blockers for heart failure patients with left ventricular dysfunction or reduced left ejection fraction.	No	No	No
22	**Heart failure:** heart failure with any ejection fraction	Digoxin (Ziff 2015: 8931a)	No: NG106 and CG108 only recommend that digoxin be used “for worsening or severe heart failure due to left ventricular systolic dysfunction despite first- and second-line treatment for heart failure”.	No	No	No

Table 3 continued. Medications that reduce emergency hospital admissions recommended in NICE resources and featured in national audits

Legend: Yes Under-Review No Reviewed and Rejected						
ID	**Broad indication:** specific indication[a]	**Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]**	**Promoted in NICE resources**			**Featured in a national audit[c] (% achievement)**
			NICE guidance	Quality standards	Quality indicators menu	
Reduces hospital admissions from out-patient, day procedure, or community settings						
23	**Inflammatory bowel disease:** crohn's disease or ulcerative colitis	Infliximab (Costa 2013: 1629a)	Yes: CG152, TA187, TA163, TA329, CG166 Under review: GID-NG10099, GID-NG10093	No	No	Yes: 2013 National clinical audit of inpatient care for adults with ulcerative colitis: UK Inflammatory Bowel Disease audit by the Royal College of Physicians (43%) 2013, 2014, 2016 National Clinical Audit of Biological therapies: UK Inflammatory Bowel Disease Audit by the Royal College of Physicians (57%, 45%, 46%) 2014, 2016 National Clinical Audit of Biological therapies: UK Inflammatory Bowel Disease Audit by the Royal College of Physicians (82%, 74%)
24	**Inflammatory bowel disease:** ulcerative colitis	Tumor necrosis factor antagonists (Lopez 2015: 8829a)	Yes: TA163, TA329, CG166 Under review: GID-NG10093	No	No	Yes: 2013 National clinical audit of inpatient care for adults with ulcerative colitis: UK Inflammatory Bowel Disease audit by the Royal College of Physicians (43%) 2014, 2016 National Clinical Audit of Biological therapies: UK Inflammatory Bowel Disease Audit by the Royal College of Physicians (82%, 74%)
25	**Hepatic encephalopathy**	Probiotics (Saab 2015: 8884a)	No	No	No	No
26	**Human immunodeficiency virus**	Cotrimoxazole (Grimwade 2003: 2933a)	No	No	No	No
27	**Dialysis**: long term hemodialysis with a central venous catheter	Topical prophylactic antibiotics (James 2008: 3657)	No	No	No	No
28	**Multiple sclerosis**	Glatiramer acetate (La Mantia 2010: 4260)	Yes: TA527	Yes: QS108	No	No

Table 3 continued. Medications that reduce emergency hospital admissions recommended in NICE resources and featured in national audits

Legend: Yes Under-Review No Reviewed and Rejected						
ID	**Broad indication:** specific indication[a]	**Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]**	**Promoted in NICE resources**			**Featured in a national audit[c] (% achievement)**
			NICE guidance	Quality standards	Quality indicators menu	
Reduces hospital admissions from out-patient, day procedure, or community settings						
29	**Pregnancy:** normal or high-risk pregnancy	Magnesium supplementation (Makrides 2014: 4844)	Reviewed and rejected: CG107 recommends against routine supplementation. NG25 and CG107 only recommend use of magnesium during acute pre-term labour or episodes of severe pre-eclampsia[e]	No	No	No
30	**Cancer:** prostate biopsy	Antibiotics (Yang 2015: 8918a)	Yes: CG175, IPG364	No	No	Yes: 2015 National Prostate Cancer Audit by the Royal College of Surgeons (85%)
31	**Schizophrenia**	Second generation antipsychotics (Kishimoto 2013: 4065a)	Yes: CG178	Yes: QS80	No	Yes: 2015 (England) Early Intervention in Psychosis Audit by the Royal College of Psychiatrists (36%) 2017 National (England and Wales) Clinical Audit of Psychosis by the Royal College of Psychiatrists (21%)

Table 3 continued. Medications that reduce emergency hospital admissions recommended in NICE resources and featured in national audits

Legend: Yes Under-Review No Reviewed and Rejected						
ID	**Broad indication:** specific indication[a]	**Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]**	**Promoted in NICE resources**			**Featured in a national audit[c] (% achievement)**
			NICE guidance	Quality standards	Quality indicators menu	
Reduces readmissions after an index hospital admission						
32	**Hospitalised:** discharged from hospital malnourished (under 65)	Oral nutritional supplements (Stratton 2013: 7484a)	Yes: CG32 (many guidelines recommend this intervention for different disease groups, all refer to CG32 for specific guidance)	Yes: QS24 Under review: GID-QS10104	No	No
33	**Heart failure:** acute decompensation	Hypertonic saline and furosemide (Gandhi 2014: 2599)	No: CG187 recommends a diuretic but does not specify a type of diuretic.	No	No	No
34	**Schizophrenia**	Antipsychotic maintenance or continuous therapy (Leucht 2012: 4508a)	Yes: CG178	Yes: QS80	No	No
35	**Schizophrenia**	Olanzapine (Komossa 2010: 4123b, 4123i)	No: CG178 no specific reference to olanzapine.	No	No	No

[a]Organisation and categories informed by the World Health Organisation's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding. The broad categories correspond to the second and third level of the ICD-10 hierarchical coding scheme. [b]References for evidence reporting moderate or high-quality evidence according to GRADE criteria. [c]Quality measurement and improvement frameworks, audits, evaluations, or surveys. National initiatives include the Quality and Outcomes Framework, Clinical Commission Group Outcomes Indicator Set, Clinical Commissioning Group Improvement Action Framework, and other initiatives by professional medical organisations and researchers. [d]NICE guideline 101 notes that: mucolytic drug therapy should be considered in patients with a chronic cough productive of sputum and continued if there is symptomatic improvement but should not be used routinely to prevent exacerbations in people with stable COPD. [e]Women planning to have pre-term labour. Abbreviations: ID No.= identifying number; NICE=national institute for health and care excellence; GP= general practitioner; CCG=clinical commissioning group; COPD= chronic obstructive pulmonary disease; NG= NICE guideline; CG=clinical guideline; QS=quality standard; NM= nice indicator menu; GID=guideline in development.

Appendix 4.5 Health systems interventions that reduce emergency hospital admissions recommended in NICE resources and featured in national audits

Table 4. Inclusion of health systems interventions that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes Under-Review No Reviewed and Rejected						
ID	**Broad indication:** specific indication[a]	**Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]**	**Promoted in NICE resources**			**Featured in a national audit[c] (% achievement)**
			NICE guidance	Quality standards	Quality indicators menu	
Reduces hospital admissions from out-patient, day procedure, or community settings						
36	**Asthma:** patients in the emergency department for an acute asthma exacerbation	Education interventions after an emergency department visit for asthma exacerbation (Tapp 2007: 7636c)	No	No	No	No
37	**Acute coronary syndrome:** unstable angina; acute myocardial infarction or **Coronary artery disease:** chronic ischaemic heart disease, stable angina or **Heart Failure:** chronic heart failure with left ventricular dysfunction	Pharmacist-involved care (Kang 2016: 9271a)	Yes (heart failure): NG106 - multi-disciplinary team including an expert in specialist prescribing No (ACS, CAD): CG126, CG95 – multi-disciplinary care recommended but pharmacists not explicitly identified. NG94 non-specific population.	No: QS21 – multi-disciplinary care recommended but pharmacists not explicitly identified	No	No
38	**Bipolar disorder**	Collaborative care (Oud 2016: 9309c)	Yes: CG185 (other guidelines recommend this intervention for bipolar subgroups, but all refer to CG185 for specific guidance)	Yes: QS95	Yes: NM108	Yes: 2016, 2017 QOF indicator MH002 by the Health and Social Care Information Centre (77.5%, 79%)
39	**Chronic obstructive pulmonary disease**	Self-management (Zwerink 2014: 8672a)	Yes: CG101 Under review: GID-NG10026	No	No	No
40	**Chronic obstructive pulmonary disease**: acute exacerbation of chronic obstructive pulmonary disease	Pharmacist-directed care or pharmacist collaborative care (Zhong 2014: 8926a)	No: multi-disciplinary care recommended but pharmacists not explicitly identified.	No	No	No

Table 4 continued. Inclusion of health systems interventions that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes Under-Review No Reviewed and Rejected						
ID	**Broad indication:** specific indication[a]	**Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]**	**Promoted in NICE resources**			**Featured in a national audit[c] (% achievement)**
			NICE guidance	Quality standards	Quality indicators menu	
Reduces hospital admissions from out-patient, day procedure, or community settings						
41	**Elderly patients:** elderly in the community or being discharged from hospital	Community-based multifactorial interventions (Beswick 2008: 725a)	Yes: NG27, NG32, NG22, CG161	Yes: QS86	No	Yes: 2012-2017, English Adult Social Care Outcomes Framework by UK government (3.2%, 3.2%, 3.3%, 3.1%, 2.9%, 2.7%)
42	**Frequent health care users**	Self-management (Tricco 2014: 8899g)	No	No	No	No
43	**Heart failure:** chronic heart failure, ejection fraction unspecified	Multidisciplinary care (Holland 2005: 3400b)	Yes: NG106, CG108	No	No	No
44		Non-invasive telemonitoring (Inglis 2015: 8787w)	No: reviewed and rejected	No	No	No
45		Specialist heart-failure clinics (Thomas 2013: 7723c, 7723i, 7723m)	Yes: NG106, CG108	Yes: QS9 supplement - 2011 quality standards recommended for local implementation, but no longer national priorities	No	No
46	**Heart failure:** chronic heart failure with reduced ejection fraction on medication	Nurse-led titration of medication (Driscoll 2015: 8761a, 8761b)	Yes: NG106 (Nurse titration recommended for Ivabridine but not other drugs)	No	No	No
47	**Schizophrenia:** schizophrenia and other types of schizophrenia-like psychoses	Case management (intensive) (Dieterich 2017: 9370b)	Yes: CG178	No	No	No
48	**Patients presenting to primary care**	Nurse-led primary care (Martínez-González 2014: 4987a)	No	No	No	No

Table 4 continued. Inclusion of health systems interventions that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes Under-Review No Reviewed and Rejected

ID	Broad indication: specific indication[a]	Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]	Promoted in NICE resources			Featured in a national audit[c] (% achievement)
			NICE guidance	Quality standards	Quality indicators menu	
Reduces readmissions after an index hospital admission						
49	**Chronic obstructive pulmonary disease**	Pulmonary rehabilitation programs (Puhan 2016: 9316a)	Yes: CG101	Yes: QS10	Yes: NM47	Yes: 2014x2, 2017x2 National (England, Wales) COPD audit Programme: secondary care, by the Royal College of Physicians (92%, 38%, 45%, 94%) 2015x4 National (England, Wales) COPD audit Programme: pulmonary rehabilitation by the Royal College of Physicians (68%, 96%. 81%, 97%) 2017 CCG OIS indicator CCG08 (unclear)
50	**Chronic obstructive pulmonary disease**: acute exacerbation of chronic obstructive pulmonary disease	Early supported discharge (Echevarria 2016: 8762a)	Yes: CG101	No	No	No
51		Hospital at home (Jeppesen 2012: 3709a)	Yes: CG101	No	No	No
52	**Heart failure:** chronic heart failure, ejection fraction unspecified	Case management (hospital initiated) (Takeda 2012: 7600c, 7600e) (Huntley 2016: 9178a, 9178c, 9178e, 9178h)	Yes: NG106 refers to use of a named health care coordinator as part of the written care plan	No: reviewed and rejected- 2011 quality standards recommend for local implementation, but no longer a national priority	No	No
53		Clinical service organisation interventions (analysis of case management, specialist clinic care, multi-disciplinary care) (Takeda 2012: 7600n)	Yes: NG106, CG108	Yes: QS9	Yes: NM116	Yes: 2016, 2017 QOF indicator HF002 by the Health and Social Care Information Centre (91%, 91%) 2014 x2 National Heart Failure Audit by the National Institute for Cardiovascular Outcomes Research (31%, 55%)
54		Disease management programs with multi-disciplinary teams (Roccaforte 2005: 6552m, 6552l, 6552p)	Yes: NG106, CG108	No: reviewed and rejected- 2011 quality standards recommend for local implementation, but no longer a national priority	No	No

Table 4 continued. Inclusion of health systems interventions that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes Under-Review No Reviewed and Rejected						
ID	**Broad indication:** specific indication[a]	**Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]**	**Promoted in NICE resources**			**Featured in a national audit[c] (% achievement)**
			NICE guidance	Quality standards	Quality indicators menu	
Reduces readmissions after an index hospital admission						
55	**Heart failure:** chronic heart failure, ejection fraction unspecified	Disease management programs with nurse-led discharge planning (Lambrinou 2012: 4305a, 4305f, 4305i)	No	No	No	No
56		Discharge planning with post-discharge support (Phillips 2004: 6099e, 6099f, 6099h)	Yes: NG106, CG108	No: reviewed and rejected- 2011 quality standards recommend for local implementation, but no longer a national priority	No	No
57		Home-visiting programs (Feltner 2014: 2359c)	Yes: NG106 (refers to use of cardiac rehabilitation programs in the home), CG108	Yes: QS9	No	No
58		Multidisciplinary care post-discharge (Raman 2008: 6360f)	Yes: NG106, CG108	No: reviewed and rejected- 2011 quality standards recommend for local implementation, but no longer a national priority	No	Yes: 2014 x2 National Heart Failure Audit by the National Institute for Cardiovascular Outcomes Research (31%, 55%)
59		Pre-discharge multidisciplinary patient education programs (Gwadry-Sridhar 2004: 3030a)	Yes: NG106	No: reviewed and rejected- 2011 quality standards recommend for local implementation, but no longer a national priority	No	No
60		Structured telephone support: monitoring; education; or self-care management (Inglis 2015: 8787v) (Inglis 2015: 8787t) (Feltner 2014: 2359h)	No: reviewed and rejected (NG106)	No	No	No
61		Specialist heart failure clinics (multi-disciplinary) (Feltner 2014: 2359l)	Yes: NG106, CG108	No: reviewed and rejected- 2011 quality standards recommend for local implementation, but no longer a national priority	No	Yes: 2014 x2 National Heart Failure Audit by the National Institute for Cardiovascular Outcomes Research (31%, 55%)

Table 4 continued. Inclusion of health systems interventions that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes Under-Review No Reviewed and Rejected

ID	Broad indication: specific indication[a]	Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]	Promoted in NICE resources			Featured in a national audit[c] (% achievement)
			NICE guidance	Quality standards	Quality indicators menu	
Reduces readmissions after an index hospital admission						
62	**Heart failure:** chronic heart failure, ejection fraction unspecified	Transitional care interventions: telecare and pre-arranged direct patient contact (Vedel 2015: 8902d, 8902i)	Yes: NG106	No: reviewed and rejected- 2011 quality standards recommend for local implementation, but no longer a national priority	No	No
63	**Hospitalised patients**	Discharge planning from hospital (Gonçalves-Bradley 2016: 8776a)	No: individual guidelines refer to in-patient discharge planning but there is no guidance on discharge for all hospitalised patients.	No	No	No
64		Nurse-led early discharge planning programs (Zhu 2015: 8929a, 8929c, 8929f, 8929g 8929i)	No: individual guidelines refer to in-patient discharge planning but there is no guidance on discharge for all hospitalised patients.	No	No	No
65		Peri-discharge interventions (analysis of 17 types of interventions) (Leppin 2014: 4494a)	No: many individual guidelines refer to in-patient discharge planning but there is no guidance on discharge for all hospitalised patients.	No	No	No
66	**Cancer:** patients receiving gastrointestinal cancer surgery	Fast-track rehabilitation after laparoscopic surgery any gastrointestinal cancer surgery (Wang 2014: 8910d)	No	No	No	No
67	**Mental illness:** severe or chronic mental disorder or illness	Education/self-management (Morriss 2013: 5399d, 5399j)	Yes: CG136, CG123 - other guidelines include reference to education and self-management but are for specific disease groups. Under review: GID-NG10092	Yes: QS14	No	Yes: 2013 - 2016 Community mental health survey (England) by the Care Quality Commission (55%, 55%, 56%)

[a]Organisation and categories informed by the World Health Organisation's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding. The broad categories correspond to the second and third level of the ICD-10 hierarchical coding scheme. [b]References for evidence reporting moderate or high-quality evidence according to GRADE criteria. [c]Quality measurement and improvement frameworks, audits, studies, evaluations, or surveys. National initiatives include the Quality and Outcomes Framework, Clinical Commission Group Outcomes Indicator Set, Clinical Commissioning Group Improvement Action Framework, and other initiatives by professional medical organisations and researchers. Abbreviations: ID No.= identifying number; NICE=national institute for health and care excellence; GP= general practitioner; CCG=clinical commissioning group; COPD= chronic obstructive pulmonary disease; NG= NICE guideline; CG=clinical guideline; QS=quality standard; NM= nice indicator menu; GID=guideline in development.

Appendix 4.6 Diagnostics, medical, and surgical interventions that reduce emergency hospital admissions recommended in NICE resources and featured in national audits

Table 5. Inclusion of diagnostics, medical, and surgical interventions that reduce emergency hospital admissions in NICE resources and national audits

Legend: Yes Under-Review No Reviewed and Rejected

ID	**Broad indication:** specific indication[a]	**Description of intervention that reduces emergency hospital admissions (Review/estimate ID)[b]**	**Promoted in NICE resources**			**Featured in a national audit[c] (% achievement)**
			NICE guidance	Quality standards	Quality indicators menu	
Reduces hospital admissions from out-patient, day procedure, or community settings						
68	**Atrial fibrillation:** persistent or permanent atrial fibrillation receiving atrioventricular junction ablation	Cardiac resynchronization therapy (Stavrakis 2012: 7417a)	Yes: CG180, TA314, IPG603	No	No	No
69	**Heart failure:** Heart failure with reduced ejection fraction or left ventricular dysfunction	Cardiac resynchronization therapy (Kang 2015: 8797a)	Yes: NG106, CG108, TA314, MTG33, IPG516	No	No	No
70	**Heart failure:** Heart failure with reduced ejection fraction or left ventricular dysfunction	Natriuretic peptide (B-type and N-terminal Pro B-type) guided therapy (McLellan 2016: 9300g, 9300l, 9300k)	Yes: NG106	No	No	No
Reduces readmissions after an index hospital admission						
71	**Acute coronary syndrome:** unstable angina or non–ST-segment elevation myocardial infarction	Early/routine coronary angiography (Fanning 2016: 9247a, 9247c)	No: reviewed and rejected Under-review: GID-NG10085	No	No	No
72	**Acute coronary syndrome:** acute coronary syndromes with non-ST segment elevation and stages 3 to 5 chronic kidney disease	Early/routine coronary angiography (Charytan 2009: 1340a)	No: reviewed and rejected Under-review: GID-NG10085	No	No	No
73	**Pneumothorax**: idiopathic spontaneous pneumothorax	Percutaneous aspiration of plural cavity (Aguinagalde 2010: 119a)	No	No	No	No

[a]Based on the 3-character coding level using the World Health Organisation's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10). bReferences for evidence reporting moderate or high-quality evidence according to GRADE criteria. [c]Quality measurement and improvement frameworks, audits, studies, evaluations, or surveys. National initiatives include the Quality and Outcomes Framework, Clinical Commission Group Outcomes Indicator Set, Clinical Commissioning Group Improvement Action Framework, and other initiatives by professional medical organisations and researchers. Abbreviations: ID No.= identifying number; NICE=national institute for health and care excellence; GP= general practitioner; CCG=clinical commissioning group; COPD= chronic obstructive pulmonary disease; NG= NICE guideline; CG=clinical guideline; QS=quality standard; NM= nice indicator menu; GID=guideline in development.

Appendix 4.7 NICE guidelines, quality standards, and quality indicators with recommendations about evidence-based interventions that reduce emergency hospital admissions

Table 6. NICE resources with recommendations about evidence-based interventions that reduce emergency hospital admissions

Guidelines	Quality standard	Quality indicator
CG32	QS9	NM47
CG101	QS10	NM79
CG108	QS14	NM80
CG123	QS24	NM89
CG126	QS80	NM90
CG136	QS86	NM108
CG152	QS95	NM116
CG161	QS100	
CG166	QS108	
CG172	GID-QS10104	
CG175		
CG178		
CG180		
CG181		
CG185		
GID-NG10026		
GID-NG10092		
GID-NG10093		
GID-NG10099		
IPG364		
IPG516		
IPG603		
MTG33		
NG106		
NG22		
NG27		
NG32		
TA163		
TA187		
TA314		
TA329		
TA388		
TA527		

Abbreviations: CG= clinical guidance; GID- guidance in development; NG= nice guidance; IPG= interventional procedure guidance; MTG= medical technology guidance; TA= technology appraisal; QS= quality standard; NM= nice indicator menu

Appendix 4.8 Nationally audited quality indicators for NICE recommended interventions that reduce emergency hospital admissions

Table 7. Nationally audited quality indicators for NICE recommended interventions that reduce emergency hospital admissions

ID-Indicator No.	Quality indicator *(Investigator/Organisation)*	Setting Year: % Achievement
11-1	The proportion of patients discharged from medical care following heart attack that are eligible and received a prescription for either angiotensin converting enzyme inhibitor or angiotensin receptor blocker. *(National Institute for Cardiovascular Outcomes Research)*	England, Wales, Northern Ireland 2015: 94.6%
11-2	The proportion of patients discharged from medical care following heart attack that are eligible and received a prescription for either angiotensin converting enzyme inhibitor or angiotensin receptor blocker. *(National Institute for Cardiovascular Outcomes Research)*	England, Wales, Northern Ireland 2016: 94.7%
12-1	Proportion of patients with heart failure who were prescribed an angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker on discharge for left ventricular systolic dysfunction. *(National Institute for Cardiovascular Outcomes Research)*	England, Wales 2014: 85% 2015: 84%
12-2	HF003: In those patients with a current diagnosis of heart failure due to left ventricular systolic dysfunction, the percentage of patients who are currently treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. *(Health and Social Care Information Centre)*	England[a] 2016: 84.7% 2017: 83.9%
13-1	Proportion of patients with heart failure who were prescribed an angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker on discharge for left ventricular systolic dysfunction. *(National Institute for Cardiovascular Outcomes Research)*	England, Wales 2014: 85% 2015: 84%
13-2	HF003: In those patients with a current diagnosis of heart failure due to left ventricular systolic dysfunction, the percentage of patients who are currently treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. *(Health and Social Care Information Centre)*	England[a] 2016: 84.7% 2017: 83.9%
13-3	Proportion of patients with heart failure who were prescribed an Angiotensin II receptor antagonists on discharge for left ventricular systolic dysfunction. *(National Institute for Cardiovascular Outcomes Research)*	England, Wales 2014: 19% 2015: 19%
16-1	Proportion of patients with heart failure who were prescribed a beta blocker on discharge for LVSD. *(National Institute for Cardiovascular Outcomes Research)*	UK 2014: 85% 2015: 86%
16-2	In those patients with a current diagnosis of heart failure due to left ventricular systolic dysfunction who are currently treated with an ACE-I or ARB, the percentage of patients who are additionally currently treated with a beta-blocker licensed for heart failure. *(Health and Social Care Information Centre)*	England[a] 2015: 76.4% 2016: 77.7% 2017: 78.6%
22-1	Percentage of adult patients in their first admission prescribed anti-tumour necrosis factor alpha following failure to respond to corticosteroids. *(Royal College of Physicians)*	UK 2013: 43%
22-2	Proportion of adult patients on biological therapy who were appropriately prescribed anti-tumour necrosis factor alpha in compliance with National Institute of Health and Care Excellence technology appraisal 187 for the treatment of Crohn's disease. *(Royal College of Physicians)*	UK 2013: 57% 2014: 45% 2016: 46%
22-3	Proportion of adult patients on biological therapy who were appropriately prescribed anti-tumour necrosis factor alpha therapy in compliance with National Institute for Health and Care Excellence technology appraisal 329 for treating moderately to severely active ulcerative colitis. *(Royal College of Physicians)*	UK 2014: 82% 2016: 74%
23-1	Percentage of adult patients in their first admission prescribed anti-tumour necrosis factor alpha following failure to respond to corticosteroids. *(Royal College of Physicians)*	UK 2013: 43%

Table 7 continued. Nationally audited quality indicators for NICE recommended interventions that reduce emergency hospital admissions

ID-Indicator No.	Indicator *(Investigator/Organisation)*	Setting Year: % Achievement
23-2	Proportion of adult patients on biological therapy who were appropriately prescribed anti-tumour necrosis factor alpha therapy in compliance with National Institute for Health and Care Excellence technology appraisal 329 for treating moderately to severely active ulcerative colitis. *(Royal College of Physicians)*	UK 2014: 82% 2016: 74%
29-1	Proportion of men with prostate cancer who had a biopsy who received a transrectal ultrasound biopsy before treatment. *(Royal College of Surgeons)*	England 2015: 85%
30-1	The proportion of people having a first episode or suspected psychosis who did not have an adequate response to a full trial of two antipsychotic drugs and were prescribed clozapine. *(Royal College of Psychiatrists)*	England 2015: 36%
30-2	Proportion of adults in the community, with a diagnosis of schizophrenia or schizo-affective disorder, who were recorded as being prescribed clozapine as a single anti-psychotic. *(Royal College of Psychiatrists)*	England, Wales 2017: 21%
37-1	The percentage of patients with schizophrenia, bipolar affective disorder and other psychoses who have a comprehensive care plan documented in the record, in the preceding 12 months, agreed between individuals, their family and/or carers as appropriate. *(Health and Social Care Information Centre)*	England[a] 2016: 77.5% 2017: 79%
40-1	Proportion of older people (65 and over) who were offered reablement services following discharge from hospital. *(UK government)*	England 2012: 3.2% 2013: 3.2% 2014: 3.3% 2015: 3.1% 2016: 2.9% 2017: 2.7%
48-1	The proportion of people with chronic obstructive pulmonary disease and Medical Research Council dyspnoea scale 3 and above referred to a pulmonary rehabilitation program. *(Health and Social Care Information Centre)*	England[a] 2017: unclear
48-2	Proportion of units with a pulmonary rehabilitation service available to patients discharged after exacerbation. *(Royal College of Physicians)*	England, Wales 2014: 92% 2017: 94%
48-3	Proportion of units with a pulmonary rehabilitation service, available to patients who had an exacerbation, where it was available within 4 weeks of discharge. *(Royal College of Physicians)*	England, Wales 2014: 38% 2017: 45%
48-4	Proportion of pulmonary rehabilitation programmes that offer pulmonary rehabilitation following hospitalisation for exacerbation of chronic obstructive pulmonary disease. *(Royal College of Physicians)*	England, Wales 2015: 68%
48-5	The proportion of pulmonary rehabilitation programmes that accept patients with chronic obstructive pulmonary disease who report significant exercise limitation and report Medical Research Council grade 3. *(Royal College of Physicians)*	England, Wales 2015: 96%
48-6	The proportion of pulmonary rehabilitation programmes that accept patients with chronic obstructive pulmonary disease who report significant exercise limitation and report Medical Research Council grade 4. *(Royal College of Physicians)*	England, Wales 2015: 97%
48-7	The proportion of pulmonary rehabilitation programmes that accept patients with chronic obstructive pulmonary disease who report significant exercise limitation and report Medical Research Council grade 5. *(Royal College of Physicians)*	England, Wales 2015: 81%

Table 7 continued. Nationally audited quality indicators for NICE recommended interventions that reduce emergency hospital admissions

ID-Indicator No.	Indicator *(Investigator/Organisation)*	Setting Year: % Achievement
52-6	Proportion of patients with heart failure who had a follow-up appointment with multi-disciplinary team scheduled within two weeks of discharge. *(National Institute for Cardiovascular Outcomes Research)*	England, Wales 2014: 31%
52-7	Proportion of patients with heart failure who had a follow-up appointment with multi-disciplinary team scheduled. *(National Institute for Cardiovascular Outcomes Research)*	England, Wales 2014: 55%
52-8	The percentage of patients with a diagnosis of heart failure (diagnosed on or after 1 April 2006) which has been confirmed by an echocardiogram or by specialist assessment 3 months before or 12 months after entering on to the register. *(Health and Social Care Information Centre)*	England[a] 2016: 91% 2017: 91%
57-1	Proportion of patients with heart failure who had a follow-up appointment with multi-disciplinary team scheduled within two weeks of discharge. (National Institute for Cardiovascular Outcomes Research	England, Wales 2014: 31%
57-2	Proportion of patients with heart failure who had a follow-up appointment with multi-disciplinary team scheduled. *(National Institute for Cardiovascular Outcomes Research)*	England, Wales 2014: 55%
60-1	Proportion of patients with heart failure who had a follow-up appointment with multi-disciplinary team scheduled within two weeks of discharge. *(National Institute for Cardiovascular Outcomes Research)*	England, Wales 2014: 31%
60-2	Proportion of patients with heart failure who had a follow-up appointment with multi-disciplinary team scheduled. *(National Institute for Cardiovascular Outcomes Research)*	England, Wales 2014: 55%
66-1	Percentage of community mental health service users who answered 'Yes, definitely' to the question 'Were you involved as much as you wanted to be in deciding what treatments or therapies to use?' *(Care Quality Commission)*	England 2013: 55% 2014: 55% 2015: 56%

[a]Does not adjust for the exception rate calculated and applied by the Health and Social Care Information Centre.

Chapter 5. Prioritising research on the utilisation of interventions that reduce emergency hospital admissions

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5.0 Chapter overview

This chapter describes a process to prioritise research to investigate in this thesis. The process was guided by principles and methods used by the National Institute for Health Research and the National Health Service to prioritise research. It involved engagement of key stakeholders and a review of the academic literature. The eight-step process led to selection of research on heart failure medication treatment gaps and dosage regimens in primary care.

5.1 Introduction

5.1.1 Building on the findings of previous chapters

Improving utilisation of evidence-based interventions has been shown to produce benefit for patients and the health system in the UK.[1,2] This thesis aims to inform such strategies for reducing emergency hospital admissions by identifying effective evidence-based interventions and exploring their utilisation in practice.

Chapter 3 identified evidence-based interventions that reduce emergency hospital admissions. Chapter 4 identified which of these interventions were supported in guidelines and, therefore, had been judged by key stakeholders to be clinically appropriate and to have an acceptable balance of benefit to harm. Chapter 4 also provided a cursory indication of utilisation rates for some of the interventions that had been nationally audited. However, many of the interventions had not been audited and only certain aspects of utilisation had been examined. This indicated a need for primary investigation. Ideally, utilisation of all the evidence- and guideline-based interventions identified in chapters 3 and 4 could have been explored in this

thesis however, this would not have been feasible. Therefore, to select a sub-set of interventions and specific research questions to investigate in-depth a prioritisation process was needed.

5.1.2 Prioritising health research

Given finite resources for research and the need to demonstrate accountability for the use of public funds, national funding agencies and health systems prioritise research topics using transparent criteria and methods. In the UK, the National Institute for Health Research[3] and the National Health Service[4] publicly report their principles and methods for prioritisation of research. The core prioritisation activities include various types of stakeholder engagement to obtain patient, carer, and practitioner perspectives, and use of the academic literature to address clear evidence gaps. The result of these activities are lists of specific research topics and questions that are deemed worthy of investigation and funding given their potential to improve patient outcomes, improve health care services, and achieve national health priorities.

5.1.3 Prioritising research on the use of interventions that reduce emergency hospital admissions

The results of chapters 3 and 4 were a list of 43 evidence- and guideline-based interventions that reduce hospital admissions. To prioritise these interventions and the aspects of their utilisation that would be studied, a multi-step prioritisation process was conducted. This process was informed by established principles and methods used by the National Institute for Health Research[3] and the National Health Service[4] to ensure that the research was valuable for patients, practitioners, and the health system in the UK.

5.2 Aims and objectives

5.2.1 Aims

This aim of this chapter was to prioritise a set of interventions and research questions to explore in an academic study as part of this thesis.

5.2.2 Objectives

To meet this aim, the objective of this chapter was:

1) To engage key stakeholders and the academic literature to prioritise interventions and research questions that could feasibly be investigated in an academic study as part of this thesis.

5.3 Methods and results

The methods and results of this chapter are reported concurrently to ease interpretation and readability.

5.3.1 Principles for prioritising the research

Core principles for prioritising research in the National Health Service and National Institute for Health Research were used to guide the design and conduct of the prioritisation process in this chapter.[3,4] Furthermore, this research was undertaken within the Oxford University Nuffield Department of Primary Care Health Sciences. The core goal of the Department is to inform resolution of contemporary issues in primary care using high-quality research. This goal was also considered when designing methods to prioritise research.

The principles guiding the prioritisation of research in this chapter were:

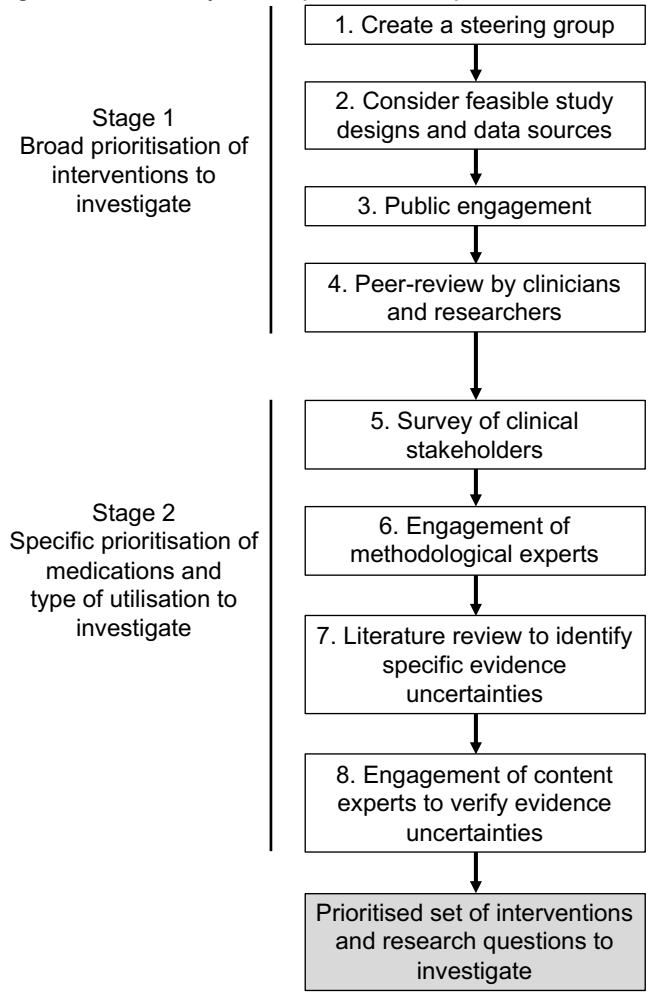
A) The research should target a contemporary issue in primary care
B) Perspectives of patients, carers, and clinicians must be considered
C) The research should address a defined evidence gap
D) The research should provide rigorous and relevant results that could improve patient outcomes, improve health care services, and help to achieve national health priorities
E) Completion of the research should be feasible within the context of a DPhil thesis

5.3.2 Methods and results of the prioritisation process

The prioritisation process was developed in a step-wise manner and guided by the *a priori* principles described in section 5.3.1. Three core elements were used to develop the outline for the process: creation of a steering group to monitor the process; engagement with the public and clinicians; and searching of the academic literature to identify gaps in the evidence. With these core elements in place, the process was allowed to develop organically based on the results of each step.

Ultimately, eight specific activities were conducted to prioritise the research. These activities are summarised in Figure 1 and described in the next eight sections.

Figure 1. Summary of the prioritisation process



Stage 1. Broad prioritisation of interventions and research questions to investigate

1) Creation of a steering group

The steering group was composed of the thesis author and his primary and secondary supervisor. This group, led by the thesis author, guided the process based on the principles described in section 5.3.1. Each activity in the process was designed and agreed upon by the group.

2) Consideration of study designs and data sources

Methods: The steering group met in-person to discuss the sources of data and study designs required to examine the different types of interventions (i.e. medications; health systems; diagnostic, medical, surgical). Emphasis was placed on the feasibility of designing and completing a study within the context of the thesis.

Results: It was agreed that retrospective analysis of routinely collected data would be a feasible and robust approach to exploring utilisation of interventions in primary care. It was anticipated that prospective data collection would be resource intensive, time-consuming, and would likely yield a small sample. Sources of routinely collected data in UK primary care were then discussed. The Clinical Practice Research Datalink was identified as a high-quality data source. Data on use of medications was thought to be the most reliable data collected. It was anticipated that other types of interventions from chapters 3 and 4 may not be coded in individual consultations (i.e., multi-disciplinary care) or may be coded less reliably in free text (i.e., educational interventions) compared to the established coding system for medication data.

3) Public engagement

Methods: To obtain input from members of the public, messages were posted on two health forums (patient.co.uk; daily mail forum), Facebook, and twitter which described the broad intentions of the proposed research - to explore utilisation of evidence-based medications in primary care and whether it was associated with emergency hospital admission rates. Feedback was invited on the importance of the research topic and methodology.

Results: Twenty-six responses were received from 20 individuals. Ninety-five percent of the respondents identified this as an important research topic. Feedback on the proposed research objectives was provided. For example, one respondent identified potential unintended consequences of the study: "*…saying things like primary care doctors don't use the best treatments for their patients, might actually be potentially harmful in losing people's trust for their doctors*". All feedback was recorded in order to inform the framing of the study that would ultimately result from this process.

4) Peer-review by clinicians and researchers

Methods: Once medications had been prioritised and the value of the broad research objectives had been verified by members of the public, the thesis author assembled a team and applied for a School for Primary Care Research NIHR grant (internal round 9). The proposed project was to examine the use of evidence-based medications in primary care using CPRD data. See Appendix 5.1 for a copy of the original SPCR application. The proposal did not specify which medications would be examined as this had not yet been determined, but it did describe the general methodological approach that would be used in the investigation (i.e., CPRD data and a longitudinal study design). This application served as a method to obtain peer-review feedback from clinicians and researchers (i.e., grant review board) while securing the funds necessary to complete the study.

Results: After reviewing the proposed research, the grant committee approved the application**.** The thesis author and his team were awarded £33,442 to complete a project examining the utilisation of evidence-based medications in primary care and associations with emergency hospital admissions.

Stage 2. Specific prioritisation of medications and aspects of utilisation to investigate

Once research on use of medications in primary care had been prioritised, more detailed input was required from key stakeholders and the academic literature to identify specific medications and elements of utilisation worthy of investigation.

5) Engagement of clinical stakeholders

Methods: Detailed input from clinicians on the types of medications to investigate was obtained using a survey. The Clinical Trials and Research Governance team was contacted to inquire about this activity. They stated that engaging clinical stakeholders to prioritise evidence-based medications was “pre-research” and did not require formal approval. Evidence of this correspondence is located in Appendix 5.2.

Once this approval was waived, a small purposive convenience sample was approached. The sample included qualified general practitioners, physicians in the Nuffield Department of Primary Care Health Sciences, pharmacists, clinical pharmacologists, and clinical commissioners. Participants of different ages and genders were approached to provide diversity within the sample. Participants were contacted by email and invited to complete a short survey. Participants were told they could complete the survey attached in the email or contact the thesis author to administer the survey in-person or by phone.

The survey included a list of 10 medications and instructions to complete the survey. These 10 medications were prioritised in chapters 3 and 4 of this thesis because they reduced emergency hospital admissions, were supported by high or moderate quality evidence, and were recommended in NICE guidelines. Although there were 12 medications that met these criteria in chapters 3 and 4, two medications were excluded from this survey as they focused on patients in the emergency department and, therefore, were not relevant in primary care.

The survey included validated 9-point scales for participants to rate their level of agreement with four statements:

A) This medication is sub-optimally utilised
B) Optimising use of this medication would reduce emergency hospital admission rates
C) Optimising use of this medication in primary care is feasible
D) Utilisation of this medication should be studied

Medications with median scores of 7 or higher for all four statements were candidates for investigation in the CPRD. The validated 9-point scales and consensus scoring method was developed by RAND corporation and have been widely used for priority setting in health care research.[5]

The survey included one open-ended question asking participants to justify their ratings. In telephone surveys, participant responses were summarised in handwritten notes by the interviewer (NB). Comments during informal discussions after survey completion were also summarised in handwritten notes. The survey and list of medications can be found in Appendix 5.3.

Prior to administration, the survey was pilot-tested for clarity with two researchers (AA, JA) in the Nuffield Department of Primary Care Health Sciences.

Results: 10 stakeholders were invited to participate. Eight participants from three CCGs in England completed the survey in person or by phone. Table 1 describes the characteristics of the participants. Eight medications were prioritised as candidates for investigation in the CPRD. Table 2 shows the results of the survey.

Table 1. Participant characteristics

Characteristic	Participants % (n=8)[a]
Gender	
Male	75% (6)
Female	25% (2)
Age	
20-39	38% (3)
40-59	50% (4)
60-79	13% (1)
Primary clinical speciality	
General practice	63% (5)
Internal medicine	13% (1)
Clinical pharmacology	13% (1)
Pharmacy	13% (1)
Member of a CCG board[b]	25% (2)[c]
Currently licensed to work as a clinical practitioner in the UK	88% (7)

[a]Percentages may not add up to 100 due to rounding. [b]CCG = clinical commission group.[c]1 was a GP prescribing lead.

Table 2. Summary of the survey of clinical stakeholders to prioritise medications for investigation in the Clinical Practice Research Datalink

Clinical indication	Medication	This medication is sub-optimally utilised	Optimising use of this medication would reduce emergency hospital admissions	Optimising use of this medication in primary care is feasible	Utilisation of this medication should be studied
Heart failure with reduced left ventricular ejection fraction or left ventricular dysfunction.	ACE inhibitors	✓	✓	✓	✓
	Angiotensin-II receptor blockers	✓	✓	✓	✓
	Aldosterone antagonists	✓	✓	✓	✓
	Beta-blocking agents	✓	✓	✓	✓
	Digoxin	✓	✓	✓	✓
Stable coronary artery disease	Intensive statin therapy	✓	✓	✓	✓
Stable moderate to severe chronic obstructive pulmonary disease	Long-acting beta-2 agonists	✓	✓	✓	✓
	Long-acting muscarinic antagonists	✓	✓	✓	✓
Schizophrenia	Anti-psychotic maintenance therapy	✓	✓	X	✓
	Second generation anti-psychotics	✓	✓	X	✓

✓=consensus achieved, indicating that the medication was a candidate for investigation in the CPRD. X=no consensus achieved, indicating that the medication was not a candidate for investigation in the CPRD. Consensus was defined as a median score of 7 or higher.

Three themes emerged from review of open-ended feedback. Firstly, the majority of participants based their prioritisation decisions on disease prevalence and burden of the disease on admission rates, rather than on the features on any single medication. They identified all the conditions as prevalent, difficult to manage or prevent, and as major contributors to admission rates. They suggested that optimisation of medications for these patient groups was challenging in practice and, therefore, worthy of investigation.

Secondly, although use of antipsychotic medication in schizophrenia patients was identified as potentially sub-optimal, some participants suggested that titrating or changing these medications may not be in the remit of primary care physicians. Therefore, optimisation in primary care may not be feasible. Similarly, some participants expressed uncertainty about the feasibility of optimising use of digoxin in primary care as it is often initiated and titrated by specialists however, a consensus score was still achieved.

Thirdly, some participants believed that key medications were missing from this list including warfarin, aspirin, proton pump inhibitors, and oral hypoglycaemics. They believed the evidence underpinning these medications was strong and may have been missed in the overview in chapter 3. An examination of the overview results showed that several reviews examining these medications were included however, they were not the highly-cited, landmark reviews which the participants believed had been missed. The included reviews were recently published and examined efficacy in novel populations, but showed no effect on admissions (i.e., warfarin in patients with systolic heart failure and sinus rhythm)[6–8] or were reviews to determine whether the medications actually increased hospitalisations due to adverse events, but showed no such increase (i.e., pioglitazone and cardiovascular risk).[9]

Many of the landmark randomised controlled trials for these medications did not directly measure hospitalisations, but instead measured major events which may have necessitated a hospital admission (e.g., stroke or non-fatal re-infarction).[10,11] Therefore, despite convincing evidence showing reductions in major events from use of some of these medications (i.e., reductions in stroke from use of

warfarin)[10,11], highly-cited systematic reviews and meta-analysis[12–15] have not reported hospital admissions as an outcome, and therefore, were not included in the overview.

6) Engagement of methodological experts

Methods: Once the list of eight medications was prioritised, an expert (MS) in the use of CPRD data was contacted to determine which medications could feasibly be studied.

Results: The expert advised that targeting a single patient population/clinical indication would be most efficient and allow for analysis of multiple medications. Therefore, to maximise the number of medications that could be studied, medications for patients with heart failure were prioritised. All five medications had a common underlying clinical indication (heart failure with reduced left ventricular ejection fraction or left ventricular dysfunction).

7) Literature review

Methods: A structured literature search was conducted to map existing evidence on utilisation of medications among heart failure patients in the UK and to identify potential gaps in the evidence base. Pubmed and Google scholar were searched using keyword search terms (Appendix 5.4). The related articles function in Pubmed and reference lists of relevant articles were also reviewed to identify pertinent studies. The results of the content analysis in chapter 4 were also reviewed to identify which of the medications had been targeted in national audits.

Results: The literature review and review of the content analysis results showed that studies on utilisation of heart failure medications in the UK had focused mainly on prescribing for in-patients or at hospital discharge. Few studies had targeted medication use during ongoing management in primary care. Reports on the Quality and Outcomes Frameworks quality indicators for heart failure medication (identified in chapter 4) provided the only insights on primary care prescribing. However, the QOF did not measure the supply of medications or the prescribed doses. From the literature that was reviewed, it was unclear whether patients were experiencing interruptions in medication coverage and whether primary-care physicians were

prescribing target doses. This was concerning, given that patients with heart failure are managed mostly in primary care and general practitioners are responsible for a large proportion of heart failure medication prescribing.[16] In their 2016 report, the British Society for Heart Failure highlighted these gap in knowledge and noted the need for investigations on heart failure medication use in primary care.[16] Therefore, these specific research gaps were selected as targets for assessment in the CPRD. An in-depth description of this literature is provided in the introduction section of the next chapter (Chapter 6: Utilisation of heart failure medication and associations with emergency hospital admissions: a national cohort study in UK primary care).

8) Engagement of content experts

Methods: Once specific research objectives had been established, a leading global expert in management of heart failure in primary care (RH) was approached and asked to provide input on the scope and value of the project.

Results: The expert verified that the research objectives were novel and worth pursuing.

5.4 Discussion

5.4.1 Summary of findings

This chapter described a process to prioritise research to conduct in this thesis. The process was guided by principles and methods for prioritising research used by the NHS and NIHR. It involved engagement of key stakeholders and a review of the academic literature. The eight-step process led to selection of research on treatment gaps and dosage regimens in primary care for five heart failure medications: ACE inhibitors, angiotensin-II receptor blockers, aldosterone antagonists, beta-blocking agents, and digoxin.

5.4.2 Findings in the context of existing research

The value of the research prioritised in this study is corroborated by ongoing randomised controlled trial research. For example, a 2017 trial protocol to reduce medical admissions into hospital through optimising medicines[17] had the following inclusion criteria: “patients taking five or more long-term medicines or whose reason for [recent hospital] admission was related to heart failure or chronic obstructive pulmonary disease.” Medications for these two patient groups were prioritised in this chapter. This indicates that there is some consensus in the research community on the value of exploring utilisation and optimisation of these medications.

5.4.3 Strengths

This project had two key strengths.

Firstly, the multi-step prioritisation process in this chapter was robust. The process was informed by the same principles used by the NHS and NIHR to prioritise research and used validated scales as part of the clinical stakeholder survey.

Secondly, the process was comprehensive. It included quantitative and qualitative input from 38 stakeholders: 20 members of the public; eight physicians, researchers, and clinical commissioners; and eight members of the SPCR peer-review grant panel. The process also included evidence from the academic literature.

5.4.4 Limitations

This project had some limitations.

Firstly, input from members of the public was restricted to those using the internet and social media. Therefore, the views of the sample may not be representative of the general public.

Secondly, although a structured literature review was conducted, it was not a systematic review and, therefore, relevant literature may have been missed. However, a world leading expert on the subject was consulted, and he verified the novelty and value of the research objectives. Furthermore, the research objectives had been identified as a core priority by a major professional cardiovascular medical society in the UK, which suggests they represent an important gap in the evidence base.[16]

5.4.5 Implications for policy and practice

The results of this chapter serve to inform future research, rather than policy or practice.

5.4.6 Future research

The research in the next chapter of this thesis was directly informed by this prioritisation process. The chapter describes a national cohort study in UK primary care examining utilisation of five medications in heart failure patients.

Five other medications were also identified as worthy of investigation. Researchers with an interest in reducing hospital admissions may consider examining utilisation of intensive statin therapy in patients with stable coronary artery disease; long-acting beta-2 agonists and long-acting muscarinic antagonists in patients with stable moderate to severe COPD; or anti-psychotic maintenance therapy and second-generation anti-psychotics in patients with schizophrenia.

5.5 Conclusion

Improving utilisation of evidence-based interventions has been shown to produce benefit for patients and the health system in the UK.[1,2] This thesis aims to inform such strategies for reducing emergency hospital admissions by identifying effective evidence- and guideline-based interventions and exploring their utilisation in practice.

Previous chapters identified 43 relevant evidence- and guideline-based interventions. Studying utilisation of all of these interventions in clinical practice would not have been feasible as part of this thesis. Therefore, this chapter served to prioritise the research agenda using input from key stakeholders and the academic literature. The process led to selection of research on treatment gaps and dosage regimens in primary care for five heart failure medications. This research is described in chapter 6 – a national cohort study in UK primary care.

5.6 Chapter summary

- This chapter described a process to prioritise research to conduct in this thesis
- The process was guided by principles and methods used by the NHS and NIHR to prioritise research topics
- Key stakeholders were engaged, and the academic literature was reviewed
- The process led to selection of research on heart failure medication treatment gaps and dosage regimens in primary care

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Chapter 5. Appendix

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Appendix 5.1 School for Primary Care Research grant application

SPCR Funding Round 9 – Application Form 2015

PLEASE ENSURE that you submit both this Word document and the Excel spreadsheet detailing the project costs. You should name the documents with the following file name structure: PI name_FR9

Project title: The Association Between Evidence-Based Medication Use And Unplanned Hospital Admissions: A National Observational Study in Primary Care.
Project short name: Evidence-Based Medication Use and Unplanned Hospital Admissions.

SECTION A - Details of Co-Principal Investigator

Title: Mr.
Surname: Niklas
Forename: Bobrovitz
Lead university: University of Oxford
Address: Nuffield Department of Primary Care Health Sciences University of Oxford Radcliffe Observatory Quarter Woodstock Road Oxford, OX2 6GG Tel: +44 (0) 1865617861 Fax: +44 (0)1865 289290
Email: niklas.bobrovitz@phc.ox.ac.uk
Contribution (role and fte on project): Co-principal investigator (16 hour/week DPhil).

Details of Co-Principal Investigator

Title: Dr.
Surname: Kamal
Forename: Mahtani
Lead university: University of Oxford
Address: Nuffield Department of Primary Care Health Sciences University of Oxford Radcliffe Observatory Quarter Woodstock Road Oxford, OX2 6GG
Email: kamal.mahtani@phc.ox.ac.uk
Contribution (role and fte on project): Co-principal investigator (1% FTE).

Details of Joint Applicant (s) (copy box as required)

Title: Professor
Surname: Heneghan
Forename: Carl
University: University of Oxford
Email: carl.heneghan@phc.ox.ac.uk
Contribution (role and fte on project): Senior advisor (1% FTE).

Title: Ms.
Surname: Stevens

Forename: Sarah
University: University of Oxford
Email: sarah.stevens@gtc.ox.ac.uk
Contribution (role and fte on project): CPRD specialist and statistician (5% FTE).

Title: Dr.
Surname: Shinkins
Forename: Bethany
University: University of Oxford
Email: bethany.shinkins@phc.ox.ac.uk
Contribution (role and fte on project): Senior statistical advisor (3% FTE).

Details of Collaborator (s) (copy box as required)
A collaborator is a person employed outside of the SPCR partner departments and cannot receive any SPCR funds

Title: Dr.
Surname: Kearley
Forename: Karen
Address**:** Jericho Health Centre, New Radcliffe House, Walton Street, Oxford**,** OX2 6NW
Email: karen.kearley@phc.ox.ac.uk
Contribution (role): Facilitator of patient and public involvement; act in her role as a GP commissioner in Oxfordshire to disseminate study results.

Title: Ms.
Surname: Cook
Forename: Jennifer
Address**:**
Email: jen.io.cook@gmail.com
Contribution (role): Patient advisor.

Study Team Expertise:

The team has expertise in managing and analysing large databases. They have conducted analysis for 15 projects using the Clinical Practice Research Datalink and 5 projects using the Hospital Episode Statistics database. The General Practitioner applicants are experts in evidence-based medicine and have 24 years of clinical experience. One GP co-applicant is an expert in managing non-communicable diseases in primary care.

SECTION B – Plain English Summary

The UK has experienced a 47% increase in unplanned hospital admissions over the last 15 years that has seriously strained the healthcare system. In 2012-2013 there were 5.3 million unplanned hospital admissions representing 67% of hospital bed days in England and costing approximately £12.5 billion. This represents a huge problem that is unsustainable and needs to change. As a result, admission reductions are a priority of the National Health Service.

Unplanned hospital admissions are unpredictable and occur at short notice because of a perceived need for immediate health care. Primary care physicians- as the gate keepers of patient care- have a crucial role to help reduce unplanned admissions. Research shows that some primary care practices are more successful than others in controlling rates of hospital admissions among their patients but the reasons for this are unclear. Studies attempting to identify the keys to success have found few conclusive results. However, one of the most fundamental components of effective primary care has not been assessed; the use of evidence-based medications. There is wide variation in primary care prescribing practices, including both under- and over-utilization of medications. These variations may explain why some physicians more successfully manage hospitalisation rates among their patients compared to others.
Therefore, the objective of this study is to assess the association between evidence-based medication use in primary care and unplanned hospital admissions. We will use national databases with primary care and hospital data for all patients registered with a primary care practice in England from 2011-2014. Our multidisciplinary team includes experts in evidence-based medicine, general practitioners, and researchers with expertise in analysing large databases. Ethics approval is not required as we will use anonymous data.
This project will help to determine the extent to which improving prescribing practices in primary care could reduce hospital admissions in England. The project will lead to future research and policy recommendations to improve primary care and to help resolve the hospital admissions crisis.

SECTION C – Expert Summary

The UK has experienced a 47% increase in unplanned hospital admission over the last 15 years that has seriously strained the healthcare system. In 2012-2013 there were 5.3 million unplanned hospital admissions representing 67% of hospital bed days in England and costing approximately £12.5 billion. This represents a huge problem that is unsustainable and needs to change. As a result, admission reductions are a priority of the National Health Service.

Unplanned hospital admissions are unpredictable and occur at short notice because of a perceived need for immediate health care. There is large variation in unplanned admission rates across the UK. Social deprivation and non-modifiable population factors (e.g., age) account for a large portion of the variation however, a substantial amount may be due to factors within the control of primary care physicians and managers. Studies have consistently found that access to care and continuity of care impact admission rates. However, the use of evidence-based medications, a core component of effective primary care practice, has not been well-studied. Evidence shows there is wide variation in primary care prescribing practices, including under- and over-utilization of medications, but the impact of those variations on unplanned admissions is unclear.

Therefore, the objective of our study is to assess the association between evidence-based medication use in primary care and unplanned hospital admissions. We will examine 10 medications that have been shown in randomized clinical trials to reduce unplanned admissions. We will obtain primary care and hospital data for all people registered with a primary care practice in England from 2011- 2014. We will use multi-level modelling to explore the association between the prescription of each medication to eligible patients and unplanned hospital admissions. Our multidisciplinary team includes experts in evidence-based medicine, general practitioners, and statisticians with expertise in analysing large databases. Ethics approval is not required as we will use anonymous data.

This project will help to determine the extent to which evidence-based medication use impacts hospital admissions in England. To our knowledge, this will be the largest ever analysis of this type. The results could be used to guide local optimization of prescribing. Nationally, the results

could inform new clinical indicators for medications as part of the Quality and Outcomes Framework.

SECTION D – Project overview

Start Date: **01/10/2015**	
End Date: **30/09/2016**	
Duration (months):12 (Gant Chart in Appendix 1).	
Total SPCR budget: **£33 442** (Full costing breakdown in Appendix 3- attached).	
SPCR Theme*	**Acute Care**
To which health category in the UK Health Research Classification System** would this project belong?	**Generic Health Relevance**

SECTION E – Key Information

Has this or any related application been submitted elsewhere? **No**
If yes, please provide details of the application, its outcome or any changes made to the protocol since feedback received:
Have you received a research project award from the SPCR previously? **Yes**
If yes, please provide details of the short title and project number: **SPCR Project 222 - Reduced dietary salt intake in heart failure patients**
How does this project add to the existing research in the SPCR? The SPCR has strong research programmes in long-term condition management, multi-morbidity and ageing, and prevention and diagnosis. Our project to explore variations in the use of evidence-based medications and impacts on admissions aligns with the goals of these programs. It also builds on previous work funded by the SPCR. Studies on unscheduled secondary care funded by the SPCR have identified factors in primary care that influence admission rates, but have not robustly examined the role of variations in medication use. Therefore, this project will fill an important knowledge gap and complement the SPCR research profile in unscheduled secondary care.
How will this proposal contribute to capacity building in academic primary care? Our program of work to identify under-utilized interventions/medications to reduce admissions is already of interest to commissioners in Oxfordshire and researchers in NHS Grampian. The results may inform modifications of GP contracts locally and potentially lead to the development and testing of new Quality and Outcomes Framework indicators to optimize the use of select medications in primary care. Sponsorship of this project will support research training and career development for four early career scientists (BS, SS, KM, NB) including both clinical (KM) and non-clinical researchers (BS, SS, NB). Support for hardware/software purchases will increase the capacity of the research team to conduct future, high-quality research using large datasets, including new analyses of the datasets used in this study. Our PPI and dissemination activities will serve to inform patients and the public of the commitment of the School to solve one of the largest problems in healthcare in the UK, thereby garnering support for the SPCR and academic primary care.
How will this project lead to further competitive grant funding or other significant impact? To our knowledge, this will be the largest ever analysis of the association between evidence-based medication use in primary care and unplanned hospital admissions. We will obtain impact through submission of our results to high impact journals and wide dissemination in the public domain. We also believe the results will have impact on policy. We will disseminate significant

findings to the local NHS trust and Clinical Commissioning Group who have mutual interests in preventing unplanned admissions. The results could guide local optimization of prescribing. Nationally, these activities could inform the development of new clinical indicators for prescribing medications as part of the Quality and Outcomes Framework.

The results will stimulate future research and applications to competitive grant funding. If we find evidence of variations in prescribing and associations with admissions this will lead to prospective studies to explore reasons for variations from the patient, provider, and system perspective; to map pathways from poor prescribing to admissions; and to implement strategies to reduce admissions. We will submit an application for researcher-led funding from the NIHR Health Services and Delivery Research (HS&DR) Programme and for the SPCR Round 12 and 13 to support these projects.

SECTION F – Patient and Public INVOLVEMENT

Our PPI activities were developed with guidance from a PPI expert (Lynne Madocks) and the NIHR Handbook for Patient and Public Involvement in Health and Social Care.[1]

Our PPI strategy integrates patient and public stakeholders throughout the research process. We have pre-specified PPI activities in four key phases: designing the study; drafting grant applications; data interpretation and analysis; and dissemination of findings.

A family friend (Jennifer Cook) of the co-principal investigator has diagnoses of cancer and hypertension and frequently uses primary and secondary care services. She is a named collaborator on this grant and will be providing ongoing advice on the drafting of patient-related study materials. She is a writer and has won journalism awards. She has been a member of 2 cancer support groups and has been nominated for membership to a provincial patient advisory panel due to her articulate and approachable nature. She has been involved in research before as a participant and patient advisor.[2,3] She has refused remuneration for her involvement.

Designing the study: To determine the value of this research topic we posted messages on 2 health forums (patient.co.uk; daily mail forum), Facebook, and twitter which described our intention to explore whether variation in treatment practices in primary care impact on unplanned hospital admissions. We invited feedback on the importance of the research topic and the potential methodology. We have received 26 responses from 20 individuals including students, practicing physicians, and members of the general public. Ninety-five percent of the respondents identified this as an important research topic and we have designed the study to incorporate the feedback they provided. For example, one respondent suggested potential unintended consequences of the study: "*…saying things like primary care doctors don't use the best treatments for their patients, might actually be potentially harmful in losing people's trust for their doctors*". This has informed the framing of our lay summary and background, and will inform how we report our results.

Drafting grant applications: The lay summary in this grant was drafted and revised with input from our patient advisor.

Data interpretation and analysis, formulating results: Once we have analysed the data we will approach 10 patients from patient participation groups (PPGs) at 2 GP practices in Oxfordshire. Two GP applicants (KM, CH) and our GP collaborator (KK) will provide access to these groups. The GPs will identify patients with relevant conditions that are eligible to receive at least one of the medications on our top 10 list. We will meet with each patient for 0.75 hours at the Nuffield Department of Primary Care Health Sciences to ask about their knowledge regarding the medications on the list and discuss their experiences with medication prescribing in primary care. The patients will be presented with results from the study drafted with guidance from our patient advisor and the NIHR PPI Handbook.[1] We will ask whether the research findings make sense and will get input on draft lay summaries of the results. A rate of £20 per hour will be paid for the consultation in addition to £10 for travel expenses.

Dissemination of findings: Once the results have been published, we will disseminate our lay summaries for readership by the public. We will utilise the University and Departmental websites to publish the summaries. We will also disseminate the results through patient participation groups in two GP surgeries in Oxfordshire and by approaching broadcast media outlets in the UK.

SECTION G– Project Details

General Aim

The aim of this study is to assess the association between evidence-based medication use among eligible patients in primary care practices in England and unplanned hospital admissions.

Specific Aims

1. Quantify the variation in the use of 10 evidence-based medications in primary care which have been shown to reduce unplanned hospital admissions.
2. Determine if eligible patients treated with evidence-based medications are less likely to experience an unplanned hospital admissions compared to eligible patients not treated with evidence-based medications.
3. Determine differences in the odds of an unplanned admission for patients from primary care practices that treat larger proportions of eligible patients with evidence-based medications compared to patients from practices that treat smaller proportions of eligible patients with evidence-based medications.
4. Identify patient and practice characteristics that are associated with variation in the use of evidence-based medications among eligible patients.
5. Estimate potential reductions in unplanned admissions if a greater proportion of eligible patients were treated with evidence-based medications.

Background (references listed in Appendix 2)

The UK has experienced a 47% increase in admission over the last 15 years that has seriously strained the healthcare system.[4] In 2012-2013 there were 5.3 million unplanned hospital admissions representing 67% of hospital bed days in England and costing approximately £12.5 billion.[4] This represents a huge problem that is unsustainable and needs to change. As a result, reducing admissions is a priority for the National Health Service.[4]

Unplanned hospital admissions are unpredictable and occur at short notice because of a perceived need for immediate health care.[5] There are large variations in unplanned admissions rates across health regions[6] and primary care practices in the UK.[4,7,8] Studies have shown a 3.4 fold variation in admission rates between health regions[6] and GP referral rates for hospital admissions have been shown to vary from 0 to 95 per 1000 population.[4] Although social deprivation and non-modifiable population factors (e.g., age) account for a large portion of these variations[6], a substantial amount may be due to factors within the control of primary care physicians and managers.

A recent systematic review by Huntley et al. (2014) examined primary care factors associated with admission rates and found consistent evidence across studies for three elements of care: access to care, patient satisfaction, and being able to see the same doctor on repeat visits.[9] While this is an encouraging start, a core component of effective primary care practice has not been well-studied; the use of evidence-based medications. For example, a meta-analysis of 22 randomized controlled trials has shown that use of Tiotropium (an anticholinergic) compared to placebo among adults with Chronic Obstructive Pulmonary Disease results in a 15% reduction in hospital admissions due to COPD exacerbations.[10] In children with acute viral bronchiolitis, a meta-analysis of 5 RCTs has shown that use of Epinephrine versus placebo reduces admissions within 24 hours of outpatient presentation by 33%.[11] Variations in use of these medications and their impacts on hospital admissions in England have not been evaluated.

Evidence suggests there is variation in prescribing in England. The National Health Service (2012) reports wide variation in primary care prescribing practices, including both under- and over-utilization of medications however, the impact of these variations on admissions is unclear.[12] Huntley et al. (2014) found only 1 study examining the relationship between

achievement levels for prescription quality indicators and admission rates; achievement for three coronary heart disease prescription indicators had no association with admission rates.[9] An additional two studies in heart failure[13] and epilepsy[14], not captured by the review, have examined 3 prescription focused quality measures but also found no evidence of an association with admissions.

This limited work does not represent a robust evaluation of the potential impact of evidence-based medication use in primary care on unplanned admissions. However, there is some evidence showing that drug-related admissions contribute to the hospitalization burden. A 2006 systematic review in the British Journal of Clinical Pharmacology reported that 3.7% (range 1.4% – 15.4%) of all hospital admissions may be due to preventable drug-related events, a large proportion of which are related to prescribing problems.[15] However, only a sub-set of studies examined under-treatment as a cause for admissions and there were only 2 studies from the UK, both of which are now over ten years old.

As a result of the paucity of investigation, it is unclear if variations in evidence-based medication use in primary care are contributing to the burden of unplanned hospital admissions. Determining the association between the prescription of effective medications and hospitalisations could inform strategies to reduce admission rates. These strategies could be implemented using the existing national infrastructure to guide and incentivise physicians to prescribe appropriate medications, including the National Institute for Health and Care Excellence guidelines and the Quality and Outcomes Framework indicators.

Description of Project Protocol

Objective

The objective of this study is to assess the association between evidence-based medication use among eligible patients in primary care in England and unplanned hospital admissions.

Methods

Foundational Work: We are currently in the process of completing an overview of systematic reviews of interventions to reduce unplanned hospital admissions.[16] Based on current progress we expect to include and analyse approximately 200 systematic reviews, with over 50 reviews of medications that have been shown to reduce admissions. This list will be hierarchically ranked based on the quality of the evidence and size of effect estimates for absolute reductions in admissions. From this list we will select the top 10 medications that have been shown to reduce unplanned admissions and are supported by strong evidence. The results will also include details of the indications and contraindications for use of the medications as defined in the reviews. The list of 10 medications and descriptions of treatment-eligible patients will form the basis of our national observational study.

Design: National observational study.
Unit of Analysis: Patients in primary care practices in England.
Data Sources: We will use three data sources to obtain the patient-level and practice-level information necessary to meet our study aims.

1. Clinical Practice Research Datalink (CPRD): The CPRD includes primary care observational data for all patients registered with a GP practice in England. We will use this database to identify patients that are eligible for treatment with medications on our top 10 list and to quantify the proportion of patients at each practice that are being treated with evidence-based medications. We will aim to obtain the following information to identify the indications and contraindications for treatment, and to adjust for potential confounding: patient demographic information; medical diagnoses; time since diagnoses; prescriptions issued in primary care including brand or generic name, strength, and dosing; records of immunisations/vaccinations; referrals to specialists and secondary care settings; diagnostic testing; lifestyle information (e.g. smoking and alcohol status); and Index of Multiple Deprivation (including separate scores for the employment and income deprivation domains).

2. Hospital Episode Statistics Database (HES): The HES contains hospital admissions data for all NHS funded hospitals in England. Patient-level linkage of the CPRD data with

the HES is necessary to identify unplanned patient admissions to hospital and to identify the primary diagnoses upon admission.

3. Health and Social Care Information Centre: We will coordinate with the Health and Social Care Information centre to adjust for key practice level confounders including supply of GPs in each practice (full-time equivalents per 100 000 practice patient population) and QOF scores for access to care (calculated from the GP patient survey).

Population: All people registered with a primary care practice in England from April 1, 2011-March 31, 2014. We will exclude practices with less than 500 registered patients as they are more likely to serve atypical populations or deliver atypical services. We will also exclude practices that are not linked to the hospital episode statistics database.

Eligible Patients: The indications/contraindications for treatment using each medication will be supplemented with current clinical practice guidelines and reviewed by General Practitioners on our team. They have 24 years of experience treating patients in primary care and are experts in evidence-based medicine. The finalized list of indications and contraindications will allow us to define eligible patients for the analysis. We will identify indications and contraindications using patient-level data from the CPRD including comorbidities, prescriptions, lifestyle factors, and demographic characteristics. Patients with contraindications will be excluded from the eligible patient denominator in each practice.
Key Independent Variable: Whether eligible patients were treated with evidence-based medication.
Outcome Measure: Whether each patient experienced an unplanned admission to hospital. We will exclude admissions that are transfers between hospitals. Our decision to measure cause-specific or all-cause unplanned admissions will vary for each medication, depending on what the evidence from our systematic overview (foundational work) supports.

Statistical Analysis: For each of the 10 evidence-based medications assessed, we will report the overall proportion of unplanned hospital admissions broken down by whether the patient received this treatment. We will then use multi-level mixed effects logistic regression to explore the association between the prescription of each medication and unplanned hospital admission. The analyses will be clustered by both hospital and general practice. We may cluster by GP if numbers are sufficient. We will identify possible confounders using a combination of the clinical expertise of the lead and co-applicants and previous published evidence that has identified patient and primary care factors that affect admission rates. In the case of an overly complex model, stepwise selection will be used to produce a simplified model that adjusts for the most significant covariates. All analyses will be carried out using STATA 13.
Strengths: To our knowledge, this will be the largest analysis of the association between evidence-based medication use in primary care and unplanned hospital admissions. All previous studies that we could identify have conducted aggregate level analyses. We will use individual patient data, therefore allowing more nuanced and powerful analyses with adjustment for patient-specific factors.
Anticipated Challenges and Limitations: We anticipate two challenges/limitations. First, it is possible that patients will be misclassified as eligible or non-eligible. However, we will have access to individual level demographic, prescription, and clinical data that should allow for robust identification of eligible patients. Second, we anticipate encountering some missing data in the CPRD and HES databases. This is a limitation of using large databases. If values for medication dosing or frequency are encountered we will use substitution of the most recent observation. If we cannot determine the name of a medication a patient is prescribed or the nature of a hospital admission (unplanned vs. planned), the observation will not be included. However, with such a large sampling frame (2011-2014) we expect to have a robust sample of millions of patients with the data necessary to complete analysis.
Project Timetable: See Gant chart in Appendix 1.

SECTION H– Justification of costs requested

Our costings have been developed in accordance with the Attributing the costs of health and social care research (AcoRD) guidance. We believe the cost of **£33 442** offers good value to the NIHR SPCR: to our knowledge, this will be the largest ever analysis of the association of evidence-based medication use in primary care and unplanned admissions; we will submit our work for publication in high impact journals (Lancet, BMJ; Annals of Internal Medicine); the hardware/software purchased will increase the capacity of our team to conduct large scale, high-quality data analyses; and, given the large volume of analyses to conduct, the staff costs are minimal as the co-principal investigator (NB- committing 40% FTE for 12 months) is a DPhil student fully funded by a Clarendon scholarship and will not receive salary support.

The majority of our request for support is to cover the CPRD data management fee (£10 500) and cost for the basic HES database with linkage for over 100 000 patients (£15 750). Both the HES database and linkage to CPRD are necessary to complete the project. The CPRD provides individual patient data, which is a key strength of this study. However, it does not provide information on the nature of hospital admissions (i.e., unplanned vs. planned) or the primary admission diagnosis. Once we identify eligible patients, we must link their primary care data to hospital data to identify those that experience an unplanned admission and the reason for admission.

To handle significant data storage and provide the computational power needed to analyse data for millions of patients we will purchase a desktop computer with a solid state hard drive and 16GB of RAM (£610). We will also require an advanced statistical package: Stata 13 MP, quad core, single user, perpetual licence (student price £650). Purchase of this computer and software will increase the capacity of our research team to conduct future projects with large datasets, including new analyses of the datasets from this study.

Other non-staff costs to support completion of the project include photocopying/printing and stationary (£45). £275 has been allocated to support patient and public involvement activities. This will support 7.5 hours of PPI activities with 10 patients recruited from patient participation groups in GP surgeries in Oxfordshire. We will provide £20 pounds per hour remuneration for patients. We will also provide £10 travel expenses for each patient to attend meetings at the Nuffield Department of Primary Care Health Sciences. £25 has been allocated for coffee/tea/snacks during meetings. A proportion of the budget (£200) has been allocated to allow for dissemination (travel, accommodation) of the results at a National conference i.e. the Society for Academic Primary Care Conference. This cost was scaled down (from £400) as the co-principal investigator can access guaranteed conference funds (£200) through his college affiliation (Green Templeton College).

Salary costs amount to £3938 (co-principle investigator 1% FTE, senior GP advisor 1% FTE, CPRD and statistics specialist 5% FTE, and senior statistical advisor 3% FTE). All staff have required expertise.

SECTION I – Delivery
Network involvement

Please indicate which network(s) http://www.crn.nihr.ac.uk/ you intend to work with and the extent to which any links have been established.

N/A

Is Clinical Trials Authorisation required?

No

Is a Clinical Trials Unit (CTU) involved with this research proposal?

No

If yes, what is the name of the CTU?

Does the CTU hold a UKCRC registration number?

If yes, please provide the CTU Registration Number

SECTION J – Expected Output of Research/Impact

Please describe how the outcomes of this research could be translated into the NHS and wider healthcare community to provide improvements in service delivery, patient health and/or wellbeing

This could include plans to submit papers to peer reviewed journals but it will be particularly important to identify forms of presentation that will maximise impact on practitioners and service managers if appropriate.
To our knowledge, this will be the largest ever analysis of the association between evidence-based medication use in primary care and unplanned hospital admissions. We will disseminate the results of the study through multiple channels to maximize impact of the research. First, we will submit our work for publication in high impact journals (Lancet, BMJ, Annals of Internal Medicine). Second, we will present the results at a National Conference (Society for Academic Primary Care). Third, our collaborator (KK - GP commissioner) and GP applicants (KM, CH) will facilitate dissemination of the result to the local NHS trust and Clinical Commissioning Group in Oxfordshire. Fourth, we will post lay-summaries on Departmental and University Websites. Fifth, we will disseminate the results through patient participation groups in GP surgeries in Oxfordshire. Sixth, we will approach broadcast media in the UK to communicate our findings to the public. The results will stimulate future research. If we find evidence of variations in prescribing and strong associations between prescribing and admissions this will lead to prospective studies to explore reasons for variations from the patient, provider, and system perspective; to map pathways from poor prescribing to admissions; and to implement strategies to reduce admissions. We will submit an application for researcher-led funding from the NIHR Health Services and Delivery Research (HS&DR) Programme and for the SPCR Round 12 and 13 to support these projects. This project will help to determine the extent to which improving prescribing practices in primary care could reduce hospital admissions. The results could be used by healthcare providers, commissioners, and policy makers to inform local optimization of prescribing. Nationally, these activities could inform new clinical indicators for prescribing medications as part of the Quality and Outcomes Framework.

SECTION K – Nominated Referees please provide:

- at least 2 names if your project cost is <£50k
- at least 3 names if your project cost is between £50k-£500k

Title_Forename_Surname: Dr. Nadeem Qureshi
Post Held: Clinical Professor
Organisation: University of Nottingham
Email: nadeem.qureshi@nottingham.ac.uk
Area of Expertise: Primary care, Genetics

Title_Forename_Surname: Dr. Richard Riley
Post Held: Professor of Biostatistics
Organisation: Keele University
Email: r.riley@keele.ac.uk

Appendix 5.2 Waiver of ethical approval

Dear Niklas,

Regarding your query for the project entitled, 'Prioritisation of evidence-based primary care medications to reduce hospital admissions', we think this would not need any approvals since the use of the list would be a choice based on the evidence you have compiled through this project and would be a decision made by the prescribing clinicians; as may happen anyway in clinical practice.

With best wishes

Carol

Carol Cornelius
Senior Research Support Associate I Clinical Trials and Research Governance
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https://www.admin.ox.ac.uk/researchsupport/ctrg/

Appendix 5.3 Survey to prioritise medications

Dear Participant,

Thank you for agreeing to complete this survey. On this page you will find an example of layout. In the far-left column you will see the **clinical indication/patient population**. In the next column is the name of the **medication of interest**. Please rate your level of agreement with the four statements by entering a single number in each box. In this survey, optimisation is defined as: "the action of making the best or most effective use of a situation or resource." Please think of the **Health Care and Primary Care Systems in the UK** when providing your ratings. The **rating scale** is a 1 to 9 scale: 1 is strongly disagree and 9 is strongly agree. Please provide comments at the end to justify your ratings.

Page 2 is a **demographics sheet** with 5 questions. Page 3 is the **medications survey**.

Clinical indication	Medication	This medication is sub-optimally utilised	Optimising use of this medication would reduce emergency hospital admissions	Optimising use of this medication in primary care is feasible	Utilisation of this medication should be studied
		1= Strongly disagree 9= Strongly agree	1= Strongly disagree 9= Strongly agree	1= Strongly disagree 9= Strongly agree	1= Strongly disagree 9= Strongly agree
Patients with abdominal pain	Paracetamol	X	X	X	X

Clinical indication	Medication	This medication is sub-optimally utilised	Optimising use of this medication would reduce emergency hospital admissions	Optimising use of this medication in primary care is feasible	Utilisation of this medication should be studied
		1= Strongly disagree 9= Strongly agree	1= Strongly disagree 9= Strongly agree	1= Strongly disagree 9= Strongly agree	1= Strongly disagree 9= Strongly agree
Heart failure with reduced left ventricular ejection fraction or left ventricular dysfunction	ACE inhibitors				
	Angiotensin-II receptor blockers				
	Aldosterone antagonists				
	Beta-blocking agents				
	Digoxin				
Stable coronary artery disease	Intensive statin therapy				
Moderate to severe stable chronic obstructive pulmonary disease	Long-acting beta-2 agonists				
	Long-acting muscarinic antagonists				
Schizophrenia	Anti-psychotic maintenance therapy				
	Second generation anti-psychotics				

Please provide comments about your ratings:

Participant Demographics

1. What is your gender?

☐ Male

☐ Female

2. What is your age?

☐ 20-39

☐ 40-59

☐ 60-79

☐ 80+

3. What is your primary clinical speciality?

☐ General practice

☐ Emergency medicine

☐ Other (please specify):

4. Are you a member of a clinical commissioning group board? If yes, describe.

☐ Yes (please specify):

☐ No

5. Are you currently licensed to work as a clinical practitioner in the UK?

☐ Yes

☐ No

Appendix 5.4 Structured approach to literature review

Table 1. List of structured search terms used in Pubmed and Google Scholar for identifying evidence on utilisation of the medications for heart failure patients

1. heart failure AND medication AND optimisation
2. heart failure AND medication AND optimise
3. heart failure AND medication AND optimization
4. heart failure AND medication AND optimize
5. heart failure AND medication AND utilisation
6. heart failure AND medication AND utilise
7. heart failure AND medication AND utilization
8. heart failure AND medication AND utilize
9. heart failure AND medication AND adhere*
10. heart failure AND medication AND compliance
11. heart failure AND medication AND complied
12. heart failure AND medication AND comply

Chapter 6. Utilisation of heart failure medication and associations with emergency hospital admissions: a national cohort study in UK primary care

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6.0 Chapter overview

This chapter reports a national cohort study of heart failure medication dosing and interruptions in UK primary care. Data for 8,274 patients and 383,369 prescriptions were analysed. The results showed that most patients experienced gaps in prescription coverage and average doses were well below recommended target doses. Higher doses of first line therapies were associated with reduced emergency hospital admission rates. Conversely, higher doses of Aldosterone antagonists were associated with an increased risk of emergency admissions. The results suggest that clinicians and policy makers should focus on up-titrating ACE inhibitors and Beta-blockers to guideline-recommended target doses and consider more careful dosing and monitoring for patients on Aldosterone antagonists in order to reduce rates of emergency hospital admissions.

6.1 Publication statement

An abstract summarising this research has been published on the website of the Clinical Practice Research Datalink.[1]

6.2 Introduction

6.2.1 Building on the findings of previous chapters

This chapter builds on the findings of previous chapters in order to identify evidence- and guideline-based interventions that could be optimised in clinical practice to reduce hospital admissions. Chapter 3 identified evidence-based interventions that reduce emergency hospital admissions. Chapter 4 determined which of the interventions were supported in guidelines. Chapter 5 used a multi-step process to prioritise the evidence- and guideline-based interventions for investigation. Five heart failure medications were prioritised. This chapter (chapter 6) explores utilisation of those interventions and whether gaps in utilisation are associated with hospital admission rates in the 'real-world'.

6.2.2 The burden of heart failure

Heart failure (HF) is a leading cause of morbidity and mortality globally. Approximately 2% to 3% of people have HF in high- and middle-income countries, including 15 million people in Europe and 6 million in the USA. In the UK there are approximately 500,000 people with HF.[2] Nearly 50% of HF patients die within five years of diagnosis. Furthermore, and of relevance to this thesis, HF is a significant source of emergency hospital admissions. There are approximately 67,000 hospital admissions each year in England and Wales due to heart failure[3], and this has substantial cost implications. Some countries, including the UK, spend nearly 2% of their total health care budget on managing HF patients, with 60% to 70% of the costs due to acute hospital admissions.[4] As a result, minimising the impact of heart failure is a priority for patients and health systems in the UK and other countries.

6.2.3 Optimising use of heart failure medication

Previous chapters of this thesis identified five evidence- and guideline-based medications that reduce emergency hospital admissions in heart failure patients.[5] NICE guidelines organise these medications into three lines of therapy to be used sequentially for heart failure patients with reduced ejection fraction or left ventricular systolic dysfunction:

- Renin-angiotensin system blockers (Angiotensin-converting enzyme Inhibitors [ACE} or Angiotensin-II receptor blockers [ARB]) and Beta-blockers

- Aldosterone antagonists
- Digoxin

There is currently no cure for heart failure and the goals of treatment are to extend life and to reduce burden of the disease, including reducing exacerbations resulting in emergency admissions. The most effective tool for achieving these goals is medication. Therefore, optimising use of heart failure medications is a national health priority.[6–8]

Over the last 10 years, substantial resources have been invested to improve the use of these five medications. For example, tens of millions of pounds have been invested in: developing and maintaining prescribing indicators for first-line therapies as part of the pay for performance Quality and Outcomes Framework (QOF); research grants investigating treatment optimisation; and annual audits of heart failure treatment and subsequent improvement efforts. However, despite these huge investments of resources, little research has examined prescribing in primary care.

6.2.4 Gaps in knowledge about heart failure medication utilisation

Evidence from the British Society for Heart Failure's audits have shown improvements over time in the rates of prescription of evidence-based treatments. However, these audits are of patients in secondary care[3], and do not reflect prescribing by primary-care physicians, who issue hundreds of thousands of prescriptions for heart failure medications each year.[9] Since 2009, the Quality and Outcomes Framework has tracked prescription rates in primary care for first-line therapy (ACE inhibitors, ARBs, beta-blockers) and, despite variations between practices, has shown improvements in the proportion of patients receiving therapy. However, the QOF does not measure the supply of medications prescribed or the prescribed doses. Similarly, the British Society for Heart Failure's annual does not include information on dosing or pill coverage.

Currently, the extent to which primary-care physicians are prescribing target doses of heart failure medications is unclear. It is also unclear if patients are given sufficient supplies of medication to follow the recommended regimens. This is a serious

concern given that patients with heart failure are managed mostly in primary care and general practitioners are responsible for a large proportion of heart failure medication prescribing.[9] In their 2016 report, the British Society for Heart Failure highlighted this gap in knowledge and noted the need to extend their audit to primary care.[3] They are in the early stage of pilot testing a primary care audit but, as of 2018, have not reported any information on primary care prescribing.

To address these gaps in knowledge and better understand the potential for reducing hospital admissions by optimisation of medication, this chapter examined dosage regimens and interruptions in pill coverage for heart failure patients in UK primary care and explored the extent to which these aspects of utilisation were associated with emergency hospital admission rates.

6.3 Aim and objectives

6.3.1 Aim

The aims of this chapter were to describe dosage regimens and treatment interruptions for heart failure medication prescribed in UK primary care; to identify patient characteristics associated with dosing and medications interruptions; and to explore the association between dosage, interruptions, and emergency hospital admissions.

6.3.2 Objectives

To achieve these aims, this chapter had the following objectives:

Dosage regimens

1) To quantify average doses of heart failure medications prescribed in UK primary care
2) To compare daily doses to evidence- and guideline-based target doses and quantify target dose achievement
3) To quantify the association between patient characteristics, doses of heart failure medication, and emergency hospital admissions

Treatment interruptions

1) To quantify the proportion of patients that experience interruptions in heart failure medication pill coverage
2) To quantify the average length of medication interruptions
3) To quantify the proportion of patients that experience interruptions of different lengths
4) To quantify the proportion of days for which patients have pill coverage
5) To quantify the association between patient characteristics, medication interruptions, and emergency hospital admissions

6.4 Methods

This study was reported in accordance with the EQUATOR network's "reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology" (RECORD-PE).[10]

6.4.1 Study design

This was a retrospective cohort study using six and a half years of data from 1 January 2010 to 1 July 2017.

6.4.2 Funding

To complete this study, the thesis author prepared and submitted a grant application to the School for Primary Care Research National Institute for Health Research (project number 271). After peer-review, funding in the amount of £33,442 was awarded to the thesis author and the team he assembled. The grant application can be found in Appendix 6.1.

6.4.3 Data sources

This study used data from the Clinical Practice Research Data Link (CPRD) with data linkages to Hospital Episode Statistics Admitted Patient Care Data, Office of National Statistics Death Registration Data, and Patient Level Index of Multiple Deprivation Data.

The CRPD is a national database that collects de-identified patient data from a network of GP practices across the UK. Primary care data are linked to a range of

other health related data to provide a longitudinal, representative UK population health dataset. As of 2018, the database included 10 million patients registered with a GP practice.[11]

Access to the CPRD data and linked data required protocol approval by the Independent Scientific Advisory Committee (ISAC).[12] The study protocol was peer-reviewed by the committee and approved. The application, which contains the detailed study protocol, can be found in Appendix 6.2. CPRD policies did not allow a DPhil student to apply as chief investigator and, therefore, Prof Carl Heneghan was named chief investigator. However, the author of this thesis (NB) designed the study, assembled the support team, wrote the study protocol, obtained SPCR grant funding to support the project, wrote the ISAC application, acted as corresponding applicant on the ISAC application, coordinated with data managers, and completed all analysis.

6.4.4 Source population

The population of interest was patients who were 18 years of age or older at the time they received a documented diagnosis of heart failure with left ventricular systolic dysfunction or reduced ejection fraction. Diagnostic codes from primary care (Read) coding schemes and ICD-10 coding schemes were used to identify eligible patients with heart failure.[13] The code list is 300 pages long and can be provided by the thesis author upon request. Read codes were used to identify patients with heart failure in the CPRD while ICD-10 codes were used to identify heart failure patients from the Hospital Episode Statistics Database. These include all codes specifying heart failure with left ventricular systolic dysfunction or reduced ejection fraction used in the Quality and Outcomes Framework, with additional codes from previously published literature[14] and online clinical code repositories.[15] Included records had to be of research quality according to CPRD criteria and have data linkage to the Hospital Episode Statistics Database, ONS death registry, and Index of Multiple Deprivation.[16]

6.4.5 Inclusion criteria

Patients were included in this study if they received “regular” prescriptions of at least one medication in any of the five designated medication groups between 1 January 2010 and 1 July 2017. “Regular” prescriptions were defined as a series of three prescriptions with no more than 90 days between the first and third prescription dates. Patients who received two prescriptions before 1 January 2010 were eligible if the third prescription occurred on or after 1 January 2010. All three prescriptions must have occurred after the diagnosis of heart failure. Patients must have been treatment naive for the medication being analysed, defined as being free of prescriptions for at least one year of data before the three prescriptions used for cohort entry. The three prescriptions must have had non-zero daily dose information and be for one of the following medications recommended by NICE and the BNF for treatment of heart failure: angiotensin-converting enzyme inhibitors (captopril, enalapril maleate, fosinopril sodium, imidapril hydrochloride, lisinopril, perindopril arginine, perindopril erbumine, quinapril hydrochloride, ramipril; trandolapril); angiotensin-II receptor antagonists (candesartan cilexetil, losartan potassium, valsartan); beta-blockers (bisoprolol fumarate, carvedilol, nebivolol hydrochloride); aldosterone antagonists (spironolactone, eplerenone); digoxin. January 2010 was selected as the start date for this study as this coincided with the publication of the NICE clinical guidelines that recommended use of these evidence-based medications.

6.4.6 Exclusion criteria

Patients were excluded if they had no documented left ventricular dysfunction or reduced ejection fraction code; never received a prescription for any of the medications of interest (Appendix 6.3); or never received three prescriptions without a gap longer than 90 days between the first and third prescriptions.

6.4.7 Percentage of target dose achieved and medication interruptions

A brief description of two key elements of the study is needed here to enable understanding of the data that was eligible for analysis.

A. **Percentage of target dose achieved**: this value was used to characterise the dosage regimen for medications and used as a predictor in the analysis

of associations with patient characteristics and hospital admissions. It was calculated by dividing the median daily dose of prescribed medication by the maximum target dose as recommended in NICE and BNF guidelines.

B. **Medications interruptions**: an interruption in treatment was defined as seven days or longer without medication. Patients with complete medication coverage and those experiencing gaps of six days or less without medication were considered to have no treatment interruptions. This buffer allowed for imprecision in the estimate of the number of days covered by each prescription (i.e., patients may have pills saved from multiple previous prescriptions or from family members/friends and used them to fill gaps in their current prescription). Previous highly-cited research on utilisation of medication for cardiovascular disease has used the same threshold to define gaps in treatment.[17]

6.4.8 Details of cohort entry

Patients entered the cohort and could contribute data once they received three prescriptions of the same medication within 90 days with non-zero daily dose information. The index date was the date of the third prescription. The third prescription and all subsequent prescriptions were included in the analysis. There was no minimum follow-up period.

6.4.9 Details of cohort exit

Patients exited the cohort at death, at permanent stoppage of medication, or at the end of the study window (1 July 2017). Permanent stoppage of medication was defined as 365 days without coverage from a primary care prescription. A permanent stoppage threshold was selected in order to restrict observation to periods during which patients may be still considered receivers of “regular” prescriptions. Previous studies have shown that among patients that experience an interruption of 180 days (6 months) or longer only 30% restart treatment. In this chapter, 365 days was selected as the threshold for permanent stoppage in order to capture some of the estimated 30% of patients that do restart treatment after 180 days.

6.4.10 Caveats to cohort entry/exit

Patients could switch medications within medications groups. Permanent stoppage did not occur if patients began receiving prescriptions of another medication within the same group within 365 days from the end of the last prescription coverage (i.e. switch from lisinopril to ramipril, both ACE inhibitors).

NICE guidelines recommend ACE inhibitors as first line therapy and suggest ARBs as an alternative if ACE inhibitors are intolerable. Therefore, patients that transition from ACE inhibitors to ARBs may not actually experience an interruption in first line therapy. To account for this potential transition and to ensure that estimates of treatment interruption were not inflated, treatment interruptions for ACE inhibitors ended if routine ARBs were initiated (3 or more prescriptions within 90 days). Upon ARB initiation, ACE inhibitor patients stopped contributing data to the ACE cohort. The same rule was applied to patients on ARBs that transitioned to ACE inhibitors.

6.4.11 Data management

Extraction of data from the CPRD system was conducted by a senior member of the CPRD and Nuffield Department of Primary Care Health Sciences (MS) according to the specifications requested by the thesis author (NB). A summary description of data extracted from the CPRD is shown in Appendix 6.4. Once extracted, the data was downloaded by the thesis author from an encrypted and password protected online platform and stored in excel files on a secure Network Drive. The thesis author then cleaned the datasets, merged and reshaped files as needed, derived key variables, and analysed the data.

6.4.12 Data analysis

Data were analysed using STATA 14.[18] Binary and categorical variables were presented as percentages. For continuous variables, means with standard deviations or medians with interquartile ranges were used, depending on the distribution of data. The threshold for statistical significance was set at $p<0.01$, as opposed to 0.05, to reduce the chance of type 1 errors in the presence of multiple comparisons. Robust standard errors were used to account for the fact that some of the data was nested within primary care practices.

6.4.13 Methods for descriptive analyses

There were three sets of descriptive analyses.

A. Descriptive analysis of patient characteristics

Descriptive statistics of patient baseline characteristics were produced. The following characteristics were analysed: age, sex, cholesterol, smoking status, alcohol consumption, co-morbidities, concomitant heart failure/cardiovascular medications, patient level of deprivation, and number of months since heart failure diagnosis. For details about the derivation or classification of these variables see Appendix 6.2 section M.

B. Descriptive analysis of dosage regimens

The median daily dose for each patient was calculated to represent the average dose a patient received during their treatment. The percentage of the target dose achieved was calculated each day for each patient by dividing the daily dose by the recommended target dose. A median of these values was calculated for each patient and used in subsequent analyses. Appendix 6.3 includes a list of the medications analysed along with guideline recommended target doses.

C. Descriptive analysis of treatment interruptions

Treatment interruptions were determined by subtracting the number of days of pill coverage by the number of days between prescriptions. Excess tablets from the last prescription were carried over. Seven days was selected as the threshold for a treatment interruption to allow for imprecision in the estimation of the number of days covered by each prescription. This categorisation has been used in previous studies.[17] These data were then used to characterise treatment interruptions in four ways. Firstly, the proportion of patients experiencing any treatment interruption (i.e., seven days or longer) was calculated. Only the first occurrence of an interruption was counted. Secondly, the proportion of patients experiencing treatment interruptions of different lengths was calculated. Thirdly, the median length in days per episode of a treatment interruption was calculated. Fourthly, the proportion of days within the observation period with medication coverage was calculated.

6.4.14 Methods for inferential analyses

There were four sets of inferential analyses.

A. Associations between patient characteristics and achievement of target dose

Univariate and multi-variate logistic regressions were used to determine whether patient characteristics were associated with achievement of target dose, defined as a binary variable (median daily achievement of 50% or greater of target dose vs. less than 50%). This cut-off (50%) has been used in previous studies of recently discharged heart failure patients and has been shown to be significantly associated with important patient outcomes such as mortality.[19,20]

B. Associations between patient characteristics and interrupted treatment

Univariate and multi-variate Cox proportional hazards regressions were used to determine whether patient characteristics were associated with the time to first treatment interruption of 90 days or longer. This threshold was selected as previous research on use of CVD medication in patients with heart failure or recent myocardial infarction has shown that gaps of 90 days or longer are associated with increased risk of mortality.[21]

C. Associations between achievement of target dose, treatment interruptions, and emergency hospital admissions

Uni-variate and multi-variate Cox proportional hazards regressions were used to explore the association between target dose achievement, treatment interruptions, and time to first all-cause and cardiovascular-related emergency hospital admission. Patients were censored at the date of death, permanent stoppage of medication (365 days without medication from a primary care prescription), or the end of the data collection period (July 1, 2017). The following two sections provides details of the two main exposure variables (i.e., dosing and interruptions).

Dosing exposure variable

As has been done in previous studies, the cumulative average achievement of target dose was used in the regression as a time-varying variable.[22] Given that doses of

heart failure medication are often up- and down-titrated, the goal of this analysis was to examine associations between admissions and prescribing trends, rather than any single prescription dose. At each prescription date, the cumulative median achievement of target dose was categorised as a binary variable and entered into the model (50% or greater achievement vs. less than 50%). The median was selected as the data for dosing were skewed.

The interaction of dosing and interruptions in medication was explored by including a time-varying interaction term to model a decline in dose during interruption periods. This time-varying variable was created by using the elimination half-life of the medication multiplied by the length in days of treatment interruption, starting seven days after pill coverage ended (i.e., start of a treatment interruption as defined in this study).[23,24] This time-varying variable was then similarly classified in a binary manner as 50% or greater of target dose and less than 50% of target dose. Elimination half-life may be defined as the time required for the amount of drug present in the body, or its concentration in serum or plasma, to be reduced by half.[24] This variable served to estimate the approximate amount of medication remaining in a patient's system during treatment interruption periods. The elimination half-life was chosen as it is commonly reported in medication profiles and is reported by the BNF.[23,24]

Medication interruption exposure variable

Treatment interruptions were treated as time-varying variables to indicate that patients were only exposed during treatment interruptions of 90 days or longer. This threshold was selected as it has been used in previous research on utilisation of CVD medication and has been associated with mortality.[21]

6.4.15 Sensitivity analysis

Two sets of sensitivity analyses were conducted. Firstly, Cox regressions were conducted to determine if patient characteristics were associated with time-to-first interruption of seven days or longer. Secondly, Cox regressions were conducted to determine if interruptions of seven days or longer were associated with emergency admissions.

6.4.16 Co-variate adjustment

The following co-variates were explored in all univariate and multi-variate analysis: age; sex; chronic kidney disease status; coronary heart disease status; number of comorbidities; number of concomitant heart failure and cardiovascular medications; use of the other five heart failure medications of interest in this study; patient level of deprivation; length of time between heart failure diagnosis and entry into the medication cohort; total cholesterol; smoking status; and alcohol consumption. Additional variables explored in specific medication groups included: atrial fibrillation status; diabetes status; hypertension status; and use of amiodarone. These variables were selected based on the results of previous studies and consultation with experts (JL, RH, JA, MS). These variables have been associated with aspects of prescribing or adherence for the medications of interest, or associated with important outcomes in patients with cardiovascular disease.[17,19] Additional details about these co-variates can be found in Appendix 6.2 (section M).

6.4.17 Missing data

Missing data patterns were investigated. Missing data for co-morbidities or outcomes was assumed to indicate that the condition was not present. Missing data for concomitant medications was assumed to indicate that the medications were not prescribed. Missing data for smoking status was assumed to indicate non-smoker. Missing data for cholesterol and patient-level deprivation was imputed using multiple imputation with chained equations under the missing at random assumption.[25] Alcohol consumption was not imputed given the large prevalence of missing data (44%), results from univariate analysis showing non-significant associations with outcomes, and research indicating that alcohol consumption data in UK primary care databases is not missing at random and, therefore, fails to meet the key assumption of multiple imputation.[26] Sensitivity analyses were conducted to compare results using imputed data and complete cases.

6.4.18 Model building

For analysis of time to event outcomes, univariate relationships were examined using the log-rank test of equality for categorical predictor variables and Cox proportional hazard regression for binary and continuous predictor variables. For analysis of binary outcomes, univariate relationships were examined using chi-

square tests for categorical predictor variables and logistic regression for continuous predictor variables. Given the large prevalence of missing data for alcohol consumption (44%), it was excluded from multi-variate models in order to increase the available sample size for analysis. Other than alcohol consumption, all co-variates were entered and retained in multi-variate models as they have been shown in previous research or suggested by experts to be important predictors of medication dosing, adherence, or outcomes in patients with cardiovascular disease.

6.4.19 Assessing model assumptions

Key model assumptions were evaluated and shown to be valid unless otherwise specified.[27,28] For cox regressions, the proportional hazards assumption was assessed by examining Schoenfeld and scaled Schoenfeld residuals plots and significance tests. When variables were found to violate the proportional hazards assumption they were retained in the model as time varying co-variates. Linearity between the predictors and the log hazard was assessed by examining plots of the Martingale residuals against each predictor.

6.4.20 Sample size considerations

A detailed discussion of sample size considerations can be found in Appendix 6.2 section I. Descriptive estimates were expected to have reasonable precision given that the sample was to include hundreds of thousands of prescription data points. Based on previous research examining CVD medication use and the expected number of events in the data, all regression analyses were expected to have sufficient power. In the hospital admissions analyses, in which dosing and interruptions were binary predictor variables, 318 events were required to achieve 80% power at the 0.05 level of significance.[17] Analyses examining patient characteristics as predictors of dosing (<50% vs. >=50%) and interruptions (<90 days vs. >=90 days) were also expected to have sufficient power given that the sample contained 8,274 patients, thousands of prescription data points, and approximately 50% of the patient sample was expected to fall into each outcome category (i.e., <90 days vs. >=90 days; <50% target dose vs. >=50% target).[17]

6.5 Results

6.5.1 Patient characteristics

Overall, 8,274 heart failure patients were included in the study. Baseline patient characteristics are summarised in Table 1. The majority of patients in the study had a recent HF diagnosis. The median time from HF diagnosis to entry into the study was 2.6 months (IQR 1.9 to 9.3). Patients were observed for a median of 21 months (IQR 10 to 35). Some patients received regular prescriptions for multiple types of heart failure medications and, therefore, contributed data to multiple cohorts. Of the 8,274 patients in the study, 45% (n=3,743) contributed data to one cohort, 34% (n=2,782) contributed data to two, 17% (n=1,412) contributed data to three, 4% (n=309) contributed data to four, and <1% (n=28) contributed data to all five medication cohorts. Comorbidities and polypharmacy were common; patients had a mean of 4 (SD 2) comorbid conditions and were on 7 (SD 2) concomitant medications. Details of specific comorbidities and concomitant medications can be found in Appendix 6.5. During the observation period, 50% of patients (n=4,152) had at least one all-cause emergency hospital admission; 24% (n=2,008) had at least one cardiovascular-related emergency admission; and 20% (n=1,644) died.

6.5.2 Heart failure medication prescriptions

A total of 383,369 prescriptions were analysed. Table 2 reports the number of prescriptions for each medication. Patients received a median of 26 prescriptions (IQR 10 to 58) for these medications during the study period.

6.5.3 Description of medication dosages

Table 2 and Figure 1 show patients' median daily dose compared to target dosages for each medication group. Most patients received below target doses of heart failure medication. Comparison of median daily doses to the recommended dosages showed that 76% (n=6,345) of patients were below recommended targets. Many patients on ACE inhibitors, Angiotensin-II receptor blockers, and Beta-blockers had a median daily dose less than 50% of the recommended target. Achievement of target dosing was highest for Digoxin; 53% (n=748) of patients had a median daily dose at the target leve

Table 1. Characteristics of patients

Patient characteristics[a]	Overall (n=8,274)	Patients by medication cohort				
		ACE Inhibitors (n=4,011)	Angiotensin-II receptor blockers (n=1,603)	Beta-blockers (n=5,383)	Aldosterone antagonists (n=2,498)	Digoxin (n=1,424)
Age[b]	71 ±13	70 ±13	71 ±12	70 ±13	70 ±13	73 ±12
Male	66% (5,451)	67% (2,702)	61% (978)	67% (3,594)	69% (1,730)	64% (914)
Months since HF diagnosis[c,d]	2.6 (1.9 to 9.3)	2.5 (1.9 to 3.8)	4.4 (2.4 to 22.4)	2.6 (2.0 to 5.4)	3.9 (2.4 to 24.3)	3.6 (2.3 to 30.0)
Deprivation[e]						
Quintile 1 (least)	16% (1,358)	17% (667)	15% (248)	17% (928)	17% (435)	15% (218)
Quintile 2	20% (1,645)	20% (816)	19% (298)	20% (1,084)	20% (507)	20% (284)
Quintile 3	21% (1,743)	21% (844)	21% (340)	21% (1,119)	20% (501)	21% (302)
Quintile 4	23% (1,893)	23% (913)	24% (382)	23% (1,213)	24% (587)	23% (322)
Quintile 5 (most)	20% (1,631)	19% (769)	21% (335)	19% (1,036)	19% (467)	21% (298)
Smoking[f]						
No	88% (7,241)	85% (3,420)	91% (1,461)	86% (4,647)	85% (2,130)	88% (1,260)
Yes	12% (973)	14% (551)	9% (137)	13% (694)	14% (349)	11% (152)
Drinking						
Non/Former	29% (2,434)	29% (1,175)	28% (456)	30% (1,620)	30% (747)	30% (432)
Occasional	27% (2,198)	26% (1,047)	28% (445)	26% (1,415)	27% (679)	26% (372)
Mod/Heavy	5% (425)	5% (219)	5% (82)	5% (288)	5% (129)	5% (75)
Missing	44% (3,667)	39% (1,570)	39% (620)	38% (2,060)	38% (943)	38% (545)
Cholesterol (mmol/L)[g]						
Total	4.4 ±1.2	4.4 ±1.1	4.5 ±1.2	4.4 ±1.2	4.3 ±1.2	4.3 ±1.2
HDL	1.3 ±0.4	1.3 ±0.4	1.3 ±0.4	1.3 ±0.5	1.3 ±0.4	1.3 ±0.4
LDL	2.5 ±1.0	2.5 ±1.0	2.5 ±1.0	2.5 ±1.0	2.4 ±1.0	2.4 ±1.0
No. of comorbidities[h]	4 ±2	3 ±2	4 ±2	3 ±2	4 ±2	4 ±2
No. of medications[h]	7 ±2	6 ±2	8 ±2	7 ±2	8 ±2	8 ±2
Months of observation	21 (10 to 35)[c]	21 (10 to 37)	22 (12 to 38)	21 (11 to 38)	18 (9 to 32)	19 (10 to 32)
Had one or more all-cause admission	50% (4,152)	47% (1,884)	45% (724)	47% (2,554)	49% (1,218)	55% (779)
Had one or more CVD admission	24% (2,008)	22% (876)	22% (348)	23% (1,215)	24% (595)	26% (370)
Died during the observation period	20% (1,644)	16% (652)	15% (233)	17% (910)	21% (515)	25% (350)

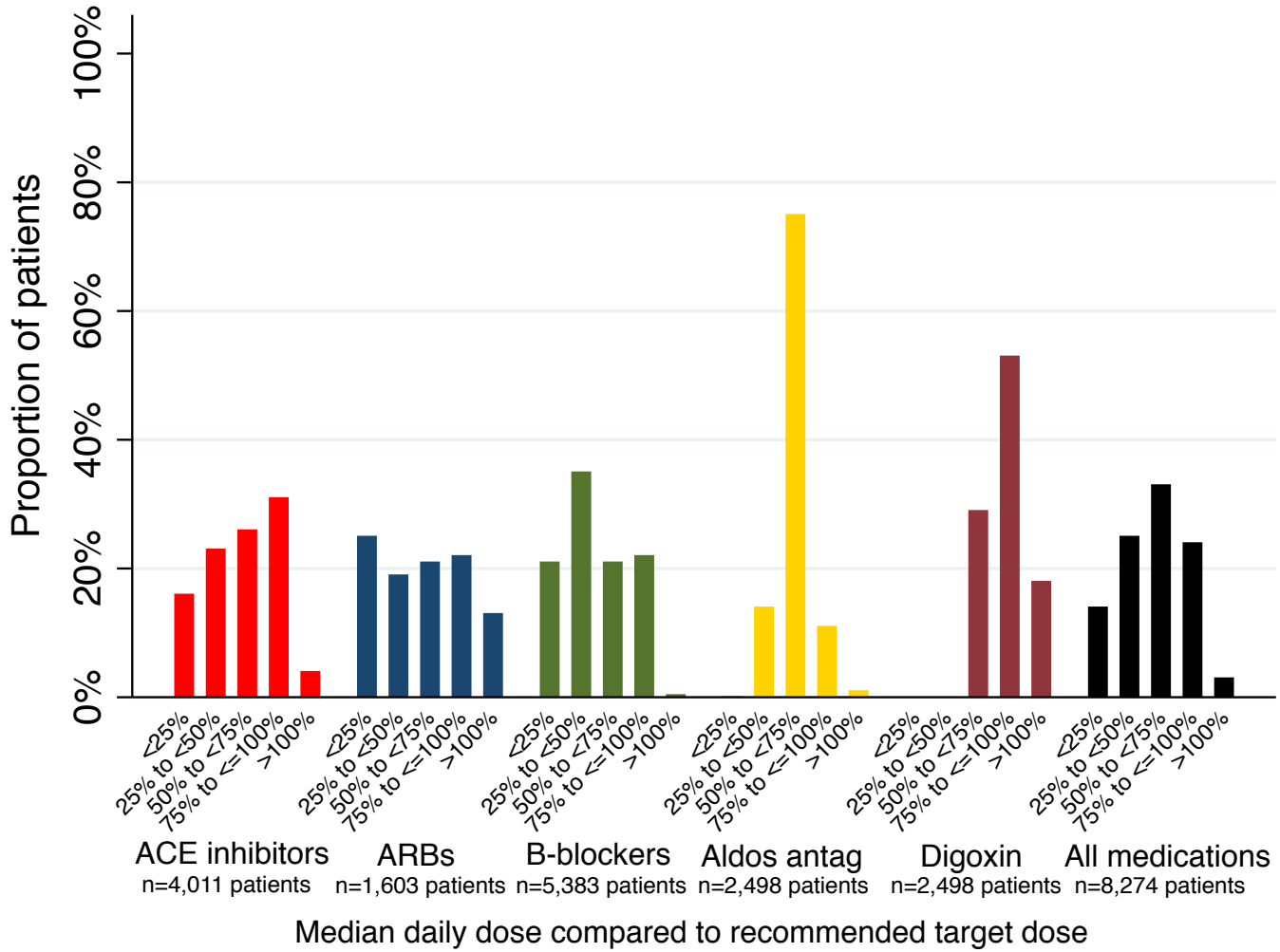
[a]For patients in multiple medication cohorts, characteristics from the earliest cohort entry date were used. [b]Age at cohort entry. [c]Median and interquartile range. [d]Number of months between date of heart failure diagnosis and first cohort entry date. [e]Index of multiple deprivation deciles collapsed into quintiles. [f]Patients with missing smoking status were assumed non-smokers. [g]Mean and standard deviation. Most recent measurement before index date. [h]Mean and standard deviation rounded to nearest whole number. Abbreviations: ACE= angiotensin converting enzyme; HDL= high-density lipoprotein; LDL= low-density lipoprotein; No.=number. Number of patients with missing data: socioeconomic status (n=4); smoking (n=60); total cholesterol(n=544): high-density lipoprotein (n=1,010): low-density lipoprotein(n=1,587).

Table 2. Description of the utilisation and dosing of heart failure medications among patients receiving regular prescriptions

Medication	Patients receiving regular prescriptions[a]	Number of prescriptions	No. of pescriptions per patient[b]	Average daily dose per patient[c]	Guideline target dose[d]	Patients categorised by their average dose			
						<50% of target dose	>=50% to <100% of target dose	100% of target dose	>100% of target dose
ACE Inhibitors	4,011	98,839	16 (6 to 34)	-	-	39% (1,553)	29% (1,160)	28% (1,140)	4% (158)
Captopril	10	220	12 (3 to 42)	50.0 mg (25.0 to 100.0)	150mg	70% (7)	30% (3)	0%	0%
Enalapril maleate	97	1,949	15 (5 to 29)	15.0 mg (5.0 to 20.0)	40mg	51% (49)	43% (42)	6% (6)	0%
Fosinopril sodium	3	75	26 (5 to 44)	40.0 mg (10.0 to 40.0)	40mg	33% (1)	0%	67% (2)	0%
Lisinopril	576	14,439	16 (6 to 33)	10.0 mg (5.0 to 20.0)	35mg	64% (366)	30% (175)	<1% (1)	6% (34)
Perindopril arginine	7	31	5 (2 to 6)	5.0 mg (2.5 to 10.0)	5mg	0%	43% (3)	29% (2)	29% (2)
Perindopril erbumine	521	13,411	18 (6 to 37)	4.0 mg (2.0 to 4.0)	4mg	0%	36% (187)	41% (215)	23% (119)
Quinapril hydrochloride	2	94	47 (11 to 83)	30.0 mg (20.0 to 40.0)	40mg	0%	50% (1)	50% (1)	0%
Ramipril	2,905	68,485	16 (6 to 32)	5.0 mg (2.5 to 10.0)	10mg	41% (1,192)	27% (773)	32% (928)	<1% (12)
Trandolapril	4	135	27 (15 to 53)	3.0 mg (1.5 to 4.0)	4mg	25% (1)	25% (1)	50% (2)	0%
Angiotensin-II receptor blockers	1,603	40,160	17 (7 to 35)	-	-	43% (694)	22% (358)	21% (338)	13% (213)
Candesartan cilexetil	898	22,022	16 (7 to 34)	8.0 mg (4.0 to 16.0)	32mg	69% (621)	19% (173)	12% (104)	0%
Losartan potassium	733	16,540	15 (6 to 31)	50.0 mg (25.0 to 100.0)	50mg	9% (64)	26% (191)	35% (256)	30% (222)
Valsartan	74	1,598	13 (6 to 28)	80.0 mg (40.0 to 160.0)	320mg	72% (53)	27% (20)	1% (1)	0%
Beta-blockers	5,383	143,652	18 (8 to 36)	-	-	56% (3,008)	28% (1,487)	16% (867)	<1% (21)
Bisoprolol fumarate	4,912	128,381	18 (7 to 35)	3.125 mg (2.5 to 5.0)	10mg	56% (2,770)	27% (1,343)	16% (784)	<1% (15)
Carvedilol	393	10,285	17 (6 to 35)	12.5 mg (6.25 to 25.0)	50mg	58% (228)	23% (90)	17% (68)	1% (7)
Nebivolol hydrochloride	212	4,986	16 (5 to 29)	5.0 mg (2.5 to 5.0)	10mg	46% (97)	41% (88)	13% (27)	0%
Aldosterone antagonists	2,498	55,464	14 (6 to 29)	-	-	14% (344)	75% (1,875)	10% (248)	1% (31)
Spironolactone	1,986	40,709	13 (5 to 26)	25.0 mg (25.0 to 25.0)	50mg	16% (317)	74% (1,462)	9% (175)	2% (32)
Eplerenone	626	14,755	15 (7 to 31)	25.0 mg (25.0 to 25.0)	50mg	7% (45)	79% (497)	13% (83)	<1% (1)
Cardiac glycosides	1,424	32,254	16 (6 to 34)	-	-	0%	30% (423)	53% (748)	18% (253)
Digoxin	1,424	32,254	16 (6 to 34)	125.0 mcg (62.5 to 125.0)	125mcg	0%	30% (423)	53% (748)	18% (253)
Overall	8,274	373,369	26 (10 to 58)	-	-	39% (3,215)	37% (3,130)	20% (1,646)	3% (283)

[a]A regular prescription was defined by an initial set of three or more prescriptions within a 90-day period and any subsequent prescriptions of that specific medication. Stoppage of regular prescriptions was defined as 365 days without medication. [b]Median and interquartile range. All prescriptions before treatment stoppage. [c]Median and interquartile range of medians calculated for each patient. [d]Target doses were the maximum target daily dose recommended by the National Institute for Health and Care Excellence Guidelines and the British National Formulary. Did not include the first two prescriptions to allow for initial titration. Abbreviations: no.= number; mg= milligrams; mcg=microgram.

Figure 1. Median daily dose compared to target dosages for patients in each medication group



Abbreviations: ACE= angiotensin converting enzyme inhibitors; ARBs= angiotensin-II receptor blockers; B-blockers= beta-blockers; Aldos antag=aldosterone antagonists

6.5.4 Associations between patient characteristics and medication dosages

Appendices 6.6 to 6.10 show the results of univariate analyses between patient characteristics and dosage. Results from multi-variate logistic regression are presented in Table 3. Ten patient characteristics were associated with dose achievement: age; gender; months since HF diagnosis; number of comorbidities; atrial fibrillation status; chronic kidney disease status; hypertension status; number of concomitant CVD medications; concomitant use of Aldosterone antagonists; and concomitant use of digoxin. The associations varied by medication group.

ACE inhibitors

Patients on ACE inhibitors were more likely to have a median daily dose that was 50% or greater than the target dose if they were male, had comorbid hypertension, and took concomitant Aldosterone antagonists. The odds of achieving that level of dosing declined with increased age and as more time passed since HF diagnosis.

Angiotensin-ll receptor blockers

For patients on Angiotensin-ll receptor blockers, comorbid hypertension was associated with a median daily dose in the higher achievement category.

Beta-blockers

Patients on Beta-blockers were more likely to have a median daily dose in the higher category if they had comorbid atrial fibrillation, comorbid hypertension, took an increased number of concomitant CVD medications, and concomitantly used Digoxin. They were less likely to have that level of dosing if they were older and if more time has passed since their HF diagnosis.

Aldosterone antagonists

Older patients on Aldosterone antagonists were less likely to have median daily dose that was 50% or greater than the target dose.

Digoxin

Patients on Digoxin were less likely to have a median daily dose in the higher achievement category if they were older or had chronic kidney disease. They were more likely to have a median dose in the higher category if they had atrial fibrillation.

Table 3. Results of multi-variate logistic regression of patient characteristics and median achievement of 50% or greater of target dose

	ACE (n=4,011)		ARB (n=1,603)		Beta-blockers (n=5,383)		Aldosterone antagonists (n=2,498)		Digoxin[g] (n=1,424)	
Characteristics	**OR (95% CI)[a]**	**p**	**OR (95% CI)[a]**	**p**	**OR (95% CI)[a]**	**p**	**OR (95% CI)[a]**	**p**	**OR (95% CI)[a]**	**p**
Age	**0.98 (0.97 to 0.98)**	**<0.001**	0.99 (0.98 to 1.00)	0.036	**0.96 (0.96 to 0.97)**	**<0.001**	**0.96 (0.95 to 0.97)**	**<0.001**	**0.96 (0.95 to 0.98)**	**<0.001**
Male[b]	**1.30 (1.12 to 1.51)**	**<0.001**	1.11 (0.89 to 1.38)	0.368	1.08 (0.95 to 1.22)	0.243	1.14 (0.87 to 1.48)	0.347	1.22 (0.93 to 1.60)	0.146
Index of multiple deprivation quintile[c]										
2	0.93 (0.76 to 1.14)	0.458	0.84 (0.62 to 1.13)	0.251	1.02 (0.86 to 1.22)	0.806	0.97 (0.68 to 1.37)	0.852	1.01 (0.70 to 1.45)	0.976
3	1.00 (0.81 to 1.22)	0.974	0.87 (0.63 to 1.18)	0.364	0.98 (0.82 to 1.18)	0.872	0.97 (0.68 to 1.40)	0.881	1.33 (0.91 to 1.95)	0.143
4	0.86 (0.69 to 1.06)	0.161	0.78 (0.56 to 1.07)	0.125	1.05 (0.87 to 1.25)	0.623	1.13 (0.78 to 1.66)	0.517	0.94 (0.63 to 1.38)	0.736
5 (most deprived)	0.92 (0.73 to 1.15)	0.471	0.81 (0.57 to 1.15)	0.235	1.10 (0.91 to 1.33)	0.310	0.92 (0.62 to 1.36)	0.672	0.69 (0.46 to 1.05)	0.083
Months since heart failure diagnosis	**0.99 (0.98 to 0.99)**	**<0.001**	1.00 (0.99 to 1.00)	0.551	**0.99 (0.99 to 0.99)**	**<0.001**	0.99 (0.99 to 1.00)	0.328	1.00 (1.00 to 1.00)	0.929
Smoking[d]	0.97 (0.79 to 1.19)	0.762	0.88 (0.62 to 1.28)	0.528	0.95 (0.80 to 1.13)	0.601	1.27 (0.84 to 1.93)	0.253	1.83 (1.12 to 3.01)	0.017
Cholesterol (mmol/L)	0.98 (0.92 to 1.04)	0.505	1.01 (0.92 to 1.10)	0.879	0.97 (0.92 to 1.03)	0.327	0.91 (0.82 to 1.01)	0.067	1.08 (0.96 to 1.21)	0.222
No. of comorbidities	1.01 (0.95 to 1.07)	0.825	0.98 (0.89 to 1.08)	0.696	**0.92 (0.87 to 0.98)**	**0.009**	0.93 (0.84 to 1.04)	0.189	0.96 (0.86 to 1.07)	0.440
Atrial fibrillation[e]	-	-	-	-	**1.42 (1.22 to 1.65)**	**<0.001**	-	-	**1.99 (1.41 to 2.82)**	**<0.001**
Chronic kidney disease[e]	0.84 (0.71 to 0.98)	0.030	0.90 (0.71 to 1.14)	0.383	1.20 (1.04 to 1.38)	0.014	0.74 (0.56 to 0.98)	0.035	**0.56 (0.42 to 0.74)**	**<0.001**
Coronary heart disease[e]	0.83 (0.70 to 0.97)	0.022	0.99 (0.77 to 1.28)	0.960	0.93 (0.80 to 1.07)	0.321	1.20 (0.91 to 1.60)	0.197	0.94 (0.69 to 1.26)	0.661
Diabetes[e]	0.99 (0.84 to 1.16)	0.864	1.21 (0.94 to 1.55)	0.135	1.15 (1.00 to 1.31)	0.049	0.92 (0.70 to 1.22)	0.578	1.28 (0.95 to 1.73)	0.100
Hypertension[e]	**1.73 (1.47 to 2.03)**	**<0.001**	**1.80 (1.41 to 2.30)**	**<0.001**	**1.33 (1.15 to 1.54)**	**<0.001**	1.16 (0.87 to 1.55)	0.318	-	-
No. of concomitant CVD medications	1.04 (0.98 to 1.11)	0.164	0.97 (0.88 to 1.06)	0.479	**1.12 (1.07 to 1.16)**	**<0.001**	1.04 (0.94 to 1.15)	0.446	0.96 (0.86 to 1.07)	0.440
ACE inhibitors[f]	-	-	0.81 (0.59 to 1.14)	0.238	0.89 (0.72 to 1.11)	0.310	0.97 (0.57 to 1.64)	0.906	1.00 (0.62 to 1.61)	0.986
ARB[f]	0.81 (0.68 to 0.97)	0.020	-	-	0.85 (0.74 to 0.97)	0.015	1.18 (0.90 to 1.56)	0.226	0.81 (0.60 to 1.08)	0.147
Amiodarone[f]	-	-	-	-	-	-	-	-	0.70 (0.51 to 0.96)	0.026
Beta-blockers[f]	1.03 (0.87 to 1.21)	0.767	1.00 (0.79 to 1.28)	0.987	-	-	1.19 (0.91 to 1.55)	0.216	0.95 (0.71 to 1.29)	0.758
Aldosterone antagonists[f]	**1.24 (1.05 to 1.45)**	**0.009**	0.75 (0.59 to 0.97)	0.025	0.99 (0.87 to 1.14)	0.992	-	-	0.77 (0.58 to 1.03)	0.082
Digoxin[f]	0.90 (0.75 to 1.07)	0.235	0.98 (0.75 to 1.28)	0.525	**1.25 (1.07 to 1.46)**	**0.005**	0.88 (0.67 to 1.16)	0.357	-	-
Diuretics[f]	1.03 (0.81 to 1.30)	0.814	1.26 (0.85 to 1.86)	0.251	1.14 (0.92 to 1.40)	0.223	-	-	-	-

[a]Outcome was median achievement of 50% or greater of target dose. Statistically significant associations are bolded. [b]Reference group was female. [c]Reference group was least deprived. [d]Reference group was non-smokers. [e]Reference group was no disease. [f]Reference group was non-users of the medication. [g]No patients had a cumulative median of less than 50% therefore the outcome for Digoxin users was achievement of 75% or greater of target dose. Abbreviations: ACE= angiotensin converting enzyme inhibitors; ARB= angiotensin-II receptor blockers; OR= odds ratios; No.= number; p= probability value. Hosmer and Lemeshow's model fit values were: ACE p=0.327; ARB p=0.351; Beta-Blockers p=0.419; Aldosterone antagonists p=0.432; Digoxin p=0.341.

6.5.5 Description of medication interruptions

Interruptions in medication coverage were highly prevalent. Details of medication interruptions are presented in Table 4. Patterns in medication interruptions were similar across all medication groups. Overall, 82% (n=6,785) of patients experienced an interruption in medication coverage (seven days or longer) during the observation period. The median length per episode of a treatment interruption was 16 days (IQR 8 to 31), indicating that the majority of interruptions lasted less than one month. However, a considerable proportion of patients experienced very long gaps in coverage. Twenty percent (n=1,665) of patients experienced gaps of 180 to 364 days without medication, then resumed prescription coverage. Fifteen percent of patients (n=1,271) had interruptions of 365 days or longer, which were defined as medication stoppage in this study. Only 7% (n=95/1,271) of these patients received another prescription after their 365-day gap. Despite the high prevalence of interruptions, the overall proportion of days with pill coverage was fairly high (median= 89%, IQR 72% to 97%).

6.5.6 Associations between patient characteristics and medication interruptions of 90 days or longer

Appendices 6.6 to 6.10 show the results of univariate analyses between patient characteristics and time to first interruption of 90 days or longer. Results from multi-variate cox proportional hazards regression are presented in Table 5. Five patient characteristics were significantly associated with time to first interruption of 90 days or longer. The associations varied by medication group.

ACE inhibitors

For patients on ACE inhibitors, a greater period of time since HF diagnosis and concomitant use of Angiotensin-ll receptor blockers were associated with an increased risk of medication interruption of 90 days or longer, while concomitant use of Beta-blockers was associated with a reduction in risk.

Angiotensin-ll receptor blockers

Comorbid chronic kidney disease was associated with an increased risk of medication interruption of 90 days or longer among patient on Angiotensin-ll receptor blocker.

Beta-blockers

For patients on Beta-blockers, a greater period of time since HF diagnosis was associated with an increased risk of medication interruption of 90 days or longer.

Aldosterone antagonists

For patients on Aldosterone antagonists, increasing age was associated an increased risk of medication interruption of 90 days or longer, while comorbid coronary heart disease was associated with a reduced risk.

Digoxin

For patients on Digoxin, increasing age was associated with a reduce risk of medication interruption of 90 days or longer.

6.5.7 Associations between patient characteristics and medication interruptions of seven days or longer (sensitivity analysis)

Results of the sensitivity analysis examining associations between patient characteristics and time to first interruption of seven days or longer are shown in Appendix 6.11. Six patient characteristics were associated with time to first interruption of seven days or longer: deprivation; months since heart failure diagnosis; cholesterol; number of comorbidities; number of concomitant medications; concomitant use of Angiotensin-II receptor blockers; and concomitant use of Beta-blockers. These results differed from the main analyses.

ACE inhibitors

Similar to the main analysis of 90-day interruptions, a greater period of time since HF diagnosis and concomitant use of Angiotensin-II receptor blockers were associated with an increased risk of medication interruptions of seven days or longer however, the sensitivity analysis also showed that higher cholesterol and concomitant use of Aldosterone antagonists were associated with increased risk of interruptions. These did not appear in the main analysis. Furthermore, unlike the main analysis, concomitant use of Beta-blockers was not associated with medication interruptions of seven days or longer.

Angiotensin-II receptor blockers

No significant associations were found.

Beta-blockers

In sensitivity analysis, a greater period of time since HF diagnosis was no longer associated with an increased risk of medication interruption. However, two other relevant factors emerged: cholesterol and deprivation. Higher cholesterol was associated with an increased risk of medication interruption and the highest level of deprivation was associated with a reduced risk of interruption (compared to patients at the lowest level of deprivation).

Aldosterone antagonists

Number of comorbidities was associated with an increased risk of medication interruptions of seven days or longer. Unlike the main analysis, age and coronary heart disease were not significant.

Digoxin

For patients on Digoxin, an increased number of concomitant medications was associated with a higher risk of medication interruptions of seven days or longer. Unlike the main analysis, age was not associated with medication interruptions.

Table 4. Description of interruptions in heart failure medication coverage

	Overall[a] (n=8,274)	Patients by medication cohort				
		ACE Inhibitors (n=4,011)	Angiotensin-II receptor blockers (n=1,603)	Beta-blockers (n=5,383)	Aldosterone antagonists (n=2,498)	Digoxin (n=1,424)
Days of observation	638 (304 to 1,064)[b]	638 (304 to 1,125)	669 (365 to 1,155)	638 (334 to 1,155)	547 (274 to 973)	578 (304 to 973)
Interruptions in treatment[c]						
>= 7 days	82% (6,778)	80% (3,190)	78% (1,256)	76% (4,106)	76% (1,900)	77% (1,092)
>=30 days	51% (4,190)	45% (1,817)	40% (645)	36% (1,919)	44% (1,107)	36% (518)
>=90 days	29% (2,417)	24% (967)	22% (346)	16% (880)	24% (598)	20% (281)
>=180 days	20% (1,665)	16% (655)	15% (234)	10% (542)	16% (400)	13% (188)
Medication stoppage (>=365 days)	15% (1,271)	11% (448)[g]	10% (165)[g]	7% (398)	12% (299)	11% (160)
Restarted therapy after >=365 days without medication	7% (95/1,271)	6% (25/448)	10% (16/165)	7% (29/398)	4% (12/299)	9% (15/160)
Length per episode of a treatment interruption[d]	16 days (9 to 31)[e]	17 days (10 to 33)	15 days (9 to 30)	15 days (9 to 28)	18 days (10 to 37)	15 days (9 to 29)
Proportion of treatment days with pill coverage[d]	89% (72% to 97%)[f]	90% (62% to 98%)	92% (69% to 98%)	93% (78% to 99%)	89% (61% to 98%)	92% (65% to 98%)

[a]Some patients were on multiple concurrent or partially overlapping medication regimes. The events in this column apply to one or more medications that a patient was taking, unless otherwise specified. For example, overall, 82% (n=6,778) of patients experienced a gap of 7 days or longer for one or more of the medications they were taking. [b]Median and interquartile range of the median amount of time observed for each medication a patient was taking. [c]Does not include patients that experienced an interruption in prescriptions of 365-days or longer. Patients experiencing these interruptions resumed treatment within 365 days of the interruption start date. [d]Median and interquartile range. [e]Median and interquartile range of interruptions across all medications. [f]Median and interquartile range of the percentage of days with coverage for all relevant medications. Coverage for each medication was considered separately. The denominator was the total number of days within the treatment window for each medication. The numerator was the total number of days covered with pills from primary care prescriptions. [g]This did not include patients that ended treatment in order to switch first line therapies from ACE to ARB or vice versa. 202 patients switched from ACE inhibitors to ARBs and 15 patients switched from ARBs to ACE inhibitors.

Table 5. Results of multi-variate logistic regression of patient characteristics and time to first treatment interruption of 90 days or longer

	ACE Patient years= 7,450 No. events= 1,222		**ARB** Patient years= 3,101 No. events= 433		**Beta-blockers** Patient years= 10,560 No. events= 1,137		**Aldosterone antagonists** Patient years= 4,028 No. events= 735		**Digoxin** Patient years= 2,449 No. events= 1,424	
Characteristics	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**
Age	1.00 (0.99 to 1.01)	0.113	1.00 (0.99 to 1.01)	0.416	0.99 (0.99 to 1.00)	0.908	**1.02 (1.01 to 1.03)**	**<0.001**	**0.98 (0.97 to 0.99)**	**<0.001**
Male[b]	0.85 (0.75 to 0.97)	0.012	0.87 (0.70 to 1.107)	0.178	0.96 (0.84 to 1.09)	0.523	0.94 (0.80 to 1.11)	0.475	0.93 (0.73 to 1.18)	0.539
IMD quintile[c]										
2	1.05 (0.88 to 1.26)	0.561	1.02 (0.77 to 1.35)	0.898	0.98 (0.81 to 1.17)	0.789	1.23 (0.98 to. 1.54)	0.071	1.10 (0.81 to 1.49)	0.535
3	1.00 (0.84 to 1.20)	0.979	0.81 (0.60 to 1.11)	0.188	1.04 (0.86 to 1.25)	0.710	1.13 (0.89 to 1.43)	0.307	1.03 (0.75 to 1.41)	0.860
4	1.23 (1.02 to 1.48)	0.026	1.10 (0.81 to 1.50)	0.522	1.09 (0.90 to 1.31)	0.386	0.99 (0.78 to 1.26)	0.944	0.96 (0.70 to 1.33)	0.823
5 (most deprived)	1.12 (0.92 to 1.37)	0.258	0.88 (0.63 to 1.2)	0.442	0.94 (0.77 to 1.15)	0.575	1.11 (0.86 to 1.43)	0.431	1.00 (0.70 to 1.44)	0.979
Months since heart failure diagnosis	**1.005 (1.003 to 1.007)[h]**	**<0.001**	1.00 (0.99 to 1.00)	0.444	**1.002 (1.001 to 1.005)[h]**	**0.009**	1.00 (0.99 to 1.00)	0.034	0.99 (0.99 to 1.00)	0.262
Smoking[d]	0.92 (0.77 to 1.09)	0.341	1.29 (0.92 to 1.82)	0.140	1.01 (0.84 to 1.21)	0.924	1.21 (0.96 to 1.51)	0.108	0.83 (0.57 to 1.21)	0.336
Cholesterol (mmol/L)	1.03 (0.97 to 1.08)	0.311	0.99 (0.91 to 1.00)[g]	0.093	1.04 (0.99 to 1.10)	0.144	1.00 (0.93 to 1.07)	0.902	1.05 (0.96 to 1.15)	0.266
No. of comorbidities	1.05 (0.99 to 1.11)	0.073	1.01 (0.93 to 1.10)	0.745	1.07 (1.00 to 1.13)	0.036	0.99 (0.99 to 1.00)[g]	0.265	1.06 (0.96 to 1.16)	0.266
Atrial fibrillation[e]	-	-	-	-	0.94 (0.81 to 1.11)	0.471	-	-	1.23 (0.88 to 1.73)	0.229
Chronic kidney disease[e]	1.03 (0.90 to 1.18)	0.677	**1.0004 (1.0001 to 1.0007)[g,h]**	**0.004**	0.85 (0.74 to 0.98)	0.028	1.22 (1.04 to 1.44)	0.017	1.19 (0.93 to 1.53)	0.163
Coronary heart disease[e]	0.95 (0.83 to 1.09)	0.491	0.86 (0.68 to 1.09)	0.208	0.85 (0.73 to 0.98)	0.031	**0.79 (0.66 to 0.94)**	**0.009**	0.75 (0.58 to 0.98)	0.032
Diabetes[e]	0.90 (0.77 to 1.03)	0.120	1.08 (0.86 to 1.35)	0.516	0.93 (0.80 to 1.07)	0.289	1.00 (0.99 to 1.00)[g]	0.208	0.78 (0.61 to 0.99)	0.048
Hypertension[e]	0.88 (0.77 to 1.02)	0.087	0.78 (0.62 to 0.97)	0.028	0.87 (0.75 to 1.01)	0.064	1.24 (1.04 to 1.47)	0.017	-	-
No. of concomitant CVD medications	1.06 (1.00 to 1.12)	0.019	1.07 (0.98 to 1.16)	0.133	1.05 (1.00 to 1.10)	0.046	1.07 (1.01 to 1.14)	0.024	1.00 (1.00 to 1.00)[g]	0.036
ACE inhibitors[f]	-	-	1.18 (0.84 to 1.67)	0.332	0.83 (0.67 to 1.03)	0.095	0.99 (0.99 to 1.00)[g]	0.422	1.06 (0.69 to 1.63)	0.783
ARB[f]	**1.0003 (1.0001 to 1.0005)[g,h]**	**0.006**	-	-	1.10 (0.96 to 1.26)	0.167	1.05 (0.87 to 1.24)	0.574	1.00 (0.79 to 1.27)	0.973
Amiodarone[f]	-	-	-	-	-	-	-	-	1.00 (1.00 to 1.00)[g]	0.034
Beta-blockers[f]	**0.82 (0.71 to 0.94)**	**0.006**	1.07 (0.85 to 1.35)	0.542	-	-	0.90 (0.75 to 1.07)	0.227	0.86 (0.69 to 1.09)	0.211
Aldosterone antagonists[f]	1.11 (0.97 to 1.27)	0.144	0.97 (0.77 to 1.23)	0.802	0.99 (0.86 to 1.13)	0.871	-	-	1.13 (0.90 to 1.42)	0.305
Digoxin[f]	0.90 (0.78 to 1.05)	0.174	0.99 (0.77 to 1.28)	0.939	1.07 (0.91 to 1.25)	0.425	1.07 (0.89 to 1.27)	0.477	-	-
Diuretics[f]	0.95 (0.77 to 1.18)	0.667	0.94 (0.64 to 1.41)	0.779	1.00 (0.99 to 1.00)[g,h]	0.269	-	-	-	-

[a]Outcome was time to first treatment interruption of 90 days or longer. Statistically significant associations are bolded. [b]Reference group was female. [c]Index of multiple deprivation. Reference group was least deprived. [d]Reference group was non-smokers. [e]Reference group was no disease. [f]Reference group was non-users of the medication. [g]Entered as a time-varying covariate to meet the proportional hazards assumption. [h]When necessary for interpretation, greater than two decimal places are reported for significant continuous predictors and time-varying co-variates. Abbreviations: ACE= angiotensin converting enzyme inhibitors; ARB= angiotensin-II receptor blockers; HR=hazard ratio; No.= number; p= probability value.

6.5.8 Associations between medication dosage and emergency hospital admissions

Appendices 6.6 to 6.10 show the results of univariate analyses between medication dosage and time to first emergency hospital admission. Results of multi-variate regressions are presented in Table 6 (all-cause) and Table 7 (CVD-related). The time-varying dosing interaction term was eliminated from multi-variate models as it was found to be collinear with the interruption variable. After adjusting for key co-variates, medication dose was significantly associated with emergency hospital admissions in three of the heart failure medication groups while treatment interruptions were associated with admissions in all five medication groups.

ACE inhibitors

Patients with median daily doses of ACE inhibitors greater than or equal to 50% of target dosages had a significantly lower risk of emergency hospital admissions than patients with median doses less than 50% of the target. Patients exposed to the higher doses of ACE inhibitors had an 18% lower risk of all-cause admissions (HR: 0.82, 95% CI 0.74 to 0.90, p<0.001) and a 23% lower risk of CVD-related emergency admissions (HR: 0.77, 95% CI 0.67 to 0.88, p<0.001).

Angiotensin-II receptor blockers

Achievement of 50% or greater of the target dose for Angiotensin-II receptor blockers was not associated with the risk of all-cause or CVD-related emergency hospital admissions.

Beta-blockers

Patients exposed to the higher doses of Beta-blockers had a 15% lower risk of all-cause admissions (HR: 0.85, 95% CI 0.78 to 0.92, p<0.001) and an 18% lower risk of CVD-related emergency admissions (HR: 0.82, 95% CI 0.72 to 0.92, p<0.001).

Aldosterone antagonists

Patients with median daily doses greater than or equal to 50% of the target dose for Aldosterone antagonists had a 29% higher risk of all-cause emergency admission (HR: 1.29, 95% CI 1.08 to 1.53, p=0.005) and a 65% higher risk of CVD-related

emergency admission compared to patients on less than 50% of the target dose (HR: 1.65, 95% CI 1.32 to 2.07, p<0.001).

Digoxin

No patients on Digoxin had a median daily dose less than 50% of the target dose. Therefore, a threshold of 75% was used. Analysis using this threshold showed no association between median dose achievement and emergency hospital admissions.

6.5.9 Associations between medication interruptions and emergency hospital admissions

Appendices 6.6 to 6.10 show the results of univariate analyses between medication interruptions of 90 days or longer and time to first emergency hospital admission. Results of multi-variate regression are presented in Table 6 (all-cause) and Table 7 (CVD-related).

Surprisingly, in univariate and multi-variate analyses, patients were at significantly lower risk of all-cause and CVD-related hospital admissions during interruptions in medication coverage of 90 days or longer. These findings were the same across all five medication groups. Point estimates for all hazard ratios ranged from 0.03 to 0.17 with all p-values significant at the <0.01, indicating that patients had a reduction of 83% or more in the risk of emergency admission during interruptions of 90 days or longer. Sensitivity analysis similarly showed similar results for interruptions of 7 days or longer.

However, these findings are based on analyses of the time to first admission after starting regular prescriptions with patients censored at the time of first admission. Therefore, the results need to be interpreted with caution. A detailed discussion of these findings can be found in the discussion section of this chapter.

Table 6. Results of multi-variate cox proportional hazards analysis of dosing, treatment interruptions, and time to first all-cause emergency hospital admission

	ACE Patient years= 5,879 No. events= 1,884		**ARB Patient years= 2,408 No. events= 724**		**Beta-blockers Patient years= 8,015 No. events= 2,554**		**Aldosterone antagonists Patient years= 3,195 No. events= 1,218**		**Digoxin Patient years= 1,849 No. events= 779**	
Variables	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**
>=50% of target dose[b]	**0.82 (0.74 to 0.90)**	**<0.001**	0.88 (0.76 to 1.01)	0.079	**0.85 (0.78 to 0.92)**	**<0.001**	**1.29 (1.08 to 1.53)**	**0.005**	-	-
>=75% of target dose[b]	-	-	-	-	-	-	-	-	0.91 (0.77 to 1.07)	0.242
Interruptions >= 90 days[c]	**0.05 (0.02 to 0.13)**	**<0.001**	**0.03 (0.01 to 0.23)**	**<0.001**	**0.04 (0.01 to 0.11)**	**<0.001**	**0.05 (0.02 to 0.15)**	**<0.001**	-[k]	-
Interruptions >= 7 days[c]	**0.07 (0.04 to 0.12)**	**<0.001**	**0.03 (0.01 to 0.11)**	**<0.001**	**0.05 (0.03 to 0.09)**	**<0.001**	**0.08 (0.04 to 0.13)**	**<0.001**	**0.09 (0.04 to 0.18)**	**<0.001**
Age	1.02 (1.01 to 1.02)	<0.001	1.01 (1.00 to 1.02)	0.006	1.02 (1.01 to 1.02)	<0.001	1.02 (1.01 to 1.02)	<0.001	1.0004 (1.0002 to 1.0006)[i,j]	<0.001
Male[d]	0.85 (0.76 to 0.94)	0.901	0.94 (0.80 to 1.10)	0.415	0.97 (0.89 to 1.06)	0.570	0.99 (0.87 to 1.12)	0.847	0.86 (0.74 to 1.01)	0.063
IMD quintile[e]										
2	0.97 (0.84 to 1.12)	0.648	1.04 (0.83 to 1.30)	0.731	1.04 (0.92 to 1.17)	0.537	1.03 (0.86 to 1.23)	0.760	0.97 (0.77 to 1.20)	0.757
3	1.02 (0.89 to 1.18)	0.747	1.06 (0.84 to 1.34)	0.609	1.07 (0.95 to 1.21)	0.263	1.12 (0.93 to 1.35)	0.226	1.19 (0.95 to 1.48)	0.132
4	1.10 (0.95 to 1.27)	0.206	1.01 (0.78 to 1.31)	0.949	1.19 (1.05 to 1.35)	0.006	1.06 (0.88 to 1.27)	0.558	1.14 (0.91 to 1.44)	0.252
5 (most deprived)	1.17 (0.99 to 1.37)	0.056	1.31 (1.02 to 1.67)	0.034	1.27 (1.11 to 1.44)	<0.001	1.32 (1.09 to 1.60)	0.005	1.39 (1.08 to 1.78)	0.009
Months since HF diagnosis	1.00 (0.99 to 1.00)	0.735	0.99 (0.99 to 1.00)	0.189	0.99 (0.99 to 1.00)	0.581	1.00 (0.99 to 1.00	0.733	1.00 (0.99 to 1.00)	0.355
Smoking[f]	1.00 (0.86 to 1.16)	0.985	1.30 (0.99 to 1.69)	0.056	1.07 (0.94 to 1.21)	0.309	1.10 (0.92 to 1.31)	0.320	0.85 (0.64 to 1.12)	0.242
Cholesterol (mmol/L)	0.98 (0.94 to 1.02)	0.442	0.99 (0.92 to 1.07)	0.860	0.99 (0.95 to 1.03)	0.528	1.02 (0.97 to 1.07)	0.563	0.95 (0.89 to 1.02)	0.198
No. of comorbidities	1.20 (1.15 to 1.25)	<0.001	1.16 (1.09 to 1.24)	<0.001	1.22 (1.18 to 1.27)	<0.001	1.17 (1.11 to 1.24)	<0.001	1.19 (1.12 to 1.27)	<0.001
Atrial fibrillation[g]	-	-	-	-	0.86 (0.78 to 0.95)	0.004	-	-	0.77 (0.61 to 0.97)	0.029
Chronic kidney disease[g]	0.89 (0.80 to 0.99)	0.032	0.95 (0.80 to 1.13)	0.561	0.94 (0.85 to 1.03)	0.158	0.92 (0.80 to 1.05)	0.205	0.88 (0.75 to 1.04)	0.143
Coronary heart disease[g]	0.98 (0.88 to 1.10)	0.775	0.97 (0.81 to 1.17)	0.761	0.97 (0.88 to 1.07)	0.573	0.82 (0.71 to 0.94)	0.005	0.93 (0.77 to 1.11)	0.413
Diabetes[g]	0.96 (0.86 to 1.07)	0.446	1.00 (0.85 to 1.19)	0.987	0.93 (0.85 to 1.02)	0.134	0.98 (0.86 to 1.11)	0.735	0.87 (0.74 to 1.03)	0.108
Hypertension[g]	0.84 (0.75 to 0.94)	0.003	0.72 (0.60 to 0.86)	<0.001	0.80 (0.73 to 0.89)	<0.001	0.85 (0.74 to 0.97)	0.019	-	-
No. of concomitant CVD medications	1.08 (1.03 to 1.12)	<0.001	1.15 (1.07 to 1.23)	<0.001	1.08 (1.04 to 1.11)	<0.001	1.13 (1.07 to 1.19)	<0.001	1.05 (0.98 to 1.12)	0.205
ACE inhibitors[h]	-	-	0.84 (0.65 to 1.09)	0.196	0.82 (0.70 to 0.96)	0.012	0.88 (0.68 to 1.15)	0.355	0.81 (0.61 to 1.07)	0.152
ARB[h]	1.09 (0.96 to 1.24)	0.138	-	-	0.84 (0.77 to 0.92)	<0.001	0.85 (0.74 to 0.98)	0.021	0.80 (0.67 to 0.96)	0.013
Amiodarone[h]	-	-	-	-	-	-	-	-	1.09 (0.90 to 1.31)	0.385
Beta-blockers[h]	0.91 (0.81 to 1.02)	0.108	0.96 (0.80 to 1.13)	0.599	-	-	0.85 (0.74 to 0.97)	0.016	0.94 (0.78 to 1.12)	0.479
Aldosterone antagonists[h]	1.17 (1.05 to 1.30)	0.004	1.14 (0.95 to 1.36)	0.161	1.07 (0.97 to 1.17)	0.156	-	-	1.25 (1.06 to 1.49)	0.010
Digoxin[h]	0.96 (0.85 to 1.08)	0.482	0.97 (0.80 to 1.18)	0.789	1.08 (0.97 to 1.20)	0.138	1.00 (0.87 to 1.15)	0.991	-	-
Diuretics[h]	1.25 (1.03 to 1.52)	0.026	0.95 (0.66 to 1.36)	0.778	-	-	-	-	-	-

[a]Outcome was time to first all-cause hospital admission. Statistically significant associations for the main exposure variables are bolded. [b]Compared to patients with a median dose <50% of the target dose. For Digoxin, no patients had a median <50% so analysis compared >=75% vs <75%. [c]Main analysis compared patients with interruptions >= 90 days to <90 days or no interruptions while sensitivity analysis examined the 7-day threshold. [d]Reference was female. [e]Index of multiple deprivation. Reference was least deprived. [f]Reference was non-smokers. [g]Reference was no disease. [h]Reference was non-users of the medication. [i]Entered as a continuously time varying co-variate to satisfy the proportionality hazards assumption. [j]When necessary for interpretation, greater than two decimal places were reported. [k]Excluded as no admissions occurred during the interruption period. Abbreviations: ACE= angiotensin converting enzyme inhibitors; ARB= angiotensin-II receptor blockers; CVD=cardiovascular disease; HF=heart failure; HR=hazard ratio; No.= number; p= probability value.

Table 7. Results of multi-variate cox proportional hazards analysis of dosing, treatment interruptions, and time to first CVD emergency hospital admission

	ACE Patient years= 7,402 No. events= 876		**ARB Patient years= 3,014 No. events= 348**		**Beta-blockers Patient years= 10,075 No. events= 1,215**		**Aldosterone antagonists Patient years= 3,996 No. events= 595**		**Digoxin Patient years= 2,378 No. events= 370**	
Variables	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**
>=50% of target dose[b]	**0.77 (0.67 to 0.88)**	**<0.001**	0.82 (0.66 to 1.01)	0.075	**0.82 (0.72 to 0.92)**	**0.001**	**1.65 (1.32 to 2.07)**	**<0.001**	-	-
>=75% of target dose[b]	-	-	-	-	-	-	-	-	0.88 (0.70 to 1.11)	0.284
Interruptions >= 90 days[c]	**0.17 (0.10 to 0.31)**	**<0.001**	**0.05 (0.01 to 0.36)**	**0.003**	**0.13 (0.06 to 0.28)**	**<0.001**	**0.17 (0.08 to 0.33)**	**<0.001**	-[k]	-
Interruptions >= 7 days[c]	**0.19 (0.13 to 0.28)**	**<0.001**	**0.09 (0.03 to 0.24)**	**<0.001**	**0.10 (0.06 to 0.17)**	**<0.001**	**0.13 (0.08 to 0.22)**	**<0.001**	**0.10 (0.04 to 0.24)**	**<0.001**
Age	1.03 (1.02 to 1.03)	<0.001	1.02 (1.00 to 1.03)	0.013	1.02 (1.01 to 1.02)	<0.001	1.01 (1.00 to 1.02)	0.003	1.01 (0.99 to 1.02)	0.108
Male[d]	0.94 (0.81 to 1.10)	0.473	0.99 (0.79 to 1.27)	1.000	1.03 (0.90 to 1.17)	0.713	0.99 (0.81 to 1.20)	0.889	0.78 (0.62 to 0.99)	0.040
IMD quintile[d]										
2	0.93 (0.76 to 1.15)	0.525	1.03 (0.74 to 1.44)	0.840	1.01 (0.85 to 1.21)	0.906	1.12 (0.85 to 1.46)	0.416	0.91 (0.66 to 1.26)	0.585
3	1.00 (0.82 to 1.23)	0.984	1.13 (0.80 to 1.58)	0.489	0.96 (0.80 to 1.15)	0.649	1.19 (0.91 to 1.56)	0.210	1.10 (0.81 to 1.51)	0.535
4	1.08 (0.87 to 1.34)	0.473	1.15 (0.79 to 1.66)	0.464	1.18 (0.98 to 1.41)	0.078	1.08 (0.82 to 1.42)	0.600	1.07 (0.77 to 1.48)	0.677
5 (most deprived)	1.18 (0.94 to 1.49)	0.154	1.21 (0.83 to 1.76)	0.328	1.24 (1.03 to 1.49)	0.026	1.29 (0.97 to 1.72)	0.084	1.43 (0.99 to 2.05)	0.054
Months since HF diagnosis	0.99 (0.99 to 1.00)	0.759	0.99 (0.99 to 1.00)	0.712	0.99 (0.99 to 1.00)	0.356	1.00 (0.99 to 1.00)	0.407	1.00 (0.99 to 1.00)	0.959
Smoking[f]	1.05 (0.86 to 1.30)	0.619	1.67 (1.15 to 2.43)	0.007	1.11 (0.93 to 1.33)	0.243	1.18 (0.92 to 1.51)	0.193	1.06 (0.73 to 1.54)	0.761
Cholesterol (mmol/L)	0.96 (0.90 to 1.03)	0.274	0.93 (0.83 to 1.04)	0.208	0.96 (0.91 to 1.02)	0.173	0.95 (0.88 to 1.03)	0.245	0.91 (0.81 to 1.03)	0.134
No. of comorbidities	1.0002 (1.0001 to 1.0003)[i,j]	<0.001	1.08 (0.98 to 1.19)	0.127	1.16 (1.11 to 1.22)[i]	<0.001	1.11 (1.03 to 1.20)	0.005	1.12 (1.01 to 1.23)	0.020
Atrial fibrillation[g]	-	-	-	-	0.92 (0.79 to 1.06)	0.252	-	-	0.68 (0.50 to 0.92)	0.014
Chronic kidney disease[g]	0.97 (0.84 to 1.12)	0.634	1.06 (0.83 to 1.36)	0.630	1.00 (1.00 to 1.00)[i]	0.041	1.11 (0.92 to 1.35)	0.283	0.97 (0.75 to 1.24)	0.782
Coronary heart disease[g]	1.00 (0.99 to 1.00)[i]	0.722	1.01 (0.78 to 1.32)	0.924	1.10 (0.95 to 1.27)	0.094	1.24 (1.02 to 1.51)	0.034	1.07 (0.82 to 1.40)	0.620
Diabetes[g]	0.99 (0.99 to 1.00)[i]	0.085	1.18 (0.92 to 1.52)	0.192	0.99 (0.99 to 1.00)[i]	0.083	1.08 (0.89 to 1.30)	0.458	0.81 (0.62 to 1.05)	0.105
Hypertension[g]	0.87 (0.74 to 1.03)	0.098	0.72 (0.55 to 0.93)	0.012	0.80 (0.69 to 0.92)	0.002	0.87 (0.71 to 1.06)	0.166	-	-
No. of concomitant CVD medications	1.30 (1.22 to 1.37)	<0.001	1.23 (1.11 to 1.36)	<0.001	1.21 (1.16 to 1.27)	<0.001	1.0002 (1.0001 to 1.0003)[i,j]	<0.001	1.07 (0.97 to 1.17)	0.166
ACE inhibitors[h]	-	-	0.79 (0.54 to 1.15)	0.218	0.70 (0.55 to 0.89)	0.004	0.76 (0.54 to 1.06)	0.106	0.84 (0.53 to 1.31)	0.433
ARB[h]	0.86 (0.72 to 1.03)	0.109	-	-	0.71 (0.62 to 0.81)	<0.001	0.90 (0.75 to 1.08)	0.249	0.90 (0.70 to 1.16)	0.421
Amiodarone[h]	-	-	-	-	-	-	-	-	1.23 (0.94 to 1.60)	0.133
Beta-blockers[h]	0.81 (0.69 to 0.96)	0.014	1.02 (0.79 to 1.31)	0.901	-	-	1.00 (0.83 to 1.19)	0.978	1.00 (1.00 to 1.00)	0.030
Aldosterone antagonists[h]	1.35 (1.14 to 1.60)	<0.001	1.37 (1.04 to 1.81)	0.026	1.20 (1.05 to 1.37)	0.009	-	-	1.63 (1.27 to 2.11)	<0.001
Digoxin[h]	0.89 (0.76 to 1.06)	0.185	0.90 (0.68 to 1.19)	0.459	0.96 (0.83 to 1.12)	0.606	1.30 (1.08 to 1.56)	0.005	-	-
Diuretics[h]	1.12 (0.81 to 1.56)	0.486	0.78 (0.45 to 1.34)	0.370	-	-	-	-	-	-

[a]Outcome was time to first cardiovascular-related emergency hospital admission. Statistically significant associations for the main exposure variables are bolded. [b]Compared to patients with a median dose <50% of the target dose. For Digoxin, no patients had a median <50% so analysis was conducted comparing >=75% vs <75%. [c]Main analysis compared patients with interruptions >= 90 days to <90 days or no interruptions while sensitivity analysis examined the 7-day threshold. [d]Reference was female. [e]Index of multiple deprivation. Reference was least deprived. [f]Reference was non-smokers. [g]Reference was no disease. [h]Reference was non-users of the medication. [i]Entered as a continuously time varying co-variate to satisfy the proportionality hazards assumption. [j]When necessary for interpretation, greater than two decimal places were reported. [k]Excluded as no admissions occurred during the interruption period. Abbreviations: ACE= angiotensin converting enzyme inhibitors; ARB= angiotensin-II receptor blockers; CVD=cardiovascular disease; HF=heart failure; HR=hazard ratio; No.= number; p= probability value.

6.6 Discussion

6.6.1 Summary of findings

This was a national cohort study of medication dosing and interruptions in medication coverage for heart failure patients in UK primary care. The results showed that the majority of patients were on doses of HF medications that were well below guideline-recommended target doses. The results also showed that the majority of patients experienced interruptions in pill coverage. Many of these interruptions were short however, there was a considerable proportion of patients that went long periods without medication. Patient characteristics associated with lower dosing or increased risk of medication interruptions were:

- ACE inhibitor: older age, female, higher cholesterol, longer time since HF diagnosis, normotensive, using Angiotensin-ll receptor blockers, not using Beta-blockers, and not using Aldosterone antagonists
- Angiotensin-ll receptor blockers: normotensive, chronic kidney disease
- Beta-blockers: older age, higher cholesterol, less deprived, longer time since HF diagnosis, normotensive, normal sinus rhythm, taking fewer CVD medications, and not using Digoxin
- Aldosterone antagonists: older age, no coronary heart disease, more comorbidities
- Digoxin: older age, chronic kidney disease, normal sinus rhythm, more concomitant medications

Dosing and medication interruptions were associated with emergency hospital admission rates. Patients with median daily doses greater than or equal to 50% of recommended target doses for ACE inhibitors and Beta-blockers had lower rates of emergency admissions, while patient on Aldosterone antagonists at higher dosing levels had higher rates of admissions. Interruptions in medication were associated with a reduced risk of admissions for all five medication groups.

6.6.2 Findings in the context of existing research

This chapter provides novel contributions to the literature on heart failure management, primary care prescribing, and emergency hospital admissions. To the best of the thesis author's knowledge, this is the first national study of HF medication interruptions in the UK and the most comprehensive study of HF medication dosing in UK primary care. The findings complement national efforts in the UK to track and improve utilisation of heart failure medications and to improve outcomes for heart failure patients. The results add granularity to indicators reported by the Quality and Outcomes Framework (QOF) and British Society for Heart Failure National Audit, neither of which provide information on dosing or medication coverage.[3,7] This chapter showed that, despite improvements in the proportion of patients receiving heart failure medication as demonstrated by QOF and the British Society for Heart Failure, sub-target dosing and interruptions are common for patients receiving medications in the community. These findings suggest that use of HF medications in primary care may be sub-optimal and, therefore, there may be opportunities to reduce rates of emergency hospital admissions through improved utilisation.

Target dosing

Doses of ACE inhibitors, Angiotensin-ll receptor blockers, and Beta-blockers were far below recommended target doses. A "start low and go slow" titration approach is advocated for these medications, often up-titrating every two weeks. However, patients were observed for a median of 2 years and doses were still far below target.

NICE guidelines recommend up-titrating to evidence-based target doses derived from clinical trials or to the maximum tolerable dose in order to obtain maximum clinical benefit.[6] Although intolerance and side effects may limit target dose achievement in some patients, these sub-target doses may represent shortfalls in prescribing. This assertion is supported by findings in this study showing that patients on lower doses of ACE-inhibitors and Beta-blockers were at higher risk for emergency admission, even after adjusting for key co-variates.

Doses for Aldosterone antagonists and Digoxin were closer to established targets. Most patients on Aldosterone antagonists had median doses at or above 50% of the target dose and all patients on Digoxin were above 50%. Patients often receive

these drugs after a period on first line therapies, which is the sequential approach recommended in clinical guidance. Therefore, it is possible that physicians had a better understanding of the patients' physiological tolerances when initiating therapy for these second- and third-line therapies. Input from specialists is also recommended before prescribing these medications in primary care. This might explain the more aggressive dosing compared to first line therapies.

The levels of dosing found in this study match research conducted on real world cohorts of heart failure patients in Europe and Mediterranean countries.[17,22,29] For example, a study of 12,944 patients on the European Society of Cardiology Heart Failure Long-term Registry showed that only 29% of patients received target doses of ACE inhibitors, 24% received target doses of Angiotensin-II receptor blockers, 18% received target doses of Beta-blockers, and 31% received target doses of Aldosterone antagonists.[30] In this chapter, a similar minority of patients were classified at or above target levels: 32% on ACE inhibitors, 34% on Angiotensin-II receptor blockers, 16% on Beta-blockers, and 11% on Aldosterone antagonists.

This chapter builds on a previous study of ACE inhibitors and Beta-blockers in UK primary care. Calvert et al. (2009) examined prescriptions for 9,311 heart failure patients between 2001 and 2006 and found that only 35% of patients on ACE inhibitors and 12% of patients on Beta-blockers received guideline-recommended doses. This chapter updates these results to 2017. Comparing the studies suggests that achievement of target dosing for first line HF therapies has remained fairly static since the early 2000s. This chapter builds on the Calvert et al. study by examining dosing for three additional types of HF medications, all of which showed similarly low levels of target dose achievement.

Previous research has shown that older, sicker patients are less likely to be prescribed target doses of HF medication. The results of this chapter corroborate these findings. The results match previous studies showing that older age, more progressed disease (time since HF diagnosis), more comorbidities, and chronic kidney disease are associated with lower levels of dose achievement for ACE inhibitors, Angiotensin-II receptor blockers, and Beta-blockers, and Digoxin.[29,31,32]

However, there are nuances to these associations as patients with certain comorbidity clusters are more likely to receive higher levels of dosing. Previous research has shown that heart failure patients with comorbid hypertension are more likely to receive target doses of ACE inhibitors and Beta-blockers. This chapter found similar associations, but for all first line therapies (ACE inhibitors, Angiotensin-II receptor blockers, and Beta-blockers). Furthermore, this chapter showed that patients with comorbid atrial fibrillation were more likely to receive higher doses of Beta-blockers and Digoxin. It is possible that physicians make a more concerted effort to up-titrate these patients given their compounding cardiovascular clinical needs. It is also possible that patient and physician thresholds for risk and willingness to tolerate side effects change when facing compounding cardiovascular issues that may be alleviated by more aggressive use of medications that serve to treat multiple conditions.

Unlike previous UK-based research, this study did not observe socioeconomic differences in dose achievement for first line therapies.[6] This may represent an improvement in the equity of heart failure management in UK primary care.

Medication interruptions

In addition to potential shortfalls in dosing, treatment interruptions were highly prevalent. Even after discounting gaps less than seven days and adjusting for medication carry over from the last previous prescription, 82% of all patients experienced at least one interruption in medication coverage. Most interruptions were shorter than 31 days however, 29% (n=2,417) of patients experienced gaps of 90 days or longer.

The frequencies of interruptions found in this study were lower than studies from other countries. The most prominent study in the literature examined 107,000 heart failure patients in Denmark who filled prescriptions for Renin-angiotensin system blockers, Beta-blockers, and Spironolactone (Aldosterone antagonist) after a first HF hospitalisation. The authors found that breaks in therapy were common, with short breaks most prevalent. However, the proportion of patients with interruptions in each category (i.e. 7 days or longer, 30 days or longer, etc) was approximately

10% to 15% higher than in this chapter.[17] The reason for these differences is not clear but the results are encouraging for UK primary care.

There has been little research on predictors of interruptions in HF medication however, the results of this study generally match the available literature. Increasing age, time since HF diagnosis, and concomitant use of Aldosterone antagonists and ACE inhibitors have previously been associated with gaps of 90-days or longer in HF medications.[17] The ability to tolerate side effects in older age and the elevated risk of hyperkalaemia may explain these findings. Concomitant use of Renin-angiotensin system inhibitors and Beta-blockers have also previously been associated with a reduced risk of interruptions.[17] It is possible that patients find that this type of dual therapy highly effective and more vigilantly adhere to the medication regimen. It is also possible that chronic under-dosing for these medications results in fewer side effects and therefore fewer interruptions.

Some of the findings on patient characteristics and interruptions in this chapter were novel in the light of the sparse existing literature. Of note, the results of this chapter showed that concomitant use of ACE inhibitors and ARBs was associated with an increased risk of treatment interruptions. It is important to note that this analysis did not include patients that permanently switched first line therapies from ACE inhibitors to ARBs. It may be the case that some patients on ACE inhibitors attempt to switch to ARBs, perhaps due to side effects, but ultimately return to ACE prescriptions. It is also possible that dual therapy is attempted but results in intolerable side effects and patients revert to monotherapy with ACE.

Also of note, this study also showed that cholesterol was associated with an increased risk of interruption for patients on Beta-blockers and ACE inhibitors. Evidence that certain Beta-blockers may have adverse effects on lipid profiles may explain interruptions for this treatment – clinician may have concerns about dyslipidaemia and request a break in medication use – however, it is unclear why this occurred for patients on ACE inhibitors.[33]

Comparison to randomised controlled trials

The accumulating evidence of low levels of dosing achievement in 'real-world' patients contrast with randomised controlled trials, in which 50% to 60% of patients achieve target doses.[31,34–36] Differences in achievement are likely due to patient selection. Patient in trials are generally younger and have fewer comorbidities than patients observed in cohort studies.[6] Indeed, in this chapter, patients were approximately 10 years older and had a higher prevalence of comorbidities and concomitant medications compared to patients in landmark trials.[31,34–36]

Furthermore, target doses are often not met even among 'real-world' patients that are similar to trial patients. For example, a study applied the inclusion and exclusion criteria from two landmark trials to patients in a European heart failure registry.[37] The study showed that only 5% to 9% of patients would have been eligible for enrolment in the trials and, among patients that met all the eligibility criteria, only 46% achieved target doses of ACE-inhibitors and 6% achieved target doses of beta-blockers. This suggests that patients in trials are not only highly selected, but the sophisticated and robust support available in trials play a role in dosing achievement, including the availability of dedicated staff to track and monitor patients and enact up-titration protocols.

Association of dosing and emergency admissions

The results of this study match other observational studies showing that improved achievement of target dosing in ACE inhibitors and Beta-blockers reduces emergency hospital admissions. Some argue that patients that can tolerate higher doses may be healthier and, as a result, are at lower risk for admission. However, studies reporting these associations, including the current study, adjusted for key co-variates and the signal is fairly consistent across literature.[20] Furthermore, these findings are supported by randomised trial research showing that the beneficial effects of these medications may be dose-dependent.[38–40]

This study found that higher doses of Aldosterone antagonists were associated with an increased risk of all-cause and CVD-related emergency hospital admissions. Furthermore, in many of the medication groups, concomitant Aldosterone antagonists use was associated with an increased risk of emergency admissions. It

is likely that these admissions increases were due to adverse events such as hyperkalaemia, which is a common safety concern when using Aldosterone antagonists. [41,42] Use of Aldosterone antagonists have been previously associated with an increased risk of admissions for hyperkalaemia in 'real-world' patients.[42,43] These findings suggest that the beneficial effects of these drugs are not predicated on achieving a higher doses and, in fact, higher doses may cause harm.[44,45] The results also suggest that 'real-world' patients may be much less resilient to the side effects of Aldosterone antagonist than patients in RCTs.

Higher Digoxin dosing showed no association with emergency admissions in this study. Other observational studies investigating Digoxin dosing in 'real-world' HF patients have similarly shown no impact on important patient outcomes, suggesting that the beneficial effects of this medication are not dependent on dose.

Association of interruptions and emergency admissions

The associations between medications interruptions and hospital admissions were surprising. Heart failure medications have short-term effects that can be influenced by immediate medication use (i.e., reducing fluid retention to avoid acute decompensation) as well as long-term effects (i.e., cardiac remodelling reducing symptoms over time) resulting from chronic medication use.[21,46] Therefore, interruptions of any length have the potential to change the effects of medication in ways that are detrimental to patient outcomes. In this study, however, patients had a significant reduction in the risk of hospital admission during interruptions of seven days or longer and 90 days or longer.

These finding needs to be interpreting with caution. It is unlikely that gaps in medication coverage are beneficial for patients. The safest interpretation is that pill coverage may not be an important factor contributing to a patient's first emergency admission after starting new medication. More research is needed to clarify this finding and determine whether this association is maintained after the first admission.

Few studies have examined associations between interruptions in treatment and hospital admissions as a stand-alone outcome – it is often measured as part of a

composite outcome. However, the available literature conflicts with the findings in this chapter.[47–50] The largest study to date was published in 2018 by Hood et al.. The authors examined 55,000 heart failure patients in the United States and showed that every 10% increase in the proportion of days covered with medication was associated with a 6% reduction in hospital admissions (RR 0.94, 95% CI 0.94 to 0.94).[51] These findings show the opposite of what was observed in this chapter. However, the differences are likely due to methodology. The authors used Poisson regression and considered all admissions during the follow-up period. In this chapter, Cox regression was used to assess time to first admission only. The discrepancy in these findings suggests that the relationship between medication coverage and hospital admissions may change after the first admission. Further research is required to clarify the nature of the relationship between medication interruptions and the timing of emergency hospital admissions.

6.6.3 Strengths

This study had four key strengths.

Firstly, this study used data from a national data set that is representative of the UK population. The patients in the study had similar characteristics to patients in other large observational studies, indicating that the results are likely generalisable.

Secondly, the study was comprehensive. Overall, 383,369 prescriptions for 8,274 patients were analysed. This represents the largest ever UK-based study of heart failure dosing and treatment interruptions.

Thirdly, steps were taken to increase the robustness of the analysis including consideration of medication carried over from previous prescriptions and allowing up to a seven-day gap to occur before classifying patients as having an interruption in treatment. This is a more conservative approach than has been used in some previous research.

Fourthly, the use of time varying co-variates helped to reduce the risk of immortal time bias: a common and serious bias in pharmacoepidemiology.[52,53] The time-

varying variable for medication interruptions ensured that the pre-exposure window (i.e., less than 90 days) was not counted as exposure time, which would have biased the effect estimates.

6.6.4 Limitations

This study had several limitations.

Firstly, information on medication intolerance and patient and provider treatment preferences was not analysed. This would have required analysis of free text data in the CPRD, the reliability of which is unclear, and would have been resource intensive. It is also possible that much of this information is not entered into medical records at all. Therefore, the sub-target doses observed for some patients in this study may not necessarily represent failures to optimise prescribing.

Secondly, estimates of mediation coverage derived from electronic prescription data are an indirect indicator of actual medication adherence. Patients that received prescriptions may not have filled them or may not have taken the medications according to schedule. Conversely, during medication interruptions, patient may have had access to stockpiles of pills from multiples previous prescriptions. Therefore, there may be additional imprecision in the estimates.

Direct measures of adherence are considered superior, including observing medication consumption and measurement of drug metabolites however, these require prospective research, which is resource intensive and often limited to smaller sample sizes.[54]

Thirdly, at the time of analysis, data were only available on the first hospital admission for patients in each medication group. Therefore, when estimating medication interruptions, adjustment could not be made for time in hospital during which patients could not re-fill primary care prescriptions. The 2017 National Heart Failure Audit showed that the median hospital length of stay for heart failure patients was six days on general wards and nine days on cardiology wards.[3] Therefore, use of the seven day threshold for interruption may have reduced the impact of this

limitation. However, the prevalence of treatment interruptions may be overestimated.

Fourthly, the analysis of interruptions and emergency admissions may have limited utility. The results suggest that pill coverage may not be an important risk factor for the first emergency admission after initiating a new medication. However, heart failure patients experience many admissions and the associations demonstrated in this study are unlikely to persist beyond the first admission. Analysis of repeated admissions is needed. The thesis author will be obtaining additional admissions data from CPRD to complete this analysis. This data will also be used to re-estimate treatment interruptions after adjusting for in-hospital time.

Fifthly, the analysis did not consider interruption of multiple drug therapy. For example, if a patient was given both an ACE and a Beta-blocker, interruptions in coverage for one of the medications may be considered an interruption of the overall regimen. More complex multi-drug analysis may provide greater insights into the nature of medication coverage and its association with patient outcomes.

Sixthly, there were a large number of statistical tests used in this study which increased the risk of type 1 error. To guard against this risk a stricter p-value threshold of <0.01 and robust standard errors were used. However, these may be insufficient safeguards against type 1 errors in the presence of many comparisons and use of the Bonferroni correction may have been more appropriate.

Seventhly, this was an observational study and it is possible that residual confounding may be present despite efforts to control for key confounding factors. While observational data may be used to build a case for inferring causality, only the randomised controlled trial design is capable of providing high-quality evidence of casual relationships.

Finally, this study relied on accurate data input and transfer from primary practices to the CPRD. However, CPRD routinely evaluates record accuracy and only research quality data was used.

6.6.5 Implications for policy and practice

Greater efforts to optimise the use of heart failure medication in UK primary care may help to reduce emergency hospital admissions. Attainment of target doses may help to realise the full benefits of ACE inhibitors and Beta-blockers for reducing emergency admissions. Conversely, more cautious dosing may be required to reduce hospital admissions for patients on Aldosterone antagonists. Efforts to reduce the occurrence of interruptions in medication coverage are also warranted given the poor outcomes associated with non-adherence as demonstrated in other studies.[47–50]

There are effective evidence-based interventions for improving achievement of target dosing and medication adherence in HF patients.[29,39,55] The systematic review in Chapter 3 of this thesis identified evidence-based interventions that may be of use. For example, nurse-led titration of ACE inhibitors, Angiotensin-ll receptor blockers, and Beta-blockers was shown to improve target dose achievement and reduced rates of emergency admissions compared to traditional physician-led care. Incorporation of this, and other, evidence-based interventions into routine practice should be explored. A variety of patient characteristics were associated with medication dosing and interruptions in this chapter. These may be used to guide these quality improvement efforts.

Policy makers may consider adding target dose achievement indicators for ACE inhibitors and Beta-blockers to national quality improvement frameworks and audits, such as the Quality and Outcomes Framework and British Society for Heart Failure National Audit. Measuring achievement may be challenging given the requirement to document exemptions due to intolerance. However, it would place this important issue at the forefront of general practice heart failure management.

6.6.6 Future research

The findings of this study highlight several areas of valuable future research.

Firstly, future research should examine the proportion of patients in UK primary care on sub-target doses due to intolerances. This would help to identify the proportion of justified under-dosing and aid in the setting of quality improvement goals.

Secondly, additional research is needed to clarify the association between treatment interruptions and emergency hospital admissions. In this study, the analysis focused on time to first hospital admission after patients initiated a new HF medication. However, given the frequent rate of emergency admissions among HF patients, analysis of multiple admissions is needed. This research will be addressed as part of the SPCR grant which funded this project and will be carried out by the thesis author after additional data extraction from the CPRD.

Thirdly, qualitative research should explore why HF patients experience treatment interruptions. The reasons for this may not be fully understood from analysis of routinely collected data. Patients may not receive prescriptions for various reasons related to the patient, the prescriber, or the healthcare system: they may choose to break from treatment due to physiological intolerance and side effects; they may receive conflicting advice from general practitioners, cardiologists, and heart failure nurses; they may have limited access to health care, owing to geography or cost; or repeat prescriptions may not be requested or issued. These issues may be best explored using interview, focus group, or survey methodology.

Fourthly, pragmatic trials may be needed to get more realistic estimates of target doses for real-world heart failure patients. Estimates of under-dosing are widespread however, there is accumulating evidence that patients in practice are different than patients in trials. The evidence that informs practice should be based on representative populations of patients. In the case of heart failure, trials ought to include patients that are older, with more comorbidities and concomitant medications.

Fifthly, consensus on methodological approaches in pharmacoepidemiology of electronic health records is needed. There are many methods of measuring target dose achievement and gaps in medication coverage including the last prescribed dose, cumulative average dose, moving average dose, maximum dose achieved, frequency of medication interruption, medication possession ratio, proportion of days with pill coverage, etc.[54,56,57] In the current study, decisions were informed by previous heart failure literature and input from content and methods experts. However, there is a large literature comparing different methodological approaches

and there appears to be no consensus on ideal methods. A consensus processes featuring the best available evidence curated by experts may aid in future pharmacoepidemiologic research of routinely collected data and increase the comparability of studies.

6.7 Conclusions

This chapter provides evidence of potential failures to optimise use of heart failure medications in UK primary care. The study showed that majority of heart failure patients experienced gaps in coverage from their primary care prescriptions and average doses were well below recommended target doses. A variety of patient characteristics were associated with these aspects of medication utilisation and these may be used to guide quality improvement efforts.

This study also showed that increased doses of first line therapies in 'real-world' HF patients were associated with reduced emergency hospital admission rates. Therefore, in order to reduce emergency admissions for HF patients in the UK, clinicians and policy makers should focus on up-titrating ACE inhibitors and Beta-blockers to guideline-recommended target doses. Conversely, higher doses of Aldosterone antagonists were associated with an increase in the risk of emergency admissions. Therefore, stakeholders should consider more careful dosing and monitoring for patients on this medication to avoid hospitalisation from adverse events.

Further investigation is needed to explore reasons for sub-target dosing and frequent medication interruptions. Additional research is also needed to clarify the relationship between interruptions in medication coverage and hospital admissions.

6.8 Chapter summary

- This was a national cohort study of heart failure medication dosing and interruptions in UK primary care
- Data for 8,274 patients and 383,369 prescriptions were analysed
- Average doses of medications were well below recommended target doses
- Interruptions in medication coverage were common
- A variety of patient characteristics were associated with medication dosing and interruptions
- Higher doses of ACE-inhibitors and Beta-blockers were associated with a reduced risk of all-cause and cardiovascular-related emergency admissions
- Primary care stakeholders should focus on achieving target doses of first line therapies and more careful dosing and monitoring of Aldosterone antagonists in order to reduce rates of emergency hospital admissions for heart failure patients in the UK
- Reasons for sub-target dosing and medication interruptions need to be explored
- The association between interruptions in medication coverage and hospital admissions requires further investigation

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Chapter 6. Appendix

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Appendix 6.1 School for Primary Care Research grant application

SPCR Funding Round 9 – Application Form 2015

PLEASE ENSURE that you submit both this Word document and the Excel spreadsheet detailing the project costs. You should name the documents with the following file name structure: PI name_FR9

Project title: The Association Between Evidence-Based Medication Use And Unplanned Hospital Admissions: A National Observational Study in Primary Care.
Project short name: Evidence-Based Medication Use and Unplanned Hospital Admissions.

SECTION A - Details of Co-Principal Investigator

Title: Mr.
Surname: Niklas
Forename: Bobrovitz
Lead university: University of Oxford
Address: Nuffield Department of Primary Care Health Sciences University of Oxford Radcliffe Observatory Quarter Woodstock Road Oxford, OX2 6GG Tel: +44 (0) 1865617861 Fax: +44 (0)1865 289290
Email: niklas.bobrovitz@phc.ox.ac.uk
Contribution (role and fte on project): Co-principal investigator (16 hour/week DPhil).

Details of Co-Principal Investigator

Title: Dr.
Surname: Kamal
Forename: Mahtani
Lead university: University of Oxford
Address: Nuffield Department of Primary Care Health Sciences University of Oxford Radcliffe Observatory Quarter Woodstock Road Oxford, OX2 6GG
Email: kamal.mahtani@phc.ox.ac.uk
Contribution (role and fte on project): Co-principal investigator (1% FTE).

Details of Joint Applicant (s) (copy box as required)

Title: Professor
Surname: Heneghan
Forename: Carl
University: University of Oxford
Email: carl.heneghan@phc.ox.ac.uk
Contribution (role and fte on project): Senior advisor (1% FTE).

Title: Ms.

Surname: Stevens
Forename: Sarah
University: University of Oxford
Email: sarah.stevens@gtc.ox.ac.uk
Contribution (role and fte on project): CPRD specialist and statistician (5% FTE).

Title: Dr.
Surname: Shinkins
Forename: Bethany
University: University of Oxford
Email: bethany.shinkins@phc.ox.ac.uk
Contribution (role and fte on project): Senior statistical advisor (3% FTE).

Details of Collaborator (s) (copy box as required)
A collaborator is a person employed outside of the SPCR partner departments and cannot receive any SPCR funds

Title: Dr.
Surname: Kearley
Forename: Karen
Address**:** Jericho Health Centre, **New Radcliffe House, Walton Street, Oxford, OX2 6NW**
Email: karen.kearley@phc.ox.ac.uk
Contribution (role): Facilitator of patient and public involvement; act in her role as a GP commissioner in Oxfordshire to disseminate study results.

Title: Ms.
Surname: Cook
Forename: Jennifer
Address**:**
Email: jen.io.cook@gmail.com
Contribution (role): Patient advisor.

Study Team Expertise:

The team has expertise in managing and analysing large databases. They have conducted analysis for 15 projects using the Clinical Practice Research Datalink and 5 projects using the Hospital Episode Statistics database. The General Practitioner applicants are experts in evidence-based medicine and have 24 years of clinical experience. One GP co-applicant is an expert in managing non-communicable diseases in primary care.

SECTION B – Plain English Summary

The UK has experienced a 47% increase in unplanned hospital admissions over the last 15 years that has seriously strained the healthcare system. In 2012-2013 there were 5.3 million unplanned hospital admissions representing 67% of hospital bed days in England and costing approximately £12.5 billion. This represents a huge problem that is unsustainable and needs to change. As a result, admission reductions are a priority of the National Health Service.

Unplanned hospital admissions are unpredictable and occur at short notice because of a perceived need for immediate health care. Primary care physicians- as the gate keepers of patient care- have a crucial role to help reduce unplanned admissions. Research shows that some primary care practices are more successful than others in controlling rates of hospital admissions among their patients but the reasons for this are unclear. Studies attempting to identify the keys to success have found few conclusive results. However, one of the most fundamental components of effective primary care has not been assessed; the use of evidence-based medications. There is wide variation in primary care prescribing practices, including both under- and over-utilization of medications. These variations may explain why some physicians more successfully manage hospitalisation rates among their patients compared to others.
Therefore, the objective of this study is to assess the association between evidence-based medication use in primary care and unplanned hospital admissions. We will use national databases with primary care and hospital data for all patients registered with a primary care practice in England from 2011-2014. Our multidisciplinary team includes experts in evidence-based medicine, general practitioners, and researchers with expertise in analysing large databases. Ethics approval is not required as we will use anonymous data.
This project will help to determine the extent to which improving prescribing practices in primary care could reduce hospital admissions in England. The project will lead to future research and policy recommendations to improve primary care and to help resolve the hospital admissions crisis.

SECTION C – Expert Summary

The UK has experienced a 47% increase in unplanned hospital admission over the last 15 years that has seriously strained the healthcare system. In 2012-2013 there were 5.3 million unplanned hospital admissions representing 67% of hospital bed days in England and costing approximately £12.5 billion. This represents a huge problem that is unsustainable and needs to change. As a result, admission reductions are a priority of the National Health Service.

Unplanned hospital admissions are unpredictable and occur at short notice because of a perceived need for immediate health care. There is large variation in unplanned admission rates across the UK. Social deprivation and non-modifiable population factors (e.g., age) account for a large portion of the variation however, a substantial amount may be due to factors within the control of primary care physicians and managers. Studies have consistently found that access to care and continuity of care impact admission rates. However, the use of evidence-based medications, a core component of effective primary care practice, has not been well-studied. Evidence shows there is wide variation in primary care prescribing practices, including under- and over-utilization of medications, but the impact of those variations on unplanned admissions is unclear.

Therefore, the objective of our study is to assess the association between evidence-based medication use in primary care and unplanned hospital admissions. We will examine 10 medications that have been shown in randomized clinical trials to reduce unplanned admissions. We will obtain primary care and hospital data for all people registered with a primary care practice in England from 2011- 2014. We will use multi-level modelling to explore the association between the prescription of each medication to eligible patients and unplanned hospital admissions. Our multidisciplinary team includes experts in evidence-based medicine, general practitioners, and statisticians with expertise in analysing large databases. Ethics approval is not required as we will use anonymous data.

This project will help to determine the extent to which evidence-based medication use impacts hospital admissions in England. To our knowledge, this will be the largest ever analysis of this type. The results could be used to guide local optimization of prescribing. Nationally, the results

could inform new clinical indicators for medications as part of the Quality and Outcomes Framework.

SECTION D – Project overview

Start Date: **01/10/2015**	
End Date: **30/09/2016**	
Duration (months):12 (Gant Chart in Appendix 1).	
Total SPCR budget: **£33 442** (Full costing breakdown in Appendix 3- attached).	
SPCR Theme*	**Acute Care**
To which health category in the UK Health Research Classification System** would this project belong?	**Generic Health Relevance**

SECTION E – Key Information

Has this or any related application been submitted elsewhere? **No**
If yes, please provide details of the application, its outcome or any changes made to the protocol since feedback received:
Have you received a research project award from the SPCR previously? **Yes**
If yes, please provide details of the short title and project number: **SPCR Project 222 - Reduced dietary salt intake in heart failure patients**
How does this project add to the existing research in the SPCR? The SPCR has strong research programmes in long-term condition management, multi-morbidity and ageing, and prevention and diagnosis. Our project to explore variations in the use of evidence-based medications and impacts on admissions aligns with the goals of these programs. It also builds on previous work funded by the SPCR. Studies on unscheduled secondary care funded by the SPCR have identified factors in primary care that influence admission rates, but have not robustly examined the role of variations in medication use. Therefore, this project will fill an important knowledge gap and complement the SPCR research profile in unscheduled secondary care.
How will this proposal contribute to capacity building in academic primary care? Our program of work to identify under-utilized interventions/medications to reduce admissions is already of interest to commissioners in Oxfordshire and researchers in NHS Grampian. The results may inform modifications of GP contracts locally and potentially lead to the development and testing of new Quality and Outcomes Framework indicators to optimize the use of select medications in primary care. Sponsorship of this project will support research training and career development for four early career scientists (BS, SS, KM, NB) including both clinical (KM) and non-clinical researchers (BS, SS, NB). Support for hardware/software purchases will increase the capacity of the research team to conduct future, high-quality research using large datasets, including new analyses of the datasets used in this study. Our PPI and dissemination activities will serve to inform patients and the public of the commitment of the School to solve one of the largest problems in healthcare in the UK, thereby garnering support for the SPCR and academic primary care.
How will this project lead to further competitive grant funding or other significant impact? To our knowledge, this will be the largest ever analysis of the association between evidence-based medication use in primary care and unplanned hospital admissions. We will obtain impact through submission of our results to high impact journals and wide dissemination in the public domain. We also believe the results will have impact on policy. We will disseminate significant

findings to the local NHS trust and Clinical Commissioning Group who have mutual interests in preventing unplanned admissions. The results could guide local optimization of prescribing. Nationally, these activities could inform the development of new clinical indicators for prescribing medications as part of the Quality and Outcomes Framework.

The results will stimulate future research and applications to competitive grant funding. If we find evidence of variations in prescribing and associations with admissions this will lead to prospective studies to explore reasons for variations from the patient, provider, and system perspective; to map pathways from poor prescribing to admissions; and to implement strategies to reduce admissions. We will submit an application for researcher-led funding from the NIHR Health Services and Delivery Research (HS&DR) Programme and for the SPCR Round 12 and 13 to support these projects.

SECTION F – Patient and Public INVOLVEMENT

Our PPI activities were developed with guidance from a PPI expert (Lynne Madocks) and the NIHR Handbook for Patient and Public Involvement in Health and Social Care.[1]

Our PPI strategy integrates patient and public stakeholders throughout the research process. We have pre-specified PPI activities in four key phases: designing the study; drafting grant applications; data interpretation and analysis; and dissemination of findings.

A family friend (Jennifer Cook) of the co-principal investigator has diagnoses of cancer and hypertension and frequently uses primary and secondary care services. She is a named collaborator on this grant and will be providing ongoing advice on the drafting of patient-related study materials. She is a writer and has won journalism awards. She has been a member of 2 cancer support groups and has been nominated for membership to a provincial patient advisory panel due to her articulate and approachable nature. She has been involved in research before as a participant and patient advisor.[2,3] She has refused remuneration for her involvement.

Designing the study: To determine the value of this research topic we posted messages on 2 health forums (patient.co.uk; daily mail forum), Facebook, and twitter which described our intention to explore whether variation in treatment practices in primary care impact on unplanned hospital admissions. We invited feedback on the importance of the research topic and the potential methodology. We have received 26 responses from 20 individuals including students, practicing physicians, and members of the general public. Ninety-five percent of the respondents identified this as an important research topic and we have designed the study to incorporate the feedback they provided. For example, one respondent suggested potential unintended consequences of the study: "*…saying things like primary care doctors don't use the best treatments for their patients, might actually be potentially harmful in losing people's trust for their doctors*". This has informed the framing of our lay summary and background, and will inform how we report our results.

Drafting grant applications: The lay summary in this grant was drafted and revised with input from our patient advisor.

Data interpretation and analysis, formulating results: Once we have analysed the data we will approach 10 patients from patient participation groups (PPGs) at 2 GP practices in Oxfordshire. Two GP applicants (KM, CH) and our GP collaborator (KK) will provide access to these groups. The GPs will identify patients with relevant conditions that are eligible to receive at least one of the medications on our top 10 list. We will meet with each patient for 0.75 hours at the Nuffield Department of Primary Care Health Sciences to ask about their knowledge regarding the medications on the list and discuss their experiences with medication prescribing in primary care. The patients will be presented with results from the study drafted with guidance from our patient advisor and the NIHR PPI Handbook.[1] We will ask whether the research findings make sense and will get input on draft lay summaries of the results. A rate of £20 per hour will be paid for the consultation in addition to £10 for travel expenses.

Dissemination of findings: Once the results have been published, we will disseminate our lay summaries for readership by the public. We will utilise the University and Departmental websites to publish the summaries. We will also disseminate the results through patient participation groups in two GP surgeries in Oxfordshire and by approaching broadcast media outlets in the UK.

SECTION G– Project Details

General Aim

The aim of this study is to assess the association between evidence-based medication use among eligible patients in primary care practices in England and unplanned hospital admissions.

Specific Aims

1. Quantify the variation in the use of 10 evidence-based medications in primary care which have been shown to reduce unplanned hospital admissions.
2. Determine if eligible patients treated with evidence-based medications are less likely to experience an unplanned hospital admissions compared to eligible patients not treated with evidence-based medications.
3. Determine differences in the odds of an unplanned admission for patients from primary care practices that treat larger proportions of eligible patients with evidence-based medications compared to patients from practices that treat smaller proportions of eligible patients with evidence-based medications.
4. Identify patient and practice characteristics that are associated with variation in the use of evidence-based medications among eligible patients.
5. Estimate potential reductions in unplanned admissions if a greater proportion of eligible patients were treated with evidence-based medications.

Background (references listed in Appendix 2)

The UK has experienced a 47% increase in admission over the last 15 years that has seriously strained the healthcare system.[4] In 2012-2013 there were 5.3 million unplanned hospital admissions representing 67% of hospital bed days in England and costing approximately £12.5 billion.[4] This represents a huge problem that is unsustainable and needs to change. As a result, reducing admissions is a priority for the National Health Service.[4]

Unplanned hospital admissions are unpredictable and occur at short notice because of a perceived need for immediate health care.[5] There are large variations in unplanned admissions rates across health regions[6] and primary care practices in the UK.[4,7,8] Studies have shown a 3.4 fold variation in admission rates between health regions[6] and GP referral rates for hospital admissions have been shown to vary from 0 to 95 per 1000 population.[4] Although social deprivation and non-modifiable population factors (e.g., age) account for a large portion of these variations[6], a substantial amount may be due to factors within the control of primary care physicians and managers.

A recent systematic review by Huntley et al. (2014) examined primary care factors associated with admission rates and found consistent evidence across studies for three elements of care: access to care, patient satisfaction, and being able to see the same doctor on repeat visits.[9] While this is an encouraging start, a core component of effective primary care practice has not been well-studied; the use of evidence-based medications. For example, a meta-analysis of 22 randomized controlled trials has shown that use of Tiotropium (an anticholinergic) compared to placebo among adults with Chronic Obstructive Pulmonary Disease results in a 15% reduction in hospital admissions due to COPD exacerbations.[10] In children with acute viral bronchiolitis, a meta-analysis of 5 RCTs has shown that use of Epinephrine versus placebo reduces admissions within 24 hours of outpatient presentation by 33%.[11] Variations in use of these medications and their impacts on hospital admissions in England have not been evaluated.

Evidence suggests there is variation in prescribing in England. The National Health Service (2012) reports wide variation in primary care prescribing practices, including both under- and over-utilization of medications however, the impact of these variations on admissions is unclear.[12] Huntley et al. (2014) found only 1 study examining the relationship between

achievement levels for prescription quality indicators and admission rates; achievement for three coronary heart disease prescription indicators had no association with admission rates.[9] An additional two studies in heart failure[13] and epilepsy[14], not captured by the review, have examined 3 prescription focused quality measures but also found no evidence of an association with admissions.

This limited work does not represent a robust evaluation of the potential impact of evidence-based medication use in primary care on unplanned admissions. However, there is some evidence showing that drug-related admissions contribute to the hospitalization burden. A 2006 systematic review in the British Journal of Clinical Pharmacology reported that 3.7% (range 1.4% – 15.4%) of all hospital admissions may be due to preventable drug-related events, a large proportion of which are related to prescribing problems.[15] However, only a sub-set of studies examined under-treatment as a cause for admissions and there were only 2 studies from the UK, both of which are now over ten years old.

As a result of the paucity of investigation, it is unclear if variations in evidence-based medication use in primary care are contributing to the burden of unplanned hospital admissions. Determining the association between the prescription of effective medications and hospitalisations could inform strategies to reduce admission rates. These strategies could be implemented using the existing national infrastructure to guide and incentivise physicians to prescribe appropriate medications, including the National Institute for Health and Care Excellence guidelines and the Quality and Outcomes Framework indicators.

Description of Project Protocol

Objective

The objective of this study is to assess the association between evidence-based medication use among eligible patients in primary care in England and unplanned hospital admissions.

Methods

Foundational Work: We are currently in the process of completing an overview of systematic reviews of interventions to reduce unplanned hospital admissions.[16] Based on current progress we expect to include and analyse approximately 200 systematic reviews, with over 50 reviews of medications that have been shown to reduce admissions. This list will be hierarchically ranked based on the quality of the evidence and size of effect estimates for absolute reductions in admissions. From this list we will select the top 10 medications that have been shown to reduce unplanned admissions and are supported by strong evidence. The results will also include details of the indications and contraindications for use of the medications as defined in the reviews. The list of 10 medications and descriptions of treatment-eligible patients will form the basis of our national observational study.

Design: National observational study.
Unit of Analysis: Patients in primary care practices in England.
Data Sources: We will use three data sources to obtain the patient-level and practice-level information necessary to meet our study aims.

1. Clinical Practice Research Datalink (CPRD): The CPRD includes primary care observational data for all patients registered with a GP practice in England. We will use this database to identify patients that are eligible for treatment with medications on our top 10 list and to quantify the proportion of patients at each practice that are being treated with evidence-based medications. We will aim to obtain the following information to identify the indications and contraindications for treatment, and to adjust for potential confounding: patient demographic information; medical diagnoses; time since diagnoses; prescriptions issued in primary care including brand or generic name, strength, and dosing; records of immunisations/vaccinations; referrals to specialists and secondary care settings; diagnostic testing; lifestyle information (e.g. smoking and alcohol status); and Index of Multiple Deprivation (including separate scores for the employment and income deprivation domains).

2. Hospital Episode Statistics Database (HES): The HES contains hospital admissions data for all NHS funded hospitals in England. Patient-level linkage of the CPRD data with

the HES is necessary to identify unplanned patient admissions to hospital and to identify the primary diagnoses upon admission.

3. Health and Social Care Information Centre: We will coordinate with the Health and Social Care Information centre to adjust for key practice level confounders including supply of GPs in each practice (full-time equivalents per 100 000 practice patient population) and QOF scores for access to care (calculated from the GP patient survey).

Population: All people registered with a primary care practice in England from April 1, 2011-March 31, 2014. We will exclude practices with less than 500 registered patients as they are more likely to serve atypical populations or deliver atypical services. We will also exclude practices that are not linked to the hospital episode statistics database.

Eligible Patients: The indications/contraindications for treatment using each medication will be supplemented with current clinical practice guidelines and reviewed by General Practitioners on our team. They have 24 years of experience treating patients in primary care and are experts in evidence-based medicine. The finalized list of indications and contraindications will allow us to define eligible patients for the analysis. We will identify indications and contraindications using patient-level data from the CPRD including comorbidities, prescriptions, lifestyle factors, and demographic characteristics. Patients with contraindications will be excluded from the eligible patient denominator in each practice.
Key Independent Variable: Whether eligible patients were treated with evidence-based medication.
Outcome Measure: Whether each patient experienced an unplanned admission to hospital. We will exclude admissions that are transfers between hospitals. Our decision to measure cause-specific or all-cause unplanned admissions will vary for each medication, depending on what the evidence from our systematic overview (foundational work) supports.

Statistical Analysis: For each of the 10 evidence-based medications assessed, we will report the overall proportion of unplanned hospital admissions broken down by whether the patient received this treatment. We will then use multi-level mixed effects logistic regression to explore the association between the prescription of each medication and unplanned hospital admission. The analyses will be clustered by both hospital and general practice. We may cluster by GP if numbers are sufficient. We will identify possible confounders using a combination of the clinical expertise of the lead and co-applicants and previous published evidence that has identified patient and primary care factors that affect admission rates. In the case of an overly complex model, stepwise selection will be used to produce a simplified model that adjusts for the most significant covariates. All analyses will be carried out using STATA 13.
Strengths: To our knowledge, this will be the largest analysis of the association between evidence-based medication use in primary care and unplanned hospital admissions. All previous studies that we could identify have conducted aggregate level analyses. We will use individual patient data, therefore allowing more nuanced and powerful analyses with adjustment for patient-specific factors.
Anticipated Challenges and Limitations: We anticipate two challenges/limitations. First, it is possible that patients will be misclassified as eligible or non-eligible. However, we will have access to individual level demographic, prescription, and clinical data that should allow for robust identification of eligible patients. Second, we anticipate encountering some missing data in the CPRD and HES databases. This is a limitation of using large databases. If values for medication dosing or frequency are encountered we will use substitution of the most recent observation. If we cannot determine the name of a medication a patient is prescribed or the nature of a hospital admission (unplanned vs. planned), the observation will not be included. However, with such a large sampling frame (2011-2014) we expect to have a robust sample of millions of patients with the data necessary to complete analysis.
Project Timetable: See Gant chart in Appendix 1.

SECTION H– Justification of costs requested

Our costings have been developed in accordance with the Attributing the costs of health and social care research (AcoRD) guidance. We believe the cost of **£33 442** offers good value to the NIHR SPCR: to our knowledge, this will be the largest ever analysis of the association of evidence-based medication use in primary care and unplanned admissions; we will submit our work for publication in high impact journals (Lancet, BMJ; Annals of Internal Medicine); the hardware/software purchased will increase the capacity of our team to conduct large scale, high-quality data analyses; and, given the large volume of analyses to conduct, the staff costs are minimal as the co-principal investigator (NB- committing 40% FTE for 12 months) is a DPhil student fully funded by a Clarendon scholarship and will not receive salary support.

The majority of our request for support is to cover the CPRD data management fee (£10 500) and cost for the basic HES database with linkage for over 100 000 patients (£15 750). Both the HES database and linkage to CPRD are necessary to complete the project. The CPRD provides individual patient data, which is a key strength of this study. However, it does not provide information on the nature of hospital admissions (i.e., unplanned vs. planned) or the primary admission diagnosis. Once we identify eligible patients, we must link their primary care data to hospital data to identify those that experience an unplanned admission and the reason for admission.

To handle significant data storage and provide the computational power needed to analyse data for millions of patients we will purchase a desktop computer with a solid state hard drive and 16GB of RAM (£610). We will also require an advanced statistical package: Stata 13 MP, quad core, single user, perpetual licence (student price £650). Purchase of this computer and software will increase the capacity of our research team to conduct future projects with large datasets, including new analyses of the datasets from this study.

Other non-staff costs to support completion of the project include photocopying/printing and stationary (£45). £275 has been allocated to support patient and public involvement activities. This will support 7.5 hours of PPI activities with 10 patients recruited from patient participation groups in GP surgeries in Oxfordshire. We will provide £20 pounds per hour remuneration for patients. We will also provide £10 travel expenses for each patient to attend meetings at the Nuffield Department of Primary Care Health Sciences. £25 has been allocated for coffee/tea/snacks during meetings. A proportion of the budget (£200) has been allocated to allow for dissemination (travel, accommodation) of the results at a National conference i.e. the Society for Academic Primary Care Conference. This cost was scaled down (from £400) as the co-principal investigator can access guaranteed conference funds (£200) through his college affiliation (Green Templeton College).

Salary costs amount to £3938 (co-principle investigator 1% FTE, senior GP advisor 1% FTE, CPRD and statistics specialist 5% FTE, and senior statistical advisor 3% FTE). All staff have required expertise.

SECTION I – Delivery
Network involvement

Please indicate which network(s) http://www.crn.nihr.ac.uk/ you intend to work with and the extent to which any links have been established.

N/A

Is Clinical Trials Authorisation required?

No

Is a Clinical Trials Unit (CTU) involved with this research proposal?

No

If yes, what is the name of the CTU?

Does the CTU hold a UKCRC registration number?

If yes, please provide the CTU Registration Number

SECTION J – Expected Output of Research/Impact

Please describe how the outcomes of this research could be translated into the NHS and wider healthcare community to provide improvements in service delivery, patient health and/or wellbeing

This could include plans to submit papers to peer reviewed journals but it will be particularly important to identify forms of presentation that will maximise impact on practitioners and service managers if appropriate.
To our knowledge, this will be the largest ever analysis of the association between evidence-based medication use in primary care and unplanned hospital admissions. We will disseminate the results of the study through multiple channels to maximize impact of the research. First, we will submit our work for publication in high impact journals (Lancet, BMJ, Annals of Internal Medicine). Second, we will present the results at a National Conference (Society for Academic Primary Care). Third, our collaborator (KK - GP commissioner) and GP applicants (KM, CH) will facilitate dissemination of the result to the local NHS trust and Clinical Commissioning Group in Oxfordshire. Fourth, we will post lay-summaries on Departmental and University Websites. Fifth, we will disseminate the results through patient participation groups in GP surgeries in Oxfordshire. Sixth, we will approach broadcast media in the UK to communicate our findings to the public. The results will stimulate future research. If we find evidence of variations in prescribing and strong associations between prescribing and admissions this will lead to prospective studies to explore reasons for variations from the patient, provider, and system perspective; to map pathways from poor prescribing to admissions; and to implement strategies to reduce admissions. We will submit an application for researcher-led funding from the NIHR Health Services and Delivery Research (HS&DR) Programme and for the SPCR Round 12 and 13 to support these projects. This project will help to determine the extent to which improving prescribing practices in primary care could reduce hospital admissions. The results could be used by healthcare providers, commissioners, and policy makers to inform local optimization of prescribing. Nationally, these activities could inform new clinical indicators for prescribing medications as part of the Quality and Outcomes Framework.

SECTION K – Nominated Referees please provide:

- at least 2 names if your project cost is <£50k
- at least 3 names if your project cost is between £50k-£500k

Title_Forename_Surname: Dr. Nadeem Qureshi
Post Held: Clinical Professor
Organisation: University of Nottingham
Email: nadeem.qureshi@nottingham.ac.uk
Area of Expertise: Primary care, Genetics

Title_Forename_Surname: Dr. Richard Riley
Post Held: Professor of Biostatistics
Organisation: Keele University
Email: r.riley@keele.ac.uk

Appendix 6.2 Independent Scientific Advisory Committee application form

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY
1. Study Title§ (*Please state the study title below)* Dosage regimens and interrupted treatment in heart failure: a national retrospective cohort study in primary care. §*Please note: This information will be published on the CPRD's website as part of its transparency policy.*
2. Has any part of this research proposal or a related proposal been previously submitted to ISAC? Yes * ☐ No ☒ • A previous version of this protocol was selected by the National Institute for Health Research, School for Primary Care Research, Internal Round 9 for grant funding support (Study ID: 271, £33 442) • The protocol was reviewed by two external examiners (outside the University of Oxford) and by a review panel internal to the Nuffield Department of Primary Care Health Sciences
3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee) Yes* ☒ No ☐ **If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :*
4. Type of Study (please tick all the relevant boxes which apply) Adverse Drug Reaction/Drug Safety ☐ Drug Effectiveness Drug Utilisation ☒ Pharmacoeconomics Disease Epidemiology ☐ Post-authorisation Safety Health care resource utilisation ☒ Methodological Research Health/Public Health Services Research ☒ Other* **If Other, please specify the type of study here and in the lay summary below:*
5. Health Outcomes to be Measured§ §*Please note: This information will be published on CPRD's website as part of its transparency policy.* Please summarise below the primary/secondary health outcomes to be measured in this research protocol: • Primary: Mortality • Primary: All-cause emergency hospital admissions • Primary: Cardiov emergency hospi • Secondary: Treatment interruptions in heart failure medication • Secondary: Defined daily dose of heart failure medication •
6. Publication: This study is intended for (please tick all the relevant boxes which apply)**:** Publication in peer-reviewed journals ☒ Presentation at scientific conference ☒ Presentation at company/institutional meetings ☒ Regulatory purposes ☐ Other* ☐ **If Other, please provide further information:*
SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS
7. Chief Investigator§ Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol. Professor Carl Heneghan Professor of Evidence-Based Medicine Director, Centre for Evidence-Based Medicine University of Oxford Carl.heneghan@phc.ox.ac.uk §*Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy* CV has been previously submitted to ISAC ☒ **CV number:** 213_17 A new CV is being submitted with this protocol ☐ An updated CV is being submitted with this protocol ☐
8. Affiliation of Chief Investigator (full address) Radcliffe Primary Care Building

Radcliffe Observatory Quarter
Woodstock Rd, Oxford
OX2 6GG

9. Corresponding Applicant§

Please state the full name, affiliation(s) and e-mail address below:

Niklas Bobrovitz
DPhil Candidate
University of Oxford
niklas.bobrovitz@phc.ox.ac.uk

§*Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy*

Same as chief investigator ☐
CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

10. List of all investigators/collaborators§

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

§*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator: Professor Richard Hobbs
richard.hobbs@phc.ox.ac.uk
Head of Department
Professor of Primary Care Health Sciences
Nuffield Department of Primary Care Health Sciences
University of Oxford
CV has been previously submitted to ISAC ☒ **CV number:** 035_16PEL
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator: Dr Kamal Mahtani
kamal.mahtani@phc.ox.ac.uk
Clinical Scientist
Deputy Director, Centre for Evidence-Based Medicine
Nuffield Department of Primary Care Health Sciences
University of Oxford
CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

Other investigator: Mr Niklas Bobrovitz
niklas.bobrovitz@phc.ox.ac.uk
DPhil Candidate
University of Oxford CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

Other investigator: Dr Margaret Smith
margaret.smith@phc.ox.ac.uk
Senior statistician and epidemiologist
Nuffield Department of Primary Care Health Sciences
University of Oxford
CV has been previously submitted to ISAC ☒ **CV number:** 488_16ES
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator: Dr Jeffrey K Aronson
jeffrey.aronson@phc.ox.ac.uk
Clinical pharmacologist
Nuffield Department of Primary Care Health Sciences
University of Oxford
CV has been previously submitted to ISAC ☐ **CV number:**

A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

11. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work

No relevant conflicts of interest.

12. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☐	☐
> 3	☒	☒

Experience/Expertise available	Yes	No
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Margaret Smith is a senior primary care epidemiologist and statistician with significant CPRD experience.	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Professor Richard Hobbs has conducted and published studies of over 1 million records using CPRD data.	☒	☐
Is experience of practising in UK primary care available to or within the research team? Prof Carl Heneghan, Dr. Kamal Mahtani, and Prof Richard Hobbs are all general practitioners in the UK with decades of experience.	☒	☐

13. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

1. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet. 2017 Nov 21. pii: S0140-6736(17)32520-5.

2. Bobrovitz N, Heneghan C, Onakpoya I, Fletcher B, Collins D, Lee J, Tompson A, Fisher R, Nunan D, Scott B, O'Sullivan J, Van Hecke O, Nicholson B, Stevens S, Roberts N, Mahtani K. Reducing unscheduled hospital admissions using pharmacotherapy: an overview of systematic reviews and prioritisation of treatments. *Under review.*

3. National Institute for Health and Care Excellence. Chronic heart failure in adults: management. Clinical guideline (CG108). August 2010. https://www.nice.org.uk/guidance/cg108/chapter/1-Guidance#treating-heart-failure

SECTION C: ACCESS TO THE DATA

14. Financial Sponsor of study§

§*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	National Institute for Health Research, School for Primary Care Research, UK
Government / NHS	☐	*Please specify name and country:*
Charity	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*
None	☐	

15. Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	University of Oxford, UK
Government Department	☐	*Please specify name and country:*
Research Service Provider	☐	*Please specify name and country:*
NHS	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*

16. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data ☐

The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data** ☒

A data set will be provided by the CPRD¥€ ☐

CPRD has been commissioned to extract the data and perform the analyses€ ☐

Other:

☐

If Other, please specify:

* Name of CPRD Researcher Reference number (where available) Date of contact

17. Primary care data

Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐

EMIS® only* ☐

Name of CPRD Researcher Reference number (where available) Date of contact

18. Site Location of Data

a) Processing location(s)

The data received will be processed on secure network drives managed by IMSU and the Nuffield Department of Primary Care Health Sciences.

Location area - UK / EEA / Worldwide: Oxford, UK

Organisation address: Room 3A25, John Radcliffe Hospital, Oxford OX3 9DU

Note: Please enter the location details of where the data for this study will be used (processed).

b) Storage Location(s)

The data received will be stored on secure network drives managed by IMSU and the Nuffield Department of Primary Care Health Sciences.

Location area - UK / EEA / Worldwide: Oxford, UK

Organisation address: Room 3A25, John Radcliffe Hospital, Oxford OX3 9DU

Note: Please enter the location details of where the data for this study will be stored.

c) Territory of analysis - UK / EEA / Worldwide: Oxford, UK.

Organisation address: Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Rd, Oxford OX2 6GG.

Note: Please enter the details of where the data for this study will be analysed.

SECTION D: INFORMATION ON DATA LINKAGES

19. Does this protocol seek access to linked data

Yes* ☒ No☐ If No, please move to section E

Name of CPRD Researcher: Margaret Smith

Reference number (where available) N/A

Date of contact Ongoing

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

20. Please select the source(s) of linked data being requested§

§Please note: This information will be published on the CPRD's website as part of its transparency policy.

☒ ONS Death Registration Data

☒ HES Admitted Patient Care

☐ HES Outpatient

☐ HES Accident and Emergency

☐ HES Diagnostic Imaging Dataset ☐ HES PROMS (Patient Reported Outcomes Measure)**

☐ NCRAS (National Cancer Registration and Ana Registration Data *

☐ NCRAS Cancer Patient Experience Survey (CPE

☐ NCRAS Systemic Anti-Cancer Treatment (SACT

☐ Mental Health Services Data Set (MHDS)

☐ CPRD Mother Baby Link

☐ Pregnancy Register

☐ Practice Level Index of Multiple Deprivation (Standard)

☐ Practice Level Index of Multiple Deprivation (Bespoke)

☒ Patient Level Index of Multiple Deprivation***

☐ Patient Level Townsend Score ***

Name of CPRD Researcher Reference number (where available) Date of contact

21. Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **<u>not</u>** be included in this count):* 3

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

22. Is linkage to a <u>local¥</u> dataset with <1 million patients being requested?

Yes * ☐ No ☒

**If yes, please provide further details:*

¥ Data from defined geographical areas i.e. non-national datasets.

23. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

24. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

25. Does this protocol describe a purely observational study using CPRD data?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*

*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

26. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP[Ψ] Yes ☐ No ☒

Is the questionnaire a validated instrument? Yes ☐ No ☐

If yes, has permission been obtained to use the instrument? Yes ☐ No ☐

Please provide further information:

Other (please describe)

[Ψ] Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

27. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No ☒

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

28. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected:*

SECTION F: DECLARATION

29. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.
- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Carl Heneghan Date:6 February 2018 e-Signature (type name):Carl Heneghan

A. Study Title§

Dosage regimens and interrupted treatment in heart failure: a national retrospective cohort study in primary care.

B. Lay Summary (Max. 200 words)§

§*Please note: This information will be published on CPRD's website as part of its transparency policy*

Heart failure occurs when the heart does not pump blood as well as it should. Nearly one million people in the United Kingdom have heart failure. These patients experience debilitating symptoms, frequent hospitalisations, and an increased risk of death because of this condition.

Medical guidelines recommend several medications to relieve symptoms in patients with heart failure, avoid the need for hospitalisation, and help them to live longer. However, it is unclear if patients in the UK are given these medications in ways that maximise the possible benefits. We must therefore examine how many patients have an adequate supply of pills (enough for each day) and whether the doses they are given are appropriate. We must then determine the extent to which supply of pills and doses are related to better health outcomes. We will use the Clinical Practice Research Datalink and Hospital Episode Statistics databases to complete this study. The results could be used to improve prescribing of heart failure medications in UK primary care and improve health outcomes for patients.

C. Technical Summary (Max. 200 words)§

§*Please note: This information will be published on CPRD's website as part of its transparency policy*

Heart failure (HF) is a leading cause of morbidity and mortality globally, and a major financial burden on health systems. Current medical guidelines recommend use of several medications to help manage patients with heart failure and a reduced ejection fraction. Studies have shown that the use of these medications in recommended doses improves survival, reduces hospital admissions, and can reduce health costs. However, it is unclear if patients in UK primary care receive adequate supplies of medications and whether target doses are being achieved. Patients may not receive or take medications correctly or at all, for various reasons related to the patient, the prescriber, or the healthcare system:

- they may not adhere to treatment, for example because of forgetfulness or adverse reactions;
- they may receive conflicting advice from carers;
- they may have limited access to health care, owing to geography or cost;
- repeat prescriptions may not be requested or issued.

However, before studying these factors in UK primary care we must first determine the extent to which interruptions in treatment occur and if they are associated with patient outcomes.

We shall therefore describe the proportion of patients with reduced ejection fractions experiencing interrupted treatment (days without pills) and determine the extent to which their prescribed doses meet guideline recommendations. We will then examine the association between interrupted treatment and prescribed dosage regimens and important patient outcomes (emergency hospital admissions and mortality) using Cox proportional hazards modelling adjusted for key co-variates. We will also examine if patient characteristics are associated with interrupted treatment and dosage regimens using Cox proportional hazards modelling and logistic regression. The results of this study could be used to inform quality improvement initiatives and improved management of patients with heart failure in UK primary care.

D. Objectives, Specific Aims and Rationale

Objective 1: To describe interrupted treatment with heart failure medications in UK primary care and examine associations with patient characteristics and outcomes.

Aim 1.1) To quantify the proportion of patients that experience interrupted treatment with heart failure medications of 7 to 29 days; 30 to 89 days; 90 to 179 days; and 180 to 365 days.

Aim 1.2) To quantify the median interruption length (in days) per episode of a treatment interruption.

Aim 1.3) To quantify the proportion of days for which patients have coverage with heart failure medications.

Aim 1.4) To identify if patient characteristics are associated with treatment interruptions.

Aim 1.5) To quantify the association between treatment interruptions in heart failure medication and patient mortality, all-cause emergency hospital admissions, and cardiovascular-related emergency hospital admissions.

Objective 2: To describe dosage regimens of heart failure medications prescribed in UK primary care and examine their association with patient characteristics and outcomes.

Aim 2.1) To quantify the mean daily dose of heart failure medications.

Aim 2.2) To compare the mean daily doses of heart failure medications to recommended target doses and quantify the proportion of the target dose achieved for each heart failure medication drug class.
Aim 2.3) To identify if patient characteristics are associated with dosing of heart failure medications.
Aim 2.4) To quantify the association between doses of heart failure medications and patient mortality, all-cause emergency hospital admissions, and cardiovascular-related emergency hospital admissions.

Rationale: Optimising use of heart failure medications is a national health priority.[1–3] Over the last 10 years, substantial resources have been invested to improve the use of three lines of evidence-based medications that are recommended in NICE clinical guidelines. For example, tens of millions of pounds have been invested in: (a) developing and maintaining prescribing indicators for first-line therapies as part of the pay for performance Quality and Outcomes Framework (QOF); (b) research grants investigating treatment optimisation; and (c) annual audits of heart failure treatment and subsequent improvement efforts. However, despite these huge investments of resources, little research has examined prescribing in primary care.

Evidence from the British Society for Heart Failure's audits have shown improvements over time in the rates of prescription of evidence-based treatments. However, these audits are of patients in secondary care[4], and do not reflect prescribing by primary-care physicians, who issue hundreds of thousands of prescriptions for heart failure medications each year.[5] The QOF offers insights into community prescribing, demonstrating improvements over time in the number of patients receiving first-line therapy. However, this provides an incomplete picture of medication use. It is currently unclear whether patients are experiencing interruptions in medication coverage and whether primary-care physicians are prescribing target doses. Given the burden of heart failure on patients and the health system, and the tremendous resources put towards improving treatment, it is crucial to better understand primary-care prescribing and its associations with patient outcomes.

Examining the prevalence of interruptions in therapy and dosage regimens could inform quality improvement efforts to ensure that we are obtaining maximum benefit from heart failure medications. We shall examine patient factors associated with interruptions in therapy and dosage regimens, and therefore may be better able to target quality improvement initiatives. The findings of our study will also help to determine the importance of achieving target dosing in real world patients with heart failure. Observational studies and audits have shown that doses of medications used to treat heart failure are often below guideline recommended targets, despite evidence from randomised controlled trials that higher doses favourably influence clinical outcomes.[6–9] However, some clinicians and researchers argue that these reflect appropriate doses in real world populations – patients who are burdened by multi-morbidity, frailty, and polypharmacy – in contrast to the highly selected patients in controlled trials, from which target doses are derived. Our study will address this issue by examining the association between dosage regimens on patient outcomes in a real-world cohort.

The four medication groups we shall analyse correspond to the therapies recommended in NICE clinical guidelines for treating patients with heart failure and reduced ejection fractions. First-line therapy consists of Renin-Angiotensin System Blockers (Angiotensin Converting Enzyme Inhibitors or Angiotensin 2 Receptor Blockers) and Beta-Blockers; second line is Aldosterone Antagonists; and third line is Digoxin. These medications represent high-value therapies and are worthy of investigation. This is evidenced not only by their recommendation in guidelines, but also by published evidence: we have previously conducted a large systematic review and found that these four drug groups are among the best medications for helping patients to avoid emergency hospitalisation.[10,11]

E. Study Background

Heart failure (HF) is a leading cause of morbidity and mortality globally. Approximately 2-3% of people have heart failure in high- and middle-income countries, including 15 million people in Europe and 6 million in the USA. Nearly 50% of patients die within five years of diagnosis and patients living with heart failure are frequently admitted to hospital. Heart failure is also associated with a huge financial burden; for example, some countries spend nearly 2% of their total health care budget on managing patients, most of the costs being due to hospital admissions. Therefore, minimising the impact of heart failure is a priority for health systems all over the world.

There is currently no cure for heart failure and the primary goals of treatment of established disease are to minimise symptoms and extend life. The most effective tool for achieving these goals is medication. NICE clinical guidelines recommend three lines of medication therapy for managing heart failure: the first line consists of Renin-Angiotensin System Blockers (Angiotensin

Converting Enzyme Inhibitors or Angiotensin 2 Receptor Blockers) and Beta-blockers; the second line is Aldosterone Antagonists; and the third line is Digoxin. These clinical guidelines also recommend target doses. Randomised trials have shown that using these medications in the recommended doses improves patient survival, reduces use of health services, and reduces cost to the health system.

The burden of heart failure and the beneficial effects of these medications are well known. As a result, optimising use of heart failure medications is a national health priority in the UK and has received significant attention and resources. Since 2009, the Quality and Outcomes Framework has tracked prescription rates in primary care for first-line therapy (ACE inhibitors, ARBs, beta-blockers) and, despite variations between practices, has shown improvements in the proportion of patients receiving therapy. However, the QOF does not measure the supply of medications prescribed or the prescribed doses. Some of this information is captured by the British Society for Heart Failure's annual audit, which has shown that prescription rates and dosing are improving, although there are still significant problems with under-prescribing and under-dosing. However, this audit only examines trends in prescribing by cardiologists for patients recently discharged after hospitalisation for heart failure. There is therefore a significant gap in knowledge about therapy provided in primary care.

Currently, the extent to which primary-care physicians are prescribing target doses of heart failure medications is unclear. It is also unclear if patients are given sufficient supplies of medication to follow the recommended regimens. This is a serious concern, given that patients with heart failure are managed mostly in primary care and that general practitioners are responsible for a large proportion of heart failure medication prescribing.[12] In their 2016 report, the British Society for Heart Failure highlighted this gap in knowledge and noted the need to extend the audit to primary care. They are in the early stage of pilot testing a primary care audit but have not yet reported any information on primary-care prescribing.

To address this important gap in knowledge, our study will examine interruptions in treatment and dosage regimens of heart failure medications in UK primary care and will determine their association with important patient outcomes. The results will help to identify opportunities to optimise use of heart failure medications in UK primary care and inform qualify improvement efforts and allocation of resources.

F. Study Type

Our study will include both descriptive and hypothesis testing elements. We shall describe interruptions in therapy and dosage regimens for four classes of heart failure medications. We shall test the hypotheses that patient characteristics are associated with interruptions in treatment and dosage regimens. Several characteristics have been identified in previous literature. We shall examine if these associations exist in UK primary care. We shall also test the hypotheses that treatment interruptions and dosage regimens are associated with mortality and emergency hospital admissions.

G. Study Design

We have collaborated with general practitioners, pharmacists, clinical pharmacologists, health researchers, statisticians, CPRD experts, and members of clinical commissioning groups in England to inform the design of this study. This will be a retrospective cohort study using six and a half years of data from 1 January 2010 to 31 July 2017.

H. Feasibility counts

The protocol has been discussed, designed, and reviewed with CPRD scientific representatives at the University of Oxford (Bankhead, Smith). As of December 2017, the number of patients that meet our cohort inclusion criteria (see sections K and L) from January 2010 to July 2017 is 12 343. These patient records are of acceptable research quality with the necessary data linkages to the Hospital Episodes Statistics Database, the Index of Multiple Deprivation, and ONS death registry.

The **total number of patients** in each medication group is:

- Renin-angiotensin system blockers: 2902 (ACE-inhibitors 2807; ARB 956)
- Beta-blockers: 4300
- Aldosterone antagonists: 2847
- Digoxin: 1433

The anticipated **mortality event counts** are:

- Renin-angiotensin system blockers: 384 deaths
- Beta-blockers: 568 deaths
- Aldosterone antagonists: 376 deaths
- Digoxin: 189 deaths

We are not able to obtain feasibility counts of hospitalisation, as this requires access to the HES database. However, we can estimate the likely number of events. The literature indicates that the proportion of patients experiencing at least one emergency hospitalisation is approximately 33% higher than the proportion experiencing death within 5 years of diagnosis.[13] Therefore, given our feasibility count of 1632 deaths, we expect approximately 2170 patients to have at least one emergency admissions during the study period. We expect that just over half of these admissions (1128 admissions) will be cardiovascular-related[13,14]

The anticipated number of patients experiencing at least one **hospitalisation event** are:

- Renin-angiotensin system blockers: 511 all-cause, 265 cardiovascular-related
- Beta-blockers: 756 all-cause, 393 cardiovascular-related
- Aldosterone antagonists: 501 all-cause, 260 cardiovascular-related
- Digoxin: 251 all-cause, 131 cardiovascular-related

I. Sample size considerations

The primary analyses on which we shall power this study are the associations between treatment interruptions/dosage regimens and patient mortality.

Treatment interruptions and mortality: Previously published estimates show that 47% of patients experience interruptions of 90 days or longer from their heart failure medications and that this interruption threshold is associated with a significantly higher risk of death: hazard ratio 1.37 (95% CI 1.31 to 1.42).[15] Based on this estimate, we require 318 events to provide us with 80% power at the 0.05 level of significance for these analyses. Mortality counts above (section H) show that we shall have sufficient power for this analysis in three of the four medication groups. The digoxin analysis may be underpowered; however, this medication has not been examined in previous studies and the results of this analysis will yield valuable clinical information. We shall also conduct sensitivity analyses to assess the association of shorter treatment interruptions (30 days or longer, 7 days or longer) with mortality. To our knowledge, no studies of heart failure medications have analysed shorter duration treatment interruptions, and this will yield clinically useful information.

Target dosing and mortality: Previous studies show that approximately 50% of patients receive 50% or less of target doses for heart failure medication[15], and that these patients have a significantly higher risk of death: hazard ratio 1.85 (95% CI 1.26 to 2.72).[16] Therefore, to have 80% power at the 0.05 level of significance we require 83 events in this analysis. Mortality feasibility counts above (Section H) show that we have sufficient power for this analysis in all four medication groups. We shall also conduct sensitivity analyses using target dosing as a continuous predictor variable. To our knowledge, few studies have examined this relationship in a linear manner, and this will yield clinically useful information.

Our hospitalisation analyses will also have sufficient power. Emergency hospitalisation is a more frequent event than death.[13] Furthermore, the effect sizes should be equivalent to or larger than mortality, given that hospitalisation represents a less extreme clinical failure/exacerbation than death. Therefore, given that the analyses are powered for mortality, they will be powered for hospitalisations. Our calculations show that we require 82 patient hospitalisations to have sufficient power for our analyses. Our emergency hospitalisation counts above (section H) show that we shall achieve this for all medication groups.

Our sample will be sufficient for reasonable precision around our descriptive estimates. Patients with heart failure on stable treatment often take the same medications for up to 5 years[15] and receive approximately 4 to 15 prescriptions per year. We therefore anticipate between tens of thousands to hundreds of thousands of individual prescription data points. This volume of data should provide reasonable precision.

We shall examine associations between several patient characteristics and treatment interruptions/dosage regimens.[15,16] Treatment interruptions will be categorised as a binary variable: a 90 day interruption or longer vs. less than 90 days. Based on data from published literature, we expect approximately 50% of our patient sample to fall into each category.[15] Dosage regimen will also be a binary variable: 50% of target dose or greater vs. less than 50%. Based on data from previous literature, we expect approximately 50% of our patient sample to fall into each category.[6] Given that our sample will contain 12 343 patients and tens to hundreds of thousands of prescription data points, we expect that these analyses will have sufficient power.

J. Data Linkage Required (if applicable):§

§*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

The patient-level index of multiple deprivation linkage is being requested. We will use this variable in regression analysis to determine the extent to which deprivation is associated with treatment interruptions and dosage regimen. Having these data will also allow us to control for

the potentially confounding effects of deprivation, while we assess the independent associations of treatment interruptions/dosage regimen with patient outcomes. We are also requesting a linkage with the Hospital Episodes Statistics Database. We will use these data to determine when emergency hospitalisations have occurred and whether they are associated with interruptions in heart failure medication or dosage regimen.

K. Study population

Source population: The study start and end dates are 1 January 2010 and 31 July 2017. We shall examine patients who are 18 years of age or older at the time they received a documented diagnosis of heart failure with left ventricular systolic dysfunction or reduced ejection fraction. We have generated a list of diagnostic codes from primary care (Read) coding schemes and ICD-10 coding schemes to identify eligible patients with heart failure.[17] Read codes will be used to identify patients with heart failure in the CPRD while ICD-10 codes will be used to identify heart failure patients from the Hospital Episode Statistics Database. These include all codes specifying heart failure with left ventricular systolic dysfunction or reduced ejection fraction used in the Quality and Outcomes Framework, with additional codes from previously published literature[18] and online clinical code repositories.[19] Events must be in the current registration period only, and also within the up to standard registration period. Records must be of research quality to be included, with data linkage to the Hospital Episode Statistics Database, Index of Multiple Deprivation, and ONS death registry.[20]

Inclusion criteria: We shall include patients receiving "regular" prescriptions of at least one medication in any of the four medication classes between 1 January 2010 and 31 July 2017. We define "regular" prescriptions as an occurrence of a series of three prescriptions with no more than 90 days between the first and third prescription dates. Patients who received two prescriptions before 1 January 2010 will be eligible if the third prescription occurred on or after 1 January 2010. All three prescriptions must have occurred after a diagnosis of left ventricular dysfunction or reduced ejection fraction. Patients must have been treatment naïve for the medication being analysed: free of prescriptions for at least one year of data before the three prescriptions used for cohort entry. The three prescriptions must have non-zero daily dose information and be for one of the following medications recommended by NICE and the BNF for treatment of heart failure: angiotensin-converting enzyme inhibitors (captopril, enalapril maleate, fosinopril sodium, imidapril hydrochloride, lisinopril, perindopril arginine, perindopril erbumine, quinapril hydrochloride, ramipril; trandolapril); angiotensin-II receptor antagonists (candesartan cilexetil, losartan potassium, valsartan); beta-adrenoceptor antagonists (bisoprolol fumarate, carvedilol, nebivolol hydrochloride); aldosterone antagonists (spironolactone, eplerenone); digoxin. We have selected January 2010 as the start date for this study as this coincides with the publication of the NICE clinical guidelines that recommended use of these medications.

Exclusions: Patients will be excluded if they have no documented left ventricular dysfunction or reduced ejection fraction code (Appendix 2); have never received a prescription for any of the medications of interest (Appendices 2 and 3); and have never received three or more prescriptions without a 90-day gap between the first and third prescriptions.

Index date: Patients can contribute data once they have received three prescriptions of the same medication within 90 days with non-zero daily dose information. The index date is the date of the third prescription. The third prescription and all subsequent prescriptions of that medication will be included in the analysis. This index date was selected based on a large Danish study that showed that most patients who experience a gap longer than 90 days do not restart therapy. Therefore, patients experiencing this type of gap during the start of treatment are unlikely to ever receive routine prescriptions for the medication. Furthermore, the study showed that maximum prescribed doses were often achieved within 30 to 180 days after the first prescription.

Cohort end: Patients will stop contributing data at death or at the end of the study window (31 July 2017). Patients will stop contributing data to a medication group on permanent withdrawal of medications within that group, which we define as 365 days without pills. A national study in Denmark showed that longer treatment interruptions are associated with a lower probability of restarting therapy and among patients that experience an interruption of 180 days (6 months) or longer, only 30% restart treatment. We have selected one year to capture some of the estimated 30% of patients that do restart treatment. Most patients (>70%) with interruptions of 365 days or longer will have permanently stopped taking the medication.

Details of the "exposure window" and exposure caveats: If therapy is restarted within 365 days of the last date of medication coverage, the period of non-treatment will be considered a treatment interruption, rather than permanent stoppage, and hospital admissions and deaths occurring in this window will be considered to have occurred during "interruption" time. We shall analyse events occurring from the index date until permanent stoppage of medication, death, or the end of the study date window.

For the mortality survival analysis, we shall account for treatments received during hospitalisation by considering the time from admission to 28 days after discharge as being "on-drug" time. We assume that in-hospital patients will receive necessary treatments and be sent home with sufficient medication to cover a 21 day post-discharge period. Therefore, the threshold for a treatment interruption (7 days or longer) will begin if no primary care prescription**s** are recorded within 28 days after discharge.

Patients may switch drugs within drug groups. We will consider a treatment interruption to end if patients begin receiving prescriptions of another medication within the same group (i.e. switch from lisinopril to ramipril, both ACE inhibitors). The first prescription of the new drug will indicate the end of the "treatment interruption". However, data on the dosage regimen of the new medication will not be eligible for analysis until three prescriptions have been recorded within a 90-day period with non-zero daily dose information. The third and subsequent doses of these medications will be eligible for analysis. We shall only analyse data for medications listed in Appendices 2 and 3.

Minimum Follow-up: There is no minimum follow-up period.

Status of records for incidence/prevalence calculations
We shall calculate the proportion of patients experiencing treatment interruptions of 7 to 29 days; 30 to 89 days; 90 to 179 days; and 180 to 365 days. The proportions will be reported for each of the four medication classes. Only the first occurrence of an interruption will be counted in the numerator. For example, a patient may have an interruption of 8 days, restart treatment, and later experience another interruption of 10 days. This patient would only be counted once in the numerator of the 7 to 29 day interruption. Patients may contribute to the numerators of multiple categories if they experience interruptions of different lengths during their treatment. The denominator for all categories will be the same: eligible patients who have received three or more prescriptions within 90 days and non-zero daily dose information.

We shall also calculate the proportion of patients experiencing treatment interruptions of 7 days or longer. Only the first occurrence of an interruption longer than 7 days will be counted in the numerator. This proportion will be reported for each of the four medication classes. Each patient can only be counted in the numerator once. The denominator will be eligible patients who have received three or more prescriptions within 90 days and non-zero daily dose information.

Sampling: No sampling will be conducted. We will include all patients from the source population.

Linkage: To be included, patient records must have data linkage with Hospital Episodes Statistics Database, Index of Multiple Deprivation, and the ONS death registry.

L. Selection of comparison group(s) or controls
We have selected 7 days as the minimum period without medication to be considered an interruption, to allow for imprecision in the estimate of the number of days covered by each prescription. This categorisation has been used in previous studies.[15]

We shall analyse the association between patient factors and both treatment interruptions and the percentage of target dose achieved. We have selected the following patient characteristics to assess, as previous studies have shown these to be associated with aspects of prescribing and medication adherence: age; sex; number of co-morbidities; number of concomitant heart failure and cardiovascular medications: patient-level deprivation; and length of time (count of the number of days) between heart failure diagnosis and starting medication.[15,16]

We shall examine the association between treatment interruptions and patient outcomes. A treatment interruption will be defined as a binary variable: 90 days or longer without pills vs less than 90 days without pills, including patients with no interruptions. This cut-off has been selected based on previous research on heart failure medications[15] and cardiovascular disease medications,[21] which show that treatment interruptions of 90 days or longer are associated with a lower probability of restarting therapy and increased mortality.

We shall also examine the association between the percentage of target dose achieved and patient outcomes. Target dose achievement will be defined as a binary variable: 50% or greater of target achievement vs. less than 50%. This cut-off has been used in previous studies and has been shown to be significantly associated with mortality.[16]

M. Exposures, Health Outcomes[§] and Covariates
[§]*Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy*

The main outcomes in this study are all-cause mortality, all-cause emergency hospital admission, and cardiovascular-related emergency hospital admission (Aims 1.5, 2.4). Treatment interruptions and dosage regimen will be classified as predictor variables in these analyses. However, they will be classified as outcome variables in Aims 1.1 to 1.4 and 2.1 to 2.3.

1. Demographic characteristics

Source/Derivation of variables A-J: Identified from the patient file, practice file, test file, therapy files, and index of multiple deprivation linked data using Read code lists (Appendix 2). Read code lists have been created using previously published studies, a clinical codes repository[22], and lists held by CPRD experts (Bankhead, Smith) in the Nuffield Department of Primary Care Health Sciences at the University of Oxford. We shall additionally identify co-morbidities using ICD-10 codes and examining the primary diagnosis for hospitalisations during the study period. Serum cholesterol, HDL, LDL values will be extracted from CPRD data associated with the relevant entity types (163, 175, 177 respectively). Alcohol consumption values will be extracted from CPRD data associated with

Predictor variables in Aims 1.4, 2.5 and Co-variates for Aims 1.5, 2.4

A. Age (continuous)
B. Sex (binary)
C. Number of co-morbidities (count) – diagnosed at any time before cohort entry or at any point between index date and end of follow-up
    - Asthma
    - Atrial fibrillation/flutter (including paroxysmal)
    - Cancer
    - Chronic kidney disease
    - Chronic obstructive pulmonary disease
    - Coronary heart disease (including myocardial infarction, coronary artery bypass graft, and percutaneous coronary intervention)
    - Dementia
    - Diabetes
    - Hypertension
    - Peripheral vascular disease
    - Stroke and transient ischemic attack
D. Concomitant heart failure/cardiovascular medications (count) – three or more prescriptions at any point between index date and end of follow-up
    - Aldosterone antagonists
    - Angiotensin-converting enzyme inhibitors
    - Angiotensin-2 receptor blockers
    - Anticoagulants
    - Anti-platelet drugs (excluding NSAIDS other than Aspirin)
    - Amiodarone
    - Beta-blockers
    - Calcium channel blockers
    - Digoxin
    - Diuretics
    - Ivabradine
    - Nitrates
    - Statins
E. Patient level of deprivation (categorical) – derived from data closest to the index date
F. Length of time since heart failure diagnosis before starting medication (count) – on the index date

Co-variates for Aims 1.5, 2.4

G. Cholesterol – Total, HDL, LDL (continuous) - derived from data closest to the index date
H. Smoking status (binary) - derived from data closest to the index date
I. Alcohol consumption (categorical: non-drinker; former drinker; occasional drinker; moderate drinker; heavy drinker; alcohol status missing) – we shall use the most recent record of alcohol consumption in the five years before the index date to classify participants' drinking behaviour. We shall reclassify non-drinkers as former drinkers if they had any record of drinking in their entire clinical record entered on CPRD before the index date. We shall also use data fields with information describing daily and/or weekly amount of alcohol consumed to define participants as non-drinkers, moderate drinkers (drank within daily and/or weekly recommended sensible drinking limits for the UK at the time of observation), and heavy drinkers (exceeded daily and/or weekly sensible drinking limits).

2. Prescription data

Source/derivation of variables A-B: Prescribing data will be identified in therapy files. To identify treatment interruptions (Variable A) we will use product codes to identify medications and the 'Number of days' prescription variable. To identify target dose achievement we will use product codes (Appendix 2) to identify medications and the 'Numeric daily dose' variable to identify the prescribed dose. We will divide the mean prescribed dose by the target doses listed in NICE clinical guidelines and the BNF (Appendix 3).

Exposures for Aims 1.5, 2.4 and Outcomes for Aims 1.1 to 1.4 and 2.1 to 2.3

Treatment interruptions (binary – 90 day interruption or longer vs. less than 90 day interruption)

A. Percent achievement of target dosing (binary – 50% or greater target dose achievement vs. less than 50%)

3. Health outcomes

Source/derivation of variables A-C: Admissions data will be identified from the HES Hospitalisations (HES_hospital.txt) data set. To identify emergency admissions we shall use the 'admimeth' variable. To determine the diagnosis as cardiovascular-related we will use the 'ICD_PRIMARY' variable in the 'Primary diagnoses across a hospitalisation (HES_primary_diag_hosp.txt)' dataset. See Appendix 2 for ICD-10 cardiovascular codes. Death data will be identified from the ONS registry.

Outcomes for Aims 1.5, 2.4

A. All-cause emergency hospital admission (binary)
B. Cardiovascular-related emergency hospital admission (binary)
C. All-cause mortality (binary)

N. Data/ Statistical Analysis

Descriptive statistics

We shall produce descriptive statistics of baseline characteristics, treatment interruptions, and prescription dose. We shall present binary and categorical variables as percentages. For continuous variables we shall use means with standard deviations or medians with interquartile ranges, depending on data distribution. We shall derive percentage of target dose achievement by dividing the mean daily dose by guideline recommended target doses, which are listed in Appendix 3. We shall determine treatment interruptions by subtracting the 'number of days' of treatment in the CPRD dataset by the number of days between prescriptions. Excess tables from only the last prescription will be carried over.

Univariate analysis

We shall examine univariate associations between predictors and binary outcomes by using logistic regression. We shall examine time-to-event outcomes using Cox proportional hazards modelling and continuous outcomes by linear regression.

Multi-variate analysis

Aim 1.4: We shall use multi-variate Cox proportional hazards models to assess independent associations between the following predictor variables and time to first treatment interruption, defined as a binary variable (90 day interruption or greater vs. less than 90 day interruption): age; sex; number of co-morbidities; number of concomitant heart failure and cardiovascular medications; patient level of deprivation; and length of time since heart failure diagnosis before starting medication. We shall present the results as hazard ratios with 95% confidence intervals.

Aim 2.3: We shall use multi-variate logistic regression to assess the independent associations between the following predictor variables and percentage of target dose achieved, defined as a binary variable (50% or greater of target dose vs. less than 50%): age; sex; number of comorbidities; number of concomitant heart failure and cardiovascular medications; patient level of deprivation; and length of time since heart failure diagnosis prior to starting medication. We will also conduct a sensitivity analysis using multi-variate linear regression and define the percentage of target dose achieved as a continuous outcome.

Aim 1.5: We shall use multi-variate Cox proportional hazards models to assess the independent association between treatment interruptions in the use of four heart failure medications and time to first all-cause emergency hospital admission, first cardiovascular-related emergency hospital admission, and mortality. Treatment interruptions will be entered into the models as a time-dependent variable to indicate that patients are considered at-risk only during interruptions in treatment that extend beyond 90 days. We shall adjust for the following co-variates: age; sex; number of comorbidities; number of concomitant heart failure and cardiovascular medications; type of concomitant heart failure and cardiovascular medications; patient level of deprivation; length of time since heart failure diagnosis before starting medication; cholesterol; smoking status; alcohol consumption; and diabetes status. We shall test for model assumptions, such as linearity of continuous variables, the proportion hazard assumptions, and lack of interactions.

The results will be reported as hazard ratios with 95% confidence intervals for each medication class: renin-angiotensin system inhibitors; beta-blockers; aldosterone antagonists; and digoxin. We shall also conduct sensitivity analyses examining the association between mortality and interruptions of 30 days or more and 7 days or more.

Aim 2.4: We shall use multi-variate Cox proportional hazards models to assess the independent association between percentage of target dose achievement for four classes of heart failure medications and time to first all-cause emergency hospital admission, cardiovascular-related emergency hospital admission and mortality. Mean percentage of target dose achievement will be entered into the model as a binary variable (50% or greater achievement vs. less than 50%). We shall adjust for the following co-variates: age; sex; number of comorbidities; number of concomitant heart failure and cardiovascular medications; type of concomitant heart failure and cardiovascular medications; patient level of deprivation; length of time since heart failure diagnosis before starting medication; cholesterol; smoking status; alcohol consumption; and diabetes status. We shall test for model assumptions, such as linearity of continuous variables, the proportion hazard assumptions, and lack of interactions. The results will be reported as hazard ratios with 95% confidence intervals for each medication group: renin-angiotensin system inhibitors; beta-blockers; aldosterone antagonists; and digoxin. We shall also conduct sensitivity analyses examining target dose achievement as a continuous variable. This sensitivity analysis will use multi-variate linear regression with the same co-variates as the main analysis.

O. Plan for addressing confounding

We have examined previous literature to identify factors that could confound our results.[15,16,24] Based on this, we shall enter the following co-variates into multi-variate models to control for potential confounding: age; sex; number of comorbidities; number of concomitant heart failure medications; type of concomitant heart failure medications; patient level of deprivation; length of time since heart failure diagnosis before starting medication; cholesterol; smoking status; and diabetes status.

P. Plans for addressing missing data

Missing data patterns will be investigated. Missing data for co-morbidities or outcomes will be assumed to indicate that the condition was not present. Missing data for concomitant medications will be assumed to indicate that the medications were not prescribed. Missing data for smoking status will be assumed to indicate non-smokers. Missing data for alcohol consumption will be imputed using multiple imputation. Missing data for cholesterol and patient-level deprivation will be imputed using multiple imputation. Sensitivity analyses will be conducted to compare results using imputed data to complete case data. If more than 10% of records have missing data for the daily dose or number of prescribed days we shall explore imputation techniques and sensitivity analyses with complete cases.

Q. Patient or user group involvement (if applicable)

Our Patient and Public Involvement (PPI) activities were developed with guidance from a PPI expert (Lynne Madocks) and the NIHR Handbook for PPI in Health and Social Care.[1] Once we have analysed the data we shall recruit 3-5 patients with heart failure from patient participation groups (PPGs), which we access via our PPI expert. We will host a 30-minute focus group to discuss reasons for delays in visiting the GP to obtain prescriptions, whether patients inquire about their medication dose at the GP surgery, and how patients monitor themselves and their symptoms after a change in dose. Patients will also be presented with results from the study drafted with guidance from our PPI expert and the NIHR PPI Handbook.[1] We shall ask whether the research findings make sense and shall get input on lay summaries of the results which will be published in the public domain.

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The results of this study will be drafted into manuscripts for submission to peer-reviewed journals and abstracts will be sent to relevant conferences. We shall publish lay and technical summaries of the results on the website of the National Institute for Health Research School for Primary Care Research. We shall publish summaries of the results on the University of Oxford and Nuffield Department of Primary Care Health Science websites.

S. Limitations of the study design, data sources, and analytic methods

By consulting existing CPRD and clinical content experts we have attempted to mitigate the limitations of our study. However, this proposed study has some limitations. First, we may encounter missing data and losses to follow-up. We have described our plan to deal with missing data above. Second, given that this is a study of routinely collected data, our analysis is restricted to variables that are collected. As a result, there are potentially relevant patient, physician, and health system factors that may affect treatment interruptions that we are not able to analyse, such as preferences, physician experience, disagreements between providers on a treatment plan, and financial and geographic barriers to access of prescriptions. However, the CPRD does include the majority of important predictors shown to be relevant in previous literature. Thirdly, there is the possibility of misclassification bias using electronic health records. Patients may be

taking medications at times when they are categorised as not doing so, as they may have stockpiled drugs from previous prescriptions or have excess from hospital discharges. To address this we have classified treatment interruptions to begin after a seven-day period without medication. This "grace" period should mitigate some of the imprecision associated with using routinely collected data. We have also built in a 28-day "grace" period after discharge from hospitalisation to account for prescriptions collected at discharge. This period of time is evidence-based, since previous literature has shown that most patients who are discharged after a heart failure admission claim prescriptions within 28 days.[15] It is also possible that patients will be categorised as receiving medication when they are not actually taking it. This is a limitation of the available data. This kind of misclassification would lead to an underestimate of the associations between treatment effects and patient outcomes. These limitations will be considered when interpreting the results of the study. Fourthly, our analysis of the association of digoxin use with patient outcomes may be underpowered. However, this medication is commonly used and, to our knowledge, no previous analyses have examined the association between digoxin treatment interruptions/dosage regimens and patients' clinical outcomes. These analyses will therefore yield valuable clinical information and help to build the evidence base for future research. It is also possible that they will be adequately powered, but without prior estimates of this specific association that is difficult to determine. Fifthly, we have restricted inclusion to patients receiving "regular" prescriptions of heart failure medications. We shall therefore be excluding patients receiving the most variable and poorest quality care. We may also be excluding patients for whom achieving a stable prescription regimen is difficult, which is likely to include patients with multi-morbidities and patients who experience rapid progression of heart failure. However, this will not affect the internal validity of the study.

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List of Appendices *(Submit all appendices as separate documents to this application)*
Appendix 1. NIHR School for Primary Care Research funded protocol
Appendix 2. Code lists
Appendix 3. Medication list and target doses

Appendix 6.3 Medication list and target doses according to NICE clinical guidelines and the British National Formulary

Table 1. List of medications and target doses

Angiotensin converting enzyme inhibitors		Half Life[a]
Captopril	150 mg daily Initially 6.25–12.5 mg 2–3 times a day, then increased if tolerated to up to 150 mg daily in divided doses, dose to be increased gradually at intervals of at least 2 weeks.	3 hours
Enalapril maleate	40 mg daily Initially 2.5 mg once daily, increased if tolerated to 10–20 mg twice daily, dose to be increased gradually over 2–4 weeks.	11 hours[b]
Fosinopril sodium	40 mg daily Initially 10 mg once daily, then increased if tolerated to 40 mg once daily, doses to be increased gradually.	14 hours[b,c]
Imidapril hydrochloride	20 mg daily Initially 2.5 mg daily, increased if necessary to 10 mg daily, dose to be taken before food, dose to be increased at intervals of at least 3 weeks; maximum 20 mg per day.	24 hours
Lisinopril	35 mg daily Initially 2.5 mg once daily; increased in steps of up to 10 mg at least every 2 weeks; maximum 35 mg per day.	12 hours[b]
Perindopril arginine	5 mg daily Initially 2.5 mg once daily for 2 weeks, then increased if tolerated to 5 mg once daily, dose to be taken in the morning.	25 to 30 hours (27.5 hours)
Perindopril erbumine	4 mg daily Initially 2 mg once daily for at least 2 weeks, dose to be taken in the morning, then increased if tolerated to 4 mg once daily.	25 to 30 hours (27.5 hours)
Quinapril hydrochloride	40 mg daily Initially 2.5 mg daily, increased if tolerated to 10–20 mg daily in 1–2 divided doses, doses to be increased gradually; maximum 40 mg per day.	25 hours
Ramipril	10 mg daily Initially 1.25 mg once daily, increased if tolerated to 10 mg daily, preferably taken in 2 divided doses, increase dose gradually at intervals of 1–2 weeks.	13 to 17 (15 hours)
Trandolapril	4 mg daily Initially 500 micrograms once daily, then increased to up to 4 mg once daily, doses to be increased gradually.	16 to 24 hours[b] (20 hours)
Angiotensin-II Receptor Antagonists		Half Life
Candesartan cilexetil	32 mg daily Initially 4 mg once daily, increased at intervals of at least 2 weeks to 'target' dose of 32 mg once daily or to maximum tolerated dose. Candesartan cilexetil is given in an initial dose of 4 mg once daily. The dose should be doubled at intervals of not less than two weeks up to 32 mg once daily if tolerated; blood pressure should be monitored during dose increases.	9 hours
Losartan potassium	50 mg daily in those aged 60 years and over. An initial dose of 12.5 mg is given once daily, and may be doubled at weekly intervals to a usual maintenance dose of 50 mg once daily	3 to 9 hours (6 hours)
Valsartan	320 mg daily	6 hours

	Valsartan is given in an initial dose of 40 mg twice daily. The dose should be increased, as tolerated, to 160 mg twice daily.	
Beta-adrenoceptor antagonists (Beta-blockers)		Half Life
Bisoprolol fumarate	10 mg daily Initially 1.25 mg once daily for 1 week, dose to be taken in the morning, then increased if tolerated to 2.5 mg once daily for 1 week, then increased if tolerated to 3.75 mg once daily for 1 week, then increased if tolerated to 5 mg once daily for 4 weeks, then increased if tolerated to 7.5 mg once daily for 4 weeks, then increased if tolerated to 10 mg once daily; maximum 10 mg per day.	10 to 12 hours (11 hours)
Carvedilol	50mg daily Initially 3.125 mg twice daily, dose to be taken with food, then increased to 6.25 mg twice daily, then increased to 12.5 mg twice daily, then increased to 25 mg twice daily, dose should be increased at intervals of at least 2 weeks up to the highest tolerated dose, max. 25 mg twice daily in patients with severe heart failure or body-weight less than 85 kg; max. 50 mg twice daily in patients over 85 kg.	6 to 10 hours (8 hours)
Nebivolol hydrochloride	10 mg daily Initially 1.25 mg once daily for 1–2 weeks, then increased if tolerated to 2.5 mg once daily for 1–2 weeks, then increased if tolerated to 5 mg once daily for 1–2 weeks, then increased if tolerated to 10 mg once daily.	10 hours
Aldosterone antagonists		Half Life
Spironolactone	50 mg daily *Moderate to severe heart failure* Initially 25 mg once daily, then adjusted according to response to 50 mg once daily.	1.4 hours[d]
Eplerenone	50 mg daily Initially 25 mg daily, then increased to 50 mg daily, increased within 4 weeks of initial treatment.	4 to 6 hours (5 hours)
Cardiac glycosides		Half Life
Digoxin	62.5–125 micrograms once daily, reduce dose in the elderly and renal impairment.	36 to 48 hours (42 hours)

[a]Elimination/terminal half-life of the active compound and active metabolites, unless otherwise reported. Values in brackets represent the value utilised in analysis in this study. [b]Effective half-life at steady state. [c]Half-life in patients with heart failure. [d]Information not available from BNF so this half-life value was taken from regulatory documents published by the United States Food and Drug Administration.

Appendix 6.4 Data extracted from the Clinical Practice Research Datalink

Data dictionary

CPRD project on medications for heart failure

Five distinct medications groups are analysed in this study:

- Angiotensin-converting enzyme inhibitors (file prefix: “angio-inhib”)
- Angiotensin-II receptor antagonists (file prefix: “angio-anta”)
- Beta-adrenoceptor antagonists (file prefix: “beta-block”)
- Aldosterone antagonists (file prefix: “aldo-anta”)
- Digoxin (file prefix: “digoxin”)

For each medication group, two files have been generated:

- PREFIX_patients.csv, containing patient-level information
- PREFIX_prescriptions.csv, containing prescription-level information for each patient

PREFIX_patients.csv

Variable	*Description*
patid	Patient identifier
heartfailure	Date of first heart failure
indexdate	Index date (date of third prescription satisfying the inclusion criteria)
study_exit	Study exit date
gender	M/F
age_indexdate	Age at index date
comorb_X	Series of comorbidities flags (0/1)
comed_X	Series of co-medication flags (0/1)
cholesterol_date	Date of cholesterol measurement (most recent before index date)
cholesterol_value	Value of cholesterol measurement (most recent before index date)
HDL_date	Date of HDL measurement (most recent before index date)
HDL_value	Value of HDL measurement (most recent before index date)
LDL_date	Date of LDL measurement (most recent before index date)
LDL_value	Value of LDL measurement (most recent before index date)
smoking	Smoking status (0/1)
drinking	Drinking status (former, non, occasional, moderate, heavy)
IMD_decile	2010 Index of Multiple Deprivation (deciles)
death	Date of death, if any
allcause_admission	Date of first all-cause emergency hospital admission
cardiovascular_admission	Date of first cardiovascular-related emergency hospital admission

PREFIX_prescriptions.csv

Variable	*Description*
prodcode	Product code
patid	Patient identifier
prescdate	Date of prescription
qty	Quantity prescribed
daily_dose	Daily dose prescribed
dose_duration	Number of days prescribed
strength	Product strength

Appendix 6.5 Details of comorbidities and concomitant medications

Table 2. Details of comorbidities and concomitant medications

Patient characteristics	Overall (n=8274)	Patients by medication cohort				
		ACE inhibitors (n=4011)	Angiotensin-II receptor blockers (n=1603)	Beta-blockers (n=5383)	Aldosterone antagonists (n=2498)	Digoxin (n=1424)
Comorbidities						
Asthma	48% (3996)	47% (1882)	54% (866)	46% (2478)	53% (1329)	50% (716)
Atrial fibrillation	45% (3683)	40% (1615)	47% (747)	43% (2340)	45% (1134)	84% (1196)
Cancer	17% (1432)	16% (659)	18% (282)	17% (921)	16% (398)	17% (240)
Coronary heart disease	51% (4247)	51% (2057)	50% (809)	52% (2781)	55% (1386)	45% (636)
Chronic kidney disease	41% (3402)	38% (1517)	46% (730)	40% (2168)	43% (1070)	47% (669)
COPD	19% (1546)	18% (708)	21% (331)	17% (895)	21% (535)	22% (313)
Dementia	5% (444)	6% (227)	5% (77)	5% (266)	5% (124)	8% (107)
Diabetes	33% (2745)	31% (1258)	35% (560)	34% (1812)	37% (927)	37% (522)
Hypertension	64% (5332)	63% (2525)	67% (1081)	64% (3437)	64% (1599)	65% (927)
Peripheral vascular disease	9% (709)	8% (313)	9% (146)	8% (439)	8% (203)	9% (125)
Stroke	18% (1464)	17% (676)	17% (266)	17% (908)	18% (448)	21% (303)
Medications[a]						
Aldosterone antagonists	53% (4362)	50% (2003)	52% (841)	51% (2742)	-	60% (852)
Amiodarone	18% (1460)	15% (592)	20% (313)	17% (931)	21% (515)	27% (389)
ACE inhibitors	93% (7702)	-	87% (1401)	92% (4942)	94% (2355)	93% (1318)
ARB	37% (3033)	21% (833)	-	34% (1811)	37% (917)	38% (544)
Anti-coagulants	56% (4604)	52% (2102)	57% (911)	55% (2940)	59% (1472)	84% (1190)
Anti-platelets	78% (6493)	78% (3114)	80% (1278)	78% (4219)	79% (1984)	76% (1087)
Beta-blockers	70% (5849)	37% (1487)	44% (709)	-	43% (1075)	46% (648)
Calcium channel blockers	51% (4211)	48% (1936)	54% (866)	49% (2631)	50% (1237)	53% (756)
Digoxin	31% (2566)	26% (1042)	30% (476)	28% (1484)	34% (838)	-
Diuretics	88% (7297)	87% (3493)	89% (1429)	87% (4703)	-	95% (1351)
Ivabradine	6% (493)	6% (250)	7% (119)	6% (301)	10% (238)	4% (62)
Nitrates	48% (3978)	47% (1866)	51% (816)	48% (2567)	51% (1284)	45% (634)
Statins	78% (6511)	78% (3126)	80% (1281)	79% (4233)	80% (1998)	76% (1084)

[a]One or more prescriptions of any of the following medications during the study period (January 1, 2010 to July 1, 2017) qualified them as concomitant medications. Abbreviations: ACE=angiotensin converting enzyme inhibitor; ARB=angiotensin-II receptor blockers; COPD=chronic obstructive pulmonary disease.

Appendix 6.6 Summary of univariate analysis for users of angiotensin converting enzyme inhibitors

Table 3. Univariate analysis for users of angiotensin converting enzyme inhibitors

Patient characteristic variables	Outcomes[a] and p-values				
	Target dosing	Interruption		Admissions	
	>= 50%	>=90 days	>=7 days[b]	All-cause	CVD
Age (continuous)	↓<0.001	↑0.001	↑0.182	↑<0.001	↑<0.001
Male gender[c]	↑<0.001	↓0.007	↓0.076	↓<0.001	↓0.521
Index of multiple deprivation quintile[d]	0.854	0.239	0.293	0.203	0.904
Months since heart failure diagnosis (continuous)	↓<0.001	↑<0.001	↑0.001	↑0.011	↑0.039
Alcohol consumption[e]	0.006	0.270	0.670	0.001	0.067
Smoking	↑0.069	↓0.181	↓0.604	↓0.088	↓0.070
Cholesterol	↓0.727	↓0.942	↑0.002	↓<0.001	↓<0.001
No. of comorbidities (continuous)	↓0.214	↑<0.001	↑0.098	↑<0.001	↑<0.001
Chronic kidney disease status	↓<0.001	↑0.001	↑0.210	↑<0.001	↑<0.001
Coronary heart disease	↓0.048	↑0.197	↓0.454	↑<0.001	↑<0.001
Diabetes status	↑0.292	↑0.944	↓0.695	↑<0.001	↑<0.001
Hypertension	↑<0.001	↑0.560	↓0.752	↑<0.001	↑<0.001
No. of concomitant CVD medications (continuous)	↑0.531	↑<0.001	↑0.033	↑<0.001	↑<0.001
Concomitant use of angiotensin-II receptor blockers	↓0.002	↑<0.001	↑<0.001	↑<0.001	↑0.001
Concomitant use of beta-blockers	↑0.557	↓0.753	↓0.220	↑<0.001	↑0.001
Concomitant use of aldosterone antagonists	↑<0.001	↑0.003	↑0.001	↑<0.001	↑0.001
Concomitant use of digoxin	↓0.250	↑0.373	↑0.047	↑<0.001	↑0.001
Concomitant use of diuretics	↑0.269	↑0.012	↑0.180	↑<0.001	↑<0.001
Medication exposure variables					
Medication interruptions of 90 days or longer (binary)	-	-	-	↓<0.001	↓<0.001
Cumulative target dose achievement >=50% (binary)	-	-	-	↓0.001	↓<0.001
Dosing interaction term – target dose achievement >=50% (binary) considering half-life decline during interruptions	-	-	-	↓0.720	↓0.657

[a]Outcome measures were: cumulative median target dose achievement of greater than or equal to 50%; time to first treatment interruption of 90 days or longer, time to first treatment interruption of 7 days or longer; time to first all-cause emergency hospital admissions; and time to first cardiovascular-related emergency hospital admissions. For time to event outcomes, the log-rank test of equality was used for categorical variables while univariate Cox proportional hazard regression was used for binary and continuous variables. For binary dosing achievement outcomes, chi-square tests were used to assess categorical variables and univariate logistic regression was used for continuous variables. For continuous dosing achievement outcomes, the one-way analysis of variance test was used to assess categorical variables and univariate linear regression was used for continuous variables. [b]Sensitivity analysis. [c]Female was reference group. [d]Lowest level of deprivation was the reference group. [e]Three groups: non-drinker/former drinker (reference group); occasional; moderate/heavy. For binary and continuous variables, arrows represent the direction of the univariate effect estimate: ↓ indicates a decrease in the risk/odds of the outcome and ↑ indicates an increase in the risk/odds of the outcome.

Appendix 6.7 Summary of univariate analysis for users of angiotensin-II receptor blockers

Table 4. Univariate analysis for users of angiotensin-II receptor blockers

Patient characteristic variables	Outcomes[a] and p-values				
	Target dosing	Interruption		Admissions	
	>= 50%	>=90 days	>=7 days[b]	All-cause	CVD
Age (continuous)	↓0.087	↑0.083	↓0.476	↑<0.001	↑<0.001
Male gender[c]	↑0.507	↓0.480	↑0.132	↑0.336	↑0.056
Index of multiple deprivation quintile[d]	0.670	0.481	0.598	0.081	0.346
Months since heart failure diagnosis (continuous)	↑0.760	↑0.196	↑0.588	↓0.676	↑0.709
Alcohol consumption[e]	0.956	0.195	0.708	0.220	0.077
Smoking	↓0.901	↑0.502	↑0.151	↑0.173	↑0.180
Cholesterol	↑0.813	↓0.386	↑0.067	↓0.003	↓<0.001
No. of comorbidities (continuous)	↑0.883	↑0.024	↓0.826	↑<0.001	↑<0.001
Chronic kidney disease status	↓0.086	↑0.016	↓0.804	↑<0.001	↑<0.001
Coronary heart disease	↓0.496	↑0.695	↑0.391	↑<0.001	↑<0.001
Diabetes status	↑0.082	↑0.213	↓0.756	↑<0.001	↑<0.001
Hypertension	↑<0.001	↓0.409	↓0.056	↑<0.763	↑0.962
No. of concomitant CVD medications (continuous)	↓0.054	↑0.001	↑0.455	↑<0.001	↑<0.001
Concomitant use of angiotensin-converting enzyme inhibitors	↓0.152	↑0.037	↑0.980	↑0.831	↑0.542
Concomitant use of beta-blockers	↓0.835	↑0.058	↑0.592	↑<0.001	↑<0.001
Concomitant use of aldosterone antagonists	↓0.003	↑0.173	↑0.423	↑<0.001	↑<0.001
Concomitant use of digoxin	↓0.189	↑0.118	↓0.411	↑<0.001	↑0.001
Concomitant use of diuretics	↓0.829	↑0.187	↓0.883	↑<0.001	↑0.001
Medication exposure variables					
Medication interruptions of 90 days or longer (binary)	-	-	-	↓0.001	↓0.003
Cumulative target dose achievement >=50% (binary)	-	-	-	↓0.016	↓0.009
Dosing interaction term – target dose achievement >=50% (binary) considering half-life decline during interruptions	-	-	-	↑0.883	↓0.601

[a]Outcome measures were: cumulative median target dose achievement of greater than or equal to 50%; time to first treatment interruption of 90 days or longer, time to first treatment interruption of 7 days or longer; time to first all-cause emergency hospital admissions; and time to first cardiovascular-related emergency hospital admissions. For time to event outcomes, the log-rank test of equality was used for categorical variables while univariate Cox proportional hazard regression was used for binary and continuous variables. For binary dosing achievement outcomes, chi-square tests were used to assess categorical variables and univariate logistic regression was used for continuous variables. For continuous dosing achievement outcomes, the one-way analysis of variance test was used to assess categorical variables and univariate linear regression was used for continuous variables. [b]Sensitivity analysis. [c]Female was reference group. [d]Lowest level of deprivation was the reference group. [e]Three groups: non-drinker/former drinker (reference group); occasional; moderate/heavy. For binary and continuous variables, arrows represent the direction of the univariate effect estimate: ↓ indicates a decrease in the risk/odds of the outcome and ↑ indicates an increase in the risk/odds of the outcome.

Appendix 6.8 Summary of univariate analysis for users of beta-blockers

Table 5. Univariate analysis for users of beta-blockers

Patient characteristic variables	Outcomes[a] and p-values				
	Target dosing	Interruption		Admissions	
	>= 50%	>=90 days	>=7 days[b]	All-cause	CVD
Age (continuous)	↓<0.001	↑0.573	↓0.815	↑<0.001	↑<0.001
Male gender[c]	↑<0.001	↓0.286	↑0.240	↓0.798	↑0.114
Index of multiple deprivation quintile[d]	0.122	0.672	0.080	0.008	0.114
Months since heart failure diagnosis (continuous)	↓<0.001	↑0.002	↑0.096	↑0.004	↑0.025
Alcohol consumption[e]	0.571	0.098	0.243	<0.001	0.040
Smoking	↑0.042	↑0.997	↓0.836	↓0.483	↓0.268
Cholesterol	↓0.480	↑0.096	↑0.031	↓<0.001	↓<0.001
No. of comorbidities (continuous)	↓0.807	↑0.093	↑0.121	↑<0.001	↑<0.001
Atrial fibrillation	↑<0.001	↑0.030	↑0.088	↑<0.001	↑<0.001
Chronic kidney disease status	↓0.207	↓0.533	↑0.159	↑<0.001	↑<0.001
Coronary heart disease	↓0.006	↓0.308	↑0.805	↑<0.001	↑<0.001
Diabetes status	↑<0.001	↑0.953	↑0.895	↑<0.001	↑<0.001
Hypertension	↑0.081	↓0.713	↓0.262	↑<0.001	↑<0.001
No. of concomitant CVD medications (continuous)	↑<0.001	↑0.001	↑0.041	↑<0.001	↑<0.001
Concomitant use of angiotensin-converting enzyme inhibitors	↑0.247	↓0.219	↓0.164	↑0.110	↑0.056
Concomitant use of angiotensin-II receptor blocker	↓0.727	↑0.003	↑0.011	↑0.149	↑0.318
Concomitant use of aldosterone antagonists	↑<0.001	↑0.234	↓0.994	↑<0.001	↑<0.001
Concomitant use of digoxin	↑<0.001	↑0.004	↑0.110	↑<0.001	↑<0.001
Concomitant use of diuretics	↑0.010	↑0.475	↓0.450	↑<0.001	↑<0.001
Medication exposure variables					
Medication interruptions of 90 days or longer (binary)	-	-	-	↓<0.001	↓<0.001
Cumulative target dose achievement >=50% (binary)	-	-	-	↓<0.001	↓0.024
Dosing interaction term – target dose achievement >=50% (binary) considering half-life decline during interruptions	-	-	-	↓0.330	↓0.808

[a]Outcome measures were: cumulative median target dose achievement of greater than or equal to 50%; time to first treatment interruption of 90 days or longer, time to first treatment interruption of 7 days or longer; time to first all-cause emergency hospital admissions; and time to first cardiovascular-related emergency hospital admissions. For time to event outcomes, the log-rank test of equality was used for categorical variables while univariate Cox proportional hazard regression was used for binary and continuous variables. For binary dosing achievement outcomes, chi-square tests were used to assess categorical variables and univariate logistic regression was used for continuous variables. For continuous dosing achievement outcomes, the one-way analysis of variance test was used to assess categorical variables and univariate linear regression was used for continuous variables. [b]Sensitivity analysis. [c]Female was reference group. [d]Lowest level of deprivation was the reference group. [e]Three groups: non-drinker/former drinker (reference group); occasional; moderate/heavy. For binary and continuous variables, arrows represent the direction of the univariate effect estimate: ↓ indicates a decrease in the risk/odds of the outcome and ↑ indicates an increase in the risk/odds of the outcome.

Appendix 6.9 Summary of univariate analysis for aldosterone antagonists

Table 6. Univariate analysis for aldosterone antagonists

Patient characteristic variables	Outcomes[a] and p-values				
	Target dosing	Interruption		Admissions	
	>= 50%	>=90 days	>=7 days[b]	All-cause	CVD
Age (continuous)	↓<0.001	↑<0.001	↑0.021	↑<0.001	↑<0.001
Male gender[c]	↑0.002	↓0.018	↑0.833	↓0.558	↑0.356
Index of multiple deprivation quintile[d]	0.599	0.280	0.521	0.187	0.283
Months since heart failure diagnosis (continuous)	↓0.106	↑0.003	↑0.117	↑0.059	↑0.018
Alcohol consumption[e]	0.126	0.363	0.205	<0.001	0.073
Smoking	↑0.003	↓0.434	↑0.685	↓0.395	↓0.809
Cholesterol	↓0.598	↓0.145	↑0.347	↓0.009	↓<0.001
No. of comorbidities (continuous)	↓<0.001	↑<0.001	↑0.001	↑<0.001	↑<0.001
Chronic kidney disease status	↓<0.001	↑<0.001	↑0.162	↑<0.001	↑<0.001
Coronary heart disease	↑0.423	↓0.332	↓0.638	↑<0.001	↑<0.001
Diabetes status	↓0.778	↑0.350	↑0.521	↑<0.001	↑<0.001
Hypertension	↓0.154	↑<0.001	↑0.159	↑0.001	↑0.117
No. of concomitant CVD medications (continuous)	↓0.742	↑<0.001	↑0.052	↑<0.001	↑<0.001
Concomitant use of angiotensin-converting enzyme inhibitors	↓0.863	↑0.335	↓0.511	↑0.879	↓0.178
Concomitant use of angiotensin-II receptor blocker	↑0.606	↑0.005	↑0.083	↑0.062	↑0.086
Concomitant use of beta-blockers	↑0.289	↑0.273	↓0.824	↑0.045	↑0.001
Concomitant use of digoxin	↓0.095	↑0.006	↑0.037	↑<0.001	↑<0.001
Medication exposure variables					
Medication interruptions of 90 days or longer (binary)	-	-	-	↓<0.001	↓<0.001
Cumulative target dose achievement >=50% (binary)	-	-	-	↓0.230	↑0.732
Dosing interaction term – target dose achievement >=50% (binary) considering half-life decline during interruptions	-	-	-	↑<0.001	↑<0.001

[a]Outcome measures were: cumulative median target dose achievement of greater than or equal to 50%; time to first treatment interruption of 90 days or longer, time to first treatment interruption of 7 days or longer; time to first all-cause emergency hospital admissions; and time to first cardiovascular-related emergency hospital admissions. For time to event outcomes, the log-rank test of equality was used for categorical variables while univariate Cox proportional hazard regression was used for binary and continuous variables. For binary dosing achievement outcomes, chi-square tests were used to assess categorical variables and univariate logistic regression was used for continuous variables. For continuous dosing achievement outcomes, the one-way analysis of variance test was used to assess categorical variables and univariate linear regression was used for continuous variables. [b]Sensitivity analysis. [c]Female was reference group. [d]Lowest level of deprivation was the reference group. [e]Three groups: non-drinker/former drinker (reference group); occasional; moderate/heavy. For binary and continuous variables, arrows represent the direction of the univariate effect estimate: ↓ indicates a decrease in the risk/odds of the outcome and ↑ indicates an increase in the risk/odds of the outcome.

Appendix 6.10 Summary of univariate analysis for digoxin

Table 7. Univariate analysis for digoxin

Patient characteristic variables	Outcomes[a] and p-values				
	Target dosing	Interruption		Admissions	
	>=75%	>=90 days	>=7 days[b]	All-cause	CVD
Age (continuous)	↓<0.001	↓0.001	↓0.101	↑<0.001	↑<0.001
Male gender[c]	↑0.003	↓0.835	↓0.567	↓0.018	↓0.130
Index of multiple deprivation quintile[d]	0.194	0.969	0.642	0.022	0.128
Months since heart failure diagnosis (continuous)	↓0.315	↓0.566	↓0.675	↑0.061	↑0.044
Alcohol consumption[e]	0.005	0.641	0.726	0.053	0.306
Smoking	↑<0.001	↓0.641	↑0.290	↓0.252	↓0.884
Cholesterol	↑0.051	↑0.109	↓0.193	↓0.001	↓<0.001
No. of comorbidities (continuous)	↓<0.001	↓0.939	↑0.814	↑<0.001	↑<0.001
Atrial fibrillation	↑<0.001	↑0.153	↑0.885	↓0.468	↓0.032
Chronic kidney disease status	↓<0.001	↑0.199	↑0.218	↑<0.001	↑<0.001
Coronary heart disease	↓0.002	↓0.049	↓0.423	↑<0.001	↑<0.001
Diabetes status	↑0.458	↓0.109	↑0.709	↑0.048	↑0.362
No. of concomitant CVD medications (continuous)	↓0.004	↑0.126	↑0.008	↑<0.001	↑<0.001
Concomitant use of angiotensin-converting enzyme inhibitors	↑0.981	↑0.674	↑0.160	↓0.848	↑0.669
Concomitant use of angiotensin-II receptor blocker	↓0.036	↑0.353	↑0.755	↓0.994	↑0.108
Concomitant use of beta-blockers	↓0.235	↓0.307	↓0.805	↑0.039	↑0.001
Concomitant use of aldosterone antagonists	↓0.164	↑0.146	↑0.041	↑<0.001	↑<0.001
Concomitant use of amiodarone	↓0.164	↑<0.001	↑0.003	↑0.105	↑0.029
Medication exposure variables					
Medication interruptions of 7 days or longer (binary)	-	-	-	↓<0.001	↓<0.001
Cumulative target dose achievement >75% (binary)	-	-	-	↓<0.001	↓0.002
Dosing interaction term – target dose achievement >75% (binary) considering half-life decline during interruptions	-	-	-	↑0.602	↑0.714

[a]Outcome measures were: cumulative median target dose achievement of greater than or equal to 50%; time to first treatment interruption of 90 days or longer, time to first treatment interruption of 7 days or longer; time to first all-cause emergency hospital admissions; and time to first cardiovascular-related emergency hospital admissions. For time to event outcomes, the log-rank test of equality was used for categorical variables while univariate Cox proportional hazard regression was used for binary and continuous variables. For binary dosing achievement outcomes, chi-square tests were used to assess categorical variables and univariate logistic regression was used for continuous variables. For continuous dosing achievement outcomes, the one-way analysis of variance test was used to assess categorical variables and univariate linear regression was used for continuous variables. [b]Sensitivity analysis. [c]Female was reference group. [d]Lowest level of deprivation was the reference group. [e]Three groups: non-drinker/former drinker (reference group); occasional; moderate/heavy. For binary and continuous variables, arrows represent the direction of the univariate effect estimate: ↓ indicates a decrease in the risk/odds of the outcome and ↑ indicates an increase in the risk/odds of the outcome.

Appendix 6.11 Sensitivity analyses of patient characteristics and time to first interruption of seven days or longer

Table 8. Results of multi-variate cox proportional hazards analyses of patient characteristics and time to first treatment interruption of seven days or longer

	ACE **Patient years= 2,705** **No. events= 3,246**		**ARB** **Patient years= 1,127** **No. events= 1,275**		**Beta-blockers** **Patient years= 3,837** **No. events= 4,138**		**Aldosterone antagonists** **Patient years= 1,553** **No. events= 1,928**		**Digoxin** **Patient years= 964** **No. events= 1,103**	
Characteristics	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**	**HR (95% CI)[a]**	**p**
Age	1.00 (0.99 to 1.00)	0.307	1.00 (0.99 to 1.01)	0.950	0.99 (0.99 to 1.00)	0.114	1.00 (0.99 to 1.01)	0.231	0.99 (0.98 to 1.00)	0.039
Male[b]	0.96 (0.89 to 1.04)	0.334	1.10 (0.97 to 1.24)	0.136	1.06 (0.99 to 1.14)	0.088	1.05 (0.95 to 1.16)	0.360	0.93 (0.81 to 1.07)	0.332
IMD quintile[c]										
2	0.94 (0.84 to 1.03)	0.203	1.10 (0.93 to 1.29)	0.257	0.96 (0.88 to 1.06)	0.440	0.95 (0.83 to 1.09)	0.481	0.96 (0.80 to 1.15)	0.651
3	0.96 (0.86 to 1.06)	0.415	1.01 (0.86 to 1.20)	0.875	0.95 (0.86 to 1.04)	0.243	0.95 (0.83 to 1.10)	0.491	1.03 (0.86 to 1.23)	0.748
4	0.93 (0.83 to 1.03)	0.152	1.13 (0.94 to 1.36)	0.181	0.94 (0.85 to 1.03)	0.208	0.89 (0.77 to 1.03)	0.120	0.91 (0.76 to 1.10)	0.327
5 (most deprived)	0.90 (0.80 to 1.01)	0.076	1.04 (0.86 to 1.25)	0.704	**0.87 (0.78 to 0.96)**	**0.007**	0.94 (0.81 to 1.10)	0.449	1.02 (0.84 to 1.24)	0.863
Months since heart failure diagnosis	**1.002 (1.001 to 1.004)[h]**	**0.002**	1.00 (0.99 to 1.00)	0.431	1.00 (0.99 to 1.00)	0.218	1.00 (0.99 to 1.00)	0.322	0.99 (0.99 to 1.00)	0.572
Smoking[d]	0.99 (0.89 to 1.10)	0.807	1.16 (0.93 to 1.44)	0.181	0.99 (0.99 to 0.99)[g]	0.031	1.07 (0.94 to 1.23)	0.322	1.06 (0.87 to 1.28)	0.579
Cholesterol (mmol/L)	**1.06 (1.02 to 1.09)**	**0.001**	1.06 (1.01 to 1.12)	0.027	**1.04 (1.01 to 1.07)**	**0.005**	1.03 (0.98 to 1.07)	0.232	0.97 (0.92 to 1.03)	0.300
No. of comorbidities	1.03 (0.99 to 1.07)	0.073	0.99 (0.95 to 1.43)	0.644	1.03 (0.99 to 1.07)	0.082	**1.06 (1.02 to 1.10)**	**0.006**	1.00 (0.94 to 1.05)	0.931
Atrial fibrillation[e]	-	-	-	-	0.99 (0.92 to 1.08)	0.863	-	-	1.01 (0.84 to 1.23)	0.881
Chronic kidney disease[e]	0.98 (0.90 to 1.06)	0.610	0.99 (0.87 to 1.14)	0.930	1.02 (0.95 to 1.10)	0.569	0.97 (0.87 to 1.07)	0.516	1.11 (0.97 to 1.29)	0.138
Coronary heart disease[e]	0.96 (0.88 to 1.05)	0.353	1.02 (0.89 to 1.16)	0.816	0.98 (0.91 to 1.06)	0.673	0.90 (0.80 to 1.01)	0.067	0.91 (0.78 to 1.05)	0.195
Diabetes[e]	0.96 (0.88 to 1.04)	0.359	0.98 (0.86 to 1.13)	0.801	0.98 (0.91 to 1.05)	0.543	0.96 (0.87 to 1.07)	0.479	0.99 (0.86 to 1.14)	0.902
Hypertension[e]	0.95 (0.87 to 1.03)	0.204	0.89 (0.78 to 1.01)	0.080	0.92 (0.85 to 0.99)	0.026	0.97 (0.87 to 1.09)	0.641	-	-
No. of concomitant CVD medications	0.98 (0.96 to 1.01)	0.221	1.03 (0.98 to 1.08)	0.238	1.01 (0.99 to 1.04)	0.343	1.00 (0.97 to 1.05)	0.685	**1.0002 (1.0001 to 1.0003)[g]**	**0.009**
ACE inhibitors[f]	-	-	0.95 (0.79 to 1.13)	0.513	0.92 (0.82 to 1.04)	0.174	0.95 (0.79 to 1.15)	0.625	1.14 (0.90 to 1.43)	0.289
ARB[f]	**1.0005 (1.0002 to 1.0008)[g,h]**	**<0.001**	-	-	1.06 (0.98 to 1.14)	0.140	1.04 (0.93 to 1.15)	0.501	0.99 (0.87 to 1.13)	0.887
Amiodarone[f]	-	-	-	-	-	-	-	-	1.00 (0.99 to 1.00)[g]	0.395
Beta-blockers[f]	0.92 (0.85 to 1.00)	0.065	1.01 (0.88 to 1.15)	0.896	-	-	0.95 (0.86 to 1.06)	0.357	0.94 (0.83 to 1.07)	0.336
Aldosterone antagonists[f]	**1.12 (1.04 to 1.22)**	**0.005**	1.01 (0.89 to 1.15)	0.848	0.96 (0.90 to 1.03)	0.268	-	-	1.00 (0.99 to 1.00)[g]	0.345
Digoxin[f]	1.02 (0.93 to 1.11)	0.674	0.89 (0.77 to 1.04)	0.134	1.03 (0.95 to. 1.10)	0.483	1.04 (0.93 to 1.16)	0.526	-	-
Diuretics[f]	0.97 (0.85 to 1.10)	0.614	0.96 (0.78 to 1.19)	0.700	1.00 (0.99 to 1.00)[g,h]	0.257	-	-	-	-

[a]Outcome was time to first treatment interruption of seven days or longer. Statistically significant associations are bolded. [b]Reference was female. [c]Index of multiple deprivation. Reference was least deprived. [d]Reference was non-smokers. [e]Reference was no disease. [f]Reference was non-users of the medication. [g]Entered as a time-varying covariate to meet the proportional hazards assumption. [h]When necessary for interpretation, greater than two decimal places were reported. Abbreviations: ACE= angiotensin converting enzyme inhibitors; ARB= angiotensin-ll receptor blockers; HR=hazard ratio; No.= number; p= probability value.

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7.0 Chapter overview

This chapter reports a quasi-experimental study of 'real-world' interventions implemented to increase access to primary care and reduce emergency hospital admissions in a large health region in England. This chapter serves to explore the feasibility of evaluating 'real-world' interventions for reducing admissions and to build the evidence base for access to care interventions. The results showed that evaluation is feasible however, use of strong study designs may be precluded by challenges in obtaining individual patient data for creating matched controls and time and financial pressures. Time series analysis showed that the interventions increased primary care access but were not associated with a significant change in admission rates for ambulatory care sensitive conditions and may have increased all-cause admission rates. Lessons for future evaluations and primary care initiatives for reducing hospital admissions are discussed.

7.1 Introduction

7.1.1 Building on previous chapters

Chapters 3 to 6 addressed the thesis aim by identifying and prioritising existing evidence-based interventions and exploring potential gaps in the utilisation of these interventions.

The next two chapters address the thesis aim from a different angle, by examining access to care interventions emerging in 'real-world' clinical practice. This was appropriate for two reasons. Firstly, there was a need to build the evidence base for these types of interventions. Systematic reviews, including the review in chapter 3, have found little experimental or quasi-experimental evidence for access to care interventions. The government and national health care stakeholders have highlighted this evidence deficit and called for the development, implementation, and evaluation of these interventions.[1] Secondly, there was a need to explore the evaluation and implementation of innovative in-practice interventions for reducing hospital admissions. At the outset of this thesis there was growing NHS and government emphasis on service innovation as a way to solve some of the health system's biggest challenges, including rising hospitalisation rates. However, it was unclear how feasible evaluating such service innovations would be. There was also uncertainty and concern about the strength of evidence underpinning these services. The next two chapters were designed to address these needs and uncertainties.

7.1.2 The UK General Practice Access Fund Challenge

In 2013/14 the English government launched a national initiative to increase access to primary care and reduce burden on secondary care by stimulating primary care service innovations. The initiative was called "The GP Access Fund Challenge". NHS England oversaw the program and invited practices to submit bids. Nationally, £150 million was offered in two phases. While the core selection criteria targeted improvements in access, services were expected to demonstrate benefits for secondary care, including reducing emergency hospital admissions.

7.1.3 Building the evidence base for access to care interventions

The Oxfordshire Clinical Commissioning Group (CCG) was awarded £5 million as part of the GP Access Fund in March 2015 to develop and implement innovative primary care services. The Oxfordshire initiative was called “Right Time, Right Place, Right Care”. A collaboration between the CCG and the Oxford Centre for Evidence-Based Medicine (CEBM) was formed for the purpose of evaluating the interventions. As described in chapter 2, there was a paucity of evidence on access to care interventions and hospital admissions. Therefore, to explore the impact of access to care interventions on hospital admissions, the author of this thesis contacted key stakeholders in the Oxfordshire CCG (Dr. Rosie Row) and Oxford CEBM (Prof. Carl Heneghan) and requested to lead the quantitative evaluation.

The Right Time, Right Place, Right Care initiative (henceforth known as the Right Care initiative) was selected as a model initiative to study for the following reasons:

- The initiative included a specific mandate to assess the impact of access to care interventions on secondary acute care and, therefore, it offered the opportunity to build the evidence base in an area with an evidence deficit
- The close proximity of health service stakeholders would facilitate the relationship building required to negotiate data sharing agreements between multiple partners and to amicably and efficiently navigate potential challenges encountered during the course of the study
- Familiarity with the local ethics boards would ensure an efficient ethical review
- The Oxfordshire CCG health region is one of the largest in England which would make a well-powered study more feasible over a shorter period of time

7.2 Aim and objectives

7.2.1 Aim

The aim of this chapter was to evaluate the association between a set of 'real-world' primary care access interventions and emergency hospital admissions in a health region in England.

7.2.2 Objectives

To achieve this aim, the objectives of this chapter were to:

1. To quantify and describe utilisation of the Right Care interventions
2. To quantify and describe the characteristics of intervention users
3. To estimate the association between the interventions and rates of all-cause and ambulatory care sensitive emergency hospital admissions
4. To explore patterns of hospital admissions among intervention users to gain insights into the impact of the interventions
5. To establish the feasibility of evaluating innovative 'real-world' interventions for reducing emergency hospital admissions

7.3 Methods

This study is reported in accordance with the Centres for Diseases Control's TREND Statement: Transparent Reporting of Evaluations with Nonrandomized Designs.[2]

7.3.1 Context

Components of this chapter contributed to a larger mixed-methods evaluation of the Oxfordshire Right Care interventions. As lead of the quantitative evaluation the thesis author completed this embedded study on the association of the interventions with emergency hospital admissions.

7.3.2 Study design

An interrupted time-series design was used. This is the strongest of the quasi-experimental designs and well-suited to assess the impact of large scale changes in policy and practice.[3–6] The advantage of this design over other quasi-experimental

designs is the ability to consider longitudinal trends before the intervention and, therefore, control for secular trends in the outcome of interest.

Ideally, a randomised approach would have been selected, but this was not possible for ethical reasons, as the requirement to increase access across the county made assignment of a local concurrent control group unacceptable. There were also logistical challenges to randomisation. It would have been difficult to randomise patients or individual GP surgeries as the services were intended to increase access across the population. It may have been possible to randomise practice catchment areas for some of the interventions, but there may have been contamination.

7.3.3 Setting and eligible participants

Oxfordshire is a large county in Southern England. In 2015/16 (active intervention year), Oxfordshire had approximately around 600 GPs and 300 other clinical staff working in 76 GP practices.[7] The mid-year (October 2015) registered primary care population was 716,193.[8] GP practices were contracted to be open from 8:00 am to 6:30 pm. Outside of those hours, Oxford Health Foundation Trust delivered some out-of-hours services.

At the time of the GP Access Fund initiatives, health care organisation and delivery was governed by two key structures:

1. The Clinical Commissioning Group: a statutory organisation responsible for the selection, purchasing, and oversight of the majority of health services for people in Oxfordshire. All 76 GP practices were members of the CCG.
2. GP Federations: a network of member GP practices that work together to share resources, such as administration and finance support, to enable them to offer better access to service and deliver economies of scale. In 2015/16 there were three Oxfordshire GP Federations.

The three GP Federations, in partnership with the CCG, created the bid for the GP Access Fund, and designed and implemented the interventions with the intention of making the interventions available to all people registered with a GP practice in the county (n=716,193).

7.3.4 Description of interventions

Health care access may be defined as "the timely use of personal health services to achieve the best health outcomes".[9] Six interventions were designed and implemented to address local access needs identified through patient and practitioner engagement.[8] The interventions had two broad themes: “improving access” and “enhancing complex care” and were intended to target the components of good access to care[10]: physical and digital entry into the health care system; physical and digital sites of care to receive services; helping patients to find and connect to appropriate heath care providers and advice; and increasing face-to-face time for practitioners and patients to facilitate better relationships.

The target populations of the interventions varied, from general groups of patients trying to access primary care services to patient with complex long-term care conditions. Different interventions were implemented in different regions and practices. Implementation was determined by the GP Federations and was based on local need. The interventions are described in detail in Table 1.

The study period was the date the first intervention started to the end of the funded intervention period (July 1, 2015 to May 31, 2016). Due to delays in recruiting staff, training staff, and information governance approvals, there was a staged roll out with five of the six interventions implemented between July and September 2015 and one implemented in December 2016. Table 2 shows for the timeline of intervention implementation with a description of data availability.

Table 1. Detailed description of interventions

Neighbourhood Hubs	
Theme	• Improving access
Service aims	• To increase acute on-the-day general practice capacity • To provide extended 8-8 opening • To enable practices to offer more 20 min appointments for proactive care
Service form	• 6 hubs were opened in health centres and community hospitals • 4 provided additional core hours provision, 2 were open evenings and weekends • Each hub served 4-9 GP surgeries; hub appointment was scheduled for 15 minutes
Target patients	• Patients with acute, straightforward illness that required an on-the day appointment
Allocation (access route)	• Patients were triaged using referral criteria by their own surgery who booked appointments
Clinical Staffing	• GPs and advanced nurse practitioners
Early Visiting Service (EVS)	
Theme	• Improving access
Service aims	• To support GPs to respond to urgent visit requests earlier in the day • To release GPs time for more complex patients
Service form	• Four teams of approximately 2 members supported a cluster of GP surgeries • Visited patients in their own home and agreed upon management plans with their GP
Target patients	• Acutely ill housebound patients that requested a GP visit
Allocation (access route)	• Patients requesting a home visit were triaged by their own GP surgery • Surgery contacted the central EVS office to book a visit for their patient by one of the teams
Staffing	• Paramedic and emergency care practitioners
Email-Consultation (E-Consultation) Service	
Theme	• Improving access
Service aims	• To provide an alternative means of access to primary care services • To provide extended opening hours without physically opening the surgery building
Service form	• Patients used a general email-consultation address at the practice • Booked an urgent or routine appointment slot (response with 2 or 24 hours respectively) • The inbox was monitored in practice and administrative queries were triaged out • Patient's own GP, where possible, replied via email, correspondence was uploaded to the electronic medical information system
Target patients	• Commuters or other groups for whom physically attending the surgery was difficult
Allocation (access route)	• Self-referred or reception staff signposted patients to the service if there was a shortage of other types of appointments
Staffing	• Practice GPs

Table 1 continued. Detailed description of interventions

Practice Visiting Nurse Service	
Theme	• Enhancing complex care
Service aims	• To provide a practice nurse service to housebound patients unable to attend the surgery
Service form	• Four nurses each with a base practice
Target patients	• Elderly, vulnerable or frail housebound patients with chronic health conditions
Allocation (access route)	• Referred using the practice's 2% register active case finding register or by GP
Staffing	• Nurses. Some team members are on secondment from community nursing teams
Care Navigators[a]	
Theme	• Enhancing complex care
Service aims	• Location 1: Coordinating care planning and support for frail elderly living in their own homes • Location 2: To support all patients, family and carers, many with long term conditions or young families, to develop their health knowledge and access timely care and support
Service form	• Location 1: Home visits to assess patients and offer signposting and social prescribing to a range of community health, social care, voluntary sector, and private services • Location 2: Care navigators showed patients how to access health information and local services
Target patients	• Location 1: The frail elderly • Location 2: All patients, family and carers
Allocation (access route)	• Location 1: GP or practice visiting nurse referred and from patients, their relatives or carers • Location 2: GP or patients self-referred
Staffing	• Location 1: A team of non-clinical care navigators each covered a cluster of GP surgeries • Location 2: Each non-clinical care navigator covered one practice only
20 Minute Extended GP Appointments	
Theme	• Enhancing complex care
Service aims	• To provide preventative health care for patients with complex needs
Service form	• Extended appointments for patients with a GP at their usual practice
Target patients	• Patients with long term health conditions
Allocation (access route)	• Usual GP surgery booking route
Staffing	• Practice GPs

[a]Care navigators were implemented in two different forms in two different GP Federations.
Abbreviation: GP= general practitioner; EVS= early visiting service.

Table 2. Intervention implementation timelines and available data

Theme	Intervention	GP Federation and percentage of Oxfordshire population covered			Month of first recorded patient contact	Month that funded service period ended	Number of months of service utilisation data	Number of months of aggregate hospital admissions data	Number of months of IPD hospital admissions data
		Fed. 1 65%	Fed. 2 30%	Fed. 3 5%					
Improving access	Neighbourhood Hubs	✓			September 2015	May 2016	9 (May 2016)	9 (May 2016)	7 (March 2016)
	Early Visiting Service	✓			July 2015	May 2016	11 (May 2016)	11 (May 2016)	8 (March 2016)
	E-Consultation Service			✓	August 2015	May 2016	10 (May 2016)	10 (May 2016)	8 (March 2016)
Enhancing complex care	Practice Visiting Nurse Service[a]		✓		December 2015	May 2016	7 (May 2016)	7 (May 2016)	5 (March 2016)
	Care Navigators		✓	✓	September 2015	May 2016	9 (May 2016)	9 (May 2016)	6 (March 2016)
	20 Minute Extended GP appointments	✓			July 2015	May 2016	11 (May 2016)	11 (May 2016)	8 (March 2016)

[a]It was not possible to recruit practice nurses willing/able to undertake urgent home visits. Service was delayed as new provider needed to undergo CQC registration. Abbreviations: GP= general practitioner; IPD= individual patient data; Fed= Federation.

7.3.5 Excluded interventions

Three additional interventions were proposed as part of the Right Care initiative but were excluded from this study because they received near zero uptake (skype consultations), were never implemented (out-of-hours access to GP records),or were stopped pre-maturely (online health resource). See Appendix 7.1 for more details on these interventions.

7.3.6 Outcomes

The primary outcome of this study was all-cause emergency hospital admissions. The secondary outcome was emergency hospital admissions for ambulatory care sensitive conditions (ACSC admissions).[11] The list of ACSCs used is in Appendix 7.2. This is the same list used in the systematic review in chapter 3.

There were other outcomes measured as part of the larger evaluation within which this study was embedded. Workshops were held with local patients and practitioners to establish the outcomes of interest. However, given the aim of this thesis, this chapter focused on emergency admissions.

7.3.7 Sample size

There was no sample size calculation for this study. Data on all 716,193 people registered at a GP practice in Oxfordshire were analysed. Power in the time series analysis was expected to be high as there was limited variability in monthly pre-intervention admission rates and an adequate number of time points (i.e., 18+ months).[12]

7.3.8 Unit of analysis

The unit of analysis for the primary and secondary outcomes was the group level: mean monthly rates of emergency hospital admissions in Oxfordshire county. Individual rates were not analysed due to unavailable individual patient data for matched controls. This is described in the next section.

7.3.9 Control groups

Use of the county level pre-intervention admission rates served as a historic control for the post-intervention period to guard against threats to internal validity. This is the standard approach to analysis of time series data and its key feature. It accounts for trends in the outcome (i.e., increasing rates of admissions) that may have started before the intervention was implemented and that may persist post-implementation.

Individual patient data to create matched controls could not be obtained and therefore, the impact of interventions at the individual patient level could not be assessed. Other CCGs were unwilling to share individual patient data and, within Oxfordshire, access to individual patient demographic data was restricted to patients that used the interventions or that experienced a hospital admission during the period of interest. Table 3 describes the availability of data within Oxfordshire.

Table 3. Availability of individual patient demographic data within Oxfordshire

	Intervention users	Non-users
Experienced a hospital admission during the study period (July 2013 to May 2016)	✓	✓
Did not experience a hospital admission during the study period (July 2013 to May 2016)	✓	X

Pre-intervention admission rates for individual users of the interventions could have served as a historic control for their post-intervention admission rates however, this would have been susceptible to the regression to the mean phenomenon. [3,13] This is a phenomenon in which extreme values are followed by values that regress towards the “average”. Given that most of the Right Care interventions were designed for patients with urgent health needs, it was anticipated that rates of admission for these patients would increase around the time of using the interventions. Therefore, the return to “average” admission rates after intervention use may be incorrectly attributed to the interventions.

7.3.10 Datasets

Three sets of data were used in this study. Data sharing agreements for individual patient data were negotiated between GP practices, the CCG, and the University of Oxford. The final data extraction occurred in June 2016.

Data set 1. Data on intervention utilisation and characteristics of users

Intervention utilisation data were obtained from 62 of the 76 practices in Oxfordshire. The data were extracted from GP practice systems by the CSU. Every instance in which an intervention was used was recorded as a distinct episode of care. Each episode included codes for the type of intervention used, the date, and individual patient data on age, sex, and long-term conditions. Read codes to specify each intervention were developed by the University of Oxford (thesis author, Carl Heneghan, Kamal Mahtani, and Alice Tompson), the GP Federations, and the Commissioning Support Unit (CSU). Challenges arose as some GP practices used different sets of codes to describe the interventions however, the codes were harmonised prior to analysis. Data coding challenges and solutions are described in Appendix 7.3.

Data set 2. Data on emergency hospital admissions

Data on emergency hospital admissions were extracted from NHS Digital's Secondary Uses Services database by CSU. These data included the date of admission and discharge, main diagnosis, age, sex, long-term conditions included in the quality and outcomes framework registry, and the name of GP practice at which the patient was registered. Aggregate admissions data for Oxfordshire was provided for the entire requested period (July 2013 to May 2016) however, at the time of final data extraction, emergency admissions data for individual patients was only available up to March 2016 due to delays in quality checks. The availability of admissions data is described in Table 2 (above).

Linkage of data sets

The above individual patient data sets were linked by CSU then pseudo-anonymised and delivered for analysis. Data for each of the three federations were provided in separate files. These files were merged by the thesis author before analysis.

Data set 3. Data on characteristics of the Oxfordshire population

Aggregated data on characteristics of GP registered patients within Oxfordshire were obtained from NHS digital. These data included population size, age, sex, and long-term conditions included in the Quality and Outcomes framework registry. These data were used in conjunction with data on intervention users to derive the characteristics of non-users within Oxfordshire.

7.3.11 Data management

Data was delivered via a high compliance system set up by Medical Sciences Division Information Technology Services. Data were managed and analysed in the high compliance system. Summaries of the data were exported out for additional analysis.

7.3.12 Data inclusion criteria

Data on use of interventions was only analysed if it contained an NHS number, a code for the intervention used, and the date the intervention was used. The date must have fallen within the study period (July 1, 2015 to May 31, 2016) For data on individual patient admissions to be included, the individual patient record needed to include the date and reason for admission.

7.3.13 Descriptive statistical analysis

Data were managed in Excel and analysed using SPSS statistical software[14] and STATA 14.[15] The threshold for statistical significance was set at $p<0.05$.

Descriptive analysis of intervention utilisation

Monthly numbers of consultations and patients using each intervention were described using counts and proportions.

Descriptive analysis of demographic data

Demographic data for intervention users are described using counts and proportions. Demographic data for non-users within Oxfordshire were derived by subtracting counts and proportions for intervention users from aggregated counts and proportions for Oxfordshire at the mid-point of the study period (October 2015).

Chi-square tests with bonferroni corrected post-hoc comparisons were conducted on categorical data to identify differences in characteristics of intervention users and non-users.

Descriptive analysis of emergency hospital admissions

Histograms of all-cause and ACSC admissions were produced to determine the distribution of the data. Scatter plots were visually inspected for preliminary identification of trends in admissions over time.

Patterns of hospital admissions for patients that used the interventions were described to gain insights into the impact of the interventions. Given that patients accessed the interventions at different points during the year (July 2015 to May 2016), the first date that a patient used an intervention was coded as time 0. Admissions 24 months prior to this date and three months after were examined. The follow-up period was constrained as individual patient data was only available until March 2016. Therefore, only patients utilising interventions prior to January 1, 2016 could be included in this analysis to allow for the three-month follow-up period. Three months was selected to maximise the available sample size while offering the ability to visually assess the trend after utilisation. For these analyses, one month was defined as 30.4 days.

7.3.14 Inferential statistical analysis

Association between interventions and emergency hospital admissions

There are many methods for analysing time series data and approaches are varied in the literature.[13] Segmented Poisson and negative binomial regression analyses were utilised in the first instance as they are suitable for count data and were anticipated to provide simple models with interpretable results.[13]

Segmented regression is a method for statistically modelling time series data to estimate the association between an intervention and an outcome. Segmented regression is superior to standard regression as it allows estimation of changes in the trend of an outcome before and after an intervention. The time series is divided into segments based on one or more change points.[5] The change point represents

the point at which the interventions are introduced. Each segment of the time series is defined by two parameters:

A. the mean value of the outcome, known as the “level” or “intercept” (i.e. monthly admission count per 1,000 patients)
B. the rate of change in the outcome, known as the “trend” (i.e., the slope of the line mapping the trend in admissions across months)

A change in level indicates an abrupt drop in the value of the outcome while a change in trend indicates a gradual change in the value of the outcome over time.

Development of time series regression models

Development of the time series regression models occurred in three steps:

Step 1. Determining the length of time series

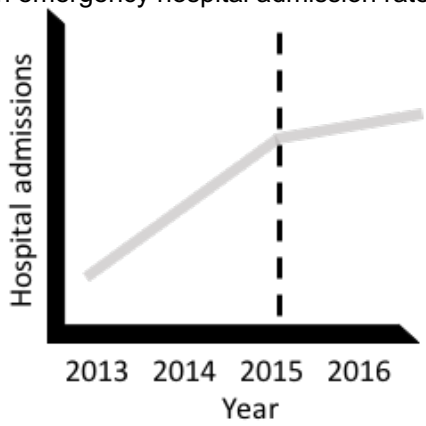
To create a time series capable of detecting seasonal trends and with adequate power data were analysed for 24 months prior to the start of the interventions (July 2013) to 11 months after the start of the interventions (May 2016, the end of the funded intervention period).[16]

Step 2. Proposing an impact model

Segmented time series regression analysis requires hypothesising how the intervention may impact on the outcome. This has implications for how the model is built. Figure 1, adapted from Bernal et al.[5], illustrates the model proposed for this study; an immediate slope change model.

A gradual change in monthly admission rates (i.e., slope change) was proposed given that the interventions were rolled out gradually and it was anticipated that their utilisation would grow over time.[16] The proposed impact was presumed to be immediate given that the interventions targeted patients with urgent or complex care issues and, therefore, if the interventions were effective, they would likely reduce admissions in the short-term (i.e., within a few days), rather than after a lag period (i.e., several months).

Figure 1. Proposed immediate slope change model of the impact of the interventions on the trend in emergency hospital admission rates



Step 3. Selection of models and assessment of model assumptions

Selection of final regression models was led by assessments of four key model assumptions[17]:

A. The outcome variable was measured as a count and its distribution was appropriate for analysis using Poisson or negative binomial regression. This was assessed visually using histograms.

B. There was a linear relationship between the outcome variable and time. This was assessed visually using scatter plots.

C. The conditional variance was equal to the conditional mean. If the conditional variance is larger (over-dispersion) or smaller (under-dispersion) than the conditional mean, estimates of standard errors using a Poisson distribution can be incorrect. This was evaluated by examining the unadjusted mean and variance in admission rates before and after implementation of the intervention (i.e. admission means and variances conditional on the presence/absence of the intervention). Chi-square goodness of fit tests were also conducted after fitting Poisson models as poor model fit, demonstrated by a significant chi-square test, can also indicate issues with over- and under-dispersion. If over- or under-dispersion was identified, then negative binomial regression was utilised. This is an extension of Poisson modelling which does not assume that the variance is equal to the mean and, therefore, provides more reliable estimates of standard error.

D. Observations were independent of one another. In time series data, correlation between observations is often an issue. This is known as autocorrelation. If autocorrelation is present, standard errors are often underestimated, leading to unreliable p-values and type 1 errors. Autocorrelation was identified by examined plots of the residuals over time, and graphs and correlogram tables of autocorrelation and partial autocorrelation values. Appropriate adjustment methods and alternative analysis approaches were considered when autocorrelation was detected.

A brief discussion of autocorrelation is relevant to understand the methods. There are two common types of autocorrelation in time series data:

A. Seasonal autocorrelation occurs when the outcome varies by season or at cyclical patterns throughout the year. If seasonal autocorrelation was detected**,** three approaches were considered: stratification by calendar month; stratification by season; and inclusion of Fourier terms, which are pairs of sine and cosine functions well-suited to modelling cyclical patterns. The approach that best resolved autocorrelation was used. All three approaches have been recommended for use in time series regression.[16,18]

B. Adjacent autocorrelation occurs when values in a given month are more correlated with values in adjacent months compared to months farther away. If adjacent autocorrelation was detected after adjustment for season, autoregressive integrated moving average (ARIMA) models were considered. Although ARIMA models assume normally distributed data, these models have been shown to function well when using large samples of count data (i.e. monthly mean counts of approximately 5000).[13,18]

7.3.15 Research governance and ethical approval

This study was reviewed by the University of Oxford Joint Research Office Study Classification Group. The study was classified as a service evaluation of procurement practice and did not require research governance or ethical approval. The thesis author was granted a Research Passport by the Oxford University Hospitals NHS Trust in order to access and analyse the data.

7.4 Results

7.4.1 Quality of data

The intervention utilisation dataset contained 40,277 records, one for each contact with an intervention. Of these records, 162 (0.4%) were duplicates, 27 (0.07%) were missing NHS numbers, and 1,032 (2.7%) were missing dates. These records were excluded. Data on sex and age were missing for 521 patients (2.1%).

7.4.2 Utilisation of interventions

Intervention utilisation is shown in Figure 2 and Table 4. The interventions were utilised 39,056 times by 28,598 patients (4% of the registered GP population). Among service users, 98% (n=27,935) used only one type of the interventions, 2% (651) used two interventions, and <0.5% (n=12) utilised three or more of the interventions. Utilisation grew in an exponential fashion from July 2015 to January 2016, then remained steady until the end of the funded intervention period in May 2016. Monthly breakdowns of utilisation for each type of intervention can be found in Appendix 7.4 and 7.5.

7.4.3 Demographic characteristics

The characteristics of the GP-registered population in Oxfordshire are described in Table 5, with a breakdown for intervention users and non-users. Compared to non-users, users were significantly different in terms of age, sex, and prevalence of chronic diseases ($p<0.001$ all comparisons). There were significantly more paediatric patients, elderly patients, and females in the user group compared to the non-user group ($p<0.001$ all comparisons). Compared to non-users, users had a higher prevalence of 15 of the 19 chronic diseases measured ($p<0.001$ all comparisons). Characteristics of patients served by each intervention can be found in Appendix 7.6.

Figure 2. Monthly service utilisation for all interventions

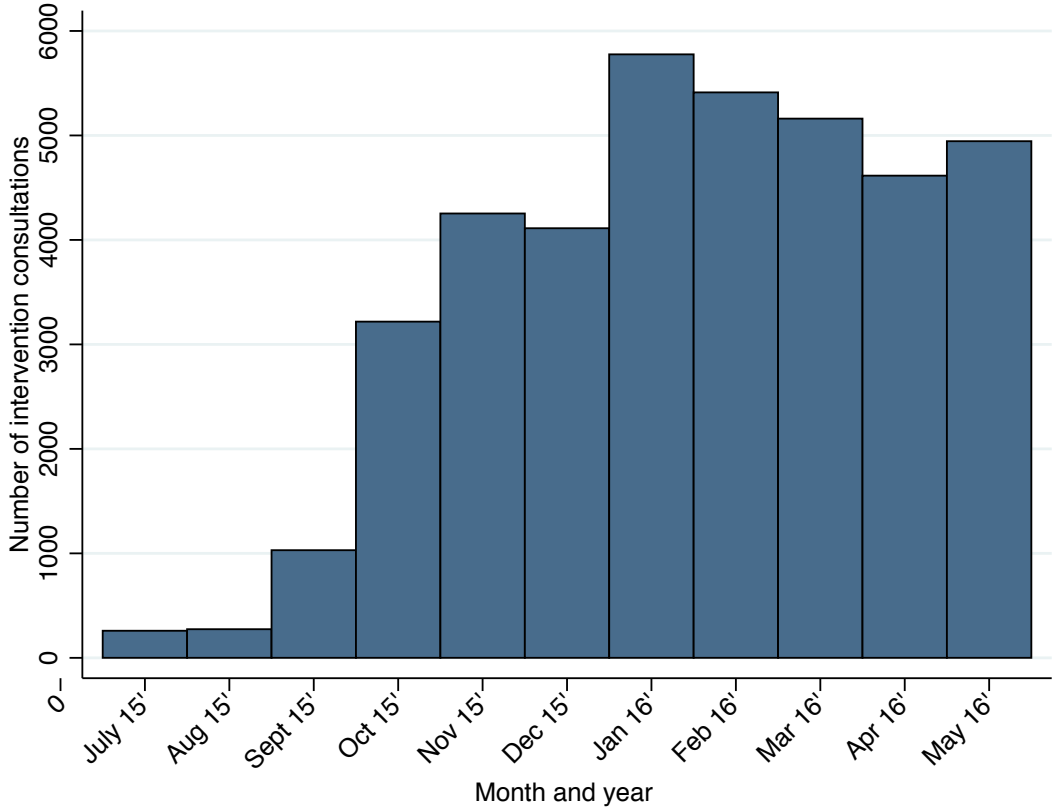


Table 4. Summary of intervention utilisation

Theme	Intervention	Total number of contacts with the interventions	Number of unique patients using the interventions	Consultations per patient
Improving access	Neighbourhood hubs	24,505	19,994	1.2
	Early visiting service	4,508	3,095	1.5
	E- consultations	1,667	1,099	1.5
Enhancing complex care	Practice visiting nurse service	994	232	4.3
	Care navigators	2,177	759	2.9
	Extended 20 minute GP appointments	5,203	4,094	1.3
	Totals	39,056	28,598[a]	1.4

[a]Overall, there were 28,598 unique patients. The column does not add up to 28,598 as 749 patients used multiple services.

Table 5. Characteristics of Oxfordshire county and intervention users and non-users

Characteristic	Oxfordshire county[a] % (n=716,193)	Intervention users % (n=28,598)	Non-users % (n=687,595)
Age in groups[b,c]			
<18	20% (143,375)	24% (6,970)	20% (136,276)
18 to 54	53% (376,532)	39% (11,079)	53% (365,247)
55 to 64	11% (77,733)	10% (2,794)	11% (74,887)
65 to 74	9% (63,869)	9% (2,545)	9% (61,77)
75+	8% (54,684)	16% (4,689)	7% (49,908)
Missing data	-	2% (521)	-
Sex[c]			
Female	50% (358,446)	57% (16,198)	50% (341,821)
Male	50% (357,747)	41% (11,665)	50% (345,774)
Missing data	-	3% (735)	-
QOF disease registry[c,d]			
Asthma	6% (41,101)	12% (3,554)	5% (37,547)
Atrial fibrillation	2% (11,798)	3% (866)	2% (10,932)
Cancer	3% (19,441)	4% (1,055)	3% (18,386)
Chronic kidney disease (18+)	3% (19,824)	5% (1,351)	3% (18,473)
Chronic obstructive pulmonary disease	1% (9,551)	2% (583)	1% (8,968)
Coronary heart disease	2% (17,748)	4% (1,114)	2% (16,634)
Dementia	1% (5,265)	2% (553)	1% (4,712)
Depression (18+)	7% (50,834)	13% (3,588)	7% (47,246)
Diabetes (17+)	4% (28,610)	2% (680)	4% (27,930)
Epilepsy (18+)	1% (4,046)	3% (971)	<0.5% (3,075)
Heart failure	1% (4,521)	2% (458)	1% (4,063)
Hypertension	12% (87,453)	14% (4,115)	12% (83,338)
Learning disability	<0.5% (2,597)	<0.5% (106)	<0.5% (2,491)
Mental health issue	1% (5,818)	1% (216)	6% (42,989)
Obesity (18+)	6% (43,205)	-	-
Osteoporosis (50+)	<0.5% (1,558)	3% (759)	<0.5% (799)
Peripheral artery disease	1% (3,641)	1% (316)	<0.5% (3,325)
Palliative care patient	<0.5% (1,857)	1% (273)	<0.5% (1,584)
Rheumatoid arthritis (16+)	1% (3,668)	1% (181)	1% (3,487)
Stroke or transient ischemic attack	2% (11,956)	3% (871)	2% (11,085)

[a]October 2015 selected as the mid-point for the intervention period (July to May) due to data availability. [b]Age at the time of first intervention use. [c]For non-users, data was derived from mid-period (October 2015) county level data by subtracting individual patient data on users of the interventions. Missing data was assumed to be proportionally distributed across groups when deriving counts for non-users. [d]Quality and Outcomes Framework disease register prevalence in April 2016 was applied to the October 2015 population distribution to get values for the mid-year intervention period, denominators were defined as they were in April 2016.

7.4.4 Description of emergency hospital admission rates

There were 192,641 all-cause admissions during the study period (July 2013 to May 2016), of which 39,102 (20.3%) were admissions for ACSC. Overall, there was a monthly mean rate of 7.78 all-cause admissions per 1,000 and 1.58 ACSC admissions per 1,000 in Oxfordshire during the study period (Table 6).

Table 6. Mean monthly emergency hospital admission rates for Oxfordshire

Type of emergency admission	Mean ±SD monthly admission rates per 1,000 patients		
	Pre-intervention period[a]	Active-intervention period[b]	Full study period
All-cause	7.69 ±0.30	7.97 ±0.35	7.78 ±0.34
ACSC	1.55 ±0.09	1.63 ±0.43	1.58 ±0.11

[a]Full study period defined as July 1, 2013 to May 31, 2016. [b]Pre-intervention period defined as July 1, 2013 to June 30, 2015. The mid-period (May 2014) population was 701,547. [c]Active-intervention period defined as July 1, 2015 to May 31, 2016. The mid-period (October 2015) population was 716,193. Abbreviations: SD=standard deviation; ACSC= ambulatory care sensitive conditions.

7.4.5 Assessment of regression model assumptions and fit

Poisson and negative binomial regression were appropriate given that histograms of admissions showed right-skewed distributions (Appendix 7.7) and scatter plots showed a linear relationship between admissions and time (Appendix 7.8).

Poisson regression models were fit in the first instance however, conditional variances were substantially greater than the conditional means (i.e., four to ten times larger), indicating over-dispersion of the data (Appendix 7.9). Poor model fit was corroborated by statistically significant results from chi-square goodness of fit tests. Therefore, negative binomial regression was used.

Segmented negative binomial regression models were initially fit without adjustment for seasonality however, assessment of autocorrelation using plots of residuals and the autocorrelation and partial autocorrelation functions showed statistically significant spikes at the 12-month lag for all-cause admissions (p=0.015), indicating seasonal autocorrelation (Appendix 7.10). Two sets of Fourier terms were included in the all-cause admissions analysis to account for the two seasonal spikes in admissions (i.e., winter and summer). Although no statistically significant seasonal autocorrelation was detected for ACSC admissions, the time series graph showed a fairly distinct cyclical pattern starting in the second year of the study period. A

single of fourier terms was therefore included to account for the single seasonal spike in admissions (i.e., winter).

7.4.6 Time series regression of all-cause emergency hospital admissions

Introduction of the Right Care interventions was associated with a significant increase in the month-to-month trend in mean all-cause admission rates (p=0.035). Figure 3 and Table 7 show details of the final regression model. The interventions were associated with an increase in the monthly rate of admissions by a factor of 1.0046 (95% CI 1.0003 to 1.0089). This association can be contextualised with reference to a specific time point; nine months after introduction of the initiative (May 2016), the mean admission rate was 8.54 per 1,000 people per month. Had the interventions not been introduced, it is estimated that the mean admission rate would have been 8.20 admissions per 1,000 (95% CI 7.91 to 8.52) per month. This represents an absolute increase of 4.1% (95%CI 0.23% to 8.0%) or 0.34 (95%CI 0.02 to 0.63) admissions per 1,000 people per month. Given that the population in Oxfordshire was 716,628 at that time, this increase equated to an additional 244 (95%CI 14 to 451) all-cause admissions in the final month (May 2016) of the intervention period. Full regression results are available in Appendix 7.11.

7.4.7 Time series regression of ACSC emergency hospital admissions

Introduction of the Right Care interventions was not associated with a change in the month-to-month trend in ACSC admission rates (p=0.072). Figure 4 and Table 8 summarise details of the regression model. Full regression results are available in Appendix 7.12.

7.4.8 Regression sensitivity analysis

Admission rates in the final month (May 2016) of the initiative appeared as an outlier. Sensitivity analysis was conducted by excluding this point and re-running the regressions. The interpretation of the ACSC admissions analysis was similar however, the interpretation of the all-cause admissions analysis changed. This sensitivity analysis showed that the interventions were not associated with a significant change in all-cause admissions rates (p=0.317). These results are presented in Appendix 7.13.

Figure 3. Segmented negative binomial time series regression of all-cause emergency admissions in Oxfordshire with adjustment for seasonality

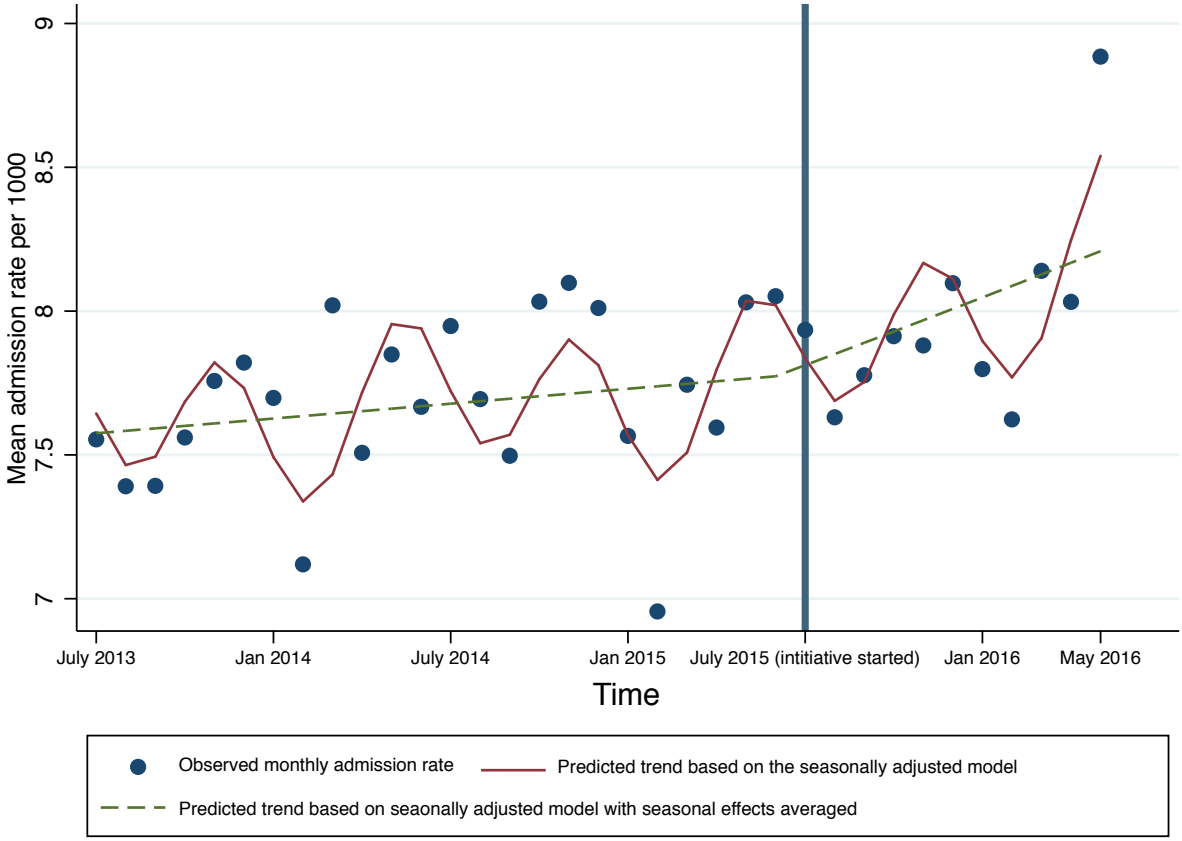


Table 7. Results of segmented negative binomial regression for all-cause emergency admissions in Oxfordshire from May 2013 to May 2016

Model terms	Incidence rate ratio	95% CI	p-value
Baseline monthly admission rates 24 months prior to the initiative	0.0044	0.0018 to 0.0111	0.000
Underlying pre-intervention trend in monthly admission rates	1.0008	0.9994 to 1.0022	0.238
Change in trend in monthly admission rates after introduction of the initiative	1.0046	1.0003 to 1.0089	0.035
Fourier cyclical season adjustment terms			
Cos1	0.9875	0.9749 to 1.0003	0.056
Cos2	0.9925	0.9801 to 1.0051	0.245
Sin1	0.9996	0.9868 to 1.0125	0.951
Sin2	0.9695	0.9572 to 0.9819	0.000

n=35 monthly observations (July 2013 to May 2016). Pseudo-R^2= 0.06

Figure 4. Segmented negative binomial time series regression of emergency admissions for ambulatory care sensitivity conditions in Oxfordshire with adjustment for seasonality

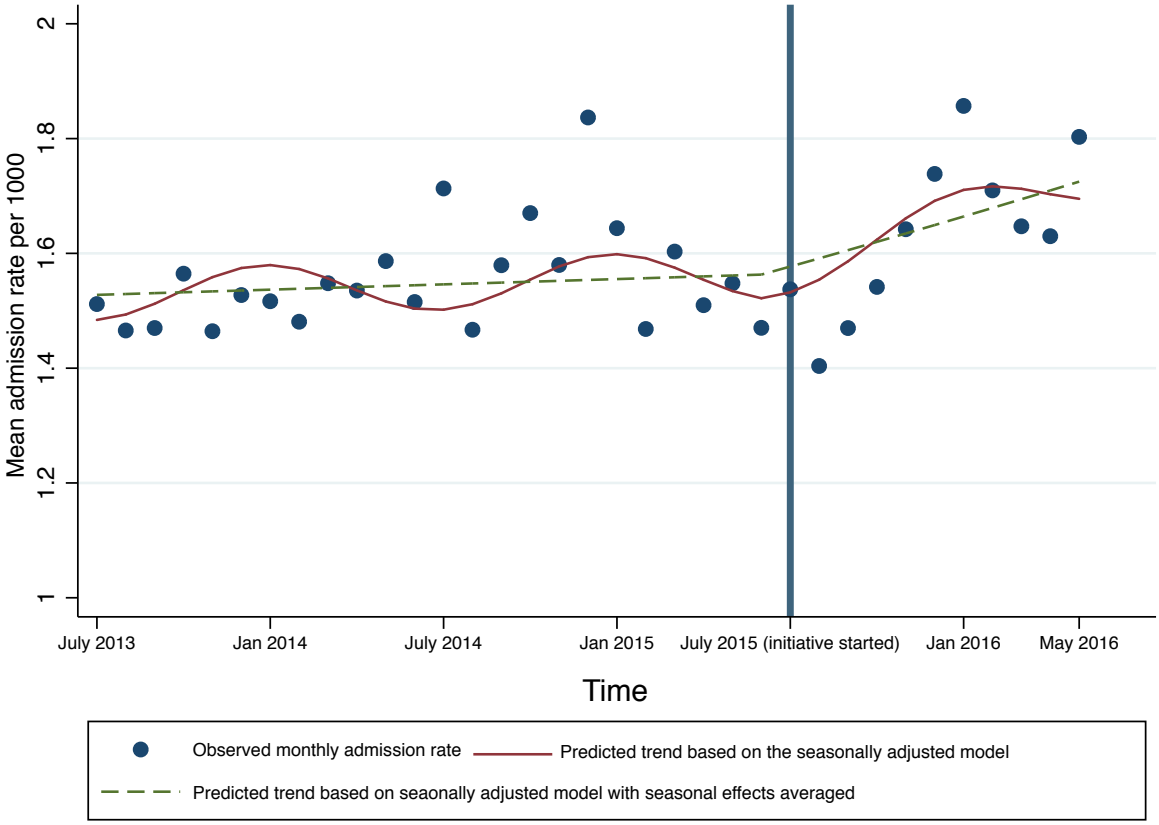


Table 8. Results of a segmented negative binomial regression for ambulatory care sensitive emergency admissions in Oxfordshire from July 2013 to May 2016

Model terms	Incidence rate ratio	95%CI	p-value
Baseline monthly admission rates 24 months prior to the initiative	0.0008	0.0001 to 0.0053	0.000
Underlying pre-intervention trend in monthly admission rates	1.0009	0.9981 to 1.0039	0.497
Change in trend in monthly admission rates after introduction of the initiative	1.0080	0.9993 to 1.0168	0.072
Fourier cyclical season adjustment terms Cos1 Sin1	 1.0286 0.9969	 1.0020 to 1.0559 0.9711 to 1.0234	 0.035 0.817

n=35 monthly observations (July 2013 to May 2016). Pseudo-R^2= 0.06

7.4.9 Patterns of emergency admissions among intervention users

During the study period, 7.4% of all-cause admissions and 10.0% of ACSC admissions in Oxfordshire were from users of the Right Care interventions. Mean monthly admission rates for intervention users are shown in Table 9. Rates for non-users are provided for context. Results for each intervention are presented in Appendix 7.14.

Table 9. Description of mean admission rates among users and non-users of the interventions

Population	Mean ±SD of emergency hospital admission rate per 1,000					
	Full study period		Pre-intervention period[b]		Active intervention period[c]	
	All-cause	ACSC	All-cause	ACSC	All-cause	ACSC
Intervention users (n=28,598)	15.01 ±4.46	4.10 ±1.37	12.59 ±1.74	21.4 ±2.45	3.39 ±0.61	6.00 ±0.95
Non-users (n=687,595)[d]	7.43 ±0.27	1.46 ±0.09	7.48 ±0.28	7.30 ±0.20	1.48 ±0.08	1.43 ±0.12

[a]July 2013 to March 2016, the time period for which there was available individual patient admissions data. [b]24 months from July 1, 2013 and start of the initiative in June 30, 2015. [c]9 month active initiative period for which there was individual patient data: July 1, 2015 to March 31, 2016. [d]Mid-period population estimate used as the denominator (October 2015).

Time series graphs of hospital admissions among intervention users revealed a common overall pattern, with three distinct sub-patterns (Figure 5). Among intervention users for which there was at least three months of follow-up data (n=10,556), there was a steady increase in admissions in the 24-months leading up to the date they accessed the interventions. This steady rise was followed by a spike in admissions in close proximity to use of the intervention. This occurred across all interventions. However, the timing of the spike relative to the date of intervention use reveals three distinct sub-patterns. Firstly, for users of neighbour hubs and the early visiting service, there was spike in the first month after use of the interventions, followed by a decrease to pre-intervention levels shortly thereafter (Figures 5a, 5b). Secondly, for users of extended 20-minute GP appointments and e-mail consultations, there was a spike in the first two months after use of the interventions (Figures 5c, 5d). Thirdly, for users of the care navigator service and practice nurse visiting service, admissions peaked in the month prior to intervention use, with a sustained high-level of admissions until after use of the interventions (Figures 5e, 5f). Across all three patterns, the rates of admissions showed a downward trend to pre-intervention levels after one to two months of follow-up.

Figure 5. Mean monthly rate of emergency hospital admissions among intervention users with at least three months of follow-up

Figure 5a.

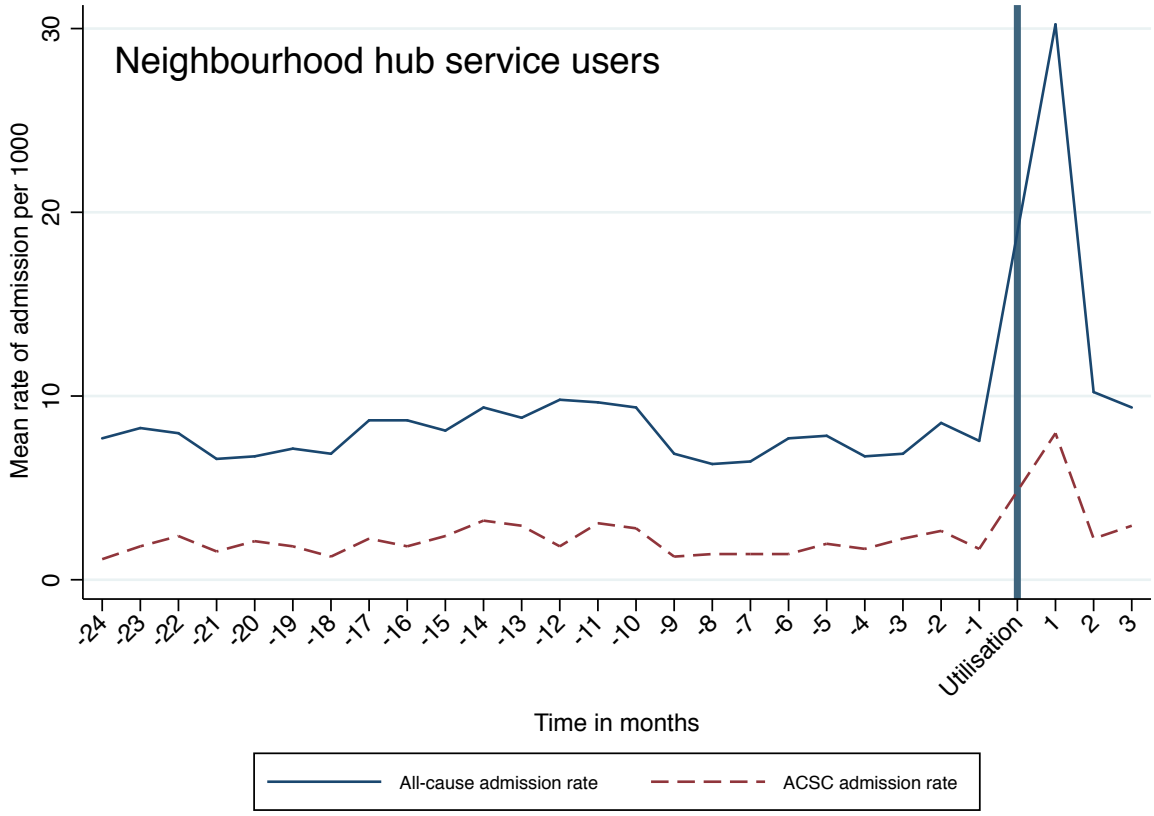


Figure 5b.

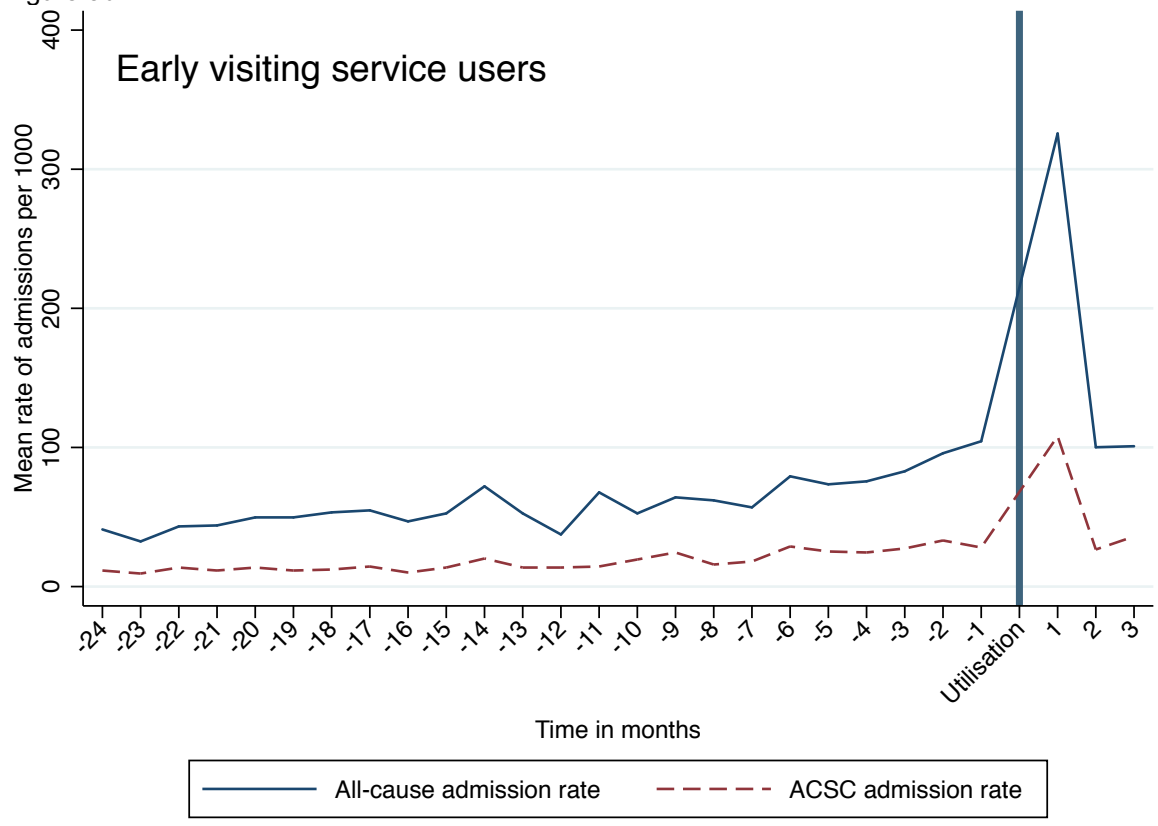


Figure 5 continued. Mean monthly rate of emergency hospital admissions among intervention users with at least three months of follow-up

Figure 5c.

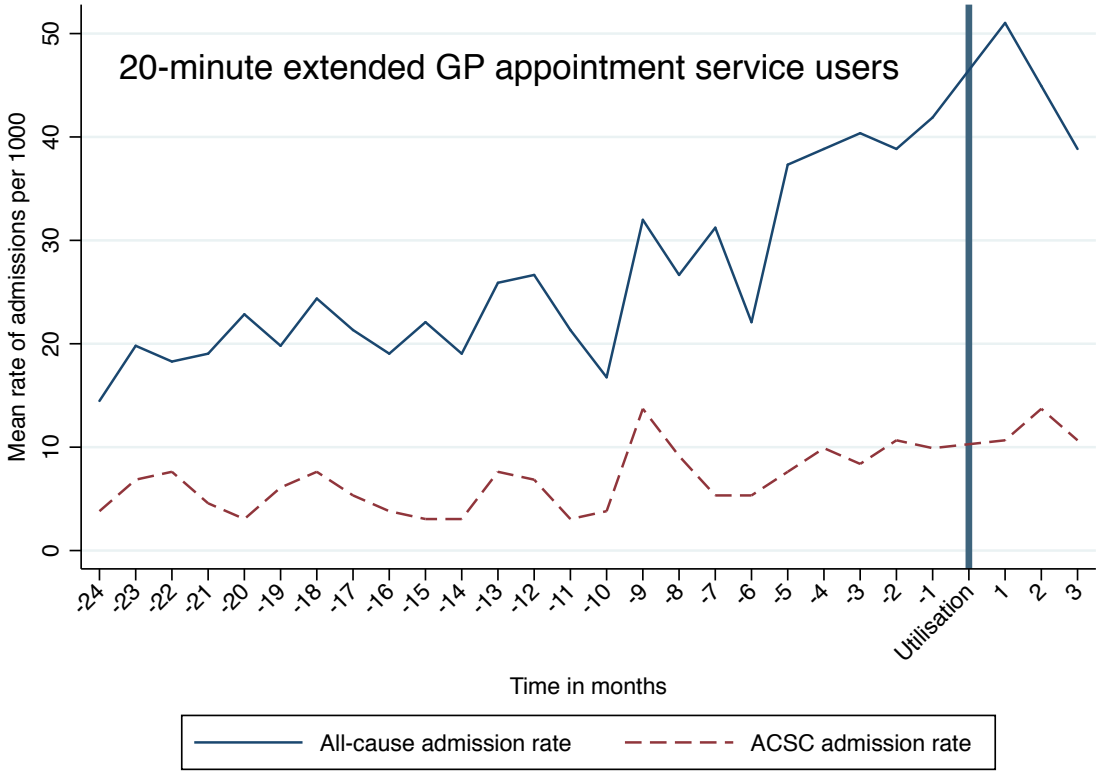


Figure 5d.

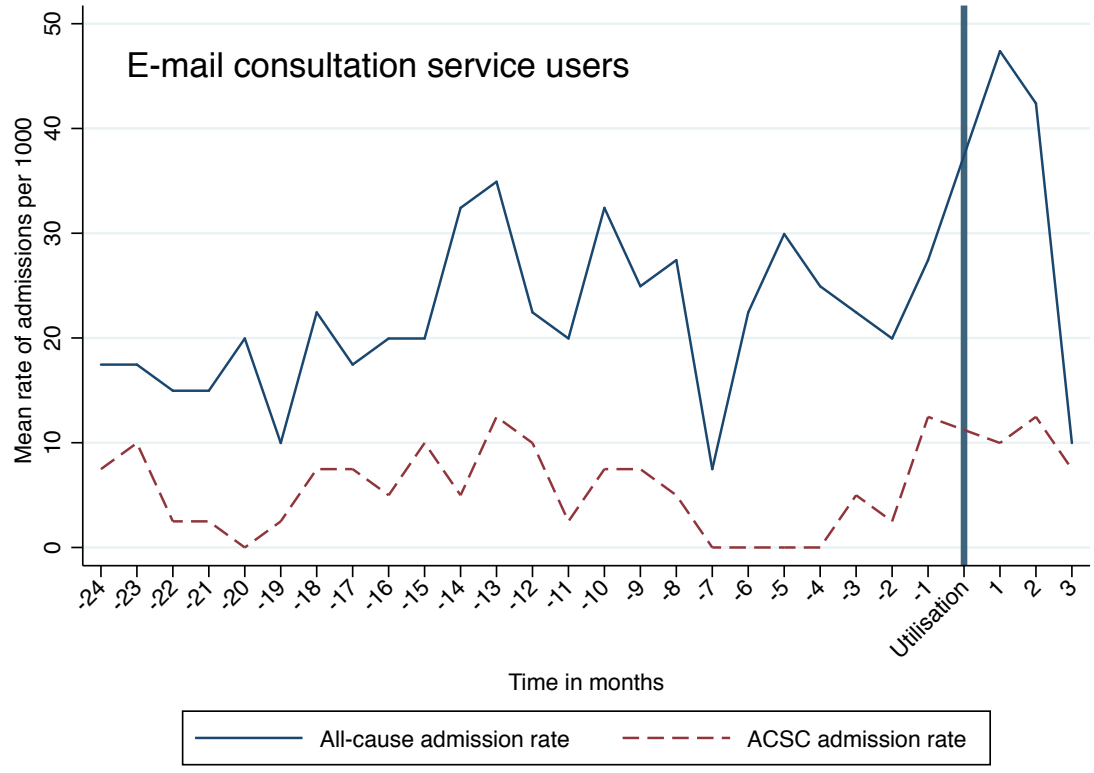


Figure 5 continued. Mean monthly rate of emergency hospital admissions among intervention users with at least three months of follow-up

Figure 5e.

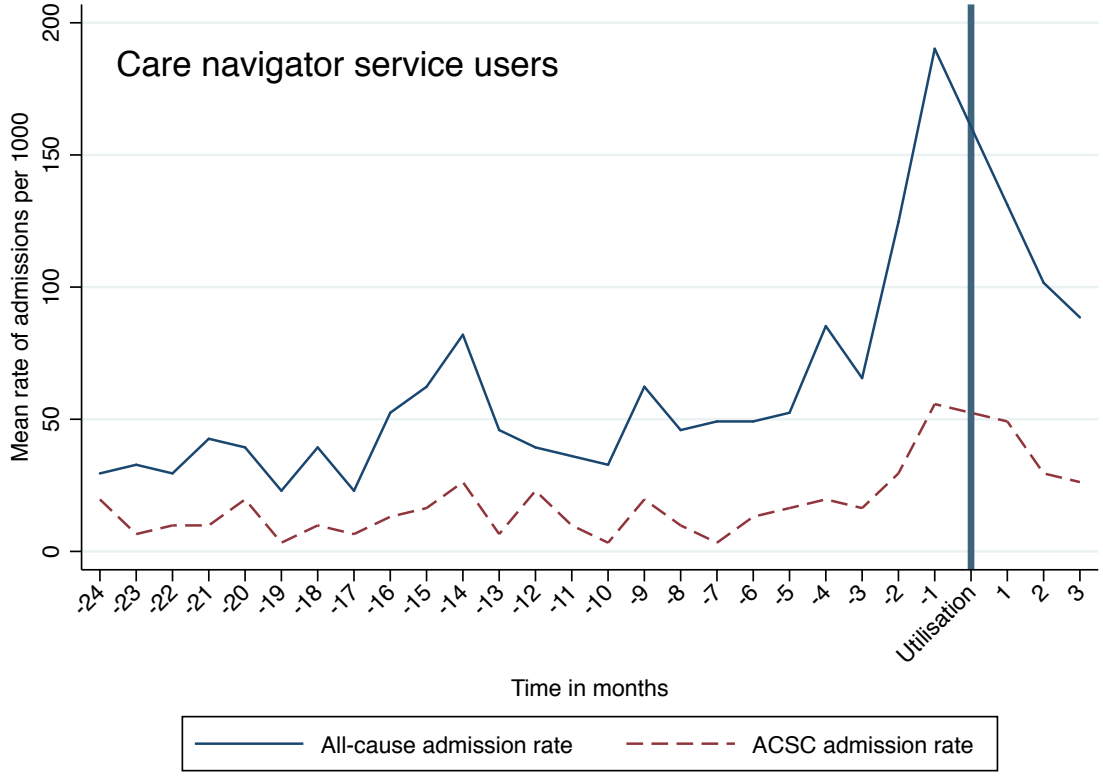
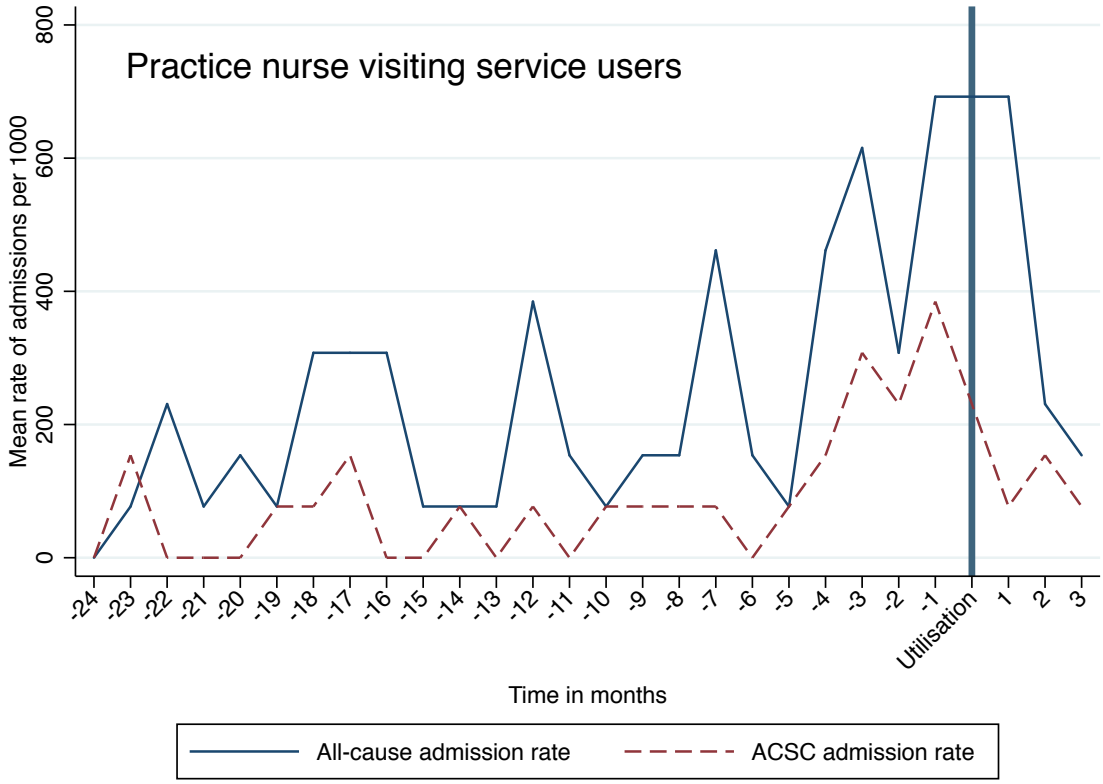


Figure 5f.



7.5 Discussion

7.5.1 Summary of findings

This study examined a set of primary care access interventions implemented in July 2015 in a large health region in England. The interventions were intended to increase access to primary care and reduce emergency hospital admission rates. This study showed that, over the 11-month study period, they did increase access; they directly provided 39,056 primary care consultations that would not have otherwise been available. However, segmented time series regression analysis showed that the interventions were not associated with a significant change in county-level hospital admission rates for ambulatory care sensitive conditions and may have even increased all-cause admissions by up to 8%. The results suggest that increasing access to primary care may not reduce EHA. This study also highlights challenges involved in evaluating real-world initiatives for reducing hospital admissions using routinely collected data shared between multiple stakeholders. These challenges include the feasibility of randomisation, inaccessibility of data to create matched concurrent control groups, and consistency of electronic health record coding across multiple primary care practices.

7.5.2 Findings in the context of existing research

The results of this study corroborate and build upon the findings of the national evaluation of interventions implemented in the Prime Minister's GP Access Challenge. The Right Care interventions in Oxfordshire were part of the second round of the GP Access Challenge. Interventions funded in the first round were nationally evaluated and the results were published after second wave interventions had been implemented.[19] Twenty initiatives were implemented across the UK in the first round. Six of these showed reductions in hospital admissions, ranging from 1% to 3% however, the statistical significance of these reductions was not reported. The overall conclusion of the national evaluation was that "for emergency admissions..., there has been no demonstrable impact and, as such, there are unlikely to be any cost savings". The national evaluation used a simple before/after comparison to assess impact on hospital admissions. Therefore, given the strength of time series analysis, the results in this chapter may be considered more valid and reliable than the national evaluation. This chapter also provides more details and insights

regarding the nature of the association between primary care access interventions and emergency hospital admissions.

The results in this chapter align with mounting evidence and discourse that increasing access to general practice may not be the solution to rising emergency hospital admission rates.[20,21] Overall, the evidence for the impact of access to care on admissions has been mixed and may be context dependent.[22,23] In contrast to the results of this chapter, and other studies from the UK and Europe, evidence from the United States has shown that better access to primary care is associated with reductions in EHA.[22–24] This discrepancy may arise from differences in the health systems. In the United States, millions of Americans lack insurance coverage and their only option for health care is self-referral to secondary acute care settings. Therefore, increasing access to primary care may be more likely to offset emergency hospital admissions compared to England, where there is universal coverage and the proportion of the population solely reliant on secondary acute care is be lower.

There are several potential explanations for the results in this study, some of which are corroborated by existing research.

Firstly, although timely access is an important goal of high-quality health systems[25], increasing access to unfamiliar health care providers may eliminate the crucial element of primary care required for avoiding admissions; familiarity with the patient.[26,27] Physicians have reported that sufficient knowledge of a patient's medical and non-medical circumstance is crucial to tolerating the risks involved in sending ill patients home or to alternative care sources as opposed to the hospital ward.[28] Large studies on continuity of care corroborate this. For example, Barker et al. evaluated 230,472 individual patient records and found that patients who see the same general practitioner a greater proportion of the time experience fewer admissions to hospital for ambulatory care sensitive conditions than other patients.[29]

With respect to the Right Care interventions, the major impetus in five of the six initiatives was to provide patients with more timely consultations, but this was achieved with someone other than their regular GP.[29] This fragmentation of care

may explain the lack of impact on ACSC admissions and the slight increase in all-cause admissions.

Secondly, increasing access to urgent primary care may have helped to avoid or delay mortality in the community, which may have increased admission rates. Improvements in survival during acute episodes of illness have been associated with subsequent increases in emergency hospital admissions due to a larger pool of frail and ill patients at-risk of admission.[30] In the context of the Right Care interventions, patients that would otherwise have died in the community may have been identified via the interventions and conveyed to hospital before death, thereby resulting in additional admissions. Some of these patients may also have survived the hospital episode and been discharged back into the community, thereby increasing the pool of patients at high-risk for acute hospitalisation.

Thirdly, increasing access to primary care may increase practitioner exposure to patients whose needs border between urgent primary care and acute secondary care. Given the rising threat of litigation[31] and practice of defensive medicine, exposure to greater numbers of these patients in primary care may increase rates of hospital admissions.[28,32,33] Most of the Right Care interventions were designed for patients with urgent care needs. Therefore, it is possible that ill patients nearing the threshold for hospitalisation were seen immediately by a primary care practitioner, who referred them to hospital. Without the interventions, these patients may have had to wait for an appointment and their issues may have subsided to the point where an admission would no longer be considered.

Fourthly, the pattern of ACSC admissions among intervention users in this chapter suggests that some of the interventions may have been too little, too late to help avoid hospitalisation. In four of the six interventions, the highest spikes in ACSC admission rates occurred in the first month after intervention use. Caution is required when interpreting this data as no individually matched controls were used however, ACSC admissions are, by definition, potentially avoidable through the provision of high-quality primary care. Therefore, increases in ACSC admissions, after having just accessed primary care services, call into question the timeliness of the service in relation to disease progression. It is possible that the urgent and complex nature

of many of the patients' health issues meant that avoiding an admission was not possible through increase primary care access.

Research on ACSC admissions supports this possibility.[34] For example, Fleetcroft et al. (2018) organised clinician-led case reviews of a random selection of 132 emergency admissions in England and showed that only 47% of admissions for ACSC were judged potentially avoidable. According to the clinicians, failure to seek timely advice from GPs had led some patients to deteriorate beyond the ability of primary care to help avoid admission. They also cited the impact of influential comorbidities as reasons why access to primary care would not have helped to avoid many of the ACSC admissions. These mechanisms may partially explain why the Right Care interventions were not associated with a reduction in ACSC admissions.

7.5.3 Strengths

This study had three main strengths.

Firstly, this study investigated the use of interventions in clinical practice. Therefore, the results may provide estimates of utilisation and effect that more accurately reflect the complexity and diversity of the 'real-world'. Furthermore, the coordination of data linkages and data sharing between multiple stakeholders was a considerable achievement.

Secondly, this study used an interrupted time series design. This is the strongest quasi-experimental design and protects against common threats to internal validity, most notably, confounding by pre-intervention secular trends that influence the outcome.

Thirdly, the results are based on a robust regression analysis that used sophisticated techniques (fourier terms) to adjust for seasonal effects on the outcome. This also served to reduce confounding and increase the validity of the results.

Fourthly, the data were analysed as counts/rates. As highlighted in chapters 3, most systematic reviews and RCTs reporting hospitalisation outcomes analyse the proportion of patients experiencing one or more admissions. This has little utility given that chronic disease patients often experience multiple admissions per year and reporting data as proportions may conceal the effect of an intervention.

7.5.4 Limitations

There were limitations to this study.

Firstly, the study did not use a randomised design. A stepped-wedge randomised cluster design was ethically and theoretically possible and would have guarded against additional threats to internal validity. However, the agreement between the CCG and Oxford University to evaluate the interventions was reached close the planned start date of the interventions. Therefore, there was little time to harmonise the existing stakeholder plan for implementation with the requirements of a robust stepped-wedge cluster design. Furthermore, funding for the interventions had to be spent by the end of the financial year, which placed limitations on how long a staged roll-out could occur. These political and financial limitations are common challenges to conducting 'real-world' evaluations. However, if decision-makers and academics maintain ongoing communication some of these challenges may be overcome and result in the generation of higher-quality service evaluations.

Secondly, the effects of individual interventions could not be evaluated because a concurrent matched control group was not available. Ideally, individual patient data from another CCG could have been used to match control patients to intervention users. Three CCGs were contacted but were unwilling to provide this type of data. Attempts were made to obtain local data but revision of the initial data sharing agreement was not feasible after the first draft of the service evaluation report drew criticisms from local stakeholders. Despite this limitation, use of a concurrent local control group would not have been appropriate. The interventions were implemented county-wide and affected nearly every GP practice. Therefore, even patients not directly exposed to the interventions may have been affected by them through increased capacity of normal primary care services. This issue is known as contamination and would have led to a confounded comparison. Use of the pre-

utilisation period for individual patients could have served as a historic control for the post-utilisation period however, this would have been at high risk of selection bias and regression to the mean.[3,13]

Thirdly, a concurrent control group for the aggregate county analysis was not used. Use of control groups in time series of aggregate data can reduce confounding from other major events that occur at the time of the intervention and that potentially influence the outcome, changes in admission reporting systems, or new criteria for admitting patients to hospital. External control groups were considered, but the potential for unknown major policy changes in other jurisdictions and limitations in adjustment for confounding using publicly available data meant that comparisons would likely have been confounded. For example, Buckinghamshire county (composed of Chiltern CCG and Aylesbury CCG) was explored as a potential concurrent control group. It is located next to Oxfordshire county and did not participate in the GP Access Fund initiative. It has a similar sized population with similar health needs according to NHS estimates of relative health care need and relative unavoidable costs for health care services.[8] The two counties also have similar levels of deprivation, a key predictor of regional rates of emergency hospital admissions. However, after detailed review and construction of age-sex adjusted admission rates, reports were found which described several major county-wide primary care health service initiatives in 2015 and 2016, some of which targeted hospital admission rates[3536] Introduction of these major initiatives during the study period, that were not present in Oxfordshire, meant that a comparison would likely have been confounded.

Fourthly, it is possible that the intervention did not reach a large enough portion of the population to have had a detectable impact. The interventions were accessed by only 4% of the population of Oxfordshire. However, the analysis showed that this was a high-risk group that may be considered “frequent-flyers”. This group of patients contributed 10% of all admissions in Oxfordshire during the study period. Prior to implementation of the interventions the mean all-cause admission rate among eventual intervention users was nearly double that of non-users (12.59 vs 7.48 admissions per 1,000 per month) while their ACSC admission rate was nearly triple that of non-users (21.49 vs. 7.30 admissions per 1,000 per month). The

analysis also showed that intervention users had a higher burden of chronic disease compared to the rest of the population. Therefore, even though only a small portion of the population used the interventions, it's feasible that modestly effective interventions could have had a demonstrable impact on admissions at the county level.

Fifthly, it is possible that the short time frame (less than one year) did not allow the interventions to mature into high-functioning services capable of reducing admission rates. It was unclear whether published research evidence or previously evaluated service initiatives were considered during the design or implementation of the Right Care interventions and, therefore, all aspects of the services may have been entirely novel and untested (this issue is explored in-depth in chapter 8). Resources for implementation, including guidance from the Medical Research Council on complex interventions, suggest that local piloting and optimisation are necessary to understand and maximise benefit from in-practice interventions. It is possible that not enough time was allowed for this process to occur.[37,38]

Sixthly, the analysis assumed that the characteristics of the population remained unchanged throughout the study period. Changes in the population base may have occurred and these may have confounded the analysis. However, the study period spanned only three years and it is unlikely that shifts in population demographics during this time would have been substantial enough to influence county-level admission rates.

Seventhly, data extracted from GP practice systems by the CSU were not validated using on-site records. Ideally, a portion of the data could have been spot checked against on-site records. However, due to limitations of resources and time this was not feasible.

7.5.5 Implications for policy and practice

The findings of this study have implications for future policies and initiatives that aim to reduce emergency admissions.

Firstly, the results suggest that funding novel access to care interventions may not be an effective or efficient strategy for alleviating the emergency care crisis. The £5 million injection into the CCG increased access but had no demonstrable impact on ACSC admissions rates and may have increased all-cause admissions. Although increasing primary care access may have other benefits for patients and the health system, reducing hospital admissions may not be one of them. Future primary care initiatives that aim to reduce hospital admissions should consider targeting optimisation of interventions whose beneficial effects have been consistently demonstrated with high-quality evidence, such as those identified in chapter 3 and 4 of this thesis.

Secondly, governments and health systems should consider facilitating local use of stepped-wedge randomised designs when testing new health care services. This approach to testing and implementation would enable high-quality comparisons of intervention areas to local concurrent control areas to establish evidence of effectiveness and to inform decisions to scale-up or de-adopt services. This approach may also serve to save resources by limiting wide-spread implementation of ineffective or potentially harmful practices.[39,40] As highlighted in this chapter there are practical challenges to using this type of design for service initiatives including the need to deliver services and allocating funding in short time frame. However, top-down structural support and collaboration with academics may help local stakeholders to overcome these challenges.

Thirdly, nationally driven service initiatives should include mechanisms to support collaborations between stakeholders in different areas. Sharing of experiences, peer to peer learning, and data sharing might benefit stakeholders during the design, implementation, and evaluation of new services. The GP Access Fund supported the systematic implementation of many interventions in large populations. Each implementation represented an important opportunity to build the evidence base, yet there was no national strategy to support local evaluation efforts or to help stakeholders collaborate. In the absence of this support, securing individual patient data for matched controls was challenging and opportunities to learn about interventions implemented in previous rounds of the initiative or in other areas may have been missed.

7.5.6 Future research

It has been suggested that the effects of access to care on emergency admissions are context dependent. Therefore, future researchers may consider exploring which contextual factors affect the relationship between primary care access and hospitalisations. Although this study showed no association with admissions, it is possible that certain types of interventions in certain population and settings may be beneficial.

Many universal health systems globally are working to improve access to primary care and the potential unintended consequence of increasing hospital admission rates may need to be considered. Therefore, future primary care research should investigate mechanisms by which increased access to primary care may result in increased emergency hospital admissions. Mechanisms include increased patient exposure to unfamiliar health care providers, reduced community-based mortality, and increased practitioner exposure to patients bordering on the need for admission.

Future research should explore whether there are circumstances under which admissions for ACSC are not avoidable. Specifically, whether ACSC admissions should be considered as potentially unavoidable due to compounding comorbid illness or after a certain level of deterioration. Exploring this topic may help researchers and health systems to more narrowly define and identify potentially avoidable hospital admissions. This may also help to more clearly determine when ACSC admissions are a valid and reliable indicator of primary care access and quality.

7.6 Conclusions

It was feasible to evaluate ‘real-world’ interventions implemented in clinical practice to reduce hospital admissions. Use of a quasi-experimental study design and time series analysis was possible after navigating data sharing arrangements between multiple stakeholders. The results showed that the interventions increased access to primary care but were not associated with a significant change in emergency admission rates for ambulatory care sensitive conditions and may have increased all-cause emergency admission rates.

Use of more robust study designs may be possible for evaluating future 'real-world' interventions if mechanisms are put in place to support ongoing collaboration and data sharing between health care stakeholders and academics in different regions. Furthermore, the government and health system may consider facilitating local use of stepped-wedge randomised designs when testing new health care services.

Future primary care initiatives aiming to reduce hospital admissions should explore improvements in continuity of care or optimisation of interventions with proven effectiveness in reducing hospital admissions, as opposed to increasing primary care access.

7.7 Chapter summary

- Evaluating 'real-world' interventions for reducing hospital admissions was feasible
- Interventions that increased primary care access were not associated with a significant change in admissions for ambulatory care sensitive conditions and may have increased all-cause admission rates
- Use of more robust study designs may be possible for evaluating future 'real-world' initiatives if mechanisms are put in place to support ongoing collaboration and data sharing between stakeholders
- Future primary care initiatives aiming to reduce hospital admissions should explore improvements in continuity of care or optimisation of interventions with proven effectiveness, as opposed to increasing access

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Chapter 7. Appendix

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Appendix 7.1 Description of interventions excluded from the study

- Skype consultations: this service was implemented in October 2015 but an interim analysis showed only nine consultations after five months of use. Evaluation of this intervention was ceased as it the CCG judged it to have minimal viability.
- Out-of-hours access to GP records: this service was proposed but, due to information governance barriers, was not implemented during the study period.
- Online health resource: a website was created that drew external information from Yelp, Facebook, YouTube and other sources, and provided contact details for local health, social care and community services. The website went active in October but the interim analysis in January showed that the website was referring patients to non-evidence-based health claims. Its continued implementation was not recommended, and its use declined rapidly.

Appendix 7.2 List of ambulatory care sensitive conditions used

Table 1. List of ambulatory care sensitive conditions used in the analysis

ACSCs in common use in the NHS (n=19)	ICD10 codes
Angina	I20, I24.0 I24.8 I24.9 I25 R072 R073 R074 Z034 Z035
Asthma	J45, J46
Cellulitis	L03 L04 L08.0 L08.8 L08.9 L88 L98.0 I891 L010 L011 L020 to L024 L028 L029
Congestive heart failure	I11.0 I50 J81 I130 I255
Convulsions and epilepsy	G40 G41 R56 O15 G253 R568
Chronic obstructive pulmonary disease	J20 J41 J42 J43 J47 J44 J40X
Dehydration and gastroenteritis	E86 K52.2 K52.8 K52.9 A69.0 A020 A04 A059 A072 A080 A081 A083 A084 A085 A09 K520 K521
Dental conditions	A69.0 K02 K03 K04 K05 K06 K08 K09.8 K09.9 K12 K13
Diabetes complications	E10.0–E10.8 E11.0–E11.8 E12.0–E12.8 E13.0–E13.8 E14.0–E14.8 H66 E139, E149
Ear, nose, and throat infections	H66 H67 J02 J03 J06 J31.2 J040
Gangrene	R02
Hypertension	I10 I11.9
Influenza and pneumonia	J10 J11 J13 J14 J15.3 J15.4 J15.7 J15.9 J16.8 J18.1 J18 J189 J120 J121 J122 J128 J129 J160 A481 A70x
Iron-deficiency anaemia	D50.1 D50.8 D50.9 D460 D461 D463 D464 D510–D513 D518 D520 D521 D528 D529 D531 D571 D580 D581 D590–D592 D599 D601 D608 D609 D610 D611 D640 to D644 D648
Nutritional deficiency	E40 E41 E42 E43 E55.0 E64.3
Other vaccine-preventable diseases	A35 A36 A37 A80 B05 B06 B16.1 B16.9 B18.0 B18.1 B26 G00.0 M01.4
Pelvic inflammatory disease	N70 N73 N74
Perforated/bleeding ulcer	K25.0–K25.2 K25.4–K25.6 K26.0–K26.2 K26.4–K26.6 K27.0–K27.2 K27.4–K27.6 K280–282 K284–K286 K920 K921 K922 K20x K210 K219 K221 K226
Pyelonephritis	N10 N11 N12 N13.6 N300 N390 N159 N308 N309

Appendix 7.3 Details of data coding challenges and solutions

Data coding challenges:

Challenges in the management of data arose as a result of different coding used in different GP practices. There were three partially overlapping variables used to describe the interventions: *patient contact clinical code* (read code)*; patient contact code term;* and *cohort*. *Patient contact code term* was a text variable that described the alphanumeric *patient contact clinical code;* both were based on read codes in the Electronic Medical Information system. The *Cohort* code variable was created by the evaluation team. Confusion arose as the variables partially overlapped and there were variations in the language used to describe each intervention. In addition, there were no read codes for the Neighbourhood hubs. These were instead identified by organisation codes akin to GP practice codes. These coding discrepancies are illustrated in Table 2.

Table 2. Coding discrepancies

Service	Three sets of variables in the datasets that identified the services used		
	Based on read codes		Defined by the evaluation team
	Patient contact clinical codes (read code)	Patient contact code terms (text description of read code)	Cohort codes
Extended appointments	66, EMISNQEX49	Chronic disease monitoring, Extended consultation for complex condition	20m
Early visiting service	6A7	Reviewed by advanced primary nurse	EVP, EVS
Practice visiting nurse service	9N2y	Seen by community nurse for older people	EVO[a]
E-mail consultation	9N3B	E-mail received from patient	ema, Ema
Care navigators	9NtA	Seen by Community Navigator	CNa, CNA
Neighbourhood access hubs[b]	-	-	Hub

[a]There were 162 cases (before de-duplication) in which patients in the non-PML dataset were coded as having received the Practice Nurse Visiting Service (*Cohort* code: EVO) however, this was incorrect as non-PML federations did not offer this service. These cases were re-coded to identify the "Early Visiting Service" (*Cohort code*: EVP). [b]There were no read codes for the Neighbourhood hubs. These were instead identified by organisation codes akin to GP practice codes.

Data coding solutions:

The *Cohort* coding variable was used for analysis this was the only variable which covered all services. Before de-duplicating, similar codes that described the same service were combined (i.e. CNa and CNA for "Care Navigators") and 162 cases originally identified as "Early visiting service" were converted to the "Practice visiting nurse service".

Appendix 7.4 Histograms of monthly service utilisation

Figure 1. Care navigator consultations

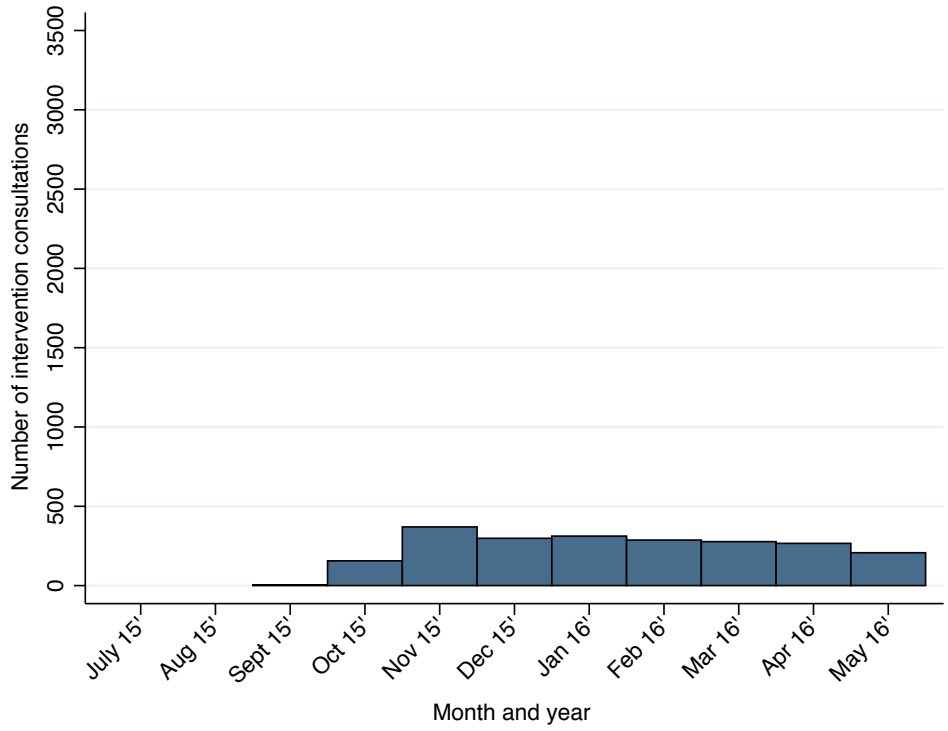


Figure 2. Early visiting service consultations

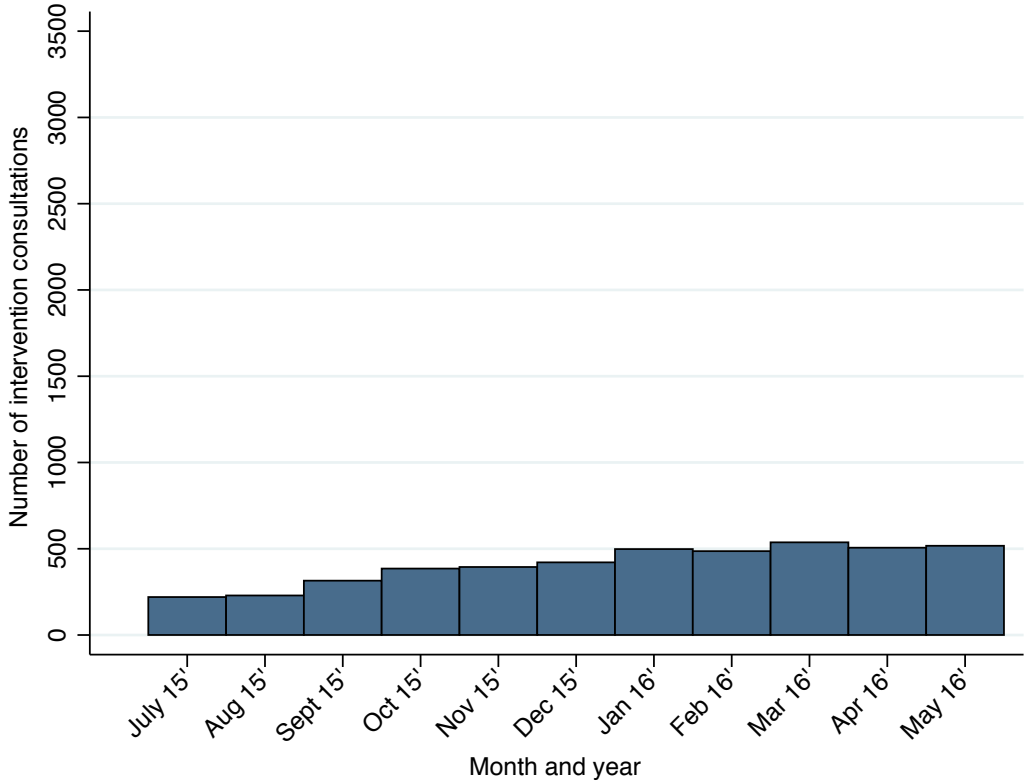


Figure 3. E-mail consultations

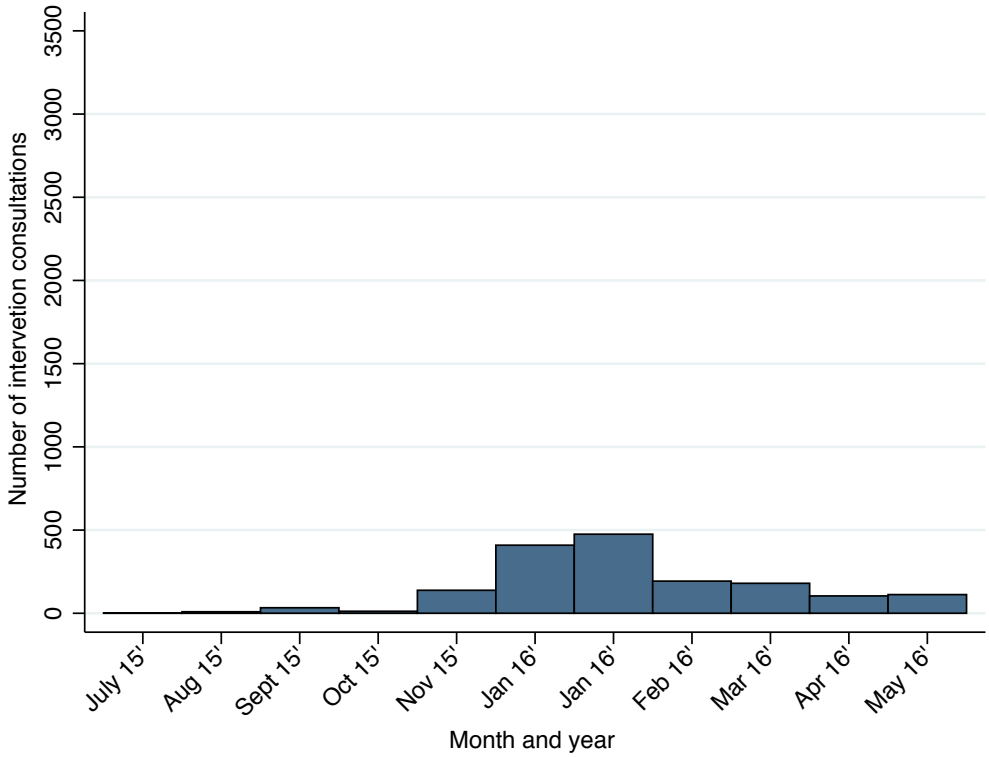


Figure 4. Extended appointment consultations

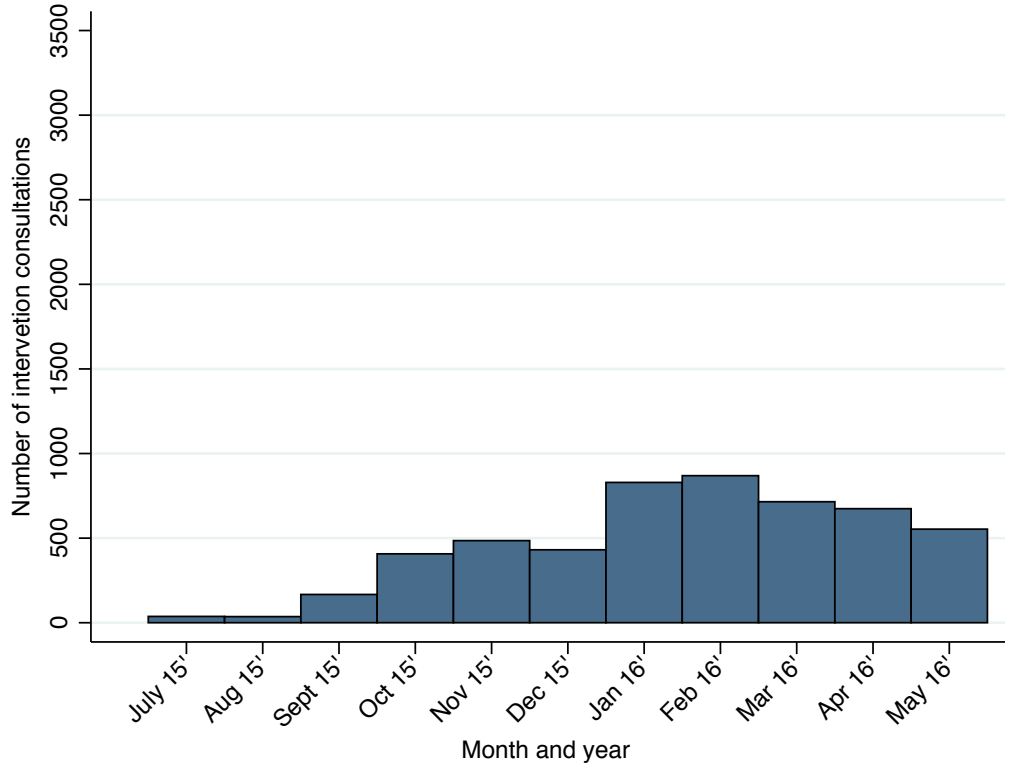


Figure 5. Neighbourhood hub consultations

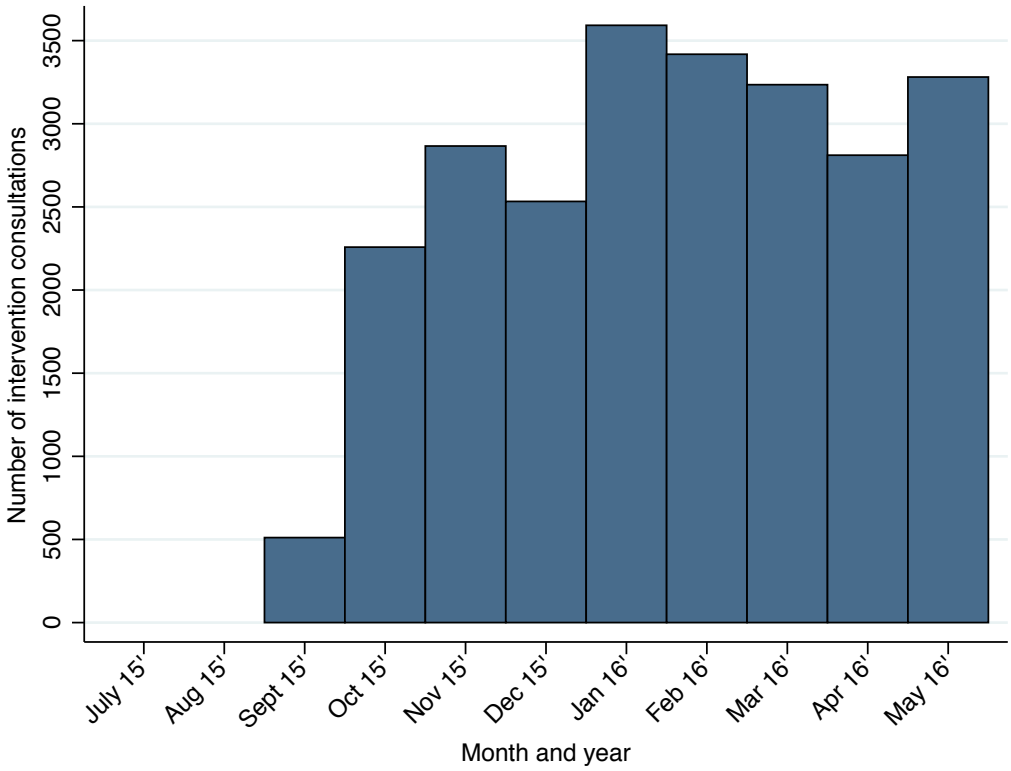
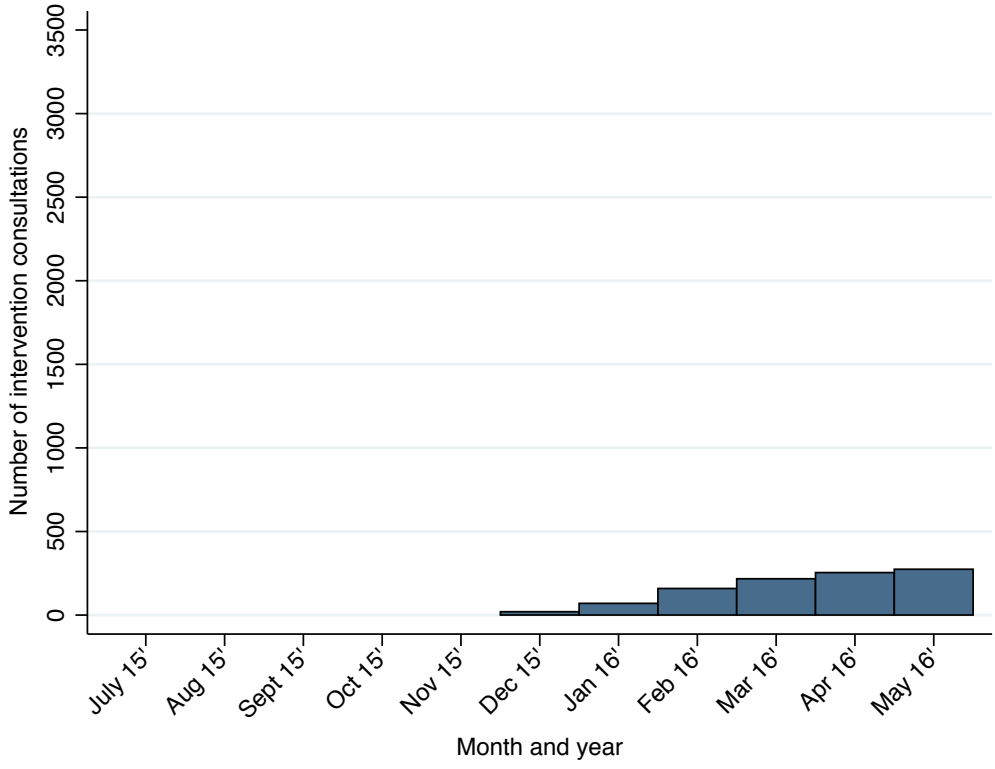


Figure 6. Practice nurse visiting service consultations



Appendix 7.5 Description of monthly service utilisation

Table 3. Description of monthly service utilisation

Services	Measure of utilisation	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Total
Care navigators	Consultations	N/A	N/A	4	156	370	298	312	287	277	266	207	2,177
	Patients	N/A	N/A	2	68	129	106	115	93	105	92	117	827
Early visiting service	Consultations	220	229	315	385	394	421	498	486	537	506	517	4,508
	Patients	146	150	221	269	291	311	366	368	409	399	393	3,323
E-mail consultations	Consultations	2	9	33	12	138	409	475	193	180	104	112	1,667
	Patients	2	6	25	7	94	267	320	141	123	77	88	1,150
Extended appointments	Consultations	37	36	167	407	485	431	829	869	715	674	553	5,203
	Patients	32	33	126	342	415	365	702	735	602	557	441	4,350
Neighbourhood hubs	Consultations	N/A	N/A	511	2,258	2,866	2,533	3,592	3,418	3,235	2,811	3,281	24,505
	Patients	N/A	N/A	449	1,982	2,514	2,201	3,168	3,037	2,892	2,519	2,938	21,700
Practice nurse visiting service	Consultations	N/A	N/A	N/A	N/A	N/A	20	70	159	217	254	274	994
	Patients	N/A	N/A	N/A	N/A	N/A	13	41	37	56	58	27	232
Total	Consultations	259	274	1030	3,218	4,253	4,112	5,776	5,412	5,161	4,615	4,945	39,055
	Patients	180	189	823	2,668	3,443	3,263	4,712	4,411	4,187	3,702	4,005	28,598[a]

[a]There were 28,598 unique patients, but some patients used multiple services or used the same services in multiple months and, therefore, the rows may not add to 28,598.

Appendix 7.6 Characteristics of intervention users

Table 4. Characteristics of patients using the interventions

	Care navigator patients % (n=759)	Early visiting service patients % (n=3,094)	E-mail consultation patients % (n=1,099)	Extended appointments patients % (n=4,094)	Neighbourhood hub patients % (n=19,994)	Practice nurse visiting service patients % (n=319)
Age [a]	76 (SD=17)	80 (SD=14)	48 (SD=23)	61 (SD=21)	32 (SD=23)	82 (SD=10)
Age in groups						
<18	1% (6)	1% (2)	11% (116)	4% (147)	34% (6 718)	-
18 to 54	11% (85)	5% (150)	51% (557)	29% (1 180)	46% (9 262)	3% (6)
55 to 64	8% (58)	4% (131)	13% (140)	15% (628)	10% (1 898)	5% (12)
65 to 74	14% (106)	10% (305)	12% (127)	20% (802)	7% (1 295)	9% (21)
75+	66% (504)	64% (1 986)	15% (159)	33% (1 337)	4% (821)	83% (193)
Missing data	-	17% (521)	-	-	-	-
Sex						
Female	59% (450)	48% (1 498)	60% (656)	58% (2 371)	58% (11 536)	58% (135)
Male	41% (309)	28% (861)	40% (443)	42% (1 723)	42% (8 458)	42% (97)
Missing data	-	25% (736)	-	-	-	-
Number of QOF registry diseases						
0	9% (71)	63% (1 943)	2% (18)	<0.5% (1)	43% (8 561)	<0.5% (1)
1	18% (134)	2% (75)	34% (377)	20% (816)	35% (7 051)	2% (5)
2	21% (158)	5% (156)	33% (365)	31% (1 249)	14% (2 860)	16% (36)
3 or more	52% (396)	30% (921)	31% (339)	50% (2 028)	8% (1 522)	82% (190)

[a]Mean and standard deviation.

Appendix 7.7 Histograms of emergency hospital admissions data

Figure 7. Histogram of all-cause admissions for Oxfordshire from July 2013 to May 2016

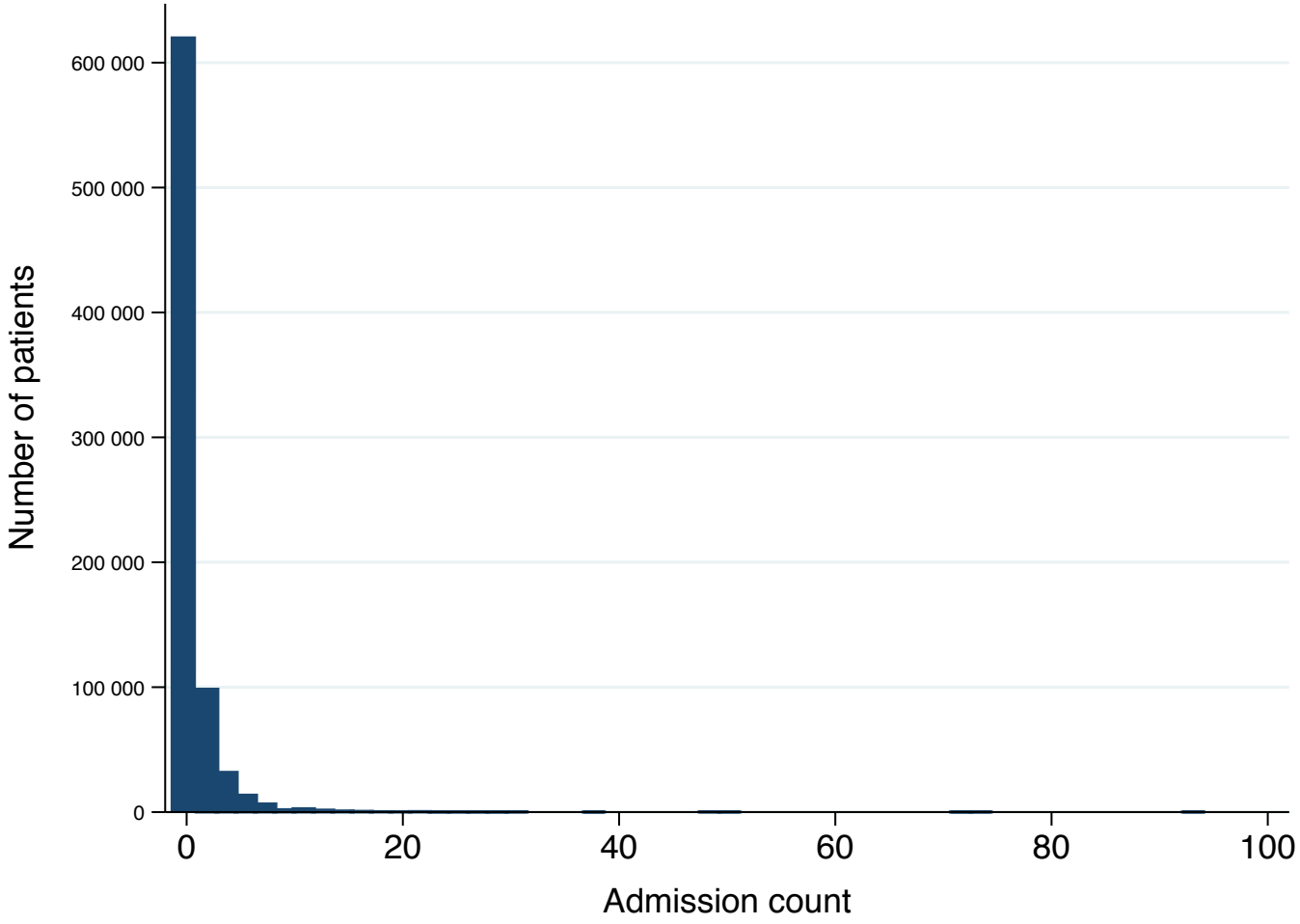
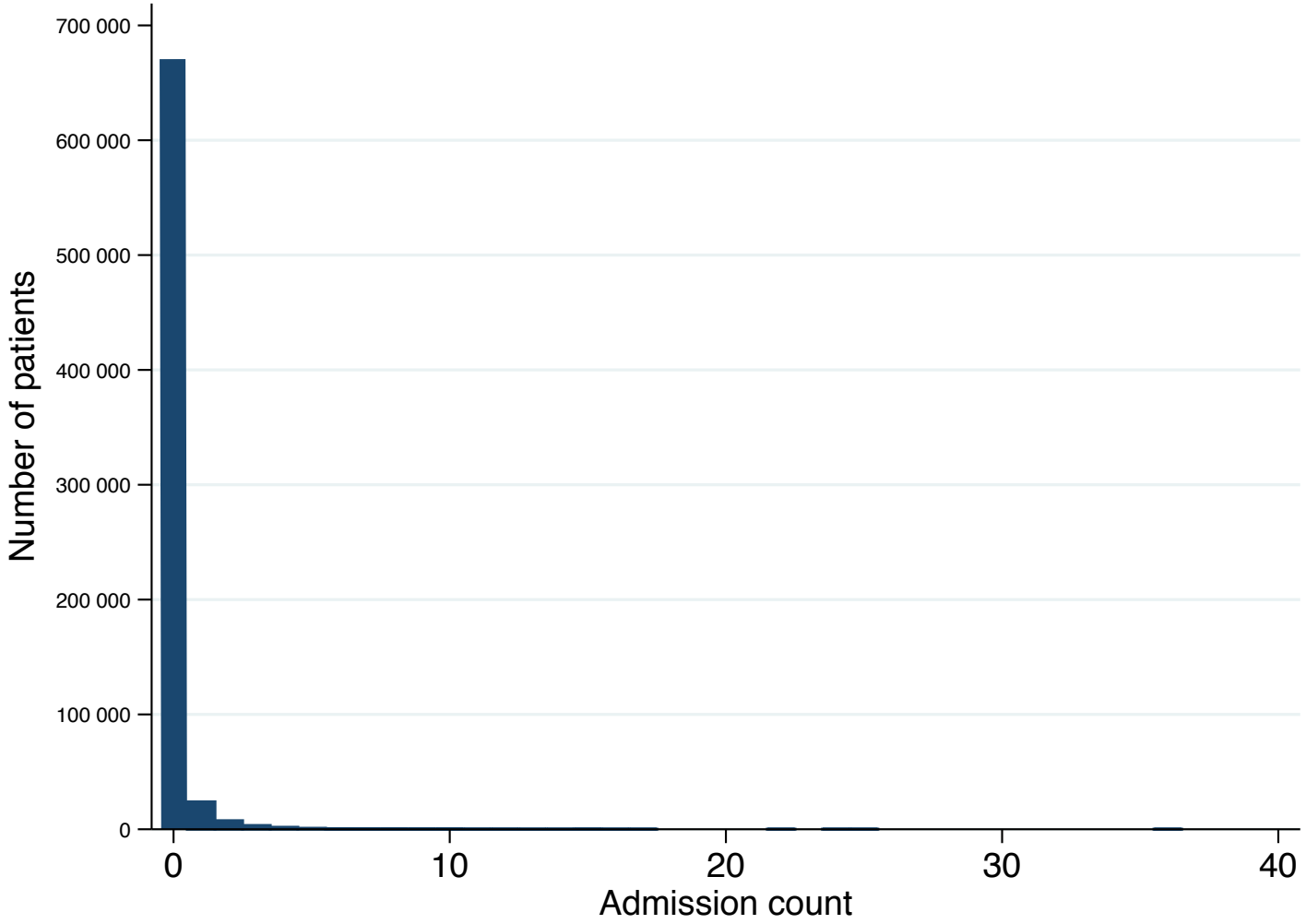


Figure 8. Histogram of ambulatory care sensitive condition admissions for Oxfordshire from July 2013 to May 2016



Appendix 7.8 Scatter plots showing linear relationship between emergency hospital admissions and time

Figure 9. Scatter plot of all-cause emergency hospital admissions with lowess smoother

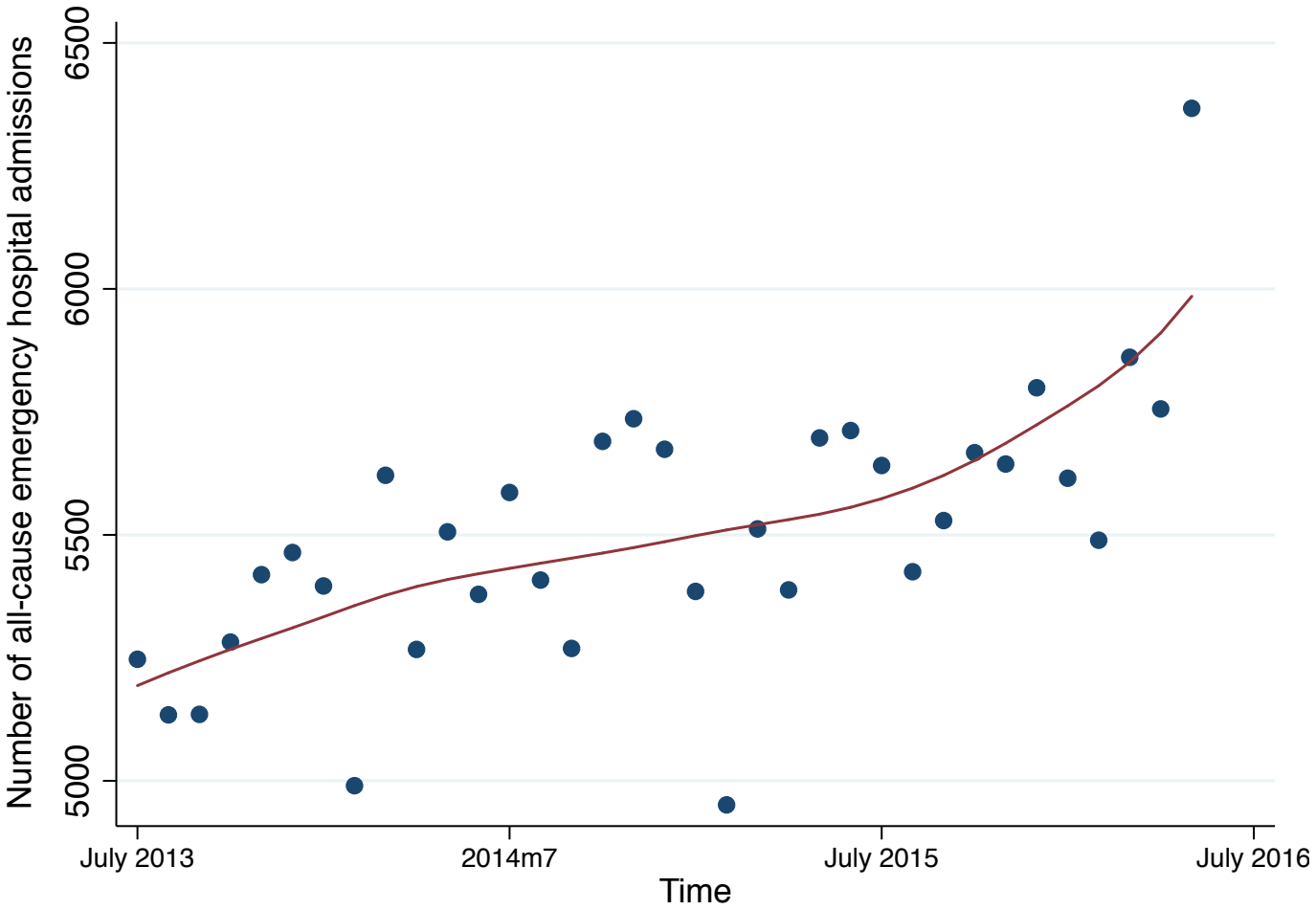
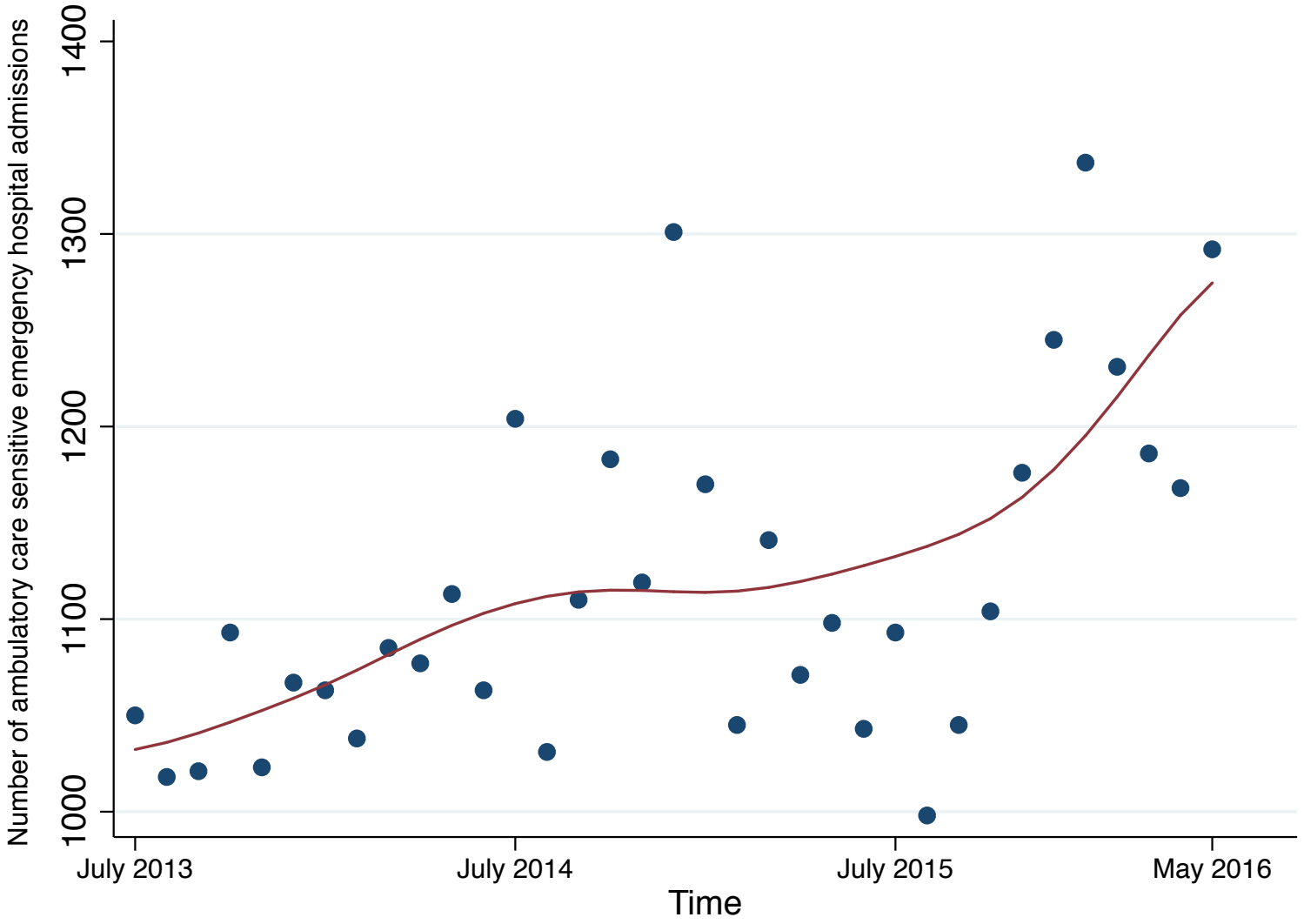


Figure 10. Scatter plot of ambulatory care sensitive emergency hospital admissions with lowess smoother



Appendix 7.9 Conditional admission means and variances showing over-dispersion of data

Table 5. Conditional admission means and variances showing over-dispersion of data

Outcome	Period	Mean	Variance
All-cause admissions	Pre-intervention period	5410.33	50021.36
	Active-intervention period	5708.45	64727.87
ACSC admissions	Pre-intervention period	1092.79	4600.78
	Active-intervention period	1170.46	10790.67

Appendix 7.10 Evidence of seasonal autocorrelation in all-cause emergency admissions data prior to statistical adjustment

Figure 11. Autocorrelation function plot for all-cause admissions

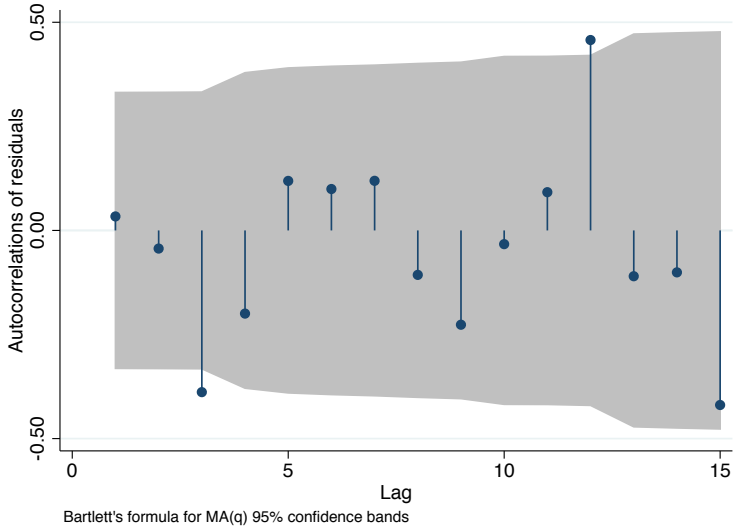


Figure 12. Partial autocorrelation function plot for all-cause admissions

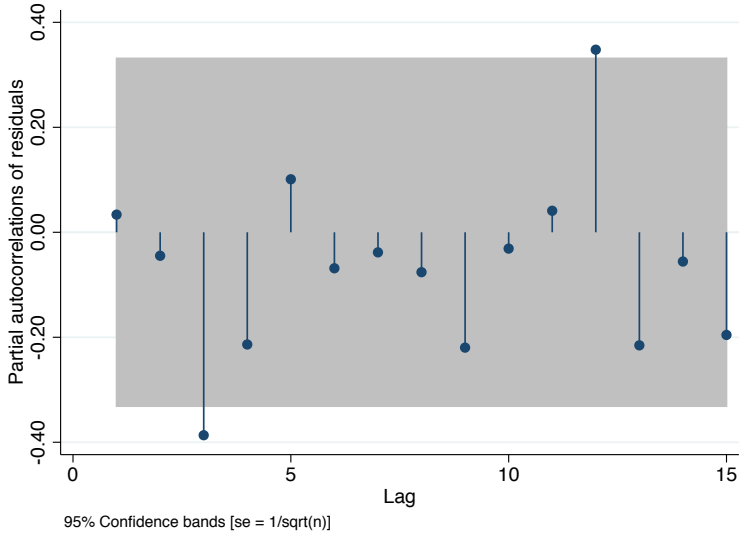


Table 6. Correlogram with autocorrelation values and p-values indicating significance

Lag	Autocorrelation	Partial autocorrelation	Q	Prob>Q
1	0.0336	0.0336	.04301	0.8357
2	-0.0436	-0.0448	.1176	0.9429
3	-0.3885	-0.3866	6.2247	0.1012
4	-0.1998	-0.2138	7.8927	0.0956
5	0.1189	0.1010	8.5029	0.1306
6	0.0994	-0.0686	8.9445	0.1767
7	0.1191	-0.0383	9.6007	0.2124
8	-0.1068	-0.0760	10.148	0.2548
9	-0.2266	-0.2198	12.705	0.1764
10	-0.0330	-0.0311	12.761	0.2373
11	0.0918	0.0410	13.216	0.2794
12	0.4573	0.3478	24.989	0.0149*

Appendix 7.11 Regression results for all-cause emergency admissions

Figure 13. Regression output for all-cause emergency admissions

```
. glm all_cause_num cos* sin* slope_term time, family(nbinomial ml) link(log)
offset(logpop) eform

Iteration 0:   log likelihood = -224.43827
Iteration 1:   log likelihood = -224.43686
Iteration 2:   log likelihood = -224.43686

Generalized linear models                         No. of obs      =         35
Optimization     : ML                             Residual df     =         28
                                                  Scale parameter =          1
Deviance         =  35.07247586                   (1/df) Deviance =   1.252588
Pearson          =  35.29734801                   (1/df) Pearson  =    1.26062

Variance function: V(u) = u+(.0005)u^2            [Neg. Binomial]
Link function    : g(u) = ln(u)                   [Log]

                                                  AIC             =   13.22496
Log likelihood   = -224.4368607                   BIC             =  -64.47727

------------------------------------------------------------------------------
             |                 OIM
all_cause_num |        IRR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       cos_1 |   .9875226   .0064983    -1.91   0.056     .9748679    1.000342
       cos_2 |   .9925485   .0063851    -1.16   0.245     .9801125    1.005142
       sin_1 |   .9995938   .0065503    -0.06   0.951     .9868374    1.012515
       sin_2 |   .9694895   .0062854    -4.78   0.000     .9572484    .9818872
  slope_term |   1.004617   .0021941     2.11   0.035     1.000326    1.008927
        time |   1.000845   .0007156     1.18   0.238     .9994431    1.002248
       _cons |   .0044227   .0020705   -11.58   0.000     .0017668    .0110707
      logpop |          1  (offset)
------------------------------------------------------------------------------
Note: Negative binomial parameter estimated via ML and treated as fixed once
      estimated.
```

Figure 14. Plot showing random distribution of residuals over time for all-cause admissions regression

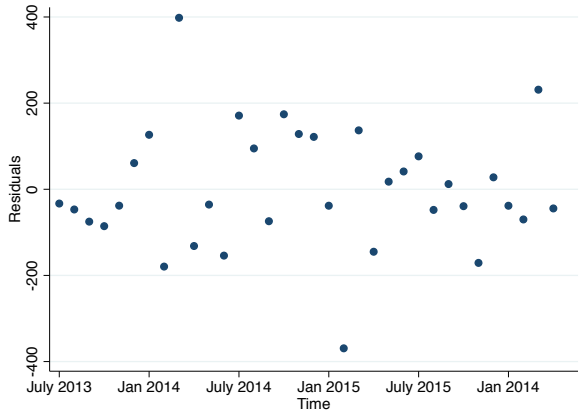


Figure 15. Autocorrelation function plot for all-cause admissions after adjustment for seasonality

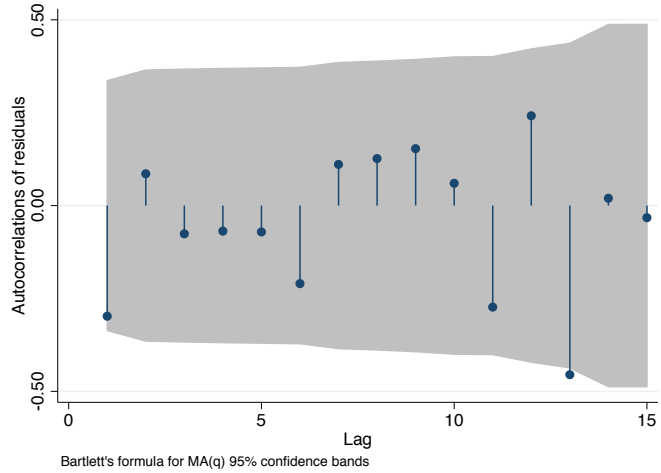


Figure 16. Partial autocorrelation function plot for all-cause admissions after adjustment for seasonality

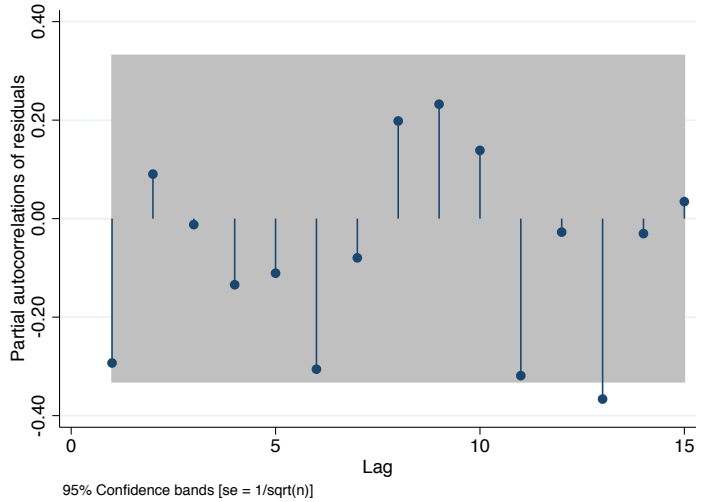


Table 7. Correlogram with autocorrelation values and p-values indicating significance after adjustment for seasonality for all-cause emergency hospital admissions

Lag	Autocorrelation	Partial autocorrelation	Q	Prob>Q
1	-0.2932	-0.2932	3.2733	0.0704
2	0.1686	0.0904	4.3882	0.1115
3	-0.0825	-0.0122	4.6635	0.1982
4	-0.0816	-0.1343	4.9414	0.2934
5	-0.0537	-0.1109	5.0661	0.4079
6	-0.2534	-0.3058	7.9329	0.2431
7	0.0858	-0.0796	8.2731	0.3091
8	0.1188	0.1983	8.9505	0.3465
9	0.1398	0.2323	9.9236	0.3567
10	0.0980	0.1385	10.421	0.4043
11	-0.2105	-0.3189	12.813	0.3058
12	0.2108	-0.0274	15.314	0.2247

Appendix 7.12 Regression results for ambulatory care sensitive emergency hospital admissions

Table 8. Regression output for ambulatory care sensitive emergency admissions

```
. glm acsc_num cos* sin* slope_term time, family(nbinomial ml) link(log)
offset(logpop) eform

Iteration 0:   log likelihood = -193.37936
Iteration 1:   log likelihood = -193.37712
Iteration 2:   log likelihood = -193.37712

Generalized linear models                         No. of obs      =         35
Optimization     : ML                             Residual df     =         30
                                                  Scale parameter =          1
Deviance         =  34.83196386                   (1/df) Deviance =   1.161065
Pearson          =  35.66996973                   (1/df) Pearson  =   1.188999

Variance function: V(u) = u+(.0021)u^2            [Neg. Binomial]
Link function    : g(u) = ln(u)                   [Log]

                                                  AIC             =   11.33584
Log likelihood   = -193.3771236                   BIC             =  -71.82848

------------------------------------------------------------------------------
             |                 OIM
    acsc_num |        IRR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       cos_1 |   1.028613   .0137541     2.11   0.035     1.002006    1.055927
       sin_1 |   .9969009    .013337    -0.23   0.817     .9711007    1.023387
  slope_term |   1.008006   .0044624     1.80   0.072     .9992975     1.01679
        time |   1.000994   .0014631     0.68   0.497     .9981304    1.003866
       _cons |   .0008067    .000772    -7.44   0.000     .0001236    .0052642
     logpop |          1  (offset)
------------------------------------------------------------------------------
Note: Negative binomial parameter estimated via ML and treated as fixed once
      estimated.
```

Figure 17. Plot of residuals against time for ambulatory care sensitive emergency admissions regression after adjustment for seasonality

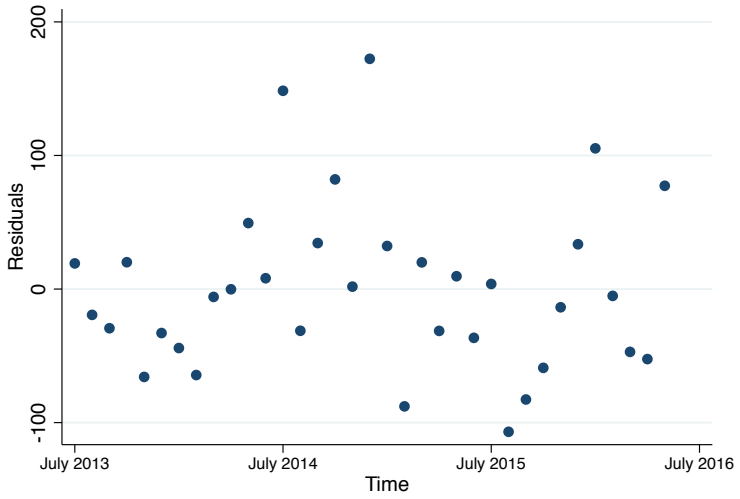


Figure 18. Autocorrelation function plot for ambulatory care sensitive emergency hospital admissions after adjustment for seasonality

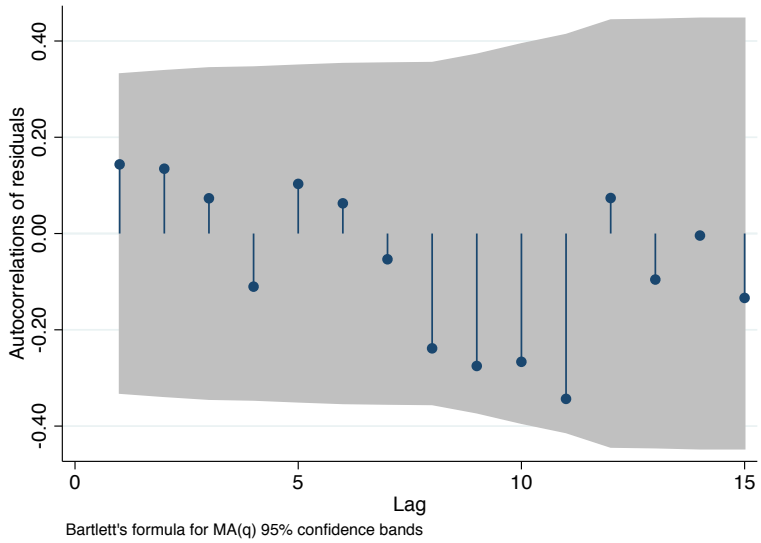


Figure 19. Partial autocorrelation function plot for ambulatory care sensitive emergency hospital admissions after adjustment for seasonality

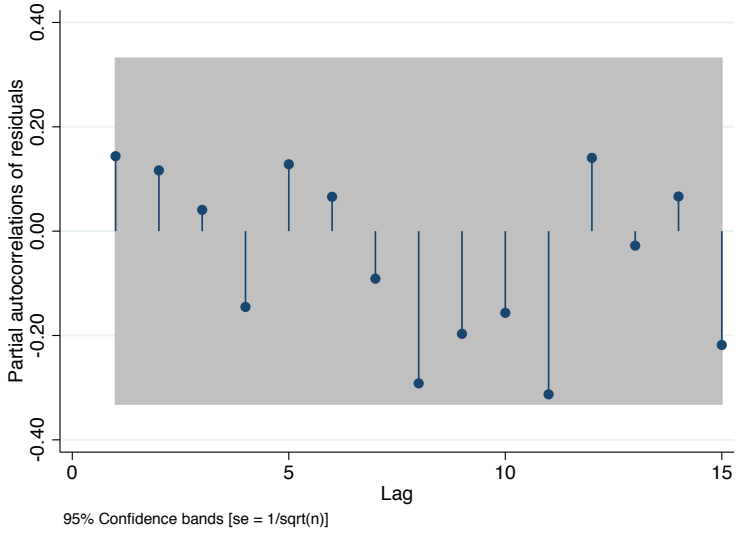


Table 9. Correlogram with autocorrelation values and p-values indicating significance after adjustment for seasonality for ambulatory care sensitive emergency admissions

Lag	Autocorrelation	Partial autocorrelation	Q	Prob>Q
1	0.1436	0.1436	0.78579	0.3754
2	0.1346	0.1164	1.4971	0.4730
3	0.0732	0.0407	1.7137	0.6339
4	-0.1104	-0.1453	2.223	0.6948
5	0.1031	0.1281	2.6821	0.7489
6	0.0627	0.0658	2.8577	0.8265
7	-0.0535	-0.0912	2.9901	0.8859
8	-0.2386	-0.2918	5.7211	0.6784
9	-0.2753	-0.1970	9.4949	0.3929
10	-0.2666	-0.1567	13.175	0.2140
11	-0.3435	-0.3129	19.543	0.0520
12	0.0737	0.1404	19.85	0.0700

Appendix 7.13 Results of sensitivity analysis of all-cause emergency hospital admissions

Figure 20. Sensitivity analysis for segmented negative binomial time series regression of all-cause admissions with adjustment for seasonality and removal of outlying data point

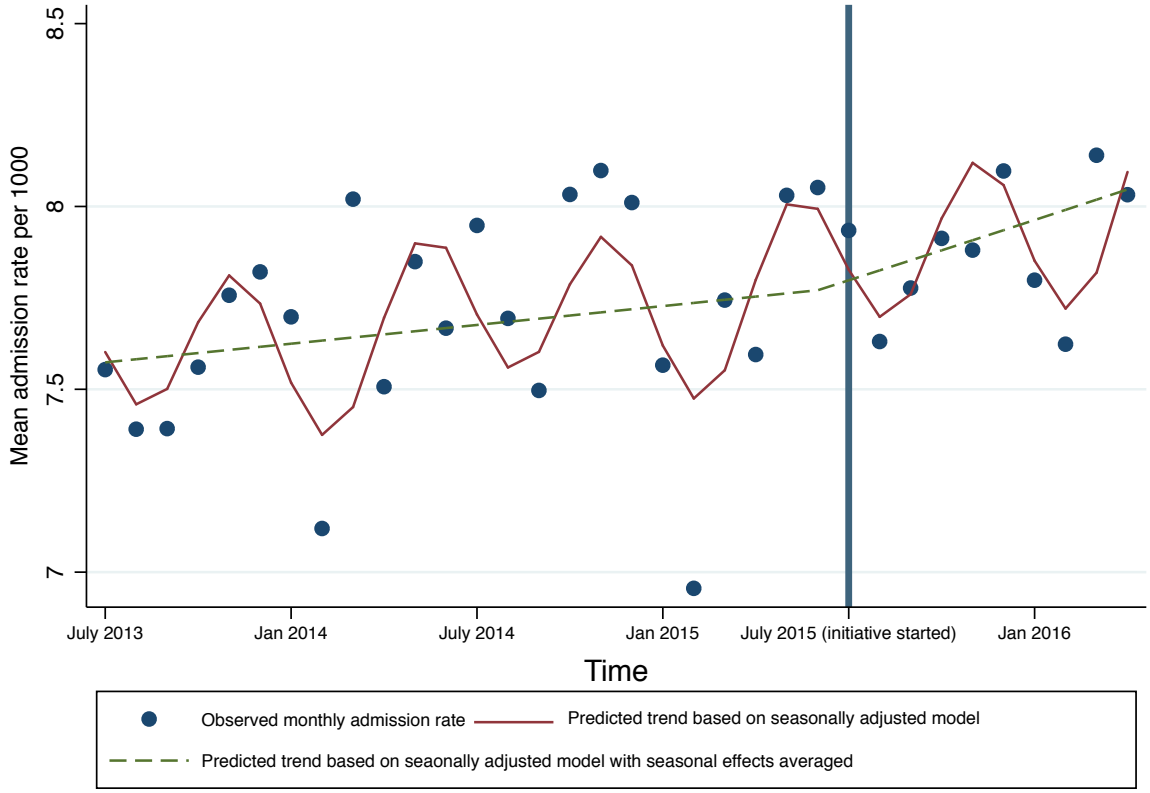


Table 10. Sensitivity analysis of all-cause emergency hospital admissions with outlying data point removed[a]

Model terms	Incidence rate ratio	95%CI	p-value
Baseline monthly admission rates 24 months prior to the initiative	0.0037	0.0015 to 0.0091	0.000
Underlying pre-intervention trend in monthly admission rates	1.0011	0.9997 to 1.0025	0.109
Change in trend in monthly admission rates after introduction of the initiative	1.0024	0.9977 to 1.0070	0.317
Fourier cyclical season adjustment terms			
Cos1	0.9911	0.9785 to 1.0040	0.175
Cos2	0.9932	0.9813 to 1.0053	0.268
Sin1	0.9974	0.9851 to 1.0010	0.687
Sin2	0.9731	0.9608 to 0.9856	0.000

[a]May 2016 outlying data point removed N=33 monthly observations (July 2013 to April 2016). Pseudo-R2= 0.05

Appendix 7.14 Mean before-after admission rates among patients using the Right Care interventions with a minimum of three months of follow-up

Table 11. Mean monthly emergency admission rates for patients using the Right Care interventions with a minimum of three months of follow-up

Population and sub-groups	Mean ±SD of emergency hospital admission rate per 1000			
	Pre-intervention	Post-intervention[c]	Pre-intervention	Post-intervention[c]
	All-cause	All-cause	ACSC	ACSC
All intervention users (n=10,556)	17.90 ±3.80	42.72 ±26.70	4.90 ±1.25	12.85 ±8.25
Neighbourhood hub users (n=7,146)	7.85 ±1.08	16.61 ±11.8	2.00 ±0.61	4.38 ±3.13
Early visiting service users (n=1,388)	60.19 ±18.18	175.55 ±130.00	17.86 ±6.91	56.91 ±44.55
E-consultation service users (n=401)	21.82 ±6.79	33.25 ±20.31	5.20 ±4.02	9.98 ±2.49
Practice nurse visiting service users (n=13)	227.56 ±184.95	358.97 ±291.23	86.54 ±102.23	102.56 ±44.41
Care navigator users (n=305)	55.60 ±36.59	107.10 ±21.83	15.30 ±11.26	34.97 ±12.41
20-minute extended GP appointment users (n=1,313)	25.83 ±8.25	44.94 ±6.09	6.51 ±2.84	11.68 ±1.76

[a]July 2013 to March 2016, the time period for which there was available individual patient admissions data. [b]24 months from July 1, 2013 and start of the initiative in June 30, 2015. [c]9 month active initiative period for which there was individual patient data: July 1, 2015 to March 31, 2016. [d]Mid-period population estimate used as the denominator (October 2015). Abbreviations: SD=standard deviation.

Chapter 8. The use of evidence when designing and implementing local interventions as part of a national campaign to reduce emergency hospital admissions: a qualitative study

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8.0 Chapter overview

This chapter explores the use of evidence by local decision makers when designing and implementing interventions as part of a national innovation campaign to reduce hospital admissions. Qualitative interviews with seven decision makers were conducted. The results showed that decision makers sought expert opinion and service evaluations, which were perceived as valuable to inform implementation. No academic research evidence was used. Decision-makers felt that the campaign's emphasis on innovation meant that robust evidence of effectiveness was not needed to inform action. Practical challenges to using evidence were identified including lack of skill, time pressures, and political constraints. Opportunities to increase the quantity and strength of evidence used in decision making were also identified. These were broadly categorised as generating evidence that better aligns with the needs of decision makers and helping decision makers to make better use of existing evidence. Lessons to facilitate future evidence-based decision making are discussed.

8.1 Introduction

"Innovation is being used as a smokescreen to smuggle poor quality evidence past the need for systematic review" - Margaret McCartney[1]

8.1.1 Building on the findings of previous chapters

The Prime Minister's GP Access Challenge was a novel national initiative to increase primary care access and reduce hospital admissions with interventions designed and implemented by local stakeholders. Chapter 7 of this thesis reported an evaluation of this initiative in a large health region in England. The analysis showed that the initiative was not associated with changes in admissions rates for ambulatory care sensitive conditions but was associated with an 4% increase in all-cause admissions. This type arrangement was becoming more frequent in efforts to reduce hospital admissions in the UK. However, the process of local decision making in the context of national campaigns to reduce admissions was unclear, including how evidence was used to design and implement interventions. To better understand this process and derive lessons for future initiatives, interviews were conducted with decision makers involved in the GP Access Challenge in Oxfordshire.

8.1.2 Gaps in knowledge about evidence-based health service decision making

To ensure that patients receive high-quality care and that scarce resources are used efficiently health care services should be designed and implemented using the best available evidence.[2–4] However, studies have shown variation in the use of evidence in health care decision making and, often, the best available evidence is not considered.[5–7] Commonly identified barriers include financial restrictions, top-down political agendas, and limitations of time and staff skill.[5,6,8]

Previous research has studied health care commissioners over multiple years and decisions, and thereby may reflect the use of evidence during "routine" commissioning. However, it is unclear if the findings of this research apply to national innovation challenges, during which local health care stakeholders are provided funding to design and implement innovative services in the pursuit of a

common national goal. These campaigns may represent a unique circumstance in the world of clinical commissioning.[9,10] In routine NHS commissioning, there is an obligation to demonstrate clinical effectiveness and value for money before installing a service. [9] However, some have argued that innovation campaigns offer a fast-track implementation pathway for interventions without evidence of efficacy or effectiveness or that bear little resemblance to previously tested interventions.[1] If so, it may be argued that resources dedicated to these campaigns may be used more appropriately and efficiently to scale-up or improve use of interventions that are supported by strong evidence.

8.1.3 An opportunity to address the gap in knowledge

The Prime Minister's GP Access Challenge was a national initiative to increase primary care access and reduce emergency hospital admissions with innovative interventions designed and implemented by local stakeholders.[10] Oxfordshire CCG was one of 57 pilot sites awarded funding to participate in the challenge. The author of this thesis completed the quantitative analysis (chapter 7) which showed that the interventions were associated with no change in admission rates for ambulatory care sensitive conditions and a 4% increase in all-cause admission rates.

This Access Challenge, and the relationship of the thesis author with key decision makers, offered the opportunity to study local decision making in the context of national campaigns to reduce hospital admissions. By exploring the types of evidence used in decision making, how evidence was used in decision making, and identifying barriers to the use of the best available evidence, lessons could be derived to reduce resource waste and increase the value of investments in future initiatives. Therefore, qualitative interviews were conducted with decision makers involved in the GP Access Challenge in Oxfordshire.

8.2 Aim and objectives

8.2.1 Aim

The aim of this chapter was to explore the use of evidence by local decision makers when designing and implementing innovative primary care interventions as part of a national initiative to reduce emergency hospital admissions.

8.2.2 Objectives

To achieve the aim, the objectives of this chapter were:

A. To describe why evidence was sought out and how it was used by local decision makers when designing and implementing interventions
B. To describe how evidence was obtained and the types of evidence that were used
C. To identify challenges to obtaining and using evidence
D. To identify opportunities to increase the quantity and strength of evidence used when designing and implementing interventions

8.3 Methods

8.3.1 Reporting

This study was reported according to the Standards for Reporting Qualitative Research (SRQR), as recommended by the Equator Network.[11]

8.3.2 Ethical approval and research governance

This study was reviewed by the University of Oxford Joint Research Office Study Classification Group. The group agreed that the study was an extension of the service evaluation reported in chapter 7 of this thesis and did not require research governance or ethics approval. The thesis author was granted a Research Passport by the Oxford University Hospitals NHS Trust prior to commencing this study.

Although ethical approval was not required, signed consent forms were obtained. Study paper was stored in locked cabinets within restricted access areas of the Nuffield Department of Primary Health Care. Electronic study files were stored on restricted access network drives. Given the small sample size, exercise was

cautioned when reporting findings to protect the anonymity of interviewees. There was no use of direct quotes or information that could be used to identify any of the interviewees.

8.3.3 Definition of evidence

In this study, evidence was broadly defined as facts or information indicating whether a belief or proposition is true or valid.[11] Any type of fact or information was considered evidence if the participant perceived it as such.

8.3.4 Study participants and sampling

Members of the Oxfordshire CCG and GP federation leads that entered the bid for the '"Right Time, Right Place, Right Care" initiative were invited to participate by email. These participants were known to the thesis author given his involvement in the quantitative evaluation of the initiative. Snowball sampling was then used to identify other decision makers that provided input on the design and implementation of the services. All participants identified in snowball sampling were contacted and invited to participate. The email included an information sheet and consent form which are located in Appendix 8.1. Participants that did not respond within 10 days were sent a reminder email. If participants did not respond after another 10 days one attempt was made to contact them by telephone. If participants did not respond after two email and one phone-call they were deemed non-responders.

8.3.5 Data collection and management

Participants that agreed to participate underwent a semi-structured qualitative interview in-person or by telephone. In-person interviews occurred in the Nuffield Department of Primary Care Health Sciences. Interviews were conducted between February and October 2017 by the thesis author, who has experience conducting telephone and in-person interviews.[12–14] Interviews were directed by a semi-structured question guide (Appendix 8.2). The question guide was informed by a modified version of the Consolidated Framework for Implementation Research, existing literature in the area, and the study objectives. [5–8,15] Questions were pilot tested for clarity on physicians and researchers in the Nuffield Department of Primary Care Health Sciences. The question guide was revised iteratively between interviews to explore emerging issues. Interviews were audio recorded.

Audio recordings were transcribed verbatim using preferred transcribers recommended by the Oxford Health Experiences Research Group. Audio files and transcriptions were transferred using the Oxfile platform.

8.3.6 Data analysis

Participant demographic data were analysed using STATA 14.[16]

Interview data were managed and analysed in NVivo 11 using a thematic analysis. This method is not strongly tied to a single underlying theory or epistemology and, therefore, offered a flexible approach to analysis.[17] Thematic analysis consists of searching across a data set to find repeated patterns of meaning. This analysis focused on semantic themes – that which was explicitly said – to describe and interpret the themes and patterns in the data, rather than examining underlying or implied meanings.

Data analysis occurred in five stages and was consistent with methodological guidance on conducting thematic analysis[17]:

A. Data familiarisation

Transcripts were read and their accuracy against the audio recording was assessed.

B. Developing the coding framework

A preliminary coding framework was developed based on the research objectives. The Oxford Levels of Evidence Table (version 2) was used to develop codes to describe the strength of evidence used by decision makers.[18] See Appendix 8.3 for the elements of the table used to inform the coding framework.

C. Piloting of the provisional coding framework

The provisional coding frameworks were piloted on two interviews, independently and in duplicate by two researchers (NB, AT) for breadth of perspective. NVivo 11 was used to organise the data and facilitate the content and thematic coding process. At this stage both coders (NB, AT) crated new codes or revised initial codes to accurately and fully capture all meaning from the transcripts. Coders then

compared and contrasted the codes, clarified meanings, and decided by consensus on a revised coding framework.

D. Indexing interviews

The revised coding framework was used to code the remaining interviews and re-code the initial two interviews. This was done independently and in duplicate by two reviewers (NB, AT). Discrepancies, including in the creation and application of new codes, were resolved through consensus and joint review of the transcripts.

E. Thematic development

Key themes in relation to the research objectives were selected based on discussion of the coded interviews. Codes were grouped into themes that accurately reflected all main issues described by the participants using the one sheet of paper analysis technique.[19] A theme captured a patterned response or meaning within the data set that was important in relation to the research objectives. The importance of the themes was not necessarily dependent on quantifiable measures – but rather in terms of whether it captured something important in relation to the research objectives. These themes were interrogated and compared to the original coded data to ensure accuracy and rigor. The occurrence of codes and themes was quantified to give some insights into their ubiquity among interview participants.

8.3.7 Interviewer characteristics and reflexivity

Reflexivity refers to the critical self-evaluation of a researcher position in relation to the research as well as an active acknowledgement that this position may impact upon the processes and outcome of the research. The findings of qualitative interviews can be made more robust by critical self-reflection on their "situatedness" within their research and the impact this may have on the participants being interviewed, the questions they chose to ask, the data collected, and the interpretation of the data.[20] Berger (2013) identified three major ways in which the position of the researcher may impact on the research.[21] These elements were reflected upon by the thesis author during the conduct of this study and are described here:

A. Access to the field

Respondents may be more willing to share their experiences with a researcher whom they think is sympathetic or shares their viewpoint. The researcher may also be more knowledgeable about the topics being discussed.

B. Nature of the researcher-researched relationship

The nature of the relationship between researcher and participant can influence the information that participants are willing to share.

C. Worldview and background of the researcher

The researcher's background can affect how they use language, pose questions, and view the information collected, and therefore shape the findings of the study.

Critical self-evaluation

In this study, interviews were conducted by a DPhil student with a background in health sciences. While the interviewer was not an NHS clinical commissioner, he had five years of experience conducting health services research and a foundational knowledge of the challenges and pressures faced by health care policy and decision makers. Furthermore, the interviewer had prior contact with some of the participants given his involvement in the quantitative evaluation of the Prime Minister's GP Access Challenge in Oxford. It was hoped that this collegial common-ground mitigated any power differential felt by the interviewees and encouraged participants to more freely share their experiences.

Given his involvement in the quantitative evaluation, the researcher also had a prior understanding of some of the issues discussed in the interviews. This knowledge was used to inform development of the interview guide and analytic framework.

The researcher was aware of previous studies suggesting that little research evidence is used in routine clinical commissioning. However, the researcher asked open ended questions and had other researchers review the interview guide to eliminate leading questions. Furthermore, to provide a range of perspective, another researcher was involved with developing the analytic framework and analysing the data.

8.4 Results

8.4.1 Response rate and characteristics of participants and interviews

Invitations to participate were sent to 18 people. Seven people agreed and completed interviews, a response rate of 40%. Two interviews were completed in person and five were completed by phone. Interviews lasted a median of 36 minutes (IQR 19 to 67). Characteristics of the participants interviewed are presented in Table 1.

Table 1 Participant demographics

Characteristic	Participants (n=7)
Female	57% (4)
Age	
40 to 59	71% (5)
60 to 79	29% (2)
General practitioner	57% (4)
Affiliations leading to involvement in the GP Access Challenge[b]	
Clinical commissioner	43% (3)
Manager within a GP Federation	43% (3)
Public/patient advisor	29% (2)
Years of experience in the role that led to involvement in the GP Access Challenge[a]	10 (3 to 10)
Highest level of education	
Vocational degree	14% (1)
University graduate/post-graduate	71% (5)

[a]Median and interquartile range. [b]One participant had dual roles that led to involvement in the Access Challenge.

8.4.2 Description of coding and theme development

The final coding framework included 54 unique codes, from which 7 themes and 11 sub-themes were identified. The full coding framework can be found in Appendix 8.4. A description and interpretation of each theme and sub-theme is provided in the next sections, along with quotes to substantiate the analytic findings. Quotes are presented in italics and represent excerpts of the verbatim transcripts. Some quotes were used repeatedly as they addressed multiple themes. Aspects of some quotes are clarified with explanatory descriptions in normal font within round brackets (example). The results are organised according to the objectives of the chapter:

- Why evidence was sought out and how it was used
- How evidence was obtained and the types of evidence that were used

- Challenges to obtaining and using evidence
- Opportunities to increase the quantity and strength of evidence used

Throughout the interviews, participants often used the terms “evidence” and “information” interchangeably. For the sake of consistency, the phrase “evidence” has been used throughout, except within direct quotations from interviews.

8.4.3 Why evidence was sought out and how it was used

Theme 1: Decision makers sought out evidence on local and national priorities to inform the design of interventions

Decision makers sought out evidence of local and national priorities to broadly inform the design and selection of interventions.

To design interventions that would address local priorities, evidence was sought on the needs of local patients, health care practitioners, and GP practices. This evidence was used to direct the design of interventions and to strengthen the bid for funding by creating a clear case for action.

A: “So, you know, for example, [um] working with local GP practices to figure out what, what their, what their reasons were, why they couldn’t see patients or what their access problems were. [um] What, what their particular gaps were, say in managing older people and a lot of that is, you know, based on quite, quite a large amount of work that we do with practices [um] on a week to week, month to month basis.

B: “Certainly some of the issues that had to be addressed when developing the ideas was about workforce, you know, how, how, if they, so the whole point about the Prime Minister’s Challenge Fund Scheme from the NHS England’s perspective and the CCGs perspective was about increasing access. And so, already at that, at point there was a shortage of GPs. Oxfordshire has difficulty in recruiting in GPs already at that point. That was experiencing that, those problems and so any, any ideas around how to extend access needed to take into account the fact that [um] the recruitment could be an issue. So that lent it to interventions that involved other professionals other than necessarily GPs. They did, the, the scheme did involve GPs but [um] it also involved emergency care practitioners. It involved nurses. It involved Care Navig-, non-clinical care navigators.”

However, evidence of local needs and circumstances was not the only driver. There were criteria associated with the national GP Access Challenge and, according to some participants, these criteria heavily shaped the design and selection of interventions.

F: "The criteria with which you had to submit the bids was the main driver of the interventions and that was looking for seven-day provision and shared resources, so, sharing practices resources rather than being specific to any individual practices and that is what we tried to test out. And it had to be GP led. And it had to be working at scale across a wider geographical area than a single practice"

To ensure that the proposed interventions aligned well with national priorities, information was sought from external organizations that had previously been successful in obtaining funding from the GP Access Fund. Decision makers wanted information on characteristics of previous successful bids, including the framing and details of proposed interventions. This information was then used to shape the interventions and the bid that was submitted.

A: "We were trying to make it fit with the overall [um] local priorities and local primary need to, to make sure that it was, it was as much towards that as it was towards a national government agenda. So, we looked at information about what had been in the Wave One schemes and some of the key criteria that needed to, to be hit [um] if a, if a bid was going to be successful."

Theme 2: Decision makers primary sought evidence on intervention feasibility and implementation

After deciding on the broad nature of the interventions, decision makers sought operational details to determine the feasibility of delivering the interventions and requirements for implementation. It was thought that this evidence would both strengthen the funding bid by demonstrating the "deliverability" of the proposed interventions, and, if the funding was awarded, guide the delivery of functional primary care services. Decision makers specifically sought evidence on staffing requirements, data sharing and information technology, and the impacts of the services on primary and secondary care utilisation. To a lesser extent, decision makers also sought evidence to inform estimates of potential intervention effects.

B: "We also had a stakeholder meeting in early January with the [um] the, with, with the some of the other providers and with some of the other commissioners in the CCGs where the Federations talked a bit about the, the ideas that they'd had and sort of tested them with them to see what issues they had. Any concerns, you know, things like, "Well, if you're going to staff this with paramedics, does that mean we're not going to be able to employ our own paramedics or recruit paramedics if you're, you know, poaching them to run this new service?" [um] So, we had that kind of stakeholder engagement to, sort of, test out some of the interventions and the ways that we're planning to, to run the programmes [um] and then they went into the, then after that the bid went in.".

A: "I think there was then further refinement even after having been selected. So, in, part of the selection process was a Deep Dive analysis and evaluation that was looking at whether from an IT perspective would really consider all the issues and whether the, not just the IT elements were dealt with effectively, but also thinking about how we were going to enable GPs to read and write into each other's notes. You know, what kind of software or data sharing software might be needed. All of those, you know, what the risks and issues were. [um] So [um] that helped to, to hone some of the ideas a bit more in terms, in terms of details."

D: "The interventions etc, those were generally [um] developed internally amongst the Federations. They then came back to, they then worked with, we had some additional project resource, one of the management trainees was helping and got seconded into the project and she provided a lot of the kind of, if you like, some of the sort of data gathering, number crunching in terms of and sort of modelling of, if you have this service and it was, it was staffed by 'x' number of paramedics, how many patients would they potentially get to see. What would that mean in terms of potential reductions in admissions. So, some of the assumptions behind the models."

8.4.4 How evidence was obtained and the types of evidence that were used

Theme 3: Various methods were used to quickly obtain expert opinion and service evaluations

Table 2 describes how evidence was obtained by decision makers, the types of evidence they gathered, and how the evidence was used. Participants reported using only two types of evidence to inform their decision making: expert opinion and service evaluations. Much of this evidence came from NHS employees or organisations affiliated with the NHS. In some instances, the source of the evidence was unclear. Most of this evidence was gathered quickly as participants only had eight weeks in which to develop the intervention proposals and submit the funding application.

Table 2. Summary of how decision makers obtained evidence, the types of evidence they obtained, and how the evidence was used

Type of evidence	Method of procurement	How the evidence was used

• Expert opinion of local stakeholders including GPs, nurses, practice managers, GP federation leads, and CCG members	• Face to face communication in routine meetings as part of local clinical practice governance
	• Face to face communication in special meetings and workshops conducted for the Access Challenge
		• Determining local needs and priorities
		• Identifying potential interventions
		• Estimating the feasibility of interventions, steps required for implementation, and potential effects of interventions
		  ○ Estimating the necessary workforce to staff the interventions
		  ○ Determining feasibility from an IT and data sharing perspective
		  ○ Estimating impact on primary care appointments, A&E attendances, and emergency admissions

• Expert opinion of external decision makers with experience obtaining funding and implementing interventions as part of the GP Access Challenge	• Face to face communication in special meetings conducted for the Access Challenge	• Identifying potential interventions
		• Aligning the design of interventions and the bid with the priorities of national decision makers
		• Estimating the feasibility of interventions and potential effects of interventions
		  ○ Identifying potential issues in delivery of the interventions
		  ○ Estimating impact on primary care appointments, A&E attendances, and emergency admissions

• Expert opinion of professional primary care organisations	• Searches of publicly available online resources	• Identifying potential interventions • Identifying national priorities
• Service evaluations from other health regions	• Informal requests for non-published and ongoing service evaluation • Searches of publicly available online resources	• Identifying potential interventions • Estimating the feasibility of interventions, steps required for implementation, and potential effects of interventions ○ Estimating impact on primary care appointments, A&E attendances, and emergency admissions

Sub-theme 3A: Expert opinion of local stakeholders

Local expert opinion was used to determine needs and preferences of the local population. Much of this evidence was gathered as part of routine meetings between front-line workers and decision makers. No participants described the use of surveys or other formalised data collection methods to determine local needs and preferences.

A: "A lot of it was quite a lot of work, almost day to day work really, and working with GPs and patients and [um] other stakeholders in the local health, health economy [um] on where the pressures are, where the gaps are, where, where the demands are. So, you know, for example, [um] working with local GP practices to figure out what, what their, what their reasons were, why they couldn't see patients or what their access problems were. [um] What, what their particular gaps were, say in managing older people and a lot of that is, you know, based on quite, quite a large amount of work that we do with practices [um] on a week to week, month to month basis. So, we have regular, regular set of meetings with lead GPs in each practice and each locality of the, the County, to talk to them about what it is they're struggling with, what they think needs to happen."

The expertise of front-line workers and local managers was also used to identify potential interventions, gauge the feasibility of the proposed interventions, identify specific steps required for implementation, and to estimate potential effects.

B: "So unfortunately, yeah, it was, you know, these things aren't, are not an exact science and they based it on their experience of how many patients a nurse could see or how many patients a GP could see [um] and it was testing out really. So, you know, can a ECP, an early visiting service travelling around and doing home visits, how many, how many people in a day can they see [um] and, in a way, testing those assumptions."

C: "And that was great and then in terms of the process of developing the ideas for the interventions and so on, we had a workshop which was led by, which was held at the CCG with all the Federations present [um]. Looking at what the bid criteria were. Getting them to think about [um] what kind of interventions would make a difference. Thinking about what, what they could mobilise and deliver realistically within, within the time frames [um] and [um] and so the Federations then went off and [um] started having internal, they then, those were the Federation leads. They then went off and had internal meetings with their kind of clinical representatives, their GP representative to develop you know some, some more ideas."

In some instances, participants referred to colloquial consensus among local experts about interventions that should be tried and what might be effective.

A: "Certainly, the Early Visiting Scheme, that, that, a lot of, sort of, a lot of that had been around for some time and it was, it was an idea that was knocking, that had been knocking round on and off over a few years, you know, in the local system and a lot of, a lot of

nearby places had tried similar things. So, it was something we were quite aware, aware of. The hubs, I was, I guess less, less involved in that as a concept but [um] again I think it was the, federations that had come up with those ideas or people who were borrowing ideas from other places, I think."

Sub-theme 3B: Expert opinion of external decision makers with experience obtaining funding and implementing interventions as part of the GP Access Challenge

Additional proposals for the design of interventions were drawn from decision makers in other health regions that had previously been awarded funding from the GP Access Challenge. The experiences of these external decision makers were also used to identify potential challenges in implementation, estimate the impact of interventions, and to align the bid and design of interventions with what national decision makers previously considered worthy of funding.

B: "So, one of the, one of the things that was picked up by one of the Federations was a [um] a website which was a kind of like a plat-, the COACH website with a, with a, which would provide an Oxfordshire platform for answering questions about health and care [um] and that website had actually been developed, or a similar one, had been developed for Wakefield in the Wave One. So, there's an, there's a direct example of how an intervention that had been developed to a certain point in Wave One was, was taken forward in Wave Two and developed further in Wave Two as well"

Sub-theme 3C: Expert opinion of professional primary care organisations

Participants accessed expert opinion and recommendations of professional primary care organisations from publicly available documents online.

B: "There were also [um] just think, I'm trying to remember which were the policy documents but some of the RCGP policy documents about primary care and its, and its future models, there were some ideas there around using ECPs and using pharmacists and care navigation. So, there were, there were some national examples. I wouldn't say it was evidence because I don't think a lot of these things hadn't been formally evaluated but they were examples of what had been tried elsewhere."

Sub-theme 3D: Service evaluations from other health regions

Published evidence from other CCGs was also accessed to inform decision making however, participants suggested that there was little evidence contained in reports and service evaluations found online, other than evidence that implementing interventions was feasible. Part of this issue was that formal evaluations from the first round of the GP Access Challenge had not yet been completed and published.

G: "When the bids were being put forward for Wave Two, the Wave One evaluation hadn't come out. But there had been [um] some sort of publicity about the, the pilots that were being run in Wave One. So, we did have some information about what that was being tried elsewhere and what had been put in place."

A: "So, so they were pulling in information and evidence from other CCGs and from Wave One to sort of inform the bids.. I mean, the information from Wave One was short case study, you know, it was that level of evidence. There wasn't any, there wasn't really any information to say, 'So this scheme it meant it, it found that, it was set up to run these hours. It needed 'x' number of work force. It saw 'x' number of patients. It stopped providing Sunday services at this point because there wasn't a demand.' You know, there was none of that kind of granular detail at that stage. All there was was 'this, this model, this intervention's been developed and it being tested in this area."

No participants reported searching in the academic literature for evidence to inform their decision making and did not believe that this type of evidence was sought or used by any decision makers involved in the design and implementation of interventions.

Theme 4: Evidence was weak but perceived as applicable to the local environment and adequate to inform pilot-testing

Sub-theme 4A: Strength of evidence for prevalence/incidence of a problem

According to the Oxford levels of evidence, much of the evidence used by decision makers was fairly weak. In terms of determining local needs and preferences, a concept which may be interpreted as estimating the prevalence and incidence of a problem, the evidence used by decision makers consisted of the two lowest levels: local non-random samples (level 3) and case-series (level 4).

A: "A lot of it was quite a lot of work, almost day to day work really, and working with GPs and patients and [um] other stakeholders in the local health, health economy [um] on where the pressures are, where the gaps are, where, where the demands are. So, you know, for example, [um] working with local GP practices to figure out what, what their, what their reasons were, why they couldn't see patients or what their access problems were. [um] What, what their particular gaps were, say in managing older people a …"

Sub-theme 4B: Strength of evidence for therapeutic benefit

In terms of the levels of evidence for intervention benefit, the evidence described by participants was again classified in the two lowest levels: case-series, case-

control studies, and historically controlled studies (level 4) and mechanism-based reasoning (level 5).

A: "I mean, the information from Wave One was short case study, you know, it was that level of evidence."

C: "Getting them to think about [um] what kind of interventions would make a difference. Thinking about what, what they could mobilise and deliver realistically within, within the time frames [um] and [um] and so the Federations then went off and [um] started having internal, they then, those were the Federation leads. They then went off and had internal meetings with their kind of clinical representatives, their GP representative to develop you know some, some more ideas."

D: "…one of the management trainees was helping and got seconded into the project and she provided a lot of the kind of, if you like, some of the sort of data gathering, number crunching in terms of and sort of modelling of, if you have this service and it was, it was staffed by 'x' number of paramedics, how many patients would they potentially get to see. What would that mean in terms of potential reductions in admissions."

B: "We also had a stakeholder meeting in early January with the [um] the, with, with the some of the other providers and with some of the other commissioners in the CCGs where the Federations talked a bit about the, the ideas that they'd had and sort of tested them with them to see what issues they had."

B: "…they based it on their experience of how many patients a nurse could see or how many patients a GP could see [um] and it was testing out really."

Sub-theme 4C: Perceived applicability of evidence

Participant perceived expert opinion and service evaluations as types of evidence with more applicability to the local environment compared to published academic research evidence. Academic research was viewed as not applicable to the local setting. Participants also expressed the perception that academic research did not contain the types of contextual and operational information required to implement an intervention in real clinical practice. When asked about whether published academic research would have been useful in developing the interventions there were mixed responses.

Interviewer: "I've heard from other people that I've talked to about this that [um] there's some reservation about using, you know, sort of published research evidence. What do you think? Is it useful?"

A: "Partially. I, I think with this especially when you're looking at, looking at pilots, you've got to [um] bear in mind that how applicable it is to, to local circumstances, given that [um] you know, there are differences between sort of the structure of primary care and how, how well it's doing and also what, what services are already in existence. So, it, to make

sure that we're not, you know, comparing apples with pears. So, we need to, to make sure that we're aware of that. But I think you've got to, you've got to use it (evidence), you've just got to make sure that you, you use it intelligently rather than using slavishly."

Sub-theme 4D: Weak evidence was deemed adequate to inform pilot studies of innovative services

Participants were asked about the strength of the evidence that they used. The majority acknowledged that the evidence may be considered weak however, they expressed the opinion that, given that this was a pilot study to test assumptions and develop new ways of working, a lower standard of evidence was required to justify implementation of interventions.

A: "I think also it doesn't have to be perfect evidence either. I think it's probably, when we're looking at pilots, it's probably enough to, to [um] see there's been some demonstration of proof of concept that, that something, you know, will, will actually be able to work but not necessarily needing enough evidence to show that it has a big effect on, for example, emergency admissions, and also, I think, make clear about what are the things we're trying to achieve."

However, a minority of participants were more critical of the strength of the evidence that was used and suggested it may not be an acceptable standard of evidence.

E: "But the problem with it is that other people in other places like to think what they're doing is good and so they say, you know, when you look at their, their evaluation, first of all they're quite often has been no evaluation, and second, if you do look at the evaluation it's not worth the paper it's written on. So nobody really knows whether it's good, bad or indifferent. So in a way, as a way of finding out things that other people are doing in other places which might or might not be useful here, I guess it's worth it from that point of view, but to say that these people over here who say what they're doing is great let's do it over here, that is not a, that is not a rigorous things."

8.4.5 Challenges to obtaining and using evidence

Participants described challenges that limited the quantity and strength of evidence used during the GP Access Fund initiative. Participants suggested that the challenges were not unique to experience of the GP Access Fund however, the issues were more pronounced during this campaign.

Theme 5: Practical and political challenges to obtaining and using evidence in decision making

Sub-theme 5A: Time pressures

Participants reported having only eight weeks to design interventions for the GP Access Challenge and submit the funding proposal. They reported feeling immense pressure during this period and commented on how quickly they had to obtain information and use it to write the proposals. They suggested that this type of time pressure was common and routinely limited their ability to obtain and use evidence when making decisions however, pressures during the GP Access Challenge were more extreme than usual.

F: "It was ridiculous and, and, and the timescales continue to be ridiculous."

B: "And, you know, the fact that the, the initial information came out in sort of mid-November [um] with essentially a lot of the work having to happen [um] in December to get things ready and not only do you have Christmas but the way that primary care works is that if you've got a GP who's working over Christmas and New Year, they tend to take time off at the beginning of December. [laughs] It was quite unreasonable."

E: "And, and it is to do with time constraints and people, and it, it's to do with the fact that if you don't give people time to consider something properly and put them under huge pressure to make decisions all the time you've actually, you've actually made it an impossible place for a true evidence-based practice to ever be able to happen."

Sub-theme 5B: Lack of expertise

Participants identified a lack of commissioner expertise in appraising and interpreting evidence. They suggested that this routinely affects the type of evidence which is sought out and used during decision making.

F: "And I think almost, you know, the majority of people working in commissioning have not had very, very much if any training. Definitely the managers have had very limited training."

E: "But then they basically Google. You know, you just Google and then you find something that supports what it is that you're planning to do. And you just, and you know, you, you want it to be, perhaps there is a level of understanding that you can't just use something really shoddy, so if you found it in the Cochrane library or, or at least it's a review or, or a pretty large apparently well-conducted randomised trial, then that's the sort of evidence they want to go for."

It was also suggested that existing support personnel lacked expertise, including commission support units, which are intended to help commissioners find and use evidence.

E: "The idea is that they're supposed to ask the commissioning support unit for, where there is a team of people who can find evidence. But my experience as someone who's, who understands about evidence having been involved in it, for some time, that they're not able to, they don't seem very skilled either."

C: "The support unit, the team are, are just coming back with, with a random collection of a whole range of, of evidence from other countries and different things and, so, so the idea that you would, that you would, would only want to be looking for high quality evidence [laughs] bring, bring something as, as simple as that, they don't seem to aware."

Sub-theme 5C: Top-down political constraints

Participants were clear that the top-down hierarchal structure of the health system constrained their autonomy and ability to use evidence to inform their decision making. Political constraints were not unique to the GP Access Fund experience, but rather, were a constant presence influencing which funding initiatives were pursued, which services and interventions could be explored, and the timescales to design and implement services.

E: "Just, the brief, and the briefs are coming down all the time, and if you do say you won't do the brief which our CCG did do (for the GP Access Challenge), *you know, you just stand out and then you get in hot water and then senior people get like pressure put on them …"*

C: "It had to be done in particular ways, and has happening all the time that, you know, the latest thing, a seven-day access that's all being set up. So the question would be, how can we help overstretched GPs locally to provide more appointment and manage their workload. We're in a crisis situation with general practice, how can we use this tranche of money that the government wish to give us? That's not what happens. They give a tranche of money and say, 'It has to be between the following hours. It has to be the following set of things'. So, actually just a lot of the time commissioners are just implementing what is coming down from above. So, what is the point of asking questions and looking at evidence? And, I mean, the whole thing, you know, is predicated on what you're talking about, about evidence-based commissioning. Would, need to be predicated on a system whereby we were trying to do, yeah, analyse the problems locally and more widely if that was appropriate, and then think about what resources we've got and how we're spending them at the moment. And then collaborate and agree and look at the evidence and talk to the, all the relevant people and then come up. That is my view of how the health service should run. But that is extremely naïve."

D: "There often is quite short timescales and what, what tends to happen is the, the deadlines that are put in place are very short notice and quite ridiculous in a way and there's a lot of [um] political and external and bureaucratic pressure to, to get things done in different, in a different time that are sort of beyond control [um] and, and don't, don't help at all. And there's a lot of, then we've also got, you know, political, managerial uncertainty about, about some of this."

8.4.6 Opportunities to increase the quantity and strength of evidence used

Decision makers were asked about the potential for using more robust evidence during initiatives like the GP Access Challenge and what would be required to facilitate that. Some participants suggested that more robust evidence was not necessarily required given the exploratory nature of innovation-focused challenges. During these challenges they perceived that a lower standard of evidence was acceptable to support decision making. However, they did acknowledge that stronger evidence of the effectiveness of interventions may be useful.

A: "I think it does, I mean, personally I think it does strengthen the bid because I think the more you get in there the better. I think it's just making sure that it's the best, the best possible evidence you can get rather than having to have perfect evidence. And [um] I don't, I don't know how well it improves how well it's received. I expect it probably does but I'm not sure how big a, how big a criteria it is when, when the funders, which is NHS England looks, looks though the list of proposals and bids, how, how much weight they put on really good evidence or the lack of it. I expect they probably put a bit more weight on deliverability."

Participants identified six opportunities to improve the quantity and strength of evidence used in decision making. The opportunities were categorised into two themes. These themes are described in Table 3 and in the next sections.

Table 3. Summary of opportunities to improve the quantity and strength of evidence used by decision makers

Theme 6: Generate high quality evidence of effectiveness with details about implementation and context	Theme 7: Optimise use of existing evidence
• Academic researchers should report contextual and implementation information • Researchers and policy makers should co-produce robust service evaluations • Improved data sharing for efficient and robust service evaluations	• More training for decision makers and support staff • Embed experts with academic and policy making experience • Establish and maintain relationships with academics

Theme 6: Generate high quality evidence of effectiveness with details about implementation and context

Participants identified three approaches to produce high-quality evidence that would be useful to them.

Researchers should report contextual and implementation information in academic studies

Participants suggested that researchers studying the effectiveness of interventions should report details to help stakeholders operationalise interventions, including information about the context within which the interventions were used. They believed that most existing published academic research did not include this type of information.

Researchers and decision makers should co-produce evaluations

The idea of co-producing service evaluations in order to improve the strength of useful evidence was proposed. Decision makers expressed an interest in collaborating with academics in order to produce such evidence.

G: "I'm quite interested in this area as well. You know, how, how we can link up the academic world with the sort of health, health service world, if you like. There's a lot of stuff that needs to be done there."

Participants felt that collaborations would strengthen service evaluations, which are often weak.

A: "I think [um] then some of what people put out there isn't great either but I don't think the commissioners necessarily going to recognise it though. So, for example, you might get a scheme in a part of the country where people can dem, can demonstrate that they've reduced A&E admissions by thirty per cent. But that evidence wouldn't be strong enough to publish and it wouldn't be, it'd have a lot of flaws in it."

Improved data sharing to increase the efficiency and strength of service evaluations

Another element that some participants felt would facilitate the production of robust service evaluations was the installation of ongoing data sharing agreements. It was thought that this would enable more efficient evaluation of services and produce stronger evidence compared to piecewise evaluations and one-off data sharing agreements.

D: "So, I think if one actually had a process that [um] was providing a dynamic access to such information on, on a regular, almost a daily basis then it would make life so much easier and everything would be much better. It's not just primary care. It's across the whole health piece. And data that is sharable without having to put up a whole framework every time for sharing agreements for specific reason. There needs to be a standing agreement for, [um] for exchange of information."

Theme 7: Optimise use of existing evidence

Participants identified three approaches to make better use of existing evidence. Each approach considered the practical challenges of 'real-world' decision making.

More training of decision makers and existing support staff

Participants suggested that additional training for CCG members could improve their ability to appraisal and interpret evidence. However, they felt that procurement of evidence would be most efficient if out-sourced to experts with appropriate infrastructure and resources.

E: "Should you be having everyone in the commissioning not really having any training and just asking some other more expert group, I think that's not the way to go. I think you definitely need everyone, absolutely everyone with a basic level of understanding of it. And then I think you need within those teams perhaps people with a bit more understanding to sort, working with, but those, those people then could be more, more useful. Because they would be with a group of people who had some back, basic training. So, that's definitely the way to go. And then if you did have, then you would need, I do think you need some external groups to help do searches and present stuff in, in a way

that is quite helpful. I mean, maybe the basic and the intermediate people who are actually intrinsically in the commissioning, they haven't got, try to go off and do the searchers, but they maybe need to be sufficiently engaged with it to know what searches are being done and then to be able to receive the information back from the expert group."

Embed experts with academic and policy making experience

The first participant interviewed suggested the idea of embedding academic experts within existing organisations to improve the quantity and strength of evidence used. Subsequent participants were questioned about this idea and all were in support.

C: "I think a more professional process where you have a, a team or unit who are very used to doing this and know where to go to look for the evidence and have the expertise to be able to properly analyse it and report on it, I think that would be a very, a very useful resource."

A: "I mean, I think it would have to be specialist, specialist enough to be able to do it properly. So, you don't necessarily want to have that done many different times. So, there is a benefit to having a team where you've got a slightly larger remit, and I think, there is also, there is also a risk in any sort of big organisation of losing that focus as well. So, if it was, it was embedded it would have to be quite, quite, a well contained discreet team who wasn't interfered with too much."

When asked about the require skill sets of such an embedded team, participants agreed that the team should be composed of academics with proficiency in evidence procurement, appraisal, and interpretation, and be familiar with the practical challenges of 'real-world' policy making.

Interviewer: "Is it feasible to have that kind of unit available and like be drawn in to these processes or is it the timeline too restrictive? Is the funding too restrictive? Would it be actually feasible to have something like that?"

D: "It would be. It would have to be, it would have to be done in the right way because it couldn't be on the, on the timescale that are done through long term academic work. There often is quite short timescales and what, what tends to happen is the, the deadlines that are put in place are very short notice and quite ridiculous in a way and there's a lot of [um] political and external and bureaucratic pressure to, to get things done in different, in a different time that are sort of beyond control [um] and, and don't, don't help at all. And there's a lot of, then we've also got, you know, political, managerial uncertainty about, about some of this. So, any such team would have to be pretty nimble and pretty flexible, and also, understand the real world as well as what, the ideal world"

Establish and maintain relationships with academics

Another suggested solution was to maintain better ongoing relationships with local academics to enable drawing in of support at times of need, as opposed to having a permanently embedded team.

E: "The, the way to go would be more, to go into more of an academic place where you've got people with all these skills, very good at this, well-placed to do it, the librarians are there, the … people like you are there, but, but that's not who you're talking to when you're currently, apparently you had, meant to be getting help from a group of people who, who blatantly hadn't got the skills to do it."

Academics were the preferred source of expertise both for embedded teams and for occasional consultations, in contrast to career health care consultants who were not perceived to be useful.

E: "And the commissioners spend an absolute ton on consultancies. All the time. And they, they basically come interview everyone and then regurgitate what they've been told. And quite often the suggestions they come up with don't work, but they've gone then. And nobody ever can, it's, that's why you need a, an embedded group of people, because then everyone has responsibility to be transparent and accountable."

G: "We are interested in working with academic departments. There is some potentially some rich work that could be done. We are looking at where we can use expertise in crunching some of these numbers around workload and building the evidence-base around activity. But there is currently a void of useful information for us to pin arguments on."

However, decision makers recognised that supporting local health care decision making may not align with current incentives in academic institutions and may not be appealing to academic researchers.

E: "I don't think researchers are in any way, it, you can, I know why researchers aren't doing it, because in order to be successful in research you have to have focus-free questions, and you have to answer them, and it takes years, and that's how you become a successful academic. That's how you get funding, that's how you keep you, you and your fellow workers in, in in a job. So, research is set up in a way that it's not going to fulfil that role. But the people within the, the res, the academic institution still have the skill-set."

8.5 Discussion

8.5.1 Summary of findings

This chapter explored the use of evidence by local decision makers when designing and implementing innovative interventions as part of a national initiative to increase primary care access and reduce emergency hospital admissions. Thematic analysis of interviews with seven decision makers showed that decisions about the design and implementation of interventions were informed by expert opinion and service evaluations. This evidence was sought out to identify feasible interventions that would address local needs and align with national priorities. This evidence was also used to determine the resources required for implementation and, to a lesser extent, the potential impact of the interventions. Decision makers perceived this evidence to be valuable given its applicability to the local environment and its ability to support implementation. They suggested that this standard of evidence, although considered weak, was adequate to justify local pilot-testing of novel interventions. Participants did not seek out or use published academic research evidence although indicated that it may be useful. Participants suggested there were challenges to obtaining and using evidence including time pressures, lack of expertise, and top-down political constraints. Opportunities to increase the quantity and strength of evidence used included better reporting of implementation and contextual information in published research, co-production of service evaluations by academics and decision makers, improved data sharing, additional training for decision makers and support staff, embedding academic researchers in decision maker support teams, and establishing and maintaining relationships with academic researchers.

8.5.2 Findings in the context of existing research

Previous studies have surveyed and interviewed health care decision makers about their use of evidence over multi-year periods without reference to a particular program or service.[5–7] These studies may be seen to represent the use of evidence during “routine” policy and decision making.

This chapter builds on this previous literature by exploring the use of evidence during a national innovation challenge. This type of innovative initiative may

represent a unique circumstance in the world of health care decision making and clinical commissioning given the flexibility afforded to local stakeholders to design and implement interventions, and the emphasis on novelty, which stands in contrast to the routine obligation of decision makers to demonstrate clinical effectiveness and value for money before installing new services.[9,10]

The results of this study are generally consistent with findings from previous research on the use of evidence by health care decision makers and the evidence-to-practice gap in primary care.

Previous studies have consistently reported that decision makers prioritise the procurement of "practical" evidence including clinicians' and users' expert opinions, needs assessments, local evaluations, and information on innovations from other health regions.[5–7] Decision makers in previous studies similarly report that these types of evidence are preferred to academic evidence as they provide more contextual information and offer insights that support implementation of services that align with local needs.

The results of this chapter are somewhat unique compared to previous studies because participants relied solely on a limited amount expert opinion, service evaluations, and information about innovations in other health regions.

Other studies have shown that decision makers use additional types of evidence, albeit to a lesser extent, including clinical guidelines and academic research.[6] This discrepancy suggests that the use of evidence during innovation initiatives may differ compared to other periods of decision making. The emphasis on innovation may lower the standard for the quantity and strength of evidence deemed adequate to justify selection and implementation of a service. Participants in this study did report having this perspective when designing and implementing services as part of the GP Access Challenge. These findings validate claims that innovation campaigns offer a fast-track implementation pathway for interventions without evidence of efficacy or effectiveness or that bear little resemblance to previously tested interventions.[1] As such, the return on investment for these challenges may be justifiably questioned.

It is also possible that the seniority of the participants played a role in the limited use of evidence. Previous research has shown that the characteristics of decision makers are associated with the type of evidence they use. Clarke et al. [6] conducted a survey of 440 staff involved in commissioning decisions in the English NHS and examined uses of "empirical" evidence (i.e., clinical guidance, National Service Frameworks, and secondary research) and "practical" evidence (i.e., local public health intelligence, expert advice, and benchmarking data). Participants more senior within the organisation reported using more practical evidence. In this chapter, decision makers were all fairly senior, with a median of 10 years in the roles that led to their involvement in the GP Access Challenge. This seniority may partly explain why there was a complete reliance on "practical" types of evidence.

Findings from studies examining how decision makers obtain evidence are also similar to the results reported in this chapter. For example, Wye et al. showed that the dominate methods of gathering evidence among commissioners in England were formal meetings, informal conversations and stories, and publicly available online documents. [5] Decision makers in the Wye study reported that these types of approaches were fast and flexible methods and met the demands of 'real-world' policy making. In this chapter, decision makers similarly reported needing to quickly obtain evidence and did so in formal and informal meetings, conversations, and by accessing publicly available documents and reports online.

Similar practical challenges to the use of evidence have been identified in previous studies including insufficient staff capacity, limited skills, cost, limited time, and the availability and quality of routine data. [5–7] Unlike other studies, access issues were not identified. For example. Wye et al. identified the lack of database access and time needed for complete locally commissioned research as key barriers to the use of research evidence.[5] Wye et al. also provided more granular information regarding the lack of decision maker skill in analysing and interrupting evidence, such as the challenge of drawing conclusions from literature reviews with substantial variations in interventions. In contrast, participants in this chapter referred broadly to lack of skills but did not give many specific details.

Opportunities to improve the access to and use of evidence have been recommended in previous studies however, this chapter adds validity and granularity to this literature. In previous studies, recommendations were developed by the authors after considering the challenges identified by participants. In this chapter, opportunities for increasing the quantity and strength of evidence were explicitly identified by the decision makers being interviewed.

Previous authors have suggested that improved skills and training for commissioners, co-production of robust local services evaluations, inclusion of detailed contextual information and operational details to inform implementation, and better access to routinely collected data may help to increase the amount of evidence used in decision making and to help decision makers make better use of existing evidence.[5] Results of this chapter confirm these findings and recommendations. Participants in this chapter expressed the sentiment that they want access to more robust evidence that is useful to them and are willing to work towards generating useful evidence and overcoming challenges to better use existing evidence.

Previous authors recommended caution when considering how to “fix” or “correct” decision makers’ use of evidence. The results of this study echo this sentiment. Decision makers in this chapter made it clear that they perceived the evidence they accessed as useful and important for their process of decision making, even though the types of evidence used may be considered “weak” according to academic research standards.

This desynchrony between the types of evidence coveted by decision makers and academic researchers may be understood by considering the different orientations that these stakeholders may have towards what constitutes evidence.[22]

Dubrowa et al. has proposed two distinct orientations adopted by these stakeholders. According to Dubrowa et al, the positivist research community adopts the “philosophical-normative orientation”. This orientation views evidence and context as mutually exclusive, neglects the role of context in evidence-based decision making, and focuses solely on what ought to be considered as evidence.

Stakeholders with this mindset emphasise evaluation of the characteristics and properties of evidence (e.g. validity, reliability) in order to establish the appropriateness and credibility of evidence for supporting decisions. Generalisable evidence that is context-independent and widely applicable is seen as highest-quality and therefore will support high-quality decision making. Support for this orientation can be seen in the policies of funding agencies, journals, and research incentive structures such as the Research Excellence Framework, all of which seek to support research that has wide relevance and can change clinical practice for the population.

In contrast, decision makers adopt the “practical-operational orientation”. This orientation defines evidence by its relevance, applicability, and generalisability to a specific context, rather than by its inherent qualities or characteristics. This orientation suggests that evidence and context are inseparable. Therefore, decision makers covet evidence that is rich in context. Certainly, in this chapter, decision makers expressed their desire for granular contextual and operational information that would allow them to deliver interventions that are functional and effective in the local environment.

According to Dubrowa et al., improving evidence-based decision making will require researchers to produce evidence that is useful and coveted by decision makers. The findings of this chapter support this assertion. Decision makers in this study identified the inclusion of contextual information and operational details in published research work as a key approach to increase their use of evidence.
They also proposed collaborations to enable the production of this type of context-rich evidence. However, decision makers also acknowledged a need for training to help them better understand and apply research evidence. This suggests that they believe there is useful academic research in the literature, although perhaps in short supply.

8.5.3 Strengths

This study had three key strengths.

Firstly, reflexivity was built into the study design to minimise the impact of the thesis author's position on the results. The question guide was reviewed by members of the Nuffield Department of Primary Care Health Sciences to ensure no leading questions were included and to increase clarity of the questions. Also, two researchers developed and applied the coding framework to ensure a diversity of perspective.

Secondly, opportunities to increase the quantity and strength of evidence used in decision making were identified directly by participants. Previous literature in this area has included recommendations for improving the use of evidence but these have been based on the judgements of authors.

Thirdly, the previously established rapport between the thesis author and some of the participants likely increased the candidness of responses to sensitive questions.

8.5.4 Limitations

There were limitations to this study.

Firstly, participant's response may have been subject to recall bias. Participants were recalling some experiences that occurred two years prior to the interview. However, the use of thematic analysis likely reduced the effect of this potential bias. Responses between participants were compared and contrasted and the main results are composed of themes that were consistent across interviews.

Secondly, the results may have limited external validity given the unique situation of the Prime Ministers GP Access Fund Challenge. However, it is likely that some of the themes are generalizable. Furthermore, this study could be replicated in other regions that participated in the Prime Ministers GP Access Fund Challenge or that participate in future innovation challenges, such as the Prime Minister's

Dementia Challenge 2020. This would allow for comparative analysis of results and an assessment of the external validity of the results.
Thirdly, the sample size was fairly small, which may also limit the generalisability of the findings. The sample was limited by the number of decision makers that contributed locally to the GP Access Challenge and the response rate. However, the major themes identified were common across participants and echo themes demonstrated in similar previous studies.

Fourthly, the response rate was fairly low, thereby increasing the risk of selection bias. It is possible that the experiences of decision makers that did not agree were different from those that did participate. Without comprising anonymity, it can be said that key decision makers did participate. Furthermore, these decision makers referred to the perspectives and experiences of their colleagues during the GP Access Challenge however, it is unclear whether their perceptions were accurate. Therefore, the results should be interpreted with some caution as it is possible that the experiences and activities of other decision makers involved in the GP Access Challenge may conflict with the themes identified in this chapter.

Fifthly, participant's responses may have been subject to social desirability bias. To limit this bias, respondents were told prior to their interview that no quotes or information that could identify them would be used. They were also told of the data protection measures including use of locked cabinets within restricted access areas for paperwork and use of restricted access network drives for electronic data. Furthermore, the familiarity of the author of this thesis with some of the respondents may have reduced the impact of this bias.

8.5.5 Implications for policy and practice

The results of this study have implications for health care and academic workforce training, academic journal publication policy, regulatory requirements for conducting and reporting of health services research and evaluations, and the organisation and conduct of future national innovation challenges in the UK.

Firstly, decision makers and academics should collaborate to develop joint training sessions supported by the NHS and research funding agencies. Training for

decision makers could focus on the basics of acquiring, appraising, and applying research evidence. Training sessions for academics could focus on the realities of 'real-world' decision making and the types of contextual and operational details that decision makers value. Regionally, these stakeholders could also work together to develop protocols for robust service evaluation that are feasible within the local health economy and that could quickly be put into action when needed.

Secondly, open-access academic journals may consider developing a "service evaluation" category within their publication operations. This would enable routine publication of service evaluations and building of an archive of evaluations in defined digital locations, as opposed to limited publication of this type of investigation scattered across different sections of the journal (i.e. brief report, analysis, etc.). This may increase the efficiency of searching for relevant evidence by decision makers.

Thirdly, similar to the requirements to register and report clinical trials in some countries, there may be a role for online registration and reporting of health service evaluations. If a central registry of service evaluations were developed, similar to clinicaltrials.gov, it may serve as a rich resource for health care policy and decision makers, increase transparency and accountability for the use of public funds in health care, and increase the value derived from the implementation and assessment of novel interventions and services in clinical practice.

Fourthly, future health care innovation initiatives in the UK should consider increasing the period of time between rounds of funding. For the GP Access Challenge, applications for funding occurred in two rounds. The first call for applications occurred in October 2013 and the second call occurred in September 2014.[23] However, the participants interviewed in this chapter reported that few evaluations of services funded in the first round had been completed and published at the time the second call for funding was announced. As a result, there was little evidence available to inform proposals. Therefore, the government may consider scheduling funding calls so that stakeholders can use evaluations findings from previous efforts.

8.5.6 Implications for research

The results of this study highlight three areas of valuable future research.

Firstly, the feasibility and impact of the opportunities identified by decision makers to increase their use of evidence should be studied. This could include assessment of skills training for decision makers, training for academic researchers to better understand the needs of policy and decision makers, embedding academic researchers within the health service, and co-production of local service evaluations.

Secondly, researchers publishing on the effectiveness or efficacy of interventions should consider including more details about context and operational delivery. There is existing guidance and literature to guide this reporting.[23,24] The Medical Research Council provides guidance on evaluation of complex interventions and identifies key contextual factors associated with variations in implementation, intervention mechanisms, and outcomes. The template for intervention description and replication (TIDieR) checklist provides guidance on the reporting of interventions in sufficient detail to allow replication.[25]

Thirdly, researchers should work with policy and decision makers to assess the feasibility and impact of an online service evaluation registry, similar to clinicaltrials.gov.

8.6 Conclusions

This interview study showed that local decision makers used expert opinion and service evaluations to inform the design and implementation of innovative interventions as part of a national campaign to increase access to primary care and reduce emergency hospital admissions. Although recognising that these types of evidence may be considered weak, they were preferred as they offered contextual and operational details required to inform delivery of functional interventions in the local setting. Furthermore, decision makers felt that a lower standard of evidence was adequate to inform decision making given the emphasis on innovation in the campaign.

Practical challenges to using evidence were identified including lack of skill, time pressures, and political constraints. However, there may be opportunities to increase the quantity and strength of evidence used in decision making including generating more evidence that decision makers find useful and making better use of existing evidence. The feasibility and impact of pursuing these opportunities should be studied.

8.7 Chapter summary

- This chapter aimed to explore the use of evidence by local decision makers when designing and implementing interventions as part of a national innovation campaign to increase primary care access and reduce emergency hospital admissions
- Decision makers sought out expert opinion and service evaluations which were perceived as valuable to inform implementation
- Academic research evidence was not used - it was perceived as not applicable to the local environment
- Decision makers felt that a lower standard of evidence was adequate to inform decision making given the emphasis on innovation in the campaign
- Practical challenges to using evidence were identified including time pressures, lack of skills, and political constraints
- There are opportunities to increase the quantity and strength of evidence used by decision makers, these will require collaborations between academics, decision makers, the health system, research funding agencies, and the government

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Chapter 8. Appendix

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Appendix 8.1 Information sheet and consent form



Centre for Evidence-Based Medicine
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The use of evidence when designing, implementing, and delivering primary care health services: a qualitative case study of the Prime Ministers GP Access Fund pilot schemes.

November 2016

Study Lead: Professor Carl Heneghan, CEBM Director

Study Team Members: CEBM - Nik Bobrovitz, Alice Tompson, Dylan Collins, Dr Kamal Mahtani

Introduction:
You are being invited to consider participating in a research study about the uses of evidence in health care decision making. This information sheet explains the purpose of the study. Please read it carefully and take your time to make your decision. Feel free to ask the study team any questions you may have.

Background:
Between October 2013 and September 2014 the Prime Minister contributed £150 million to the Prime Minister's GP Access Fund (PMAF) to improve access to general practice and to stimulate innovative methods of providing primary care services. Pilot sites chose their own specific objectives, and coordinated the design, implementation, and evaluation of new primary health care services.

The PMAF offers a unique opportunity to study decision making by health care stakeholders given that each pilot site had complete autonomy to design and deliver new services. Specifically, we are interested in the role that evidence played in decision making during the PMAF. In this context, evidence could include things like expert opinion, anecdotes, survey results, systematic reviews, etc.

Why have I been invited to take part?
Oxfordshire was one of the pilot sites in the PMAF. You have been invited to be interviewed because of your role as a member on the Oxfordshire Clinical Commissioning Group, a GP locality leadership team, as a GP or practice manager at a GP Practice served by the PMAF initiatives, or as a health care provider that delivered the interventions. In this role you may have been involved in designing, implementing, or delivering the PMAF initiatives. If so, we are interested in your use and perceptions of evidence in the decision making for the interventions.

Do I have to take part?
Taking part in the study is entirely voluntary. You may choose not to take part or, having agreed, you may change your mind about participating at any time. During the interview, you can decline to answer any questions that you do not wish to.

You will not directly benefit from participating however the findings of the study may help to inform the design of primary care services in Oxfordshire and beyond, and improve the care received by patients.

Version 1, 16 October 2016

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What will participation involve?

The interview will focus on identifying the uses and perceptions of evidence when making decisions about the design, implementation, or delivery of PMAF services.

The aims of these interviews are to:

- Describe the types of evidence that were used
- Identify facilitators and barriers to the use of evidence
- Explore potential reasons for variation in the use of evidence
- Identify ways to improve the use of evidence in decision making

With your permission the interview will be recorded.

What will happen with the data?

The findings of these interviews will be analysed for themes. The themes will be reported in a research publication in Spring 2017, in an evaluation report in Spring 2017, in a Doctoral thesis in Summer 2017, and they may be presented at meetings or conferences. All publications listed here will be available to members of the public.

Protecting your identity

We will protect your privacy and not disclose your personal information that identifies you as an individual. When the study is published or presented, your identity will not be disclosed. During the conduct of the evaluation, your personal information will be kept confidential, and no identifiable information collected for the study will be shared with anyone outside of the study team.

Governance Issues:

All study data will be stored securely in restricted access areas at the Nuffield Department of Primary Care Health Sciences in line with the data protection policies of the University of Oxford.

The researcher conducting the interviews has an enhanced CRB check and a research passport with the Thames Valley Clinical Research Partnership.

Evaluation Team Contact Details:

If you have any questions or comments about this study, please do not hesitate to contact:

Niklas Bobrovitz, DPhil Candidate
niklas.bobrovitz@phc.ox.ac.uk
01865 289414

If you wish to make a complaint about the conduct of this study, please contact:

Professor Carl Heneghan, Director of the Centre for Evidence-Based Medicine
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01865 289300

Version 1, 16 October 2016

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The use of evidence during the Prime Ministers GP Access Fund.

Interview Consent Form

	Please Initial Each Box
1. The study has been explained to me and my questions have been answered to my satisfaction.	
2. I understand that my personal information will not be accessible by anyone outside of the study team.	
3. I agree for the interview to be recorded	
4. I understand that any information given by me may be used in future reports, publications, articles or presentations by the study team.	
5. I have been informed that participation in the study is voluntary.	
6. I have been informed of the risks and benefits, if any, of participating in this interview as part of the study.	
7. I agree to be interviewed for the purposes of the study.	

Name of interview participant	Signature	Date

Name of study team member conducting the interview	Signature	Date

Version 1, 16 October 2016

Appendix 8.2 First round question guide

PART 1: USE OF EVIDENCE IN GP ACCESS CHALLENGE

1a. Were you involved in the design or implementation of the Prime Minsters GP Access Challenge services in Oxfordshire?
1b. Which ones?
1c. Could you please describe your involvement?

2. What information or evidence was used to inform the design and implementation of the interventions?

3. Where did the information or evidence come from?

4. How was that information or evidence used to inform decision making?

5. How did you know the intervention(s) would be effective in increasing primary care access and reducing hospital admissions?

6. What kind of supporting evidence or proof was needed about the effectiveness of the interventions to convince the decision makers that the interventions had value?

7. What kind of information or evidence are you aware of that shows that those intervention(s) are effective?

8a. Have other CCGs or health federations implemented similar interventions?
8b. Did that influence the decision to implement the interventions in Oxford?

9. Would you say that the interventions were evidence-based?

10. To what extent were the needs and preferences of the individuals served by the CCG/GP federation considered during the design and implementation?

PART 2: OPPORTUNITIES TO IMPROVE THE STRENGTH OF EVIDENCE

11. Did you feel the information and evidence used was adequate to support the design and implementation of the intervention?

12a. What kind of information or evidence would you want to inform decision making in future initiatives?
12b. Would published academic research evidence be of any value?
12c. What would be the best way to get you the information and evidence you want?

PART 3: DEMOGRAPHICS

13. What is your gender?

14. What is your age?

15. Please describe the affiliation or job that led you to be involved in the Access Challenge

16. How many years of experienced did you have in that role prior to the start of the Access Challenge?

17. Are you a qualified health care practitioner?

Appendix 8.3 Oxford levels of evidence used to inform the coding framework

Table 1. Oxford levels of evidence used to inform the coding framework

Source and strength of evidence for identifying prevalence or incidence of a problem	Source and strength of evidence for intervention benefit
Level 1 Local and current random sample surveys (or censuses)	**Level 1** Systematic review of randomized trials or *n*-of-1 trials
Level 2 Systematic review of surveys that allow matching to local circumstances	**Level 2** Randomized trial or observational study with dramatic effect
Level 3 Local non-random sample	**Level 3** Non-randomized controlled cohort or follow-up study
Level 4 Case-series	**Level 4** Case-series, case-control studies, or historically controlled studies
Level 5 Not applicable	**Level 5** Mechanism-based reasoning
Unclear	**Unclear**

Appendix 8.4 Final coding framework

Table 2. Final coding framework

Themes, sub-theme, and codes organised by objective	Number of interviews	Number of occurrences
Objective 1: To describe why evidence was sought out and how it was used		
Theme 1: Decision makers sought out evidence on local and national priorities to inform the design of interventions	7	49
Code: Aligning horizontal priorities	2	3
Code: Identifying local needs	3	12
Code: Aligning with local and national priorities	7	29
Code: Meeting the criteria of the bid	5	5
Theme 2: Decision makers primarily sought out evidence on intervention feasibility and implementation	5	29
Code: Presenting a strong big	1	1
Code: IT and data sharing	2	2
Code: Feasible delivery	2	6
Code: Operational details and estimated impacts	6	19
Code: Anticipating unintended consequences	1	1
Objective 2: To describe how evidence was obtained and the types of evidence that were used		
Theme 3: Various methods were used to quickly obtain expert opinion and service evaluations	6	134
Sub-theme: Expert opinion of local stakeholders	6	34
Code: Designing interventions	3	7
Code: GPs, nurses, practice managers	5	7
Code: Hub and spoke sharing of evidence	1	1
Code: Ideas for interventions	2	4
Code: Local meetings and idea generation	2	4
Code: Local needs	2	6
Code: No direct patient input	1	5
Code: Routine meetings	3	5
Code: Special meetings/workshops	2	4
Sub-theme: Expert opinion of external decision makers	3	11
Code: Designing interventions	3	7
Code: Meeting with previous successful bidders	1	1
Code: Previously attempted interventions locally	1	2
Code: Special meetings with external stakeholders	2	4
Sub-theme: Expert opinion of professional organisations	2	3
Code: Online resources from professional organisations	2	3
Sub-theme: Service evaluations from other health regions	3	10
Code: Case studies from previous rounds of the challenge	1	2
Code: Designing interventions	3	7
Code: Learning from previous bids	1	1
Code: Online reports and service evaluations	2	6

Table 2 continued. Final coding framework

Themes, categories, and codes organised by objective	Number of interviews	Number of occurrences
Theme 4: Evidence was weak but perceived as applicable to the local environment and adequate to inform pilot-testing	7	80
Sub-theme: Strength of evidence for prevalence or incidence of a problem	4	6
Code: Level 3 Local non-random sample	4	4
Code: Level 4 Case series	2	2
Sub-theme: Strength of evidence for therapeutic benefit	6	22
Code: Level 4 Case-series, uncontrolled before after, case-control studies, or historically controlled studies	3	4
Code: Level 5 Mechanism-based reasoning	6	18
Sub-theme: Perceived applicability of evidence	4	8
Code: Lack of use of published research evidence	2	3
Sub-theme: Weaker evidence deemed adequate to inform pilot studies of innovative services	4	4
Code: Lower burden of proof for pilots	5	8
Code: Proof of concept for pilot testing	1	1
Objective 3: To identify challenges to obtaining and using evidence		
Theme 5: Practical and political challenges to obtaining and using evidence in decision making	7	51
Sub-theme: Time pressure	3	8
Code: Time pressure due to political agendas	2	2
Code: Time pressure due to holidays	2	3
Code: Time pressure due to need to collaborate	1	2
Sub-theme: Lack of expertise	5	13
Code: No understanding of evidence-based practice	1	1
Code: Limited commissioner expertise in collection, appraising, interpreting evidence	3	8
Code: Limited expertise of existing support structures	2	4
Sub-theme: Top-down political constraints	7	10
Code: Centralised bid/project criteria and ties to funding	3	5
Code: Health care policy a function of political agendas	4	5

Table 2 continued. Final coding framework

Themes, categories, and codes organised by objective	Number of interviews	Number of occurrences
Objective 4: To identify opportunities to increase the quantity and strength of evidence used		
Theme 6: Generate high quality evidence of effectiveness with details about implementation and context	6	25
Code: High-quality local evaluations	3	5
Code: Service evaluations not as strong as research evidence	1	1
Code: Researchers should operational and contextual information in academic studies	2	2
Code: Real time data and data sharing for service evaluations	3	12
Code: Perceived relevance or applicability of evidence	3	5
Code: Co-produce evaluations	2	3
Theme 7: Optimise use of existing evidence	4	23
Code: Embedding teams of academic experts	3	8
Code: Maintain ongoing relationships with academics	3	3
Code: Preference for academics over consultants	2	4
Code: Training for GPs and commissioners	2	7

Chapter 9. Discussion

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9.0 Chapter overview

This chapter summarises the main findings of the thesis and discusses the overall implications; strengths and limitations; and conclusions.

9.1 Introduction

Over the past 20 years, the UK has experienced substantial increases in annual rates of emergency hospital admissions, placing enormous strain on patients, health care practitioners, and health care systems. Although small increases in admissions may be accommodated by shifting resources and increasing capacity in the system, the current rate of increase is not sustainable.[1–4] In response, there have been many initiatives to reduce admissions, yet few have been successful. The majority of initiatives have focused on care organisation and access, but these have been limited by a lack of robust evidence for effective interventions.

It is within this context that the findings of this thesis are situated. The aim of this thesis was to identify and prioritise evidence-based interventions that reduce emergency hospital admissions and explore their implementation in clinical practice.

9.2 Summary of findings

Chapters 3 to 6 focused on existing evidence, policy, and the utilisation of evidence-based interventions in practice.

Chapter 3 was a systematic review of systematic reviews to identify and prioritise evidence-based interventions that reduce EHA. Overall, 306 systematic reviews were included, with an underlying evidence base of 1,667 unique randomised controlled trials that reported hospital admissions data for over 1,000,000 patients. There was moderate or high quality evidence for 30 medications; 22 health systems interventions; two diagnostic interventions; and two medical or surgical procedures. These 56 interventions were intended for use in 31 populations, representing a total of 73 unique intervention-clinical indication combinations. The main conclusion of this chapter was that there are evidence-based interventions that could be implemented or optimised in clinical practice in order to reduce emergency hospital admissions.

Chapter 4 was a content analysis of national guidelines, quality standards, quality indicators, and audits in England. The aim was to map national efforts to promote use of effective evidence-based interventions that reduce emergency hospital admissions. The results showed that, of the 73 evidence-based intervention-clinical indications identified in the previous chapter, 43 were recommended in national guidelines. However, only 16 had been incorporated into quality standards or quality indicators and only 15 had been targeted by national audits. The main conclusion of this chapter was that there are opportunities to further promote use of evidence-based interventions that reduce emergency hospital admissions.

Chapter 5 described a multi-step prioritisation process used to select a sub-set of interventions to study in greater detail. The process included engagement of the public, clinical experts, and methodological experts; scientific peer-review; and a literature review. Ultimately, five pharmacological interventions were prioritised, all medications indicated for heart failure patients.

Chapter 6 was a national cohort study. The aim of the study was to explore the use of five heart failure medications identified in chapters 3 to 5 as high-value interventions for reducing EHA. The chapter used data on 8,274 patients and 383,369 prescriptions. The results showed that the majority of heart failure patients experienced gaps in coverage from their primary care prescriptions and average doses were below recommended target doses. Higher doses of ACE inhibitors and Beta-blockers were associated with a reduced risk of EHA, while higher doses of Aldosterone antagonists were associated with an increase in admissions. The chapter concluded by suggesting that utilisation of heart failure medications in UK primary care may be sub-optimal and there may be opportunities to reduce rates of EHA through improved medication utilisation. However, additional research and analysis are required.

Chapters 7 and 8 examined innovative interventions in clinical practice.

Chapter 7 aimed to explore the feasibility of evaluating 'real-world' interventions for reducing hospital admissions and to build the evidence base for access to care interventions. A quasi-experimental design was used to evaluate six interventions implemented in a health region in England as part of a national campaign to increase primary care access and reduce EHA. The results showed that evaluation is feasible however, use of strong study designs may be precluded by challenges in obtaining individual patient data for creating matched controls and time and financial pressures. Time series analysis showed that the interventions increased primary care access but were not associated with a significant change in admission rates for ambulatory care sensitive conditions and may have increased all-cause admission rates.

Chapter 8 aimed to explore the use of evidence by decision makers when designing and implementing local interventions as part of a national innovation campaign to reduce EHA. Qualitative interviews were conducted with seven decision makers. Thematic analysis showed that decision makers used expert opinion and service evaluations to inform the design and implementation of interventions. Although these types of evidence were considered weak, they were seen to offer crucial contextual and operational details needed for implementation. Decision makers also

felt that the campaign's emphasis on innovation meant that robust evidence of effectiveness was not needed to inform action. No academic research evidence was used. Practical challenges to using evidence were identified including lack of skill, time pressures, and political constraints. Opportunities to increase the quantity and strength of evidence used in decision making were also identified. These were broadly categorised as generating evidence that better aligns with the needs of decision makers and helping decision makers to make better use of existing evidence.

9.3 Implications for policy, practice, and patients

9.3.1 Policy

Policy and decision makers seeking to reduce emergency hospital admission rates in the UK should consider two strategies informed by this thesis: (1) optimise use of high-value interventions in clinical practice and (2) maximise the value of investments in innovation.

Strategy 1: Optimise use of high-value interventions in clinical practice

Policy and decision makers should consider optimising use of the effective evidence-based interventions identified in this thesis. Optimisation may be defined as "the action of making the best or most effective use of a situation or resource".[5] The list of 43 evidence- and guideline-based interventions may be considered in the UK (Table 1). Stakeholders in other jurisdictions may consider the evidence-based interventions identified in chapter 3 in the light of their own clinical guidelines and local priorities to define a list of high-value interventions for their settings.

Strategies to optimise clinical practices have been shown to produce benefit for patients and the health system in the UK when they target utilisation of evidence-based interventions. For example, the Bradford Healthy Hearts program targeted large-scale improvements of cardiovascular health for 350,000 residents by optimising use of evidence-based interventions, specifically, statin therapy for high cholesterol and anticoagulation for atrial fibrillation. Within 24 months, the program had initiated 13,000 eligible patients on statins or changed their statins and initiated more than 1,000 patients with atrial fibrillation on anticoagulation medication. It is

estimated that this led to 211 fewer strokes and myocardial infarctions and an estimated net cost saving to the health system of £1.2 million.[6,7]

The interventions prioritised in this thesis are supported by “gold-standard” evidence showing they reduce emergency hospital admissions; key stakeholders including patients, clinicians, economists, and health care mangers have judged them to have an acceptable overall balance of benefit to harm and to be cost-effective; and explorations of the use of the interventions in clinical practice show that some may be under-utilised, thereby indicating potential for improved utilisation. Given this strength of evidence and vetting by key stakeholders, improving the use of these interventions is more likely to bring about reductions in admission rates in comparison to initiatives targeting untested solutions. Investing in the optimisation of these interventions may therefore represent a more efficient use of resources than funding wide-spread testing and implementation of novel interventions with little supporting evidence.

Table 1. Evidence- and guideline-based interventions that reduce emergency hospital admissions

Patient populations	Interventions
Circulatory system	
Atrial fibrillation	Cardiac resynchronization therapy
Acute coronary syndrome	Pharmacist-involved care
Chronic ischaemic heart disease	Aldosterone antagonists
	Angiotensin-converting enzyme inhibitors
	Intensive statin therapy
	Pharmacist-involved care
Heart failure with reduced ejection fraction or left ventricular dysfunction	Aldosterone antagonists
	ACE- inhibitors
	Angiotensin-II receptor blockers
	ACE- inhibitors and ARB (dual therapy)
	Beta-blockers
	Cardiac resynchronization therapy
	Natriuretic peptide guided therapy
	Nurse-led titration of medication
	Pharmacist-involved care
Heart failure any ejection fraction	Case management (hospital initiated)
	Clinical service organisation (case management, specialist clinics, multi-disciplinary care)
	Discharge planning with post-discharge support
	Disease management programs (multi-disciplinary)
	Home-visiting programs
	Multidisciplinary care
	Patient education (pre-discharge, multi-disciplinary)
	Specialist heart-failure clinics
	Transitional care interventions (telecare, pre-arranged direct patient contact)
Digestive system	
Crohn's disease or ulcerative colitis	Infliximab
Ulcerative colitis	Tumor necrosis factor antagonists
Endocrine, nutritional, and metabolic	
Discharged from hospital malnourished	Oral nutritional supplements
In contact with health services	
Prostate biopsy	Antibiotics
Mental and behavioural disorders	
Bipolar disorder	Collaborative care
Schizophrenia	Antipsychotic maintenance or continuous therapy
	Case management (intensive)
	Second generation antipsychotics
Severe/chronic mental disorder/illness	Education/self-management
Mixed patient populations	
Elderly patients in the community or being discharged from hospital	Community-based multifactorial interventions
Nervous system	
Multiple sclerosis	Glatiramer acetate
Respiratory system	
Acute exacerbation of COPD	Early supported discharge
Any severity of COPD	Self-management
	Pulmonary rehabilitation programs
Stable moderate to severe COPD	Hospital at home
	Long-acting beta-2 agonists
	Mucolytics
	Tiotropium

[a]Descriptions of populations and interventions have been truncated for simplicity. Abbreviations: ACE= angiotensin-converting enzyme inhibitor; ARB= angiotensin-II receptor blocker; COPD= chronic obstructive pulmonary disease.

Optimising use of the interventions identified and prioritised in this thesis may be accomplished with the following activities:

A. leverage existing quality measurement and improvement infrastructure;
B. implement new services and expand existing services that feature the interventions; and
C. track costs and scrutinise return on investment.

A. Leverage existing quality measurement and improvement infrastructure

Health systems in many OECD countries have dedicated resources for measuring and improving the quality of health care. As a result, there are existing mechanisms for developing quality measurement tools, generating data to identify and understand variations in use of best-practice interventions, and conducting and assessing small-scale trials to improve uptake of interventions. These mechanisms may be leveraged to optimise use of the effective evidence-based interventions.

In England, all NHS organisations are legally required to engage in quality measurement and improvement activities and vast resources are dedicated to these activities.[8] Based on this mandate and using these resources, NICE may develop quality standards and indicators for each of the interventions; national quality improvement frameworks, such as the Quality and Outcomes Framework, may consider adopting standards and indicators for these interventions to incentivise uptake, compare regional achievement, and track changes over time; and local stakeholders may conduct detailed regional audits and test locally-tailored interventions to improve uptake.

There are justifiable reasons to not follow evidence-based guidelines in clinical practice which may stem from clinical judgment and patient preference. However, an exception reporting system may be used. This would allow practitioners to identify patients for whom use of the interventions is not appropriate, based on their own clinical acumen or patient preference. This type of reporting exists as part of some national improvement frameworks, such as the QOF. Although it may be cumbersome and resource intensive to have practitioners routinely document their

decision making, there may be a role for periods of detailed exception reporting for high-value interventions, especially at the local level.

B. Implement new services and expand existing services that feature the interventions

In settings where interventions prioritised in this thesis are not being utilised, clinicians, policy makers, and decision makers may consider implementing them. Stakeholders may consider these interventions in the context of existing local services, clinical expertise, and patient input to determine which of the interventions would be of value in their setting and to identify a feasible strategy for implementation.

Some of the interventions prioritised in this thesis align with NHS aims to reform health care and, therefore, may be candidates for wide-spread implementation. For example, NHS England has started pilot projects to assess expansion of the roles of pharmacists.[9–12] The findings of this thesis support this approach and may help to orient efforts towards populations that may gain the most benefit; pharmacist directed or collaborative care was shown to be effective in reducing hospital admissions in patients with heart failure, chronic ischaemic heart disease, acute coronary syndromes, and chronic obstructive pulmonary disease.

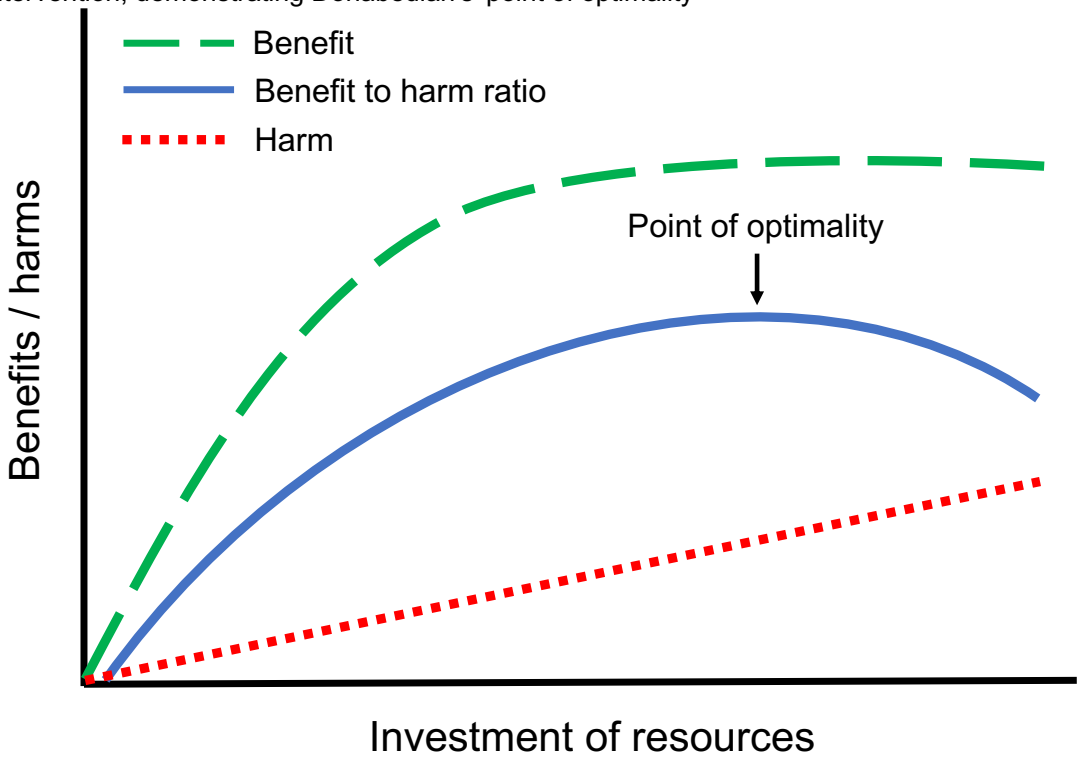
Some of the effective health system interventions identified in this thesis are components of routine care in certain settings. For example, hospital at home services and specialist heart failure clinics operate in parts of the UK.[13] In these settings, the findings of this thesis may serve to justify continued funding in times of austerity given their value for reducing emergency hospital admissions. The findings may also support the expansion of these services to ensure adequate coverage for relevant patient populations.

C. Track costs and scrutinise return on investment

Optimising use of high-value interventions offers a promising approach to reduce rates of emergency hospital admissions however, there may be a point at which additional investments in improving care no longer represent an efficient use of resources (Figure 1). Eventually, the additional benefits achieved per unit cost may

diminish while potential harms, including lost value from not investing in other services, persist. Donabedian describes this balance as the 'point of optimality': the most advantageous balancing of costs and benefits when delivering health care services.[14,15] Policy and decision makers ought to be mindful of this point of optimality. Tracking financial and human resources and scrutinising return on investment in comparison to other potential approaches may aid in determining this point.

Figure 1. The relationship between increasing resource use and the benefit and harm of an intervention, demonstrating Donabedian's 'point of optimality'



Strategy 2: Maximise the value of investments in innovation

The NHS, like many other health service organisations around the world, has made a clear commitment to innovation.[16] Development and testing of novel interventions in routine practice is being touted as a key to future adaptability and success of the health system. Therefore, financing of innovation is likely to continue, even when the interventions being implemented lack evidence of effectiveness.[17,18] Although this may not represent the best use of resources for reducing hospital admissions, two steps may be taken to increase the value of these investments: (1) conduct high quality service evaluations and (2) systematically disseminate the results of service evaluations.

A. Conduct high quality service evaluations

Service evaluations need to be high quality to obtain a clear understanding of the impact of innovations. This thesis showed that local decision makers preferentially seek out service evaluations when designing and implementing new services. They perceive this evidence to be most valuable given the inclusion of contextual and operational details to inform implementation. Therefore, to better understand the impacts of innovations in practice and to learn lessons for the future, evaluations should be developed using established methodological guidance, employ a strong study design with control groups, measure key patient outcomes, evaluate processes, and assess cost-effectivness.[19]

Often, highly quality evaluations are not possible due to strict timelines, lack of expertise and resources, or lack of coordination with researchers and academics. These challenges must be overcome. The government and health system could provide more notice of upcoming innovation initiatives, support on-job training in service evaluation, and support collaborations between local decision makers, researchers, and academics.

B. Systematically disseminate the results of service evaluations

In addition to conducting high quality evaluations, the results of evaluations need to be centrally and systematically disseminated. A registry of service evaluations could be developed to meet this need. The platform could be similar to registries for clinical trials and could host protocols and results. This type of information sharing may minimise the effort required to find useful evidence, promote peer-peer learning, and reduce duplication of efforts.

9.3.2 Practice and patients

This thesis has implications for health care practitioners and patients.

Practitioners and patients may benefit from reductions in emergency admission rates. Secondary care practitioners may directly benefit from reduced acute care demands and alleviation of workforce pressures[20–22], while other practitioners may benefit indirectly from the availability of additional resources that otherwise would have been consumed by increases in EHA rates.

Patients are the centre of the health system and, therefore, are the ultimate beneficiaries of improvement in the quality of care and reductions in emergency hospital admission rates. The results of this thesis may directly benefit patients that are seeking to avoid emergency hospitalisation, in particular patients with chronic diseases that experience frequent admissions. Other patients using the health system may benefit indirectly via reduced delays and cancellations of elective care, reduced A&E wait times, reduced risk of hospital-acquired infection, and allocation of resources to areas other than emergency care.[23–31]

Practitioners and patients have a role to play in maximising use of high-value interventions for reducing EHA. Individual practitioners may review the evidence and guidelines underpinning the prioritised interventions to ensure they are up-to-date on strategies to help their patients avoid hospitalisation. This information could facilitate dialogue in clinical consultations with patients about the benefits of these interventions, and potentially help to improve uptake and adherence. If provided the appropriate information, patients may also initiate dialogue with clinicians about the availability and benefits of the interventions. Both sets of stakeholders may need to participate in quality improvement initiatives. Practitioners may volunteer or be mandated to participate in formal quality improvement activities while patients may be asked to navigate new services or provide feedback on their experiences of new elements of care.

The Choosing Wisely campaign offers a model for engaging practitioners and patients to maximise high-value care. Choosing Wisely is a global initiative which promotes de-adoption of unnecessary tests and treatments, classified as 'low-value' care. The campaign disseminates materials to clinicians and patients including lists of low-value practices with information from evidence and guidelines about appropriate indications for use.[32] This prompts dialogue among practitioners and between practitioners and patients about the appropriate use of tests and treatments. A growing evidence base suggest that Choosing Wisely interventions can help to reduce rates of unnecessary care.[33–36] A similar approach could be used with the findings of this thesis to engage practitioners and patients in efforts to increase use of high-value interventions for reducing hospital admissions.

9.4 Future research

Future research should focus on four areas.

Firstly, researchers should further explore the value and feasibility of optimising evidence- and guideline-based interventions in this thesis as an approach to reducing rates of emergency hospital admissions. Researchers should further investigate the extent to which gaps in the use of the interventions are associated with admissions in the real-world. Five of the interventions were addressed in chapter 6 (i.e. heart failure medications). The remaining interventions should be explored.

Different methods could be used to conduct these investigations. Researchers may examine whether use of the interventions account for geographic variation in admissions or, as was done in chapter 6, whether patients' individual risk of admission is associated with the interventions. These assessments would provide estimates of potential reductions in admissions if gaps in care were closed.

Researchers could also develop and evaluate strategies to optimise use of the interventions. These assessments should measure uptake of interventions, costs, and impact on emergency hospital admissions. These studies would help to determine whether the optimisation approach represents an efficient method of reducing EHA.

Secondly, researchers should consider conducting systematic reviews and/or randomised controlled trials on interventions to reduce hospital admissions in three key patient populations: patients with multi-morbidity; patients at the end-of-life; and patients with acute ambulatory care sensitive conditions, most notably, urinary tract infection, diarrhoea and gastroenteritis, cellulitis, acute upper respiratory infections, convulsions, and viral and other specified intestinal infections. Rates of emergency admissions for these patients are high and are rapidly increasing, yet there is little evidence on how to help these patients avoid hospitalisation. Systematic reviews of RCTs are needed to identify effective interventions. If the evidence base is found to be lacking, RCTs should be conducted.[37–40]

Thirdly, researchers should explore innovations in evidence synthesis and dissemination. The methodology and software for automating systematic reviews should be developed and tested. These approaches may allow rapid and ongoing incorporation of new academic studies into “living” reviews on online platforms. Researchers may also consider testing the feasibility and impact of a database of service evaluations. These innovations would help to ensure that clinicians, decision makers, and researchers are informed by the best and most recent evidence and help to maximise the value of resources allocated to research and quality improvement.

Fourthly, health services researchers need to better understand how to produce evidence that is useful for decision makers. This may involve better integration of academic and grey literature during evidence synthesis; improved reporting of contextual and operational details required for implementation of interventions; and development and maintenance of ongoing relationships with decision makers. Although health services researchers are not functionaries in the health system, academic institutions that receive public funds have a responsibility, and often a mandate, to conduct research that could improve clinical practice and patient outcomes.

9.5 Strengths

In addition to the study specific strengths described in chapters 3 to 8, the overall thesis had four key strengths.

Firstly, this thesis was strengthened by its diverse methodological approaches. The overall aim of the thesis - identifying and prioritising interventions and exploring their implementation in practice - was achieved using multiple study designs and sources of data: a systematic review of published evidence; a content analysis of national guidelines, quality of care tools, and audits; a prioritisation activity involving multiple stakeholders; a retrospective cohort study using a national database; a quasi-experimental study using local clinical practice data; and qualitative interviews with health care decision makers.

Secondly, the linked nature of the chapters was a strength. Chapters 3 to 6 built on one another to push forward the boundary of knowledge from initial identification of effective evidence-based interventions through to exploration of intervention utilisation in practice. The linked nature of the chapters also served to increase confidence in the value of the interventions: evidence of effectiveness from the "gold-standard" academic literature (i.e., systematic reviews of RCTs) was cross-referenced with the judgements of national guideline committees and data from real clinical practice.

Chapter 7 and 8 were also linked. The results of these studies complemented one another to provide a more holistic understanding of the use of innovative 'real-world' interventions to reduce EHA. The results quantified the effectiveness of such interventions and provide insights into decisions that informed their design and implementation, with valuable lessons from both perspectives for future initiatives.

Thirdly, stakeholders were engaged throughout the conduct of this thesis. Patients, general practitioners, practice managers, pharmacologists, heart failure experts, statisticians, and clinical commissioners were engaged to prioritise the research agenda, inform the design of studies, and inform the formulation and presentation of results. Hopefully, this engagement has increased the applicability of the research to the UK context and the likelihood that the results are translated into practice.

Fourthly, this thesis was strengthened by the use of established guidance to inform the design and reporting of studies. The following guidance was used: the Cochrane Handbook of Systematic Reviews of Interventions[41]; Hsieh and Shannon's (2005) approaches to qualitative content analysis[42]; the NHS and NIHR principles for prioritising research[43,44]; the EQUATOR network's preferred reporting items for systematic reviews and meta-analysis (the PRISMA statement)[45]; the EQUATOR network's reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE)[46]; the Centres for Diseases Control's transparent reporting of evaluations with nonrandomized designs statement (TREND Statement)[47]; the EQUATOR

network's standards for reporting qualitative research (SRQR)[48]; and Docherty and Smith's (1999) recommendations for structuring the discussion of scientific papers.[49] Use of these established guides helped to ensure that the methods were robust and that reporting was complete, thereby increasing the validity, transparency, and reproducibility of the thesis.

9.6 Limitations

In addition to the study specific limitations described in chapters 3 to 8, there were limitations to the overall thesis.

Firstly, this thesis focused primarily on the UK context, which may limit the generalisability of some of the findings to other jurisdictions. The effects of prioritised interventions identified of chapter 3 may be generalisable to OECD countries; effect estimates were only downgraded if the majority of trials underpinning the effect estimates came from non-OECD countries.

Chapters 4, 5, and 6 are firmly rooted in the UK context. The purpose of these chapters was to derive recommendations for policy and practice in the UK and, therefore, used data from English guidelines, English health care stakeholders, and a UK clinical practice database. However, other researchers could repeat these studies using guidelines, stakeholders, and data in their settings.

Chapters 7 and 8 examined interventions in one setting and, therefore, may have limited generalisability. It would not have been feasible to evaluate interventions in more than one setting due to the time required to broker data sharing agreements with multiple stakeholders, and to define and implement new electronic health record coding used in the study. Furthermore, recruitment for interviews in chapter 8 was enhanced by the relationship between the thesis author and the key decision makers fostered during the evaluation. Given the somewhat sensitive nature of the interview topics, recruitment of stakeholders outside of Oxfordshire may have been difficult. However, the results of chapter 7 match findings from the National evaluation of the GP Access Challenge and the results of chapter 8 match literature on the use of evidence by UK health care decision makers.

Secondly, given the scope and timeline of a DPhil thesis, only five evidence- and guideline-based interventions were explored in-depth in chapter 6. Ideally, investigations could have been conducted on all the interventions identified and prioritised in chapters 3, 4, and 5. However, chapter 6 may serve as an model for future research on the other interventions.

Thirdly, this thesis did not develop interventions for reducing emergency hospital admissions. The thesis used existing evidence and evaluated interventions developed by others. However, the results may inform adoption of an under-utilised approach to reducing hospital admissions - optimisation of high-value clinical practices - and may inform development of novel tools, most notably, a registry to share the results of service evaluations.

Fourthly, the results of the qualitative interviews in chapter 8 suggest that the review in chapter 3 may have excluded evidence relevant for decision makers. During interviews, decision makers indicated that they seek out service evaluations and observational evidence that is context-rich to inform the design, selection, and implementation of local interventions. This type of evidence was excluded from the review, which focused on systematic reviews of randomised controlled trials, the "gold-standard" for determining intervention effectiveness.

Future reviews may benefit from using the realist approach to evidence synthesis, which aims to map out whether interventions are effective, how they work, and the circumstances that may impact on their effectiveness. That being said, the review in chapter 3 has provided a valuable list of interventions. In conjunction with the content analysis in chapter 4, the prioritised list of interventions may be considered high-value clinical practices which could be considered by decision makers for wide-spread implementation or as targets for national quality measurement and improvement. At the local level, these results may alert decision makers to interventions worthy of implementation and audit. However, approaches to optimise use of the interventions will likely be context dependent and may require use of realist approaches and locally-derived evidence.

Fifthly, this thesis did not consider social care interventions. Deficits in social care may be a major contributor to rising admission rates however, consideration of these issues was beyond the scope of this thesis. Future collaborations between social and health care stakeholders may be beneficial in addressing the emergency care crisis.

Sixthly, given the large volume of data included in this thesis there is the possibility of data errors. Chapter 3 alone included extraction and analysis of over 10,000 data points (e.g., effect estimates, follow-up periods, RCT author names). However, safeguards were built in to the design of each study to avoid errors: all data extractions, coding, and categorisations were completed independently and in-duplicate by two researchers or completed by one and verified by another.

9.7 Conclusions

This thesis represents the largest undertaking of its kind to identify and prioritise interventions that reduce emergency hospital admissions. A variety of effective evidence-based interventions were identified. However, the thesis showed gaps in the promotion and use of these interventions in clinical practice in the UK. It also called into question whether increasing access to primary care using innovative services is an effective or evidence-based approach to reducing EHA rates.

Decision makers must act diligently to use public resources in a responsible way that curbs the climbing rate of emergency admissions. This thesis provides recommended solutions that are informed by rigorous methodology and data from over 1,000,000 patients.

Stakeholders seeking to reduce admission rates may consider optimising use of the interventions prioritised in this thesis with existing quality improvement infrastructure or by developing or expanding services that feature the interventions. Given the strength of evidence underpinning these interventions and vetting by key stakeholders, investments in this strategy represent justifiable, evidence-based expenditures.

However, the emphasis on innovation in health systems suggest that some resources will continue to flow to new services with uncertain effects. Therefore, high quality service evaluations should be conducted to determine their impacts and the results should be systematically disseminated to promote peer-peer learning and to reduce duplication of efforts.

This thesis has relevance in universal health systems seeking to reduce rates of emergency admissions. As such, some of the methods and results have been disseminated in peer-review publications, on publicly available websites, and directly to health care stakeholders in multiple countries.[50–56] Eventually, all elements of the thesis will be disseminated using these approaches.

In conclusion, this thesis has identified and prioritised interventions that reduce emergency hospital admissions and explored their implementation in practice. The methods and results provide original contributions to the academic literature. The findings have been used to inform specific recommendations for policy makers, clinicians, researchers, and patients that seek to reduce rates of emergency hospital admissions and advance knowledge in this area.

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