INVESTIGATING SURGICAL SITE INFECTION AFTER HIP FRACTURE SURGERY

JAMES PETER MAGDI MASTERS

WOLFSON COLLEGE

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Abstract

James Peter Magdi Masters
Wolfson College

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Infection after surgery or surgical site infection (SSI) is a devastating complication for patients and healthcare providers. Hip fracture patients are particularly vulnerable to SSI, and its consequences. Despite its importance, there is uncertainty around the true rate of SSI. This parameter is crucially important to properly power studies that seek to assess interventions that may reduce SSI. One such intervention is the wound dressing. Some dressings including incisional Negative Pressure Wound Therapy (iNPWT) are used in high-risk surgical wounds, and may reduce SSI. There is a need to assess in this context.

Three contrasting methods were used to assess hip fracture patients. Firstly a systematic review was undertaken of patients undergoing surgery in the United Kingdom. Data were extracted and meta-analysed. Secondly, administrative data were explored to look at the incidence of SSI after hip fracture. Data were additionally interrogated for evidence of treatment for SSI and possible risk factors for SSI. Finally a randomised controlled feasibility trial was undertaken comparing standard care to incisional negative pressure wound therapy in 464 patients. These patients were allocated on a 1:1 basis across 5 centres. Each patient was assessed at 30 days and 90 days against the Centre for Disease Control definition of SSI.

The systematic review identified 20 studies of 88615 hip fracture patients. A pooled estimate of 2.08% (95% CI 1.54-2.62) was seen in studies reporting SSI in 'all hip fractures'. There was variation between types of surgery. The administrative data gave an SSI estimate of between 1.4% (95% CI 1.2%-1.6%) and 1.7% (95% CI 1.4%-2.0%). The feasibility study recruited all patients in 6 months. Eighteen patients were diagnosed with SSI according to the CDC criteria at 30 days-a rate of 4.2% (95% CI 2.5%-6.5%). At 120 days an additional new case of SSI was identified-a rate of 4.4% (95% CI 2.6%-6.8%).

The rate of SSI may be significantly higher than suggested by evidence synthesis and national screening programmes. The data from published and administrative data show higher estimates of SSI, despite possible underestimates in each data source. Prospective studies using recognised criteria show even higher rates of SSI.

The rate of surgical site infection appears to influenced by the study design and data collection procedure.

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I would like to extend my personal acknowledgement to the late Andrew Sprowson who gave me my first break in orthopaedic research, and sparked my interest in infection.

My final acknowledgement is to my wife Holly and parents whose love and patience were indispensible in completing this work.

Declaration

The work submitted here is wholly my own except where outlined. A summary of contributions from other individuals in outlined below as well as at the front of the respective chapter.

Chapter 1-The search strategy was written with support from the specialist librarian Neal Thurley at the Bodleian library. David Metcalfe reviewed a 10% randomly selected tranche of titles and abstracts, as well as all the papers under consideration at the 'full paper review stage'. The candidate undertook a review of all titles and abstracts as well as the full papers and references in their entirety. Joon Soo Ha undertook the data extraction in parallel with the candidate.

Chapter 2-Data were extracted from the parent database by Antonella Delmestri-database manager. Code lists for identifying cases of SSI in both data sets were generated with David Metcalfe as outlined in the methods.

Chapter 3- Data were extracted from the parent database by Antonella Delmestri-database manager. Code lists for identifying cases of revision were generated with David Metcalfe as outlined in the methods.

Chapter 4- The candidate was chief investigator for the trial. He was responsible for the inception, design, oversight, analysis and reporting of the trial. As with any trial there were a large number of people who contributed to its delivery. Specific thanks to the OCTRU trials team including Jonathan Cook trial

statistician who wrote the randomisation sequence and undertook the duties of trial statistician for governance and procedural purposes along with Beverly Shirkey. The sample size calculation was also undertaken in collaboration with Jonathan Cook.

The trial team within the Oxford Trauma group supported the administrative conduct of the study, in particular Lucy Sansom and Charlie Vicary.

The trial was embedded in the WHiTE cohort; this required engagement with the cohort study team and associated investigators. At each site local principal investigators and site staff recruited the patients and delivered the interventions.

Chapter 5- As for chapter 4, there was support from the OCTRU infrastructure. With regards to the trial analysis, this was undertaken by the candidate entirely with support from Beverly Shirkey and Jonathan Cook. Where OCTRU governance structures required statistician sign off and approval, this was undertaken by either Beverly Shirkey or Jonathan Cook.

Abbreviations

Abbreviated Mental Test Score	AMTS
Additional treatment, the presence of Serous discharge, Erythema, Purulent exudate, and Separation of the deep tissues, the Isolation of bacteria, and the duration of inpatient Stay	ASEPSIS
American Society of Anaesthetists	ASA
Antimicrobial Resistance and Healthcare Associated Infection	ARHAI
Arbeitsgemeinschaft für Osteosynthesefragen	AO
Body Mass Index	BMI
British National Formulary	BNF
Case Reporting Form	CRF
Centre for Disease Control	CDC
Clinical Practice Research Datalink	CPRD
Consolidated Standards of Reporting Trials	CONSORT
Data & Safety Monitoring Committee	DSMC
Data Monitoring Committees: Lessons, Ethics, Statistics	DAMOCLES
Difference Elicitation in Trials	DELTA
Hazard Ratio	HR
Health Protection Agency	HPA
Health Related Quality of Life	HRQoL
Hospital Episode Statistics	HES
Incisional Negative Pressure Wound Therapy	iNPWT
Independent Scientific Advisory Committee	ISAC
Interquartile Range	IQR

International Classification of Diseases	ICD
International Standard Randomised Controlled Trials Number	ISRCTN
Intramedullary	IM
John Radcliffe Hospital (Oxford)	JRH
Low Molecular Weight Heparin	LMWH
Major Trauma Centre	MTC
Mental Capacity Act	MCA
Meta-Analysis of Observational Studies in Epidemiology	MOOSE
Methicillin Resistant *Staphylococcus aureus*	MRSA
Minimal Clinical Important Difference	MCID
National Health Service	NHS
National Hip Fracture Database	NHFD
National Institute for Health Research	NIHR
National Nosocomial Infection Surveillance	NNIS
Newcastle-Ottawa Scale	NOS
Norfolk and Norwich	N&N
Not Otherwise Specified	NOS
Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures	OPCS
Orthopaedic Trauma Society	OTS
Oxford Clinical Trials Research Unit	OCTRU
Poole General Hospital	PGH
Principal Investigator	PI
Public Health England	PHE

Queens Medical Centre (Nottingham)	QMC
Randomised Controlled Trial	RCT
Relative Risk	RR
Research Ethics Committee	REC
Significant Adverse Event	SAE
Sliding Hip Screw	SHS
Southmead Hospital	SMH
Standard Deviation	SD
Surgical Site Infection	SSI
Surgical Site Infection Surveillance	SSIS
The National Institute for Health and Care Excellence	NICE
Total Hip Replacement	THR
Trial Management Folder	TMF
Trial Management Group	TMG
Trial Steering Committee	TSC
UK Fixation of Distal Tibial Fractures	UK FiXDT
United Kingdom	UK
World Health Organisation	WHO
World Hip Trauma Evaluation	WHiTE
Wound Healing in Surgery for Hip Fracture	WHISH
Wound Healing in Surgical Trauma	WHIST
Wound management of Open Lower Limb Fractures	WOLLF

Research Training

During the course of the thesis I attended the following training courses

1. Clinical Research Methods Course for Surgeons*, The Royal College of Surgeons of England* London UK

2. Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Postgraduate Seminar Series *Oxford University* Oxford UK

3. STATA: Data Access And Management, *Oxford University* Oxford UK

4. Statistics: Designing Clinical Research And Biostatistics, *Oxford University* Oxford UK

5. Oxford Clinical Trials Research Unit (OCTRU) training modules

- New Starter Course
- Consent
- Systematic Review
- Trial Reporting and Consent

I also undertook informal training in trial design, management and workflow whilst acting as a research fellow on the WOLLF, FiXDT and WHIST trials(1-3).

I acted as an assessor for the following course

Bristol Oxford Surgical Trials Course-BOSTIC

On behalf of the Royal College of Surgeons of England

Conferences Attended

I attended the following scientific meetings during the course of the research time, along with any contributions made to the meeting.

1. British Orthopaedic Association, Liverpool UK 2017

2. National Research Collaborative Meeting Birmingham 2017

-**Presented** *the discussion of trainee Principle Investigators at the British Orthopaedic Association (BOTA) breakout session*

3. Orthopaedic Trauma Association Vancouver 2017

- **Podium Presentation** *Rates of Surgical Site Infection After Open Fractures: Findings of the UK Wound Management of Open Lower Limb Fractures (WOLLF) Trial*

4. 7th FFN Global Congress, Dublin 2018

-**Poster Presentation** *Expanding the World Hip Trauma Evaluation (WHiTE) study to middle income countries - A feasibility study based in Cape Town*

6. Wounds UK Annual Conference Harrogate 2018

-**Podium Presentation** *Wound Healing in Surgery for Hip Fractures-WHISH/WHiTE 7. Randomised controlled feasibility trial of standard wound management versus negative-pressure wound therapy in the treatment of adult patients having surgical incisions for hip fractures.*

Awarded Best Paper on Infection for conference

7. Orthopaedic Trauma Society St George's Park, Burton 2019

-**Podium Presentation** WHISH trial summary results and pitch for definitive trial to the conference's 'Dragon's Den'.

Research Outputs

During the course of the study period I have published the following papers, papers underlined are included in appendix 16

Masters, J P M, Nanchahal, J, & Costa, M. L**.** Negative pressure wound therapy and orthopaedic trauma**.** *Bone Joint J 2016***,** 98-B (8), 1011-1013.

Masters JPM & Costa ML. Hip Fracture research: Lessons from the WHiTE cohort and beyond**.** J Traum Orthop 2016 Vol 3 Issue 4

Masters JPM & Costa ML How to build a randomised controlled trial**.** Royal Coll Surg Eng. 2017 99 (6), 227-230

Masters JPM, Achten J, Cook J Dritsaki M, Sansom L & Costa ML
Randomised controlled feasibility trial of standard wound management versus negative-pressure wound therapy in the treatment of adult patients having surgical incisions for hip fractures BMJ Open 2018; 8:e020632.

Achten J, Vadher K, Bruce J Nanchahal J, Spoors L, **Masters JPM**, Dutton S, Madan J & Costa ML Standard wound management versus negative-pressure wound therapy in the treatment of adult patients having surgical incisions for major trauma to the lower limb—a two-arm parallel group superiority randomised controlled trial: protocol for Wound Healing in Surgery for Trauma (WHIST) BMJ Open 2018; 8:e022115.

Parker B, Petrou S**, Masters JPM**, Achana F & Costa M L Economic outcomes associated with deep surgical site infection in patients with an open fracture of the lower limb Bone Joint *J* 2018; 100-B: 1506–10.

Costa ML, Achten J, Bruce J, Davis S, Hennings S, Willett K, Petrou S, Jeffery S, Griffin D, Parker B, **Masters JPM** , Lamb S E, Tutton E & Parsons N**.** Negative-pressure wound therapy versus standard dressings for adults with an open lower limb fracture: the WOLLF RCT**.** Health Technol Assess 2018; 22 (73)

Costa ML, Achten J, Hennings S, Boota N, Griffin J, Petrou S, Maredza M, Dritsaki M, Wood T**, Masters JPM**, Pallister I, Lamb S E & Parsons N R. Intramedullary nail fixation versus locking plate fixation for adults with a fracture of the distal tibia: the UK FixDT RCT. Health Technol Assess 2018; 22(25)

Research Grants

The overall project was supported by a research training fellowship grant from The Royal College of Surgeons of England and the Dunhill Medical Trust [DMT/RCS605]. £129 000

It was also supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre.

Excess treatment costs for the negative pressure wound therapy arm of the study were met by Smith and Nephew. The company had no role in the design, implementation or analysis of the study.

1. Introduction, Aims and Objectives

Declarations

Concepts and ideas from this introduction have been published

Masters, JPM, Nanchahal, J, & Costa, M. L**.** Negative pressure wound therapy and orthopaedic trauma**.** *Bone Joint J 2016***,** 98-B (8), 1011-1013.

1.1 Hip Fracture

Hip fracture is one of the biggest challenges facing patients and healthcare systems. Worldwide there are 1.3 million hip fractures and more than 60,000 occur in the UK every year (4). These figures are projected to rise to >100,000 by 2020 in the UK (4) and more than 6 million by 2050 worldwide(5). The global cost of this clinical problem is estimated at 1.75 million disability adjusted life years lost and represents 1.4% of the total healthcare burden in established market economies(6).

In Northern Europe and North America, hip fracture is an injury of the elderly, and a marker condition for osteoporosis. The vast majority of patients are over 60 years old and the median age is 82(7). There is a preponderance of female patients at a ratio of around 3:1. As a cohort hip fracture patients are typified by frailty, poor mobility, and comorbidity(8).

Most hip fractures present after a low energy fall. The cause of the fall may be innocuous, but may also be related to a medical diagnosis such as a cardiac arrhythmia or urinary infection. The effect of having a fracture of a long bone, with significant medical background and a possible acute medical problem is profound. Health related quality of life (HRQOL) studies show that before treatment, hip fracture patients have a HRQOL rated worse than death(9). From this pre-treatment, injured state, patients go on to be treated with surgery as well as any associated medical conditions. From here the HRQOL improves as the ability to weight bear is returned and rehabilitation begins. Nonetheless 4 months after treatment little further recovery takes place(10). The average loss in health related quality of life after hip fracture and treatment is akin to a major neurological diagnosis such as stroke(9). Within these averages from the hip

fracture population as a whole, lie important subgroups. One important subgroup is those patients with cognitive impairment which account for around 40% of hip fracture patients(11). Other important subgroups include the 'high functioning' elderly patient who is offered treatment with total hip replacement(12).

One of the most important contributors to the loss of health related quality of life described is loss of mobility. This in turn greatly affects personal independence. The effect of this loss of independence and the trauma of the hip fracture episode are keenly felt by patients and their carers(13).

It is also notable that the mortality associated with hip fracture is very high. Mortality rates are anywhere between 7-10% at 30 days after injury, rising to 30% at one year(14).

As well as the suffering of the patients, hip fracture and its sequelae have important costs for healthcare providers and society at large.

There are several drivers that contribute to these costs. From the perspective of healthcare institutions, hip fracture patients have long periods of inpatient care. This is a function of poor mobility, medical comorbidity, and often shifting social care arrangements. Even after treatment hip fracture patients can expect to lose one level of independence in their living arrangement(9).

Whilst in both acute and rehabilitation settings, hip fracture patients require extensive care from a wide range of members of the multidisciplinary team. The input of physiotherapists, occupational therapists as well as carers is critical to recovery. The need for formal and informal supportive care, which extends in to

the community, further explains why the costs associated with the injury and its treatment as outlined are so significant.

1.2 Treatment For Hip Fracture

The cornerstone of the acute patient care is the surgical management of the hip fracture (7). Surgery is used in over 98% of hip fracture cases and seeks to restore patients to full weight bearing as quickly as possible(7).

Surgical treatment falls into two broad areas: Internal fixation and arthroplasty. In broad terms, internal fixation is either achieved with an extramedullary plate and screw device called a sliding hip screw (SHS) or an intramedullary device called an intramedullary nail (IM nail). Internal fixation is used more generally for extracapsular and subtrochanteric fractures-AO type A1-A3 and ST(15). By contrast the majority of intracapsular fractures (AO type B1-B3) are treated with some type of joint replacement(15). This may be a half joint replacement called a hemiarthroplasty or a full joint replacement called a total hip replacement. The use of either is determined principally by the pattern of the fracture, the condition of the patient and their life expectancy (12). There are some types of intracapsular fracture that may be treated with internal fixation but this accounts for a small proportion of the total.

For most of the 1990s and before, junior members of the surgical team, often out of hours, undertook hip fracture surgery. There were frequent associated delays to surgery. There were few if any arrangements for formal care by medical teams. Since the turn of the millennium, hip fracture has experienced a progressive change in treatment paradigm. High quality modern hip fracture care involves well-defined clinical pathways and guidelines based on a growing

evidence base(12). Treatment pathways now begin in the emergency department, through surgery, and into rehabilitation with recognition of differing needs of different patient subgroups. At each stage, different members of the multidisciplinary team are engaged to address the patients needs. Instrumental to developing and refining the modern hip fracture care pathways has been the use of national audit and guidance. The National Hip Fracture Database is the United Kingdom's framework for evaluating the care at institutional level as well as disseminating best practice(7). This has provided a focus for care and development since its inception in 2007. Similar organisations and processes have evolved in other countries and are represented under the multidisciplinary and international Fragility Fracture Network(16).

1.3 Complications in hip fracture care

Given the high prevalence of comorbidity and frailty, it is unsurprising that complications are a common part of the hip fracture journey. Some of these complications relate to hip fracture surgery, and others relate to the generality of in hospital complications. Given that such a high proportion of patients undergo surgical treatment, the surgical complications will be considered in more detail.

General Complications

'Medical' Infections

As well as precipitating falls and subsequent hip fractures, medical infections such as chest and urine infections are common after hip fracture surgery(17). These infections are associated with increased mortality(17). Chest infections are one of the leading causes of death for hip fracture patients(18).

Cardiovascular problems

Other important risk factors for adverse outcomes like death include cardiovascular complications of hip fracture(19). This may include acute coronary problems or arrhythmia

Thrombosis

Clots in the deep veins of the limb, deep vein thrombosis, are a significant problem after any type of orthopaedic surgery including repair of hip fracture(20). This is a function of the reduced mobility associated with the injury as well as the trauma itself and age(21).

Anaesthetic

Closely related to the medical infections include risks associated with undergoing anaesthetic for surgery in general. There are two broad categories of anaesthesia used for hip fracture surgery-general anaesthetic or spinal anaesthetic. There is no clear evidence to support one technique over another(22).

Surgical Complications

Blood loss

As with any surgery blood loss is possible, and often significant. For hip fracture patients this can be particularly problematic as there may be pre existing anaemia(23). In turn the blood loss can bring about treatment with a blood transfusion. This may precipitate problems of its own in terms of mortality and other adverse outcomes(24, 25).

Dislocation

Where a joint replacement technique is used to treat hip fracture, it is possible for the hip to become dislocated. Either as a result of poor technical execution of the procedure or secondary to trauma-typically another fall. The outcomes for patients who befall this complication are very serious(26).

Nerve injury

Injuries to the nerves around the hip are uncommon(27). The arthroplasty category of treatment is where the greatest risk lies, particularly if a total hip replacement is performed using a 'posterior approach'. Internal fixation may be associated with injury to the sciatic nerve if excessive traction is used to reduce the fracture.

Surgical Site Infection

Infection after surgery is an important and enduring complication. This thesis is concerned with infection in the surgical field or surgical site infection (SSI) after hip fracture surgery.

1.4 Surgical Site Infection

The term surgical site infection came into broad usage in 1992, where it was suggested it as a replacement for the previously used 'surgical wound infection'(28). However the issue of infection after surgery or injury is as old as humanity. It was Joseph Lister who, with the use of carboxylic acid, helped to introduce the concept of clean surgery as a means by which the burden of infection could be reduced and surgery made safer(29). This built on the insights of germ theory from Pasteur and Koch. The next major breakthroughs would

come with penicillin, understanding of quantitative microbiology and prophylaxis(30).

Given the risk posed by surgical infection for most of history, the status today must be regarded as progressed. However it is still a grave complication, with considerable morbidity and mortality for those affected (31-34). This is particularly true in orthopaedic surgery where the extensive use of implanted materials takes place in relatively poorly vascularised tissues.

Surgical site infection is a nosocomial infection and is classified broadly into either superficial, deep or organ space. Organ space surgery is concerned with procedures of the viscera and will not be discussed further here.

Superficial infections involve the skin and subcutaneous tissues of the incision. Deep infections involve the fascial layers and beyond. In orthopaedic surgery in general, and hip fracture in particular the use of metal implants is very common, usually in association with cement and polyethelene. Deep infection typically will involve these implanted materials which act as an ineradicable nidus for microorganisms once established.

The distinction between these two types of SSI is recognised, however SSI more likely exists on a spectrum. The distinction between the two is sometimes, but not always, noted in studies concerning SSI. Indeed whilst in many areas of surgery superficial infections can be treated with antibiotics alone, many orthopaedic units undertake further debridement surgery for this problem to exclude deeper tissue involvement, and to reduce the microbial burden as quickly and aggressively as possible.

Such actions are often taken to avoid microbial contamination of the underlying implants. It is once the microbes reach the implant that treatment becomes more challenging and the process more harmful to the patient.

Treatment of infection has revolved around antimicrobials for over 70 years. These agents either kill the microbes or prevent them from dividing. It is self-evident that any orthopaedic implant has no blood supply; therefore the antimicrobial medications cannot reach microbes present on it, nor the host immune response. The microbial community can remain unharmed on the implant until such time as the medications are stopped. This is achieved using a 'biofilm' which is an extracellular polysaccharide complex used by the bacteria to adhere to inert surfaces-in this case the implanted device(35).

It is for this reason that such radical further surgery is needed to clear infection around metalwork, in combination with extended courses of medications.

The nature of treatment for SSI, combined with the disease process itself is the major driver of the economic consequences for SSI in all surgery. Estimates for this vary, depending on which healthcare system the costs are derived from, but anywhere between $25072 (US) to €3776 (Belgium) to £10523 (UK) per episode of SSI has been calculated(36-38).

Given that SSI accounts for 16-20% of all healthcare associated infections, and around 5% of all surgical procedures, annual costs to healthcare providers are extremely high(39).

1.5 Surgical Site Infection: How Common

Given the economic and clinical consequences there is an imperative to have a close understanding of how common SSI is within healthcare systems. In

England this falls under the remit of Public Health England's Surgical Site Infection Surveillance Programme(40, 41). They carry out a surveillance programme across a range of procedures, some of which are mandatory. The mandatory surveillance protocol for SSI includes hip fracture surgery. The surveillance protocol requires that for all mandatory procedures, patients be assessed for SSI against predefined criteria for one quarter of each financial year. There are two strands to the surveillance; inpatient and readmission. Their report from 2017-2018 showed a surgical site infection cumulative incidence of 1.1% (95% CI 1.0%-1.1%) in the repair of neck of femur category(41). This category encompasses both internal fixation of neck of femur fracture and treatment with joint replacement. Each report details the number of SSI identified cumulatively from April 2013 to the March of the report year (2018). There is growing evidence that the surveillance system from Public Health England is of limited use for understanding the true incidence of SSI in orthopaedic surgery(42-44). Infection rates reported in the literature for this patient group are often significantly higher, with some reports stating rates as high as 7% (32, 45).

1.6 Surgical Site Infection In Hip Fracture

Having considered hip fracture patients as a unique cohort, along with the nature and severity of SSI in general, it is worth considering the implications of SSI in hip fracture patients specifically.

Hip fracture patients are particularly vulnerable to SSI for many reasons. Sixty per cent of hip fracture patients have at least one major medical co-morbidity such as malignancy or diabetes, as well as medications such as steroid or other

immunosuppressive drugs (46). These co-morbidities sit alongside age related deterioration of immune function(47, 48).

Additional considerations relate to the risk of a wound haematoma or oozing from the wound, which predispose to SSI(49). Patients undergoing hip fracture surgery are given chemical thromboprophylaxis for up to one month after surgery to try and reduce the risk of deep vein thrombosis(50). This may contribute to the formation of haematoma and wound ooze, with downstream implications for SSI.

Deep infection has profound consequences for patients including a significantly increased hospital stay and a much greater chance of dying before discharge(51). Of those that do survive to discharge, patients with deep infection are less likely to return to their original residence(51). These worrying findings have been found in other large cohort studies(52). The impact of suffering from SSI for patients and surgeons is profound. Qualitative work discussing the impact of infection after hip replacement surgery has shed light on the deeply distressing journey each patient goes through(53). Illustrative quotes from this work highlight the burden of suffering that surgical infection can exact upon patients. In particular, the effect on mobility, the challenge of diagnosis and the antibiotic burden. Surgeons are also heavily impacted by the diagnosis of SSI. These themes have been seen in related qualitative work looking at SSI across other branches of surgery(54).

Therefore the underestimation of SSI in hip fracture by public bodies has important implications for the time, energy and resources being employed to tackle the problem. This shift in focus is already having an impact at a national level in the UK. The advisory committee on Antimicrobial Resistance and

Healthcare Associated Infection (ARHAI) meeting suggested refocusing efforts of surveillance away from orthopaedic SSI and in to other areas of surgical practice such as obstetrics(55). This thinking is also found in the literature and amongst teams in charge of surveillance (56).

1.7 Steps Taken to Reduce Surgical Site Infection

Given the significant impact for patients and surgeons, as well as healthcare systems, prevention is a major consideration of the surgical care pathway. The 2016 guideline produced by the World Health Organisation (WHO) attempts to unify the heterogenous interpretation of current evidence currently in place at national level(57, 58). This guidance provides a framework for considering the various steps that can be taken to reducing surgical site infection. Each of the three parts of the patient journey will be considered in turn and discussed with specific reference to hip fracture care.

Preoperative Preparation(58):

Hip fracture and its treatment is an emergency. By definition then, no extensive preoperative 'work-up' is possible. The NICE recommendation that surgery should take place within 36 hours means that the preoperative steps are often undertaken in parallel where possible in order to facilitate quick surgical treatment(12).

- The first two recommendations around preoperative nutrition and medication are largely not manageable within this 36 hour window. Nutritional support is part of the postoperative recovery process for hip fracture patients.

- Screening and decolonisation of *Staphylococcus aureus* is recommended particularly in orthopaedic surgery. However this is largely not possible in acute admissions such as hip fracture. Therefore this process takes place in parallel with the other aspects of acute hip fracture care.
- Hair removal is undertaken at the discretion of the treating surgeon. It is not a major consideration in hip fracture care as the surgical site is rarely covered with significant amounts of body hair.
- Surgical Antibiotic Prophylaxis (SAP). The use of antibiotic prophylaxis is considered to be a key component of SSI prevention in orthopaedic surgery. All hip fracture patients should be given SAP. The WHO recommendations support this, and identify the timing of SAP relative to the surgical incision as an important consideration. Other considerations include which antibiotics are given. This is usually determined by local patterns of infection and antibiotic resistance. One of the more influential studies around the use of SAP was by Lidwell and colleagues(59). The demonstrated that the use of antibiotics as prophylaxis led to a reduced rate of 'sepsis' in joint replacement surgery. This practice is now nearly ubiquitous in modern surgery, particularly where devices are implanted.
- The final preoperative considerations relate to the process of cleaning the surgeons' hands and the site of surgery. The WHO guidance recommends an alcohol based preparation for both. These preparations are used in the NHS alongside alternatives based on iodine.

The second part consideration for SSI prevention in the WHO guidelines aggregate intraoperative and postoperative recommendations(57).

Intraoperative and postoperative considerations

- Anaesthetically, optimisation of a patient's oxygenation, circulating volume and temperature are of benefit from an SSI prevention point of view. Consideration of each of these parameters are part of the WHO surgical checklist for all surgery including hip fracture(60).
- The use of clean drapes, wound irrigation and wound protection devices is less clear in terms of recommendation. Each is supported by weak evidence. The WHO work identifies certain categories such as abdominal surgery that may benefit from wound protection devices however no 'pan surgical' implementation is advocated. Similarly no specific recommendations are made for orthopaedic surgery.
- There are additional recommendations around antibiotics. Specifically that they should not be used to irrigate the wound, that antibiotic coated sutures (Triclosan) should be used, but that the antibiotic prophylaxis should not be continued beyond the operation itself.
- At the end of the surgical procedure, dressings are applied to the wound. This practice has long historic roots, but little evidence(61). The WHO does not recommend the use of 'advanced' dressings over primarily closed wound as in hip fractures. However it does recommend the use of incisional negative pressure wound therapy (iNPWT) dressings if available in high-risk wounds. The topic of dressings and iNPWT will be discussed more extensively below.
- Additional in theatre interventions such as laminar flow theatres may be used, particularly with regards to joint replacement. Half joint

replacement is a major strand of the treatment used for hip fracture, and therefore this is of relevance to hip fracture patients. However the effectiveness of laminar flow theatre is a subject of controversy and their use not recommended by the WHO(62).

Dressings

The role of a wound dressing is to minimise bacterial ingress into the wound, manage exudate from the wound site and protect the soft tissues whilst they heal. This is particularly important for hip fracture patients due to the difficulties in personal care, high prevalence of cognitive impairment and incontinence(63). Finally, it is suggested that the type of dressing applied to the wound may influence the healing process itself(64-68).

There is no single dressing type used in the NHS for hip fracture surgery. Clinical teams use a range of products, determined by preference and use within the institution. Often this consists of an absorbent pad secured with an adhesive. This basic system has been used for many years. Newer and alternative technologies appear, but are rarely tested rigorously. The National Institute for Health and Care Excellence (NICE) Key Therapeutic topic overview identified a cost of £106 million for advanced dressings in primary care, a wide range of products, but little robust clinical effectiveness research to guide decision making (69). No similar data were reported for in hospital care.

Cochrane's systematic review of dressings for prevention of surgical site infection drew similar conclusions about the quality of evidence; reporting high risks of bias in almost all studies (70).

1.8 Overview of Negative Pressure Wound Therapy

Negative pressure wound therapy began as a treatment for complex open wounds such as pressure ulcers and diabetic feet. Now NPWT has expanded its use into closed surgical incisions where it is proposed to help manage difficult to heal wounds. Incisional Negative pressure wound therapy (iNPWT) is a form of dressing that may be applied to closed or open surgical wounds. In this treatment, an absorbent layer overlies the incision and is covered with a semipermeable membrane that is only permeable to gas. A sealed tube is used to connect the foam to a pump, which creates a partial vacuum over the wound. This negative pressure therapy provides a sealed environment, preventing bacterial ingress and removes blood and serous fluid exuding the wound(64-68). There are studies looking at the effect of iNPWT in hip and knee replacement(71, 72), major trauma(73) and other non-orthopaedic wounds(74). Much like the rest of the wound care literature, the effectiveness of iNPWT is unclear, and reported in studies at significant risk of bias(75). Efforts to bring this evidence together have also been undertaken by Cochrane who looked at iNPWT in all branches of surgery(76).

Other evidence syntheses, whilst also acknowledging the limitations of current evidence, have identified a suggested benefit for the technology(77). Hyldig and colleagues published a systematic review and meta-analysis across all surgical disciplines that identified a significant reduction (RR 0.54 95%CI 0.33-0.89) in wound infection in the iNPWT group(77).

The Hyldig review identified a single study concerning hip fracture patients(78); Pauser and colleagues only looked at one of the two major categories of surgery (half joint replacement) and compared the iNPWT dressings to standard care.

Differences in seroma, fluid ooze and number of dressing changes were recorded. The study found that iNPWT performed better than standard dressings in all three parameters. However, the study size was only 21 patients in total, and no infections in either group were noted.

To summarise so far, it is recognised that hip fracture patients are a highly vulnerable population of considerable size who undergo surgery. As a result of their frailty and co-morbidity they are susceptible to complications like surgical site infection. Surgical site infection has catastrophic sequelae for patients and healthcare providers. Multiple steps are taken in the surgical care pathway to reduce the risk of SSI, including the application of dressings. One of the emergent technologies which is recommended in high-risk wounds is iNPWT. However, like a number of the SSI interventions the evidence basis is limited. Particularly when viewed from a hip fracture specific point of view. Both Cochrane and WHO have research recommendations to further investigate iNPWT for this purpose. The current evidence suggests the iNPWT may well offer a benefit in terms of reducing SSI, but the hip fracture population has been overlooked. Incisional negative pressure wound therapy is worthy of specific study because it is a simple intervention which if effective could be rapidly taken up across the NHS and beyond. Its use is unlikely to be controversial for treating clinical teams, which can be problematic in implementing new interventions in surgery. Furthermore adding iNPWT to current treatment pathways would not require significant system investment in terms of facilities or training.

1.9 Preparatory Systematic Review

In order to ensure all possible studies of iNPWT relevant to hip fracture surgery were considered. The candidate undertook a systematic review to update the studies Hyldig colleagues identified in their search in August 2015.

1.9.1 Study Aim

To identify any studies of the effectiveness of Negative Pressure Wound Therapy in hip fracture surgery published since January 2015 (77)

Population-Adult patients undergoing surgical treatment for hip fracture

Intervention-Negative Pressure Wound Therapy applied to a closed surgical incision

Comparator-Standard of care wound management as defined by the study

Outcome-Any wound related relevant metric noted in the existing systematic review(77).

1.9.2 Search Strategy

The search terms used in the published manuscript were entered into the MEDLINE, CINHAL and Embase databases(77) (appendix 1a & 1b). The search was limited to studies published from 1st January 2015 to 14th December 2016. Overlapping the published search strategy by 8 months.

Titles and abstracts were screened. Any primary study considering the effect of iNPWT in any type of hip fracture surgery was considered.

The ISRCTN trials registry was also searched for existing or ongoing studies considering iNPWT in hip fracture patients.

1.9.3 Search Results

Table 1-1 Overview of Search Results For Updated Systematic Review

Database	Embase	Medline	CINHAL
Search Results	101	98	67
Relevant studies identified at title and abstract stage	0	0	0

Summary of search results from the repeated and refined search of respective databases outlined in the heading of each column.

No new studies were identified on the trial registry either-table 1-1.

1.9.4 Results

The updated search failed to identify any new studies relevant to the research question.

To answer the question of whether we should use iNPWT in hip fracture surgery, further research must be undertaken. Such work must be considered important as it will either help identify a beneficial intervention for reducing SSI or it will prevent informal adoption of an expensive and non-superior treatment.

The best way to assess the effectiveness of an intervention is to undertake a randomised controlled trial (RCT)(79). This type of study was in fact recommended by the Cochrane review of incisional negative pressure wound therapy(76, 80).

In order to undertake such a study, there are a number of design considerations. Given what has been discussed so far, this RCT would compare iNPWT to current standard care, it would include the full range of hip fracture patients including the most vulnerable, and it would measure an outcome of importance to patients and healthcare providers. Surgical site infection would meet the criteria needed for suitable outcome, as a meaningful change in rate of SSI could potentially change practice.

In order to use SSI as an outcome measure, one must have confidence in the background event rate in the population of interest, one must be able to capture it reliably and one should have an idea about what size of difference in event rate would change clinical practice.

Each of these considerations contribute to the feasibility of an RCT comparing iNPWT to standard care. Given the uncertainty around the true event rate for SSI, and its implications for the sample size of a definitive RCT, confidence in this parameter must be improved.

Overarching aim and rationale

The work in this thesis therefore seeks to consider the rate of surgical site infection after hip fracture surgery with a view to informing a definitive randomised controlled trial comparing incisional negative pressure wound therapy to standard care.

The approach taken was informed by the concept of triangulation(81, 82). This concept involves using differing methodologies with ideally different sources of data and hence different sources of bias and limitations to answer the same question. The idea being that any result supported by differing approaches can

be treated with greater confidence and is less likely to be determined by systematic sources of bias peculiar to the study design.

1.10 Thesis Overview

What is the rate of surgical site infection after hip fracture surgery?

1.10.1 Objectives

- To systematically review and synthesise where appropriate the published evidence around SSI in hip fracture surgery in the UK.
- To examine the diagnosis of SSI in large scale primary and secondary care administrative datasets of patients with hip fracture.
- To undertake a feasibility randomised controlled trial comparing iNPWT and standard care in hip fracture surgery.

2. A Systematic Review Of Studies Reporting Rate Of Surgical Site Infection After Hip Fracture Surgery In The United Kingdom

Declaration

The work was undertaken in full by the candidate. Support and contributions were as follows

Writing search strategy: Mr Neal Thurley, Bodleian Library

Search of titles/abstracts and full papers: Dr David Metcalfe reviewed a random 10% tranche of the titles and abstracts in parallel to the candidate who reviewed them in their entirety. He also reviewed all studies reviewed at the full paper stage.

Extraction of data: Mr Joon Soo Ha extracted data from the final included full papers as well as the candidate to duplicate this process and check agreement.

The candidate would also like to acknowledge the corresponding authors who replied to requests for further data Mr Andrew Duckworth, Mr John Findlay, Dr George Chapman, Mr Tim Harrison, Mr Martyn Parker, Professor Keith Willett and Mr David Wright. In addition Miss Jessica Nightingale and Professor Ben Ollivere at Nottingham who provided data that the authors themselves could not.

2.1 Introduction

Having considered the overall aims of the thesis, and the critical importance of determining the accuracy of the rate of infection, the existing published literature was approached as a first data source.

Any scientific investigation should consider in detail the work already undertaken in an area and its bearing on new work proposed.

Published studies can be assessed in informal or formal ways. Systematic review is a formal methodology that identifies studies relating to the research question, and prospectively outlines the method by which the information in these studies will be extracted, analysed and reported. The process seeks to minimise the bias associated with a non-systematic approach to identifying and collating studies. This is achieved by using more than one investigator for each step in capturing and selecting studies for inclusion, in addition to formally describing and presenting the process of selection in a protocol.

Systematic reviews are most typically used to assess interventions in healthcare. The leading example of this is the Cochrane organisation whose handbook outlines a best practice in undertaking systematic review(83).

However such reviews focus on including studies reporting randomised controlled trials. The line of enquiry for this thesis relates to a question of incidence, specifically the incidence of surgical site infection after hip fracture. There is a second order consideration in how this parameter may inform a study of a new dressing intervention using surgical site infection as an outcome measure. This question does not fit in to the framework of a classic systematic review of an intervention. Therefore this chapter is a systematic review of studies that report an outcome (surgical site infection) after an exposure (hip

fracture surgery) in a particular population (patients undergoing hip fracture surgery). This 'systematic review of epidemiological studies' is a well-recognised technique that seeks to identify, report, synthesise and analyse the best available evidence to answer questions around measures such as incidence(84-86).

Each part of the research question was considered through the lens of the overarching aim of the thesis and preparatory work for the randomised controlled trial described.

Population-As outlined in the main introduction, hip fracture patients are a recognised surgical population. Clearly in order to be at risk of surgical site infection the relevant patients must undergo surgical treatment. Therefore when considering populations to be included all patients must have been treated with some form of surgery. The only surgical treatment not relevant to SSI would be external fixation. A highly unusual but described procedure for hip fracture. In order to optimise the generalisability of the population, only patients treated in the United Kingdom where considered. This decision had both methodological and pragmatic reasoning. In methodological terms, the other two work streams for this thesis were exclusively including patients treated within the United Kingdom. Therefore only including patients from the United Kingdom in the systematic review chapter offered consistency and allows comparison across the work packages. The pragmatic reasoning was that there were too many possible studies to consider if scope was expanded beyond the UK for a single candidate to manage.

Exposure- As outlined each study needed to include patients treated with surgery in order to be at risk of the outcome. All surgical interventions, excluding external fixation were included to give the best possible generalisability.

Outcome-The outcome of interest is surgical site infection. Scoping assessment of the literature showed that there was a wide range of definitions used for this clinical phenomenon and indeed sometimes no definition at all. This variation was often aligned to both institution and study design. Therefore in order to preserve the generalisability all defintions were considered, recorded and analysed within a sensitivity analysis.

2.2 Aim

To identify and analyse the published literature reporting surgical site infection after hip fracture surgery in the United Kingdom

2.3 Objectives

- To systematically search and identify relevant studies
- To extract relevant data and subject them to quality assessment processes
- Where appropriate, to synthesis the extracted data to give a pooled estimate for SSI after hip fracture surgery.
- To draw inferences on the strengths and limitations of using published literature to inform understanding of surgical site infection

2.4 Method

A systematic review of published studies from populations within the United Kingdom was carried out. The methodology was informed by the Cochrane Handbook of Systematic Reviews as well as other reviews of observational studies and conducted according to the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA)(83, 85-87). The study was registered on the Prospero registry of systematic reviews-Reference Number CRD42017050685 Appendix 2. It is reported against the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and PRISMA statement checklists –Appendices 3 & 4(87, 88).

2.5.1 Study Question

What is the rate of infection after hip fracture surgery in studies published in the UK?

2.5.2 Search Strategy

2.5.2.1 Search terms

The candidate, in collaboration with a subject specialist librarian, generated a search string designed to capture any study that may report infection after hip fracture surgery. The full string is included as appendix 5

2.5.2.2 Databases Searched

The Embase and MEDLINE databases were searched from inception to 1st May 2018.

2.5.2.3 Software Used

Each database was searched using the Ovid interface. The results of the search in each database were imported into the Rayyan systematic review software (89). Extracted data were managed in Microsoft Excel (2011) and statistical analysis undertaken using STATA version 15(Lakeway Drive, Texas, US) (90). Graphics were generated in either STATA or Tableau(90, 91).

2.5.3 Selection and Appraisal Method

2.5.3.1 Eligibility Criteria

Research Question Framework

Population Adult patients (over 18 years old) with fracture of the hip treated in the United Kingdom

Exposure Any surgical treatment for the hip fracture, excluding external fixation

Outcome Surgical Site Infection as defined by the study

2.5.3.2 Inclusion Criteria

All studies reporting surgical site infection after hip fracture surgery in the UK were included. The studies needed to report on a minimum of 100 consecutive hip fracture patients undergoing surgery. One hundred patients were chosen given the relatively low numbers of infection expected (up to 5%). The included patients needed to focus on typical hip fracture patients e.g. with an average age of greater than 60. Studies focussing on extremes of age e.g. nonagenarian or high-energy young patients were excluded. All types of original study design were included. Each study needed a minimum of 30 days of follow up. Only studies published in English were included.

2.5.3.3 Exclusion Criteria

Patients exposed to all types of hip fracture surgery were included, except for external fixation. Where patients were treated for mixed indications, and the specific hip fracture cohort are not identifiable, then the study was excluded. For

example a study reporting infection in total hip replacement; where the cases of fracture are not distinguishable from other indications such as osteoarthritis. Reviews of other studies were also excluded, this extended to systematic reviews and narrative reviews. Studies that used compound measurements such as 'surgical complications' were not included unless the SSI was independently reported. Abstracts and unpublished studies were not included.

2.5.3.4 Additional study inclusion

Once the titles and abstracts were reviewed, relevant possible full UK paper reference lists were also reviewed. Additional studies not identified in the original search were added to the list of full papers to review.

2.5.4 Selection Process

The candidate ran and managed the search process. The review of titles and abstracts was done in full by the candidate. A 10% random sample of these studies was reviewed independently by DM. A review of origin of studies was then undertaken by JM, and a list of full papers for review assembled. Both JM and DM reviewed this full list independently. Disagreement at each stage was resolved by discussion and where necessary arbitration by senior colleague undertaken (MC).

An overview of this process is outlined in the study flow diagram in the results-figure 2-1.

2.5.4.1 Categorisation Of Full Studies

Once full studies were identified, they were categorised into the respective type of surgery e.g. 'all hip fractures', 'hemiarthroplasty'. The studies identified spanned a large period of time, some of which were of questionable relevance to understanding modern hip fracture care. Modern hip fracture care encompasses many facets of the care pathway(92). These features have been introduced iteratively over the previous 20 years. Since around the year 2000, there has been a growing recognition of the value in multidisciplinary care for hip fracture patients. Deeper consideration was given to the most effective strategies for anaesthesia and intraoperative care as well as types for surgery for different fracture patterns. In 2009 the remit for the first national guidelines on hip fracture was released by NICE. This was to build on the existing guidance from the British Orthopaedic Association 'blue book' which was published in 2007. In parallel with these guidelines, the National Hip Fracture Database was set up. This national quality improvement project highlighted important variation in care and outcome. Where centres were identified as outliers, they were invited to review their arrangements and seek out examples of best practice in other units. Variation was seen in mortality, orthogeriatric input and time to surgery.

In order to reflect the evolving nature of care, and the growing distance between modern care pathways and those seen before the millenium, an arbitrary cut off of studies published after 2000 was chosen. Studies published before 2000 were labelled as historical and presented separately.

2.5.4.2 Author contact

Authors were contacted selectively if specific data were needed. This was done at the stage where the question arose. Most frequently, this was to determine a breakdown of type of surgery performed where the study presented patients exposed to different types of surgical treatment. Eleven authors were contacted, 4 failed to respond. Of the 7 who responded, 3 were unable to provide the additional information required. A summary of author correspondence is included in the declaration section at the front of the thesis.

2.5.4.3 Data Extraction

The candidate performed data extraction in parallel with JSH. Disagreement was resolved by discussion and arbitration where necessary. The data fields for extraction are outlined in the summary table in the results & appendix 6. The fields chosen were based on clinical principles and focussed on the basic patient characteristics e.g. age and gender, type of surgery and duration of follow up. A number of additional infection related descriptors, such as definition used and distinction between superficial and deep where made were also recorded where available.

Where randomised controlled trials were identified, each treatment arm was considered as to whether it was a novel intervention or used as part of routine clinical care. Where both interventions were part of routine care, then each trial arm was merged to form a cohort. If the intervention was truly novel, then only the control arm would be used, and similarly treated as a cohort.

Where surgical site infection data were reported this could be either as undifferentiated SSI (or with synonym such as 'surgical infection') or by superficial/deep. Each was recorded where possible. The data field 'total number of infections' was either the undifferentiated total number of SSI reported or a combination of superficial and deep where the study made the distinction. Where reoperation was reported as part of the SSI definition, this was assumed to be deep infection and recorded accordingly.

2.5.5 Statistical Methods

Descriptive statistics were used to represent the patient demographics included in the study. Similarly summary statistics including expressions of uncertainty were used to calculate the rate of infection as a percentage.

Selective meta analysis was undertaken where appropriate. This judgement was based on the number of cases available. This was done using a meta analysis of proportions with a random effects model. A random effects model was chosen due to anticipated methodological heterogeneity between studies. Study heterogeneity was expressed using the I^2 statistic. All proportions were transformed to percentages. No models of risk or meta regression were undertaken principally due to the lack of consistent reporting of meaningful covariates. Post hoc sensitivity analysis was done to explore stability of findings and possible drivers of observed outcomes.

2.5.6 Quality Assessment/Risk of Bias

Where studies were included for meta-analysis, the Newcastle-Ottawa scale for observational studies was used to assess quality.

The Newcastle-Ottawa tool is designed for assessing the quality of observational studies in meta-analyses (93). The Newcastle-Ottawa system reports study quality with a system of stars across three domains; selection, comparability and outcome. Each can be awarded up to three or four stars. It has precedent for use in syntheses of surgical studies in trying to understand surgical site infection after surgery(86)

The pattern of stars can then be interpreted as a 'good', 'fair' or 'poor' quality study-as described below:

"Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain"(93)

2.5.6.1 Modification

The Newcastle-Ottawa system can be used for observational studies that have comparator groups for effects or comparisons. This was not relevant here, as the research question sought to identify an incidence after an exposure. To modify this tool, only the 'selection' and 'outcome' quality assessment questions were used. The modified scoring proforma used here is included in the appendix 7. Reporting of the quality of studies also removed the 'comparator' component of the system described above.

2.6 Results

Figure 2-1- Study Flow Diagram Selection Process

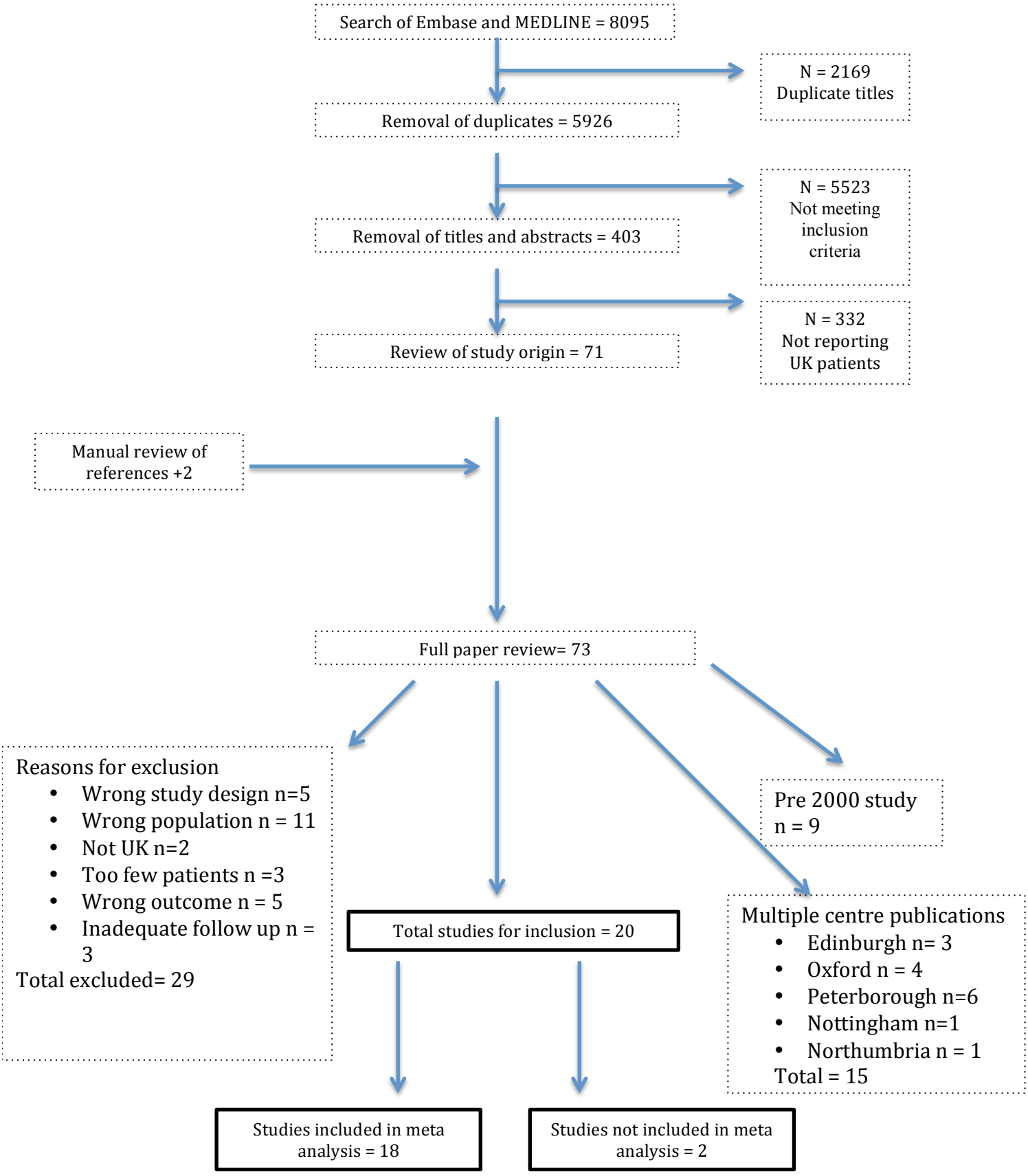


Figure 2-1 outlines the study selection process. Twenty studies were selected, with reasons for exclusion outlined in the flow diagram(94, 95) (96) (97) (98) (99) (100) (101) (102) (103) (104) (105) (106) (107) (108) (109) (110) (111) (52) (112). Of the 20 studies, 18 were included in the quantitative synthesis. This was done according to the type of surgery reported. Two studies were multicentre studies or reporting administrative data from across the UK. After contacting the authors, it was not possible to understand any possible double counting and therefore these studies were only included in a qualitative manner(102, 107). Twenty nine studies were excluded and are reported in appendix 8 along with reason for exclusion. A summary of all the studies identified and included is presented in table 2-2. A separate table of studies that were identified as 'historical' is outlined in table 2-3. These are presented here for reference only.

2.6.1 Centres

During the data extraction, the hospital or hospitals from where the study derived was recorded. Five centres published more than one study that reported infection(14, 25, 51, 113-124). Frequently these studies referred to an institutional database. The dates over which the patients were recruited, was noted. Where there was an overlap of dates and therefore patients, the largest study was included. Where the patients were derived from non-overlapping study periods, both studies were included. If there was lack of clarity about dual counting or dates from which the study came from, then the authors were contacted. Failure of response in an unclear circumstance resulted in the study being excluded. For two studies this was unclear as they were multicentre

studies without centre level reporting (102) (107). A further multicentre study conducted in Scotland was also identified, however after contact it was established that the work was conducted at board level. This study was retained and used in the meta analysis.

The centres whose data are included here are presented in figure 2-2.

Figure 2-2 Geographical Spread Of Centres Reporting Hip Fracture Data in Meta Analysis

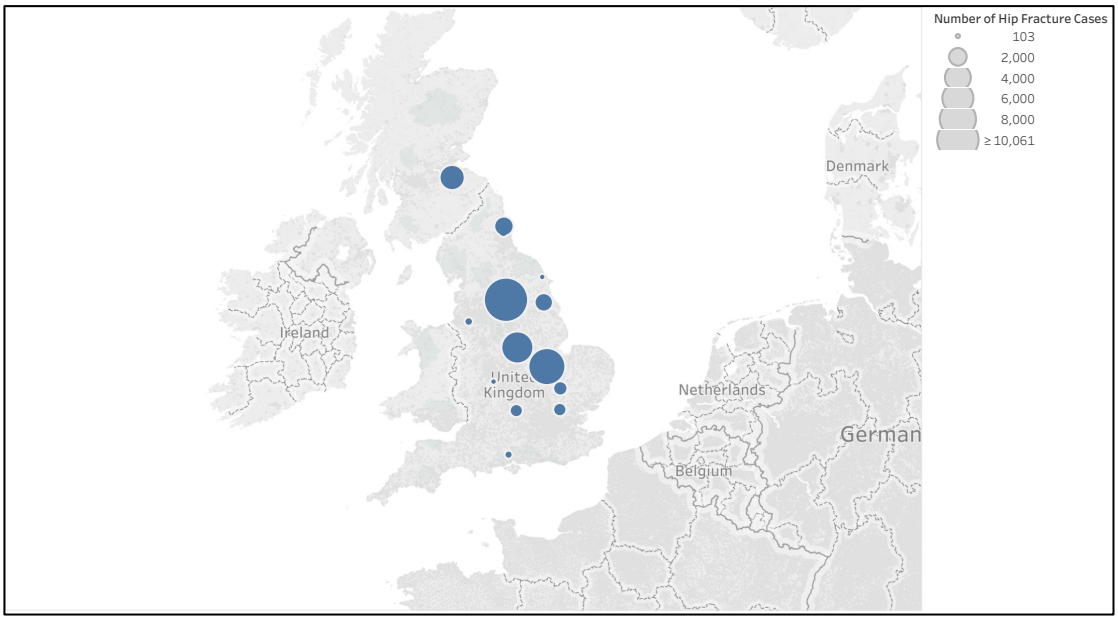


Figure outlining the distribution of reporting centres idenitified in this systematic review. Size of bubble relates to the number of cases reported in the respective studies.

2.6.2 Study Types

Most studies were single centre cohort studies. There was a mixture of prospective and retrospective study designs. A third category of 'prospective database' was also used to cover a number of the eligible studies. This refers to the use of continuously collected institutional data, including data around SSI, for hip fracture. These data were typically not collected to answer a specific research question, but reviewed at a later date.

Consideration, analysis and interpretation of these types of data should take into account several factors. This includes when the data collection was defined, and when the outcome of interest occurs. In the databases considered here, the data collection was typically prospective with regards to the patient diagnosis and surgical treatment. However the outcome data collection was varied in its nature and rarely specified. Surgical site infection is a subjective diagnosis in many respects, certainly when compared to other binary outcomes such as mortality. Even seemingly 'hard' metrics such as positive deep culture are stripped of important context such as concomitant prescription of antibiotics. Therefore whilst prospectively collected, these data are at risk of the important biases associated with retrospective outcome collection. This is considered further under the definition and discussion sections.

Other study designs include one study was of administrative data-Hospital Episode Statistics (HES) (102). There were also two randomised controlled trials(103, 111). Each used SSI as its primary outcome measure. Both were comparing interventions that are used in NHS care and therefore all patients were retained and treated as a single cohort.

2.6.3 Follow up

Each study needed a minimum of 30 days of follow up to be included. Most reported follow up for between 1 and 12 months. However, a few followed up to 4 years. The majority of follow up was passive in nature. This relates to the structure of studies that frequently interrogated institutional records. Complications were then recorded if they occurred as inpatients or brought about readmission only.

2.6.4 Definition Of Infection

There were differing definitions of infection across the included studies. Seven studies reported using either a formally recognised diagnostic system such as the Centre for Disease Control definition, or referenced a published study(125). Six studies failed to give a definition of infection, and the remainder gave their own definition. These study own definitions focus on similar parameters to those found in the formal definitions. Specifically, the presence or absence of microbes in surgical site samples, the need for further surgery or the presence of symptoms.

2.6.5 Quality Assessment Newcastle-Ottawa Scores

Table 2-1 Summary Of Modified Newcastle-Ottawa Scores

Study Author	Selection	Outcome	Global Rating
Ahmed(94)	★★	★★	Fair
Barr(95)	★★	★★	Fair
Chandran(96)	★	★★	Poor
Chaplin(98)	★	★★★	Poor
Chapman(97)	★★	★★	Fair
Duckworth(99)	★★	★★	Fair
Edwards(100)	★★	★★	Fair
Findlay(101)	★★	★★	Fair
Hargrove (103)	★★	★★	Fair
Harrison (104)	★★	★★	Fair
Jettoo (102)	★★	★★	Fair
Mackay (105)	★★	★★	Fair
Mamarelis (106)	★★	★★	Fair
Morgan (107)	★★	★	Poor
Reilly (108)	★★	★	Poor
Robinson (109)	★★	★★	Fair
Shewale (110)	★★	★★	Fair
Sprowson (111)	★★	★★★	Fair
Theodorides (52)	★★	★★	Fair
Wright (112)	★★	★★	Fair

Good quality: 3 or 4 stars in selection domain AND 2 or 3 stars in outcome/exposure domain Fair quality: 2 stars in selection domain AND 2 or 3 stars in outcome/exposure domain Poor quality: 0 or 1 star in selection domain OR 0 or 1 stars in outcome/exposure domain

Table 2-1 outlines the scores accrued for the modified Newcastle-Ottawa (NOS) system. The studies identified in this search were assessed using the modified Newcastle-Ottawa scale described in the methods. Only those studies used in the meta-analysis were subjected to this process.

Many of the studies included were awarded a similar number of stars for both the selection and outcome categories. This reflects the similarity of the study

design and source data used across most papers. As can be seen from table 2, there is a preponderance of retrospective data or 'prospective database'. Under the N-O framework, this style of study consistently attracts stars for using good evidence of exposure (in this case medical record confirming surgery) and outcome (medical record confirming SSI-however defined). Studies with a better outcome score recorded much more closely which patients left at the end of follow up(98, 111). For most studies this was not mentioned. In the outcome section an additional star is awarded for an appropriate length of follow up. This was a component part of the study selection process, and therefore all studies were awarded a star for this.

Under the measurement system for Newcastle-Ottawa, the majority of studies can be described as being of 'fair' quality.

Table 2-2 Summary Of Studies Included In Systematic Review And Meta-Analysis

Study Author	Year of publication	Journal	Hospital	Years represented	Prospective or retrospective	Patient cohort	Number of cases	Study Specified Follow up -in months	Diagnostic criteria for infection	Total number of infections (any)	Surgical Infections (Incidence Proportion)	Number Superficial Infection only (%)	Number Deep Infection only (%)	Number Reoperation for infection (%)	Summary	Mean Age of cohort	M:F ratio of cohort per 100 patients
Ahmed(94)	2016	European Journal of Orthopaedic Surgery and Traumatology	Hull	2010-2013	Retrospective	All hip fracture	1500	1	Reoperation for infection	27	1.80	-	-	27 (1.80)	Historical comparison of two different abx regimens	81.3	25.6:74.4
Barr(95)	2015	Injury	Cambridge (Addenbrooke's)	2011-2013	"Prospective"	All hip fracture > 60	841	12	Reoperation or readmission for SSI	13	1.55	9 (1.1)	4 (0.5)	-	Comparison of hip fracture care and outcomes after MTC introduction	83	28:72
Chandran(126)	2006	Acta Orthop Belg	Scarborough	1989-2000	Retrospective	Hemiarthroplasty only-specific implant	103	48	Revision for infection	1	0.97	-	1 (0.97)	1 (0.97)	Case series Furlong	77.5	-
Chaplin(98)	2013	Annals of the Royal College of Surgeons	Redditch	2004-2009	Prospective-database	Hemiarthroplasty only	110	36	None given	11	10.00	3 (2.7)	8 (7.3)	5 (4.5)	Case series with selective follow up of Austin Moore in DGH	80	25:75
Chapman(97)	2016	Clinical Biochemistry	Oxford	2012-2013	Retrospective	All hip fracture	684	1	Study's own: Wound cellulitis, persistent ooze rx with abx, return to theatre and positive wound microbiology	22	2.05	-	-	-	Cohort of operatively managed hip fractures followed up to explore utility of CRP	81.4	25:75
Duckworth(99)	2012	Injury	Edinburgh	2005-2008	Prospective-database	All hip fractures	2718	1	Positive microbiology from wound sample-superficial infections excluded	43	1.43	-	43 (1.43)	43 (1.43)	Cohort of infected cases examined for risk factors	73	-
Edwards(100)	2008	JBJS Br	Nottingham	1999-2004	Prospective-database	All hip fracture	3563	> 5 months	Study's own: Deep to fascia = deep. Abx only = superficial	80	2.25	39 (1.1)	41 (1.2)	41 (1.2)	Single centre cohort looking at numbers of infections	80.1	20.1:79.9
Findlay (101)	2011	JBJS Br	Nottingham	2007-2009	Prospective-database	All hip fracture	1578	12	None given	41	2.60	25 (1.6)	16 (1.0)	-	Within centre cohort study reporting complications in the context of service redesign	80.2	26:74
Hargrove (103)	2006	JBJS Br	4 different centres	pre 2006	Prospective	All hip hemiarthroplasty across 4 centres	356	1	The Nosocomial Infection National Surveillance System (127)	39	10.96	26 (7.3)	13 (3.7)	-	RCT comparing pulsed lavage to control in hemiarthroplasty	-	-
Harrison (104)	2012	JBJS Br	Peterborough	1986-2010	Prospective-database	All hip fracture (exclude THR)	6905	12	CDC	50	0.72	-	50 (0.7)	-	Single centre cohort of all but THR cases	80.6	22:78
Jettoo (102)	*2016*	*Journal of Orthopaedic Surgery*	*Multicentre UK*	*2007-2013*	*Administrative data*	*Internally fixed intracapsular hip fracture cannulated screws or SHS*	*52884*	*3*	*ICD codes*	*215*	*0.41*	-	-	-	*Large cohort from national data of internally fixed intracapsular hip fractures*	-	-
Mackay (105)	2000	J R Coll Surg Ed	Newcastle	1997	Retrospective	All proximal femoral fractures	357	3	Surgical Infection Study Group(128)	8	2.24	-	8 (2.24)	7 (2.0)	Single centre audit of infection rate before and after guideline implementation	80	17:83
Mamarelis (106)	2017	BJJ	Harlow	2010-2015	Retrospective	All hemiarthroplasty for intracapsular hip fractures	705	3	Positive microbiology and return to theatre	13	1.84	-	13 (1.84)	13 (1.84)	Retrospective review of return to theatre in hemiarthroplasty	83.74	25:75

Study Author	Year of publication	Journal	Hospital	Years represented	Prospective or retrospective	Patient cohort	Number of cases	Study Specified Follow up -in months	Diagnostic criteria for infection	Total number of infections (any)	Surgical Infections (& of total)	Number Superficial Infection only (%)	Number Deep Infection only (%)	Number Reoperation for infection (%)	Summary	Mean Age of cohort	M:F ratio of cohort per 100 patients
Morgan (107)	*2005*	*J Hospital Infection*	*Multicentre*	*Unknown*	*Prospective*	*Internal fixation or hemiarthroplasty*	*1127*	*12*	*CDC*	*33*	*2.93*	-	-	-	*Multicentre prospective study of CDC infection primary hip/knee and hip fracture. Only assessed as inpatients*	-	-
Reilly (108)	2006	Infection Control and Hospital Epidemiology	32 centres across Scotland	2002-2004	Prospective	Repair fracture neck of femur	2303	1	CDC	74	3.21	-	-	-	Investigation of SSI diagnosis after repair of neck of femur	-	-
Robinson(109)	2005	JBJS Am	Edinburgh	1994-2001	Retrospective	Subtrochanteric fractures	302	12	Superficial & deep needed signs and culture-study's own	42	13.91	37 (12.3)	5 (1.7)	6 (1.9)	Case series of long cephalomedullary nails	78.5	-
Shewale (110)	2004	Hip International	Southampton	pre 2004	Retrospective	Patients undergoing hemiarthroplasty	200	>12 months	None given	11	5.50	4 (2.0)	7 (3.5)	-	Single centre review of change from uncemented Austin Moore to cemented thompson.	84.9	10:90
Sprowson (111)	2016	Bone and Joint Journal	Northumbria	2008-2912	Prospective	Patients undergoing hemiarthroplasty	848	12 months	HPA SSI	17	2.00	0	17	-	RCT comparing single vs dual abx cement	82.65	
Theodorides (52)	2011	Injury	Leeds and Oxford	leeds-2004-2010 Oxford-1998-2008	Prospective-database	All patients treated surgically for hip fracture	10061	>1	Deep=reoperation and positive culture in sample deep to fascia	105	1.04	-	105 (1.04)	105 (1.04)	Review of treatment of deep infection at two centres	83	Not reported for overall cohort
Wright (112)	2008	Injury	Warrington	2002-2003	Prospective	All hip fracture	230	1	None given	28	12.17	-	-	-	Single centre review of POSSUM scoring system for predicting outcome in surgically treated hip fracture	80	-

Summary of studies included in systematic review. Studies in italics were not included in quantitative synthesis

Table 2-3 Summary Of Historical Studies Identified By Search

Study Author	Year of publication	Journal	Hospital	Years represented	Prospective or retrospective	Patient cohort	Number of patients/cases	Follow up (mean in months)	Diagnostic criteria for infection	Total number of infections (any)
Christie(129)	1988	JBJS Br	Edinburgh	Unknown-pre1988	Prospective	RCT-displaced subcapital hip fractures	127	12	None given	6
D'Arcy(130)	1976	JBJS Br	Hastings	1966-1972	Retrospective	Hemiarthroplasty only-specific implant	354	Not specified	None given	17
Hunter(131)	1969	BJS	Oxford	1963-1967	Retrospective	Hemiarthroplasty and internal fixation	186	Not specified	None given	24
Keene(132)	1993	Injury	Peterborough and Birmingham Accident Hospital	Unknown Pre 1993	Prospective	Hemiathroplasty	531	Not Specified	None given	32
McQueen(133)	1990	Injury	Edinburgh	1986-1986	Prospective	All hip fracture	502	1	None given	69
Parker(134)	1994	International Orthopaedics	Peterborough and Birmingham Accident Hospital	Pre 1993	Prospective	All hip fracture	1722	Unknown	None given	20
Robinson(135)	1994	Clin Orthop Related Research	Livingstone	1989-1991	Prospective	Intracapsular hip fractures	166	21	None given	8
Skinner(136)	1986	JBJS Br	King's College London	1980-1983	Retrospective	Displaced subcapital fracture	107	22	None given	5
Wood(137)	1980	Injury	Black Notley Hospital Essex	1972-1977	Retrospective	Displaced fracture	235	Unknown	Positive culture from wound	18

Summary of studies that met inclusion criteria but were published before 2000.

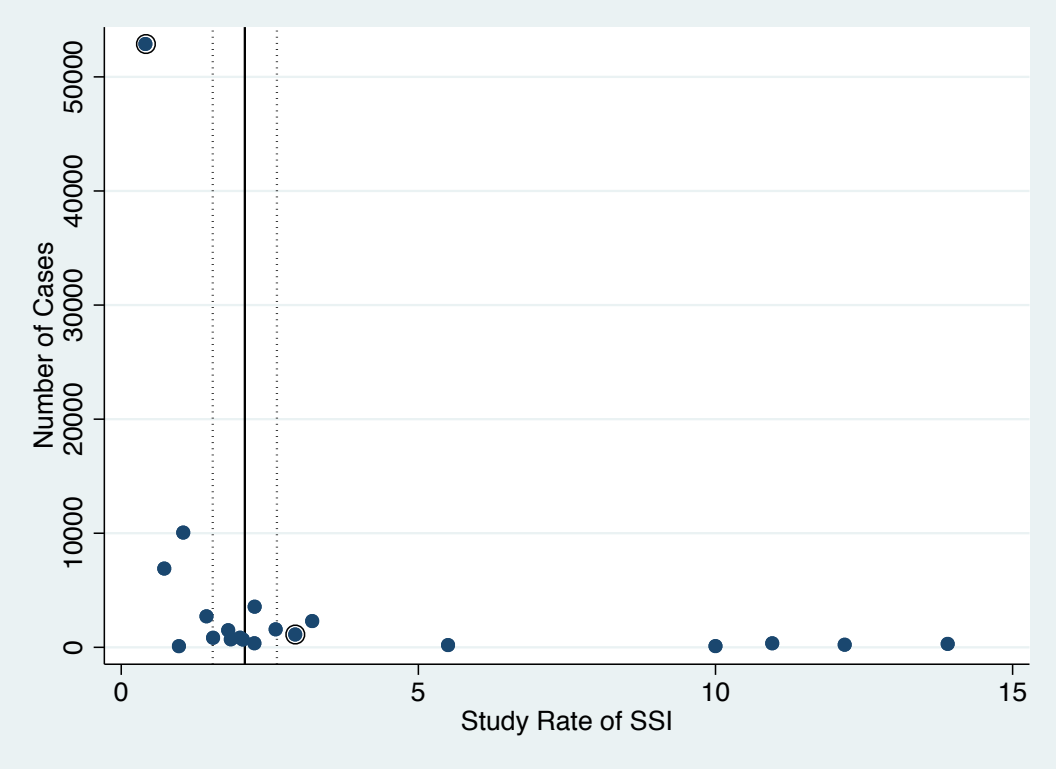
2.6.6 Studies Identified

The principle question for this review and analysis is to understand the rate of surgical site infection after hip fracture surgery. This review has identified a mixture of study types, and a range of SSI rates. Each study has its absolute numbers and percentage rate of infection presented in table 2-2. The lowest rate of infection was 0.4% and the highest was 13.9%(102, 109).

Each study in turn was considered according to the types of surgery to which the patients were exposed.

Those that report infection across all types of hip fracture surgery are described as 'All hip fractures'. Each major subtype of surgery was also examined. Where possible data from studies reporting 'all hip fracture' were extracted and contributed to the analysis of the appropriate subgroup. Where it was not possible to be confident about cases being included in more than one study, then they were excluded from the synthesis.

Figure 2-3 Percentage Rate Of SSI For Studies Included In Systematic Review By Study Population



Plot of study size against rate of SSI reported in the study. A reference line for the 'All hip fracture' pooled estimate is also demonstrated with 95% confidence intervals. The two studies not quantitatively synthesised are circled for reference.

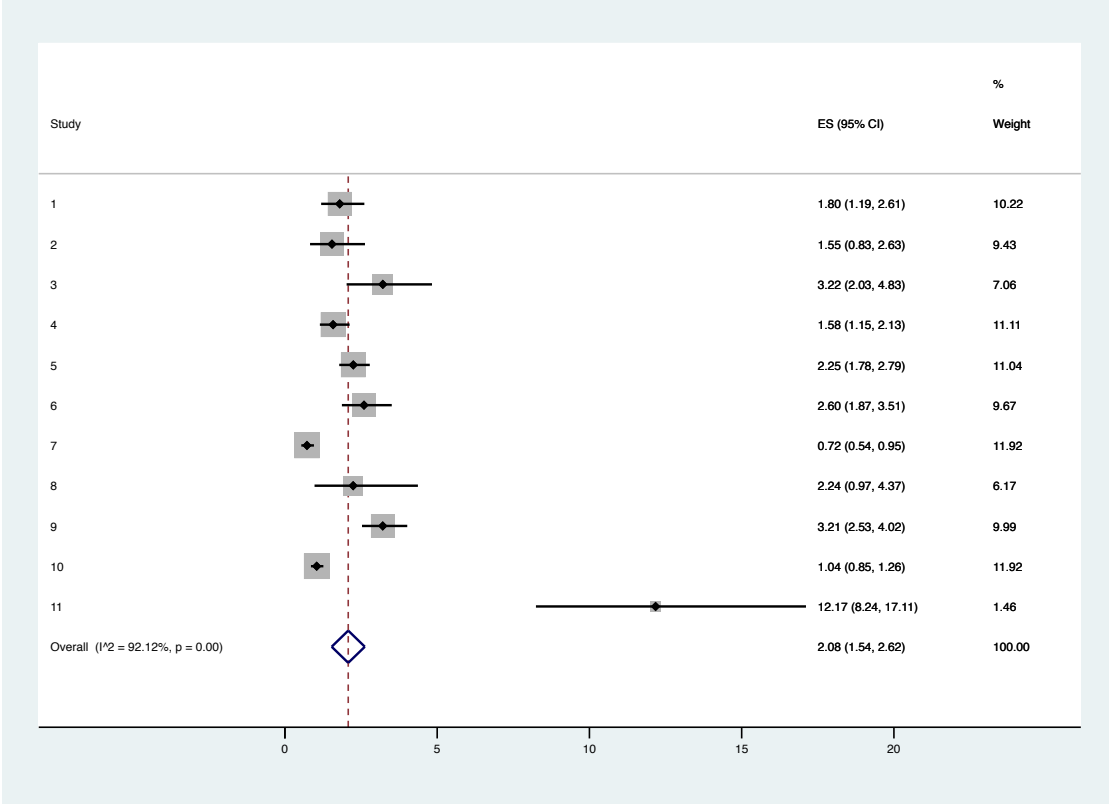
Figure 2-3 plots the percentage rate of infection against the study sample size. The largest studies also reported the lowest infection rates, however there were still a majority of studies clustered around the 2.08% rate(52, 102, 104). Jettoo and colleagues study of intracapsular fractures, focussed on two treatment modalities and used administrative data. On the plot in figure 2-3 this is the extreme outlier with over 50 000 cases. This focus on a specific population and the lack of identifiability of centres meant that the study was not incorporated into any of the pooled estimates. The outliers for high rates of infection were all smaller studies of fewer than 500 patients.

2.6.6.1 All Hip Fractures

Eleven of the 20 studies dealt with 'all types' of hip fracture surgery. Across these studies, 491 surgical infections were seen in 30 740 hip fractures.

Within these 11 studies, a range of study sizes and rates of infection were seen. The largest study reported on 105 infections from 10061 cases from two high volume centres(52). The smallest study contained only 230 cases, with 28 infections (112).

Figure 2-4 Synthesis Of Studies Reporting Surgical Site Infection For Hip Fracture Of All Surgical Types



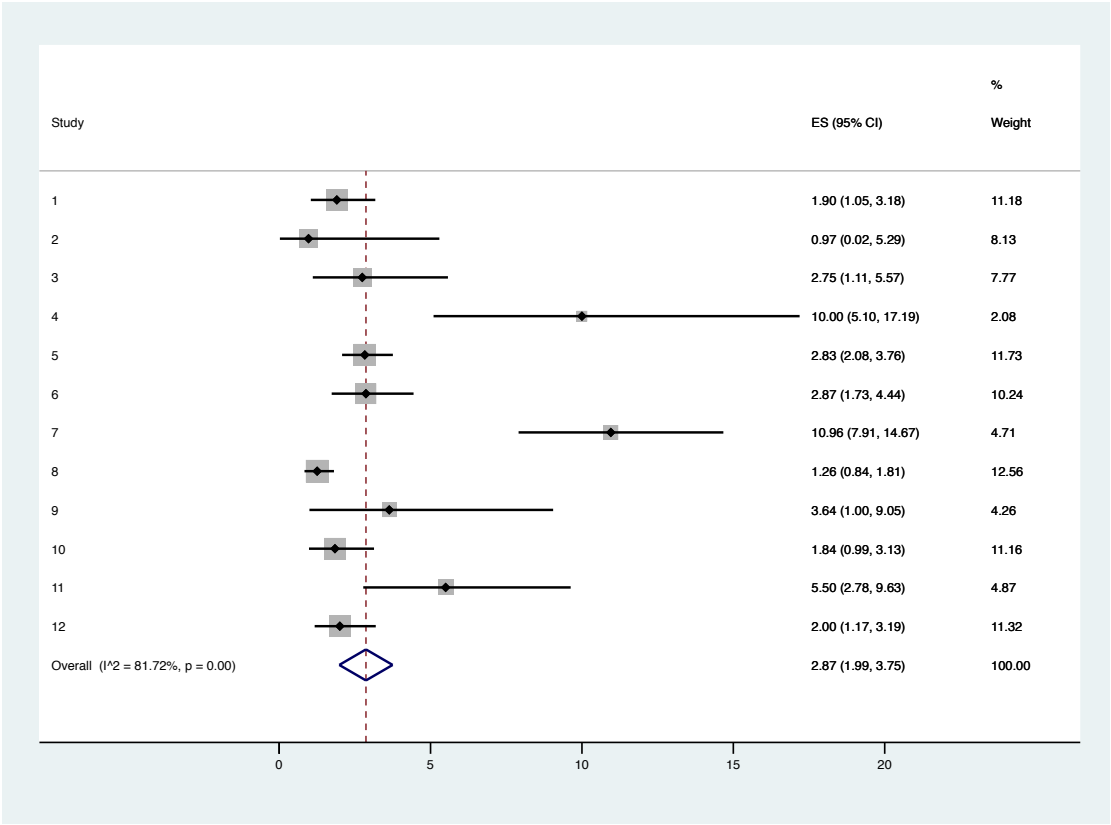
Meta-analysis of reported rates of SSI in 'All Hip Fracture Surgery'. 1 = Ahmed, 2= Barr, 3 = Chapman, 4 = Duckworth, 5 = Edwards, 6 = Findlay, 7 = Harrison, 8 = Mackay, 9 =Reilly, 10 = Theodorides, 11 = Wright. Study heterogeneity reported using the I^2 statistic was 92.1%

The pooled estimate for infection across these studies is 2.08% (95% CI- 1.54-2.62). There is significant variance between the studies as measured by the I^2 metric (92.1%). This is unsurprising given the mixture of study designs, case definitions and study sizes. Wright and colleagues study is an outlier in this group of studies, in that the infection rates are significantly higher than the other studies and the pooled estimate(112, 138). Although this study is relatively small in the context of all the studies assembled here, it still represents a sizeable study population. The outlier study does not report a specific definition for their cases of infection.

2.6.6.2 Hemiarthroplasty

Data from 12 studies reported infection after hemiarthroplasty surgery. Five of these were dedicated studies of hemiarthroplasty. The remaining studies were of hip fracture in general, and data on hemiarthroplasty were reported or obtained by contacting the authors.

Figure 2-5 Summary Of Studies Reporting Hemiarthroplasty



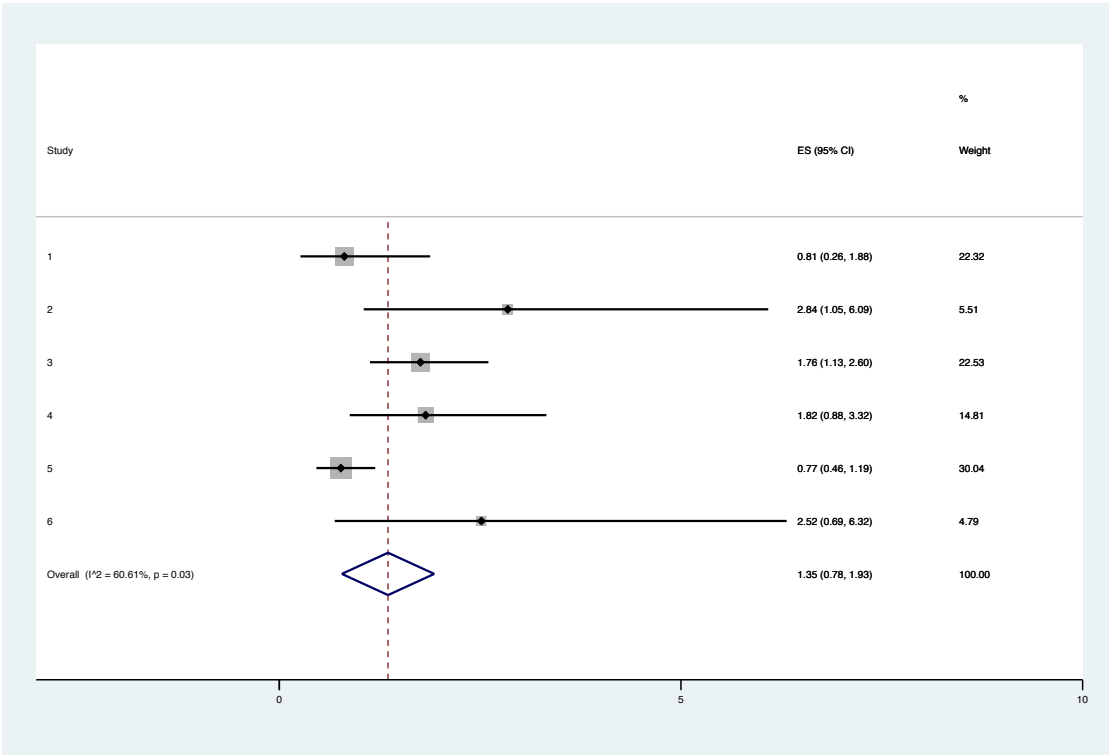
Meta-analysis of reported rates of SSI in hemiarthroplasty. 1 = Ahmed, 2= Chandran, 3 = Chapman, 4 = Chaplin, 5 = Edwards, 6 = Findlay, 7 = Hargrove, 8 = Harrison, 9 = Mackay, 10 = Mamarelis, 11 = Shewale, 12 = Sprowson. Study heterogeneity reported using the I^2 statistic was 81.7%

The pooled estimate percentage rate of infection in the 7941 hemiarthroplasty cases is 2.87% (95% CI-1.99%-3.75%). Within these studies a range of infection rates is identified. The highest being two studies of over 10% surgical infection. Similar to the 'all hip fracture' synthesis, the I^2 is high (81.7%).

2.6.6.3 Sliding Hip Screw

Fewer studies reported data on the sliding hip screw (n=6). They were all studies looking at hip fracture in general, and reported sliding hip screw as a subset. A total of 68 infections in 5383 cases treated with sliding hip screw give a pooled estimate of 1.35% (95% CI 0.78-1.93).

Figure 2-6 Summary Of Studies Reporting SSI After Sliding Hip Screw



Meta-analysis of reported rates of SSI in Sliding Hip Screw. 1 = Ahmed, 2= Chapman, 3 = Edwards, 4 = Findlay, 5 = Harrison, 6 = Mackay. Study heterogeneity reported using the I^2 statistic was 60.1%.

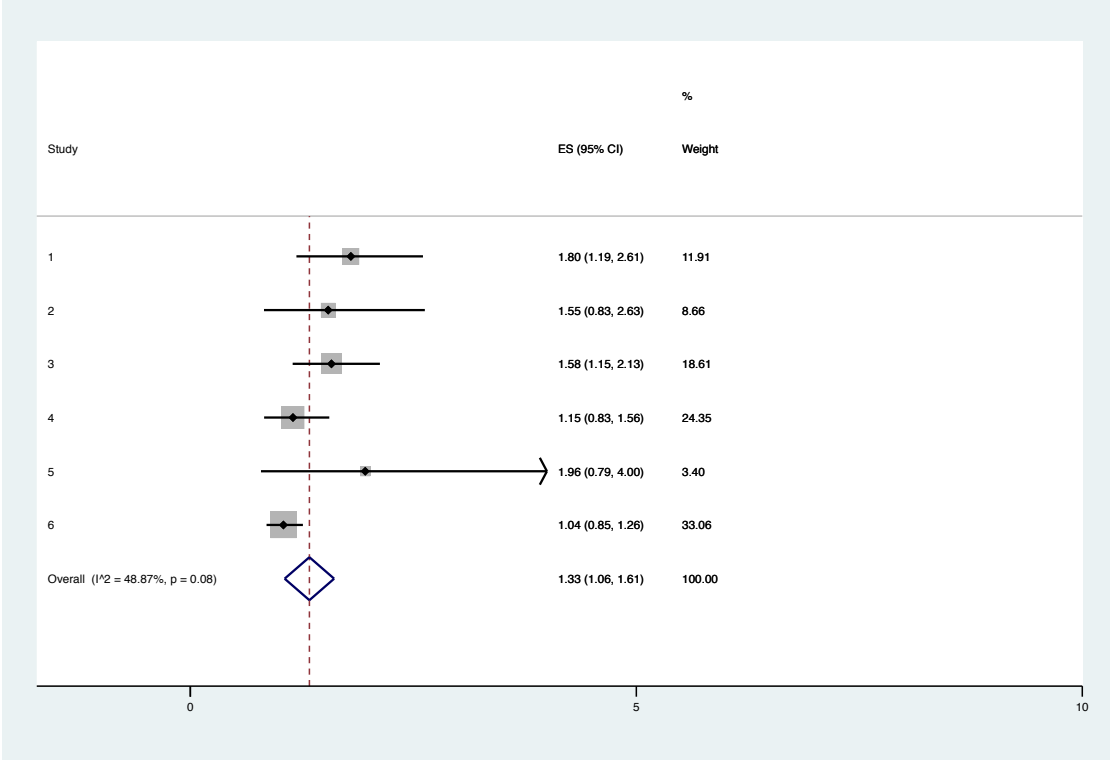
The largest study which reported data on sliding hip screw is not included in the synthesis as it was reporting administrative data, and it wasn't possible to determine which centres it reported and hence any possible overlap(102).

The study reported on 18 014 cases of intracapsular hip fractures treated with SHS. It found 80 cases of infection (0.44%).

2.6.6.4 Reoperation

Six studies reported the numbers of patients needing further surgery for infection. For some, this was implicit in their definition of infection. The rates reported in these summaries are included in figure 2-7, along with an estimate where the proportions have been collated. For this purpose, the denominator was the total number of cases under study. No effort was made to delineate by primary surgery, as this was largely not possible based on the data reported, despite author contact and correspondence.

Figure 2-7 Summary Of Studies Reporting Reoperation For Infection.



Meta-analysis of reported rates of reoperation for infection after all hip fracture surgery. 1 = Ahmed, 2= Barr, 3 = Duckworth, 4 = Edwards, 5 = Mackay, 6 = Theodorides. Study heterogeneity reported using the I^2 statistic was 48.9%.

Six studies of 19 331 cases reported reoperation for infection in 236 patients. This gives a pooled rate of 1.33% (95% CI 1.06-1.61).

2.6.6.5 Intramedullary Nail

Only 5 studies reported infection in patients treated with IM nail. This encompassed 1248 cases with 62 infections. This results in a pooled rate of SSI of 4.9% (95% CI 3.8%-6.2%).

2.6.6.6 Cannulated Screws

Five studies included data on cannulated screws. There were a total of 1990 cases treated with cannulated screws, reporting only 16 infections. This gives a combined rate of 0.8% (95% CI 0.5%-1.3%). Cannulated screws are typically used to treat undisplaced intracapsular hip fractures. Jettoo and colleagues also reported on 34870 patients treated with cannulated screws, and identified 135 infections (0.39%)(102).

2.6.6.7 Total Hip Replacement

No synthesis was undertaken for the patients treated with total hip replacement, as the studies for which data were available did not report any cases of infection.

2.6.7 Sensitivity Analysis in 'All hip fracture'

The results above summarise the results of the studies identified by this systematic review.

It is clear that whilst the broad cohorts of patients are comparable, there are notable methodological differences between the studies. In order to explore

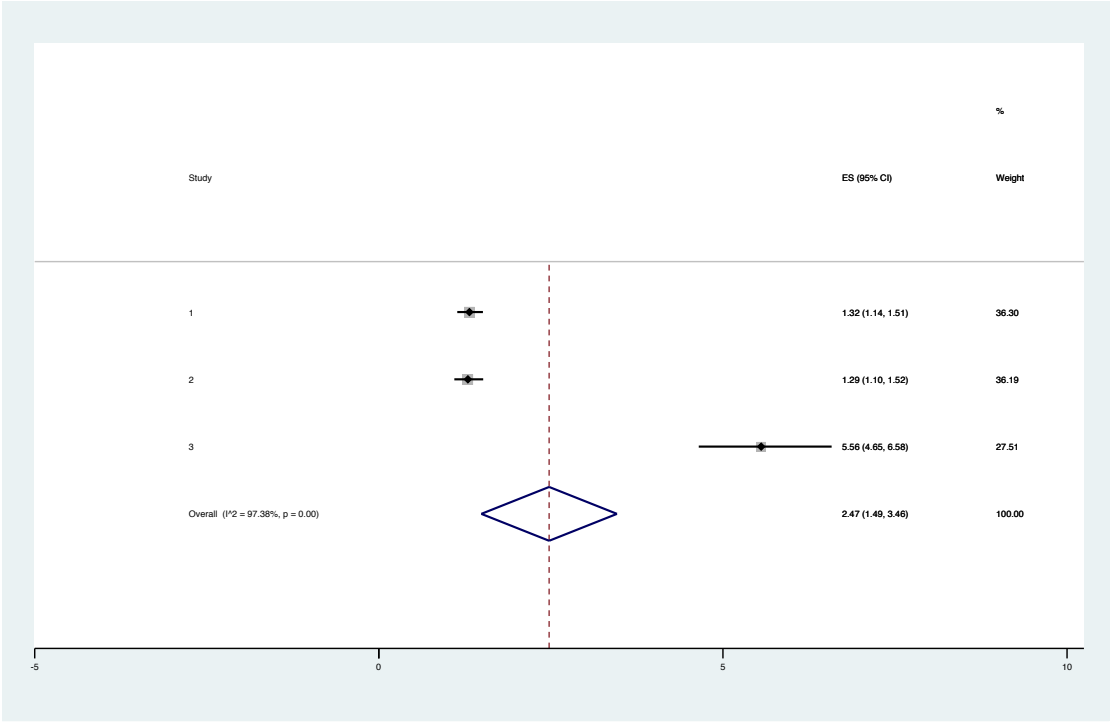
these differences, a sensitivity analysis was undertaken. This analysis sought to look at two key parameters among many possible.

2.6.7.1 Effect of study size

The relationship between study sample size and rate of infection detected is outlined in figure 2-3.

2.6.7.2 Effect of having formal definition

Figure 2-8 Summary Of Studies Clustered By Definition Of SSI.



Meta-analysis of reported rates of SSI according to study definition. 1 = Study's own definition, 2 = Formal referenced definition e.g. Centre for Disease Control, 3= No definition. *Study heterogeneity reported using the I^2 statistic was 97.4%*

Figure 2-8 outlines the effect of three types of case definition on estimated rate of SSI. Studies of 'All hip fracture' were clustered into three categories.

- Self defined or 'study's own'
- Use of formally recognised criteria e.g. CDC

- No definition given

The definition used by each study is outlined in table 2-2. The difference between clusters 1 and 2 with a definition, and cluster 3 with no definition is striking. The estimate for those studies with no definition is 5.56%, the relatively broad confidence intervals (4.65-6.58) relative to the other two clusters highlights that the absolute numbers in each are quite different. Of the two studies of 'all hip fractures' with no definition, Wright is a significant outlier with a rate of 12%(112). If this study is removed, the pooled estimate is reduced to 1.5% (95%CI 1.13-1.87). The remaining study without a definition is 2.60%(101). One must also bear in mind the differentiation between superficial and deep infections, may not have been made in the undefined cases, thereby adding additional cases to their numbers. The definitions provided in clusters 1 and 2 largely describe their infection cases as being 'deep'. Once again this is not always explicit, but the requirement for use of 'further surgery' and 'culture from deep samples' to determine infection draws a tendency for deeper infections to be reported.

2.6.7.2.1 Superficial And Deep Infections

Across studies and definitions, the reporting and differentiation between superficial and deep SSI was inconsistent. These data were extracted where reported. Of the 20 studies identified, eight distinguished between superficial and deep infection in reporting. These eight studies were a mixture of studies reporting general hip fracture population, and subgroups of procedures. Therefore it was not possible to meaningfully undertake sub analyses on this basis. However general observations suggest that those studies where this

distinction was made had a comparable rate of infection. One distinction from this was Robinson et al where a very high total rate of SSI was noted, and the overwhelming proportion of these was superficial (109). A number of the other studies reporting deep and superficial had comparable rates in each and in total.

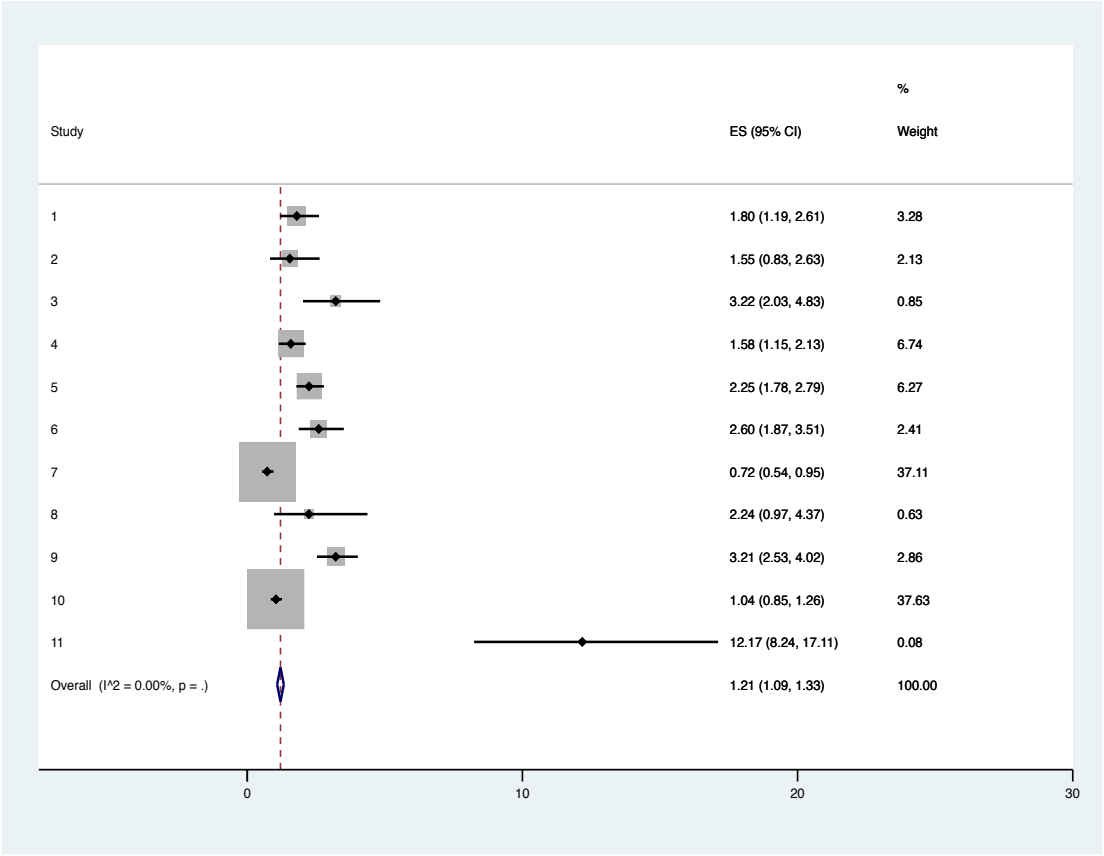
2.6.7.2.2 Historical studies

Eleven studies were deemed to be historical and their results are summarised in table 2-3. It is worth noting that all but one study did not define infection. These data are presented for context only.

2.6.7.3 Comparison of Random Effects vs Fixed Effects model

As outlined in the statistical methods section a random effects model was preferred for the meta-analysis. The alternative fixed effects model is presented here with discussion.

Figure 2-9 Synthesis Of Studies Reporting Surgical Site Infection For Hip Fracture Of All Surgical Types using Fixed Effect model



Meta-analysis of reported rates of SSI in 'All Hip Fracture Surgery' using fixed effects model. 1 = Ahmed, 2= Barr, 3 = Chapman, 4 = Duckworth, 5 = Edwards, 6 = Findlay, 7 = Harrison, 8 = Mackay, 9 =Reilly, 10 = Theodorides, 11 = Wright.

The rationale for using a random effects model was based on the anticipated differences in methodology between the studies driving the observed different rates of infection. The alternative fixed effects model assumes that the difference in observed outcome is based on sample size. The fixed effect model gives additional weight to the larger studies. The effect of this can be seen when considering figures 2-4 and 2-9. Firstly the point estimates differ, the fixed effect model gives a lower estimate and narrower confidence intervals (1.21% 95%CI 1.09-1.33). This is what would be expected given the far greater weighting afforded to the larger studies which have the lowest rate of SSI. As has been

discussed the largest sized studies used very specific definitions of infection with significant risk of bias in the design. These two issues are likely to lead to an underestimate in the rate of SSI. When the fixed effect model is used in the meta analysis, this bias becomes amplified. This highlights the benefits of the random effects model in this context.

2.7 Discussion

2.7.1 Summary Of Findings

The search process identified 20 studies that reported on 88615 cases of hip fracture and 938 cases of surgical site infection. These cases were studied in aggregate and by type of surgery. Pooled estimates of rate of infection ranged from 0.8% (95% CI 0.5%-1.3%) to 4.9% (95% CI 3.8% 6.2%). The aggregate of 'all hip fracture' identified a rate of 2.08% (95% CI- 1.84%-3.09%).

These estimates are derived from a range of study designs including case series, randomised controlled trials and cohort studies. There is a mixture of 'study focus', by which I mean the study sought to identify cases of SSI as one of its principle aims or SSI was reported incidentally as a complication.

These data are derived from studies from18 centres. Many different types of hospital are included in the analysis, improving the generalisability of the results. Similarly the types of patients included were defined in the broadest possible terms.

2.7.2 Strengths of Study

The pragmatic inclusion criteria for this review and large numbers of cases of both hip fracture and subsequent infection contribute to the generalisability of

findings. There were few multicentre studies reporting data here. Therefore in isolation, each study is really only reflective of the unit in which it was carried out. As can be seen from figure 2-1, this does not represent large areas of the UK. For example, no hospitals in the South West of England or Northern Ireland are represented here. By bringing together the combined published data, however the best possible overview of UK practice in the published literature can be represented and examined.

2.7.3 Limitations of Study

There are a number of important limitations to acknowledge in this study. First and foremost the use of only published studies does not take into account unpublished data and grey literature. This was in part a pragmatic inclusion criterion from a resource point of view. It was also clear that for such studies, it would be much more difficult to be clear about the centres from which the data were derived and any potential double counting.

This study only used studies published in English, however given the UK focus of the work; it is unlikely to have a significant effect on the findings and conclusions. The studies identified used a mixture of methods and definitions for the cases of infection. For this reason the interpretation of the synthesis undertaken here must be done so with caution. The heterogeneity seen across all of the pooled estimates could not be fully explored due to the limited reporting of the covariates. However the sensitivity analysis identified that definition, or lack thereof, seemed to significantly affect the pooled estimate. Similarly, the study size seemed to have an effect on the reported rates. An additional important consideration was the use of the random effects model to

synthesise the data. The random effects model places equal weight on all studies, compared to the fixed effect alternative that gives additional weight to larger studies. In this case, this may give additional 'over' importance to the outlier study in the 'all hip fracture' synthesis.

2.7.4 Risk of Bias

A critical consideration for a systematic review and any accompanying synthesis is to consider the sources of bias in studies identified. These can be found in both the studies themselves and the publication process.

Data presented in figure 3 attempts to address the question of publication bias. The phenomenon of publication bias is described as the propensity of studies with null or negative results to not be published. This can in turn affect the understanding of whichever clinical problem is being addressed. Publication bias is typically a phenomenon of interventional studies, and the overall effect is to have a preponderance of studies that show a positive treatment effect. The 'over represented studies' are often smaller in sample size. This is referred to as a 'small study effect'.

In interventional studies this can be visually explored using a funnel plot, which charts the individual study effects against the aggregate effect(139). Small studies are typically clustered in an asymmetrical pattern, indicating a tendency to publish small studies with 'positive' findings.

This study is not concerned with any particular effect size, but on the incidence of a particular complication. The scatter plot in figure 2-3 allows a similar inspection of the studies included.

The phenomenon of publication bias is driven by the incentives around the publication process itself, which is intrinsically interested in 'positive' findings. This would not appear to apply so obviously to studies of incidence of complication. Indeed there are compelling reasons why authors would be interested in publishing a low rate of complication. Understanding any effect of publication bias is further complicated by the mixed nature of studies identified by the search. Specifically that only a few concerned themselves with identification of SSI as the study focus.

Considering the relationship between study size and reported rate; the two largest study sizes had amongst them, the lowest rates of infection (<1.5%)(52, 104). Similarly the studies with the highest rate of infection were the smallest(112, 138). However, this observation cannot be purely attributed to the size of the study as similar small sized studies also reported much lower infection rates.

The explanation for this may be related to the study design and the case capture method. As studies become larger, the resources needed to assess many thousands of patients grow dramatically. The solution to this is often to use routinely collected data, either the medical record or an institutional database. This method was the mainstay of both the largest and some of the smaller studies. The process of retrospectively reviewing this type of data relies on the patient being diagnosed and treated in the same institution, and returning to secondary care. This type of study is therefore quite 'specific' for the SSI cases, but not very 'sensitive'. The tendency of the larger studies to rely on database data is likely to introduce an underreporting bias, as they are unable to account

for large numbers of patients who may have developed complications after discharge or presented to alternative institutions.

This reinforces the decision to use a random effects model, as the alternative use of a fixed effect model is to give larger weighting to the larger study sizes. As seen in the sensitivity analysis, the fixed effect model estimates a lower rate of SSI. This is driven by the greater weight the large studies are given in this model. That said the random effects model still requires careful interpretation. In this context, the potentially distorting effect of outlier rates of SSI. In the studies identified here, this may lead to an overestimate in the pooled estimate as Wright et al had significantly higher rate of infection relative to the other studies.

A limited number of centres report their data. The inclination to publish data on surgical site infection in general or hip fracture SSI in particular is not evenly distributed across the UK. This can be most clearly seen in the absolute numbers of studies from four specific centres (Edinburgh, Nottingham, Peterborough and Oxford). When considering the literature, this must be taken into consideration. For this study, it is important to ask whether these centres are representative of broader UK clinical practice. In many respects this study has identified a representative range of hospitals. Both major trauma centres and trauma units are included here. However in terms of numbers of cases two studies representing three hospitals account for 16966 of the 'all hip fracture cases'. These are all interested hip fracture units who have been at the forefront of hip fracture research in the UK. Therefore their representativeness must be questioned. It may well be that in these units; timely surgery and dedicated care pathways give them a lower rate of SSI than the typical hospital.

Whilst most clinicians recognise SSI as a phenomenon, the definitions used in research do vary considerably. The infections included in this review were defined using a mixture of definitions and definition types. For a number of studies, the definition appeared to be an intrinsic component of the study design. For those studies using institutional data, the retrospective nature of their study necessitated the use of particular metrics such as culture, reoperation and treatment with antibiotics. Clinical examination parameters are much more difficult to review in this way, but are equally valid means by which diagnosis can be achieved. The widespread use of reoperation and culture to define cases in this literature may therefore bring about an underreporting bias.

In particular, only considering patients who have undergone reoperation as having SSI, is potentially highly problematic. The decision to undergo further intervention is taken in the context of the 'whole patient'. Hip fracture patients often represent very high anaesthetic risk, and as such the decision to operate may well be a last resort and alternative treatments such as long term antibiotic suppression used. In addition hip fracture patients may have a concomitant palliative diagnosis, which may very reasonably reduce the willingness of both patient and surgeon to engage with further high-risk surgery.

Related to this issue is the differentiation between superficial and deep infection. In the studies included here fewer than half report both types of infection. The relative prevalence of each is unclear and cannot be determined definitively from the data extracted.

Both superficial and deep SSI is important for patients and clinicians. The obvious severe consequences of deep SSI have been outlined; in particular the further surgery needed and extended stay, cost and treatment. It does not follow that superficial infections lack consequence. At a minimum, antibiotic treatment is required. This contributes to the overall use of antibiotics that needs to be minimised given the rise of antibiotic resistance. There are also important risks to the patient such as allergy, antibiotic associated *Clostridium difficile* infection and disturbance of the patients' microbiome (140). In some centres all suspected SSI are treated aggressively and taken back to theatre to formally exclude any deep tissue involvement. Such practices perhaps indicate that SSI is a spectrum condition, all of which is important.

2. 8 Conclusion

The published literature reporting SSI after hip fracture demonstrates a range of rates, study designs and case definitions. When considered in aggregate, an estimate of 2.08% (95% CI- 1.84%-3.09%) is achieved. However, this should be interpreted with significant caution given the possible sources of bias and heterogeneity. Most of the biases identified would suggest a tendency to under report. The estimate should be understood in this context. It is also key to remember the limitations around differentiation between superficial and deep infections.

3 Exploration Of Surgical Site Infection In Administrative Data. A Study Of Primary And Secondary Care Datasets In Isolation And Combination.

Declaration

The 'Big Data' group within NDORMS, Oxford University, hold the data included in this study. The data were extracted by Dr Antonella Delmestri (database manage). Some code lists were generated in tandem with Dr D Metcalfe (DM), and this is outlined in the manuscript. The candidate undertook all analysis.

Ethics Approval was granted under an ISAC amendment for the use of these data.

3.1 Introduction

Having considered the limitations of the published data, and the difficulties around studying 'low event rate' complications, alternative sources of data were explored.

Administrative data, such as those used to codify diagnosis and treatment in primary and secondary care represent an opportunity to identify SSI cases after hip fracture. This can be either by direct diagnosis or by exploring treatment that may indicate an underlying diagnosis.

Such data may be particularly useful as it is possible to study large numbers of patients across many healthcare institutions. The use of combined primary and secondary care data may allow additional inferences to be made around risk factors and length of stay for patients affected by SSI. There are recognised limitations associated with these data sets such as the accuracy of coding for diagnosis in the administrative system(141).

Diagnoses and procedures are coded using specific code dictionaries. These dictionaries are not designed to capture specific outcomes or answer specific research questions. Therefore interpretation and analysis should take this into account.

Given the possible strengths and limitations of administrative data, this chapter has the following aims.

3.2 Aims

- To describe the incidence of surgical site infection in hip fracture cases in administrative data in isolation and in combination

- To explore the ability of different sets of administrative data to meaningfully capture the problem of surgical site infection
- To describe the rate of surgical site infection over the time of the cohort in both primary and secondary care datasets.
- To describe the length of stay for cases of SSI compared to unaffected SSI hip fracture cases
- To explore risk factors for surgical site infection

3.3 Method

3.3.1 Study Design

There are two sources of administration under consideration in this chapter.

- Clinical Practice Research Datalink (CPRD) GOLD.
- Hospital Episode Statistics (HES).

Each is described below. To address the chapter specific aims, each dataset was examined in isolation and combination according to the question. This is described throughout. The two principle sources of administrative data under study were selected based on understanding of hip fracture care pathways. Firstly most of the acute care takes place in secondary care institutions (hospitals), therefore HES data should provide both diagnostic and procedural data about the acute care episode. It should also provide information about readmission, which is particularly important in considering complications like SSI. The CPRD data were also used as this provides a rich source of baseline data, particularly around previous medical diagnoses and prescriptions of antibiotics. The CPRD were also an important source of follow up data, as routinely patients with hip fracture are not seen back in secondary care. Therefore it is feasible that

complication data may lie entirely on the primary care record. Other administrative data such as the Office for National Statistics (ONS) data were not considered as they usually inform mortality which was not directly under study here.

3.3.2 Data Source

3.3.2.1 Clinical Practice Research Datalink (CPRD) GOLD.

The CPRD is a research data source that provides the primary care records for 7% of general practices across the United Kingdom. These practices are selected for being representative of patients across the country. Each patient in the participating GP practice has their primary care record captured on the electronic records within the practice. The diagnoses and treatments-largely prescriptions-are captured within CPRD GOLD. The diagnoses are recorded using the Read code library.

It is important to note that diagnoses and treatments made in hospital care can still be entered into the CPRD data, as a result of communication (e.g. discharge summaries) between secondary and primary care. Prescription data are recorded using the British National Formulary (BNF) as a code library (142).

3.3.2.2 Hospital Episode Statistics (HES)

The Hospital Episode Statistics (HES) are derived from episodes of care in secondary care in England only for this data set. This includes admissions, attendances in accident and emergency and outpatient visits. Codes may represent diagnoses or procedures. Each of which are represented in different code libraries. Diagnoses are captured using the International Classification for

Diseases (ICD) coding system. Procedures are recorded using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4th edition). Each diagnosis or procedure can be assigned a date.

3.3.3 Data Under Study

The source data for this work was a dataset of hip fracture patients (cases), and controls. The cases were defined in CPRD. A cohort of patients (cases) were identified from CPRD GOLD practices based on a first ever record of "hip fracture" occurring between 1st January 1999 and 9th October 2013. Senior clinicians identified the diagnostic and procedural codes used to define this hip fracture cohort. In addition, the patients required at least one years up-to-standard (UTS) registration in CPRD GOLD prior to their hip fracture. Age- and sex- matched controls were identified by the CPRD in a 2:1 ratio from patients registered with practices from 1st January 1996 onwards and with at least one preceding years UTS registration.

A subset of the cases identified in CPRD had data from their hip fracture episode in hospital captured in HES as well and the record linked. Both the broader 'cases' from CPRD and the subset linked to HES were interrogated to understand the incidence of surgical site infection in hip fracture.

The reasons for difference in the two datasets relate to the availability of HES data outside of England, and a subset of the practices which contribute to the CPRD GOLD data are not able to link to HES, even in England. In addition, not all of the patients who were 'available' to HES had a record of their hip fracture

within the HES data. Therefore, when the datasets were used in combination, only the CPRD cases with confirmed HES hip fracture episode data were used. Cleaning and validation of the data was undertaken prior to the candidate receiving the data by AD. This process involved examination of data fields in turn and examining for 'improbable values' including extremes of age, body mass index and Charlson comorbidity index.

3.3.4 Capturing Data

In order to search the data under study for diagnoses of interest, code lists using the respective code dictionaries were used. These lists were either already in existence from previous work, or generated de novo, to answer specific questions for this study.

When new lists were generated, largely around the diagnosis and treatment of infection, this was done by two clinicians working independently (DM and JM). Lists were compared and disagreement resolved by discussion with arbitration by a third senior clinical member if necessary (MC).

3.3.4.1 Code Lists Of Note-Surgical Site Infection

Full discussion of each code list will not be presented here, however the diagnosis of SSI is the core remit of this study and therefore this will be explained in detail.

For both ICD and Read, two groups of code lists were generated-tables 3-1 & 3-2. A specific 'SSI' code list and a 'broad wound problem' code list. Both code dictionaries contain codes for wound related issues like dehiscence and haematoma. The analysis below explores the use of a narrow definition of SSI as

well as a broader inclusive list. The two types of code list can be combined to give a 'worst case scenario'. The code lists were generated as described above, in addition the ICD list was informed by previously published studies used in HES data(143).

3.3.4.1.1 CPRD-Read.

Table 3-1 Surgical Site Infection And Wound Problem Codes In Read

Surgical Site Infection	Wound Problem
Postoperative wound infection-superficial SP25700	Post-surgical wound care Z174O00
Postoperative wound infection-deep SP25600	Delayed healing surgical wound SP23z11
Postoperative wound infection, unspecified SP25500	Post-operative wound care 8C1M.00
Postoperative stitch abscess SP25000	Operation wound dehiscence SP23000
Postoperative wound abscess SP25100	Postoperative wound breakdown SP253011
Postoperative wound sinus SP28.00	Operation wound disruption SP23.00
ASEPSIS score for wound infection ZR1V.00	Operation wound disruption NOS SP23z00
MRSA infection of postoperative wound SP25800	

Outline of codes used to define SSI and wound problem using the Read code library in CPRD dataset

3.3.4.1.2 HES-ICD

Table 3-2 Codes Used To Define SSI In HES Database

Surgical Site Infection	Wound Problem
Infection following a procedure T81.4	Disruption of operation wound, not elsewhere classified T81.30
Infection and inflammatory reaction due to internal joint prosthesis T84.59	Other complications of internal orthopaedic prosthetic devices, implants and grafts T84.89
Infection and inflammatory reaction due to other internal fixation device [any site] T84.69	
Infection and inflammatory reaction due to other internal orthopaedic prosthetic devices, implants and grafts T84.60	
Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts-leg T84.62	

Outline of codes used to define SSI cases in HES using the ICD 9 code library

3.3.5 Applying Code Lists To Data Set

The decision to limit the coding by time was taken, as the spread of times attributed to the diagnostic codes after index admission was very broad. In addition the codes are not specific for wound infection after hip fracture. The Read codes identified describe surgical site infection at any site. Therefore in any given dataset these codes may appear for a surgical site infection after any type of surgery. A limit of 120 days was placed to increase confidence that these diagnoses were related to the hip fracture treatment in CPRD. One hundred and twenty days was chosen as this is the estimated typical time to recovery for a hip fracture, and the stage at which one might expect patients to undergo further surgery for other medical conditions(9). Similarly in the HES dataset, a limit of 365 days was applied. This extended period was used as the ICD codes in HES were more specific to implant related infection. The Centre for Disease Control

definition of surgical site infection, suggests that diagnosis can be made up to 12 months after surgery where an implant is involved(144)

Where the combined datasets were used to establish the rate of SSI across the two cohorts, the cases were defined as being all SSI in HES plus the SSI in CPRD where those CPRD patients had the possibility of returning HES data i.e. the total number of hip fracture cases defined in HES acted as the denominator for this cohort.

3.3.6 Statistical Analysis

All analysis was undertaken in STATA(90). Summary descriptive statistics were used as the principal technique to explore the rate and consistency of surgical infection diagnosis. Baseline features of patients were also analysed in this manner.

Proportions are presented with their corresponding expressions of uncertainty as 95% confidence intervals.

Where the results of different means of diagnosis were explored, Venn diagrams were created to represent their relationship to each other. Kernel density plots were constructed to express the time after index when diagnosis of SSI was recorded in both HES and CPRD.

In order to look at risk factors for infection, survival analysis was used to model time to infection as the outcome, and a Cox Proportional Hazards Regression model built. The outcome of infection was defined in CPRD and HES datasets. In consideration of model overfitting, the heuristic of '10 outcomes per covariate' was used when considering the number of parameters (predictive variables) available to include in the model(145, 146). The covariates of interest were

based on baseline patient and co-morbidity factors. Literature and the biological understanding of the system under study inform the covariates selective as potential predictive variables.

Entry into study: Index date for the CPRD GOLD cohort i.e. date of primary hip fracture

Exit: End of the follow up of the cohort

Outcome: SSI coded in CPRD within 120 days of index CPRD coded infection was used because the cases were defined in CPRD. The CPRD SSI were supplemented with those identified in HES within 365 days as well to give the greatest number of outcomes possible for the model.

Within the Cox model, there was censoring for death making the assumption that death is non-informative of infection outcome. If death were to be informative then the competing risk of death needs to be accounted for. In hip fracture, mortality is high therefore death before coding for infection was possible.

Covariates: A number of recognised covariates was selected. Either they were binary or converted to categorical e.g. age.

Reference Categories

Within the model each covariate has a reference category which is assigned a baseline hazard of 1. The model then assigns a hazard to the other covariates in its category. For this model a the largest number of observations for the relevant category was taken as the baseline hazard. For example in the age category, the largest number of patients were in the 80-90 category therefore this was the reference category.

Test of proportional hazards

The underlying critical assumption for using a Cox regression model is that the hazards are proportional. This means that the ratio of the hazard between variables is constant over time. For this model, the follow up period was only 365 days, and the covariates were unlikely to change during this relatively short period of follow up, hence the likelihood of the assumption being violated was low. Nonetheless this assumption of proportional hazards was tested using Shoenfelds residuals.

Censoring All cases were censored at 365 days

3.4 Results

3.4.1 Data Cut

Table 3-3 Data Extracted From CPRD And HES Databases

	CPRD Patients	With any HES data	With hip fx HES data	Without hip fx HES data
Case	13,920	7,981	6,239**	1,742
Control	26,729	13,345	367*	13,384
Totals	40,649	21,326	6,606	14,720

*Overview of numbers of cases and controls with numbers in each dataset. *These patients did have an ICD-10 code for hip fracture, but no record in CPRD. **These cases had evidence of hip fracture in both HES and CPRD, therefore this was the population used for combined analysis using data from both populations where outcome of SSI was defined in HES and CPRD and the cases were defined in both.*

The hip fracture cohort was defined in CPRD of which there were 13,974 cases. As outlined in the methods not all of these cases had HES data due to variation in linkage and usage of HES within the UK. The HES cases, totalling 6,239, were

analysed individually and combined with their relevant CPRD data where needed and described.

3.4.2 Baseline Demographics: Hip Fracture Cases

Table 3-4 Hip Fracture Cases: Baseline CPRD

	Female (N=10 461)	Male (n=3459)
Mean Age (SD)	81.3 (10.2)	76.7 (13.7)
Gender proportion (%)	75.2	24.9
BMI (SD)	24.2 (4.8)	24.9 (4.2)
Charlson Comorbidity Index (%of total)		
0 (%)	*5,635 (53.9)*	*1,730 (50.0)*
1 (%)	*3,306 (31.6)*	*1,066 (30.8)*
2 (%)	*1,042 (10.0)*	*411 (11.9)*
3 (%)	*478 (4.6)*	*252 (7.3)*

Summary data of hip fracture cases as defined in CPRD only.

The demographic features of the CPRD cases are as would be expected in a cohort of hip fracture cases in a high-income country. There is a preponderance of females, who are on average older than their male counterparts. There is a spread of co-morbidities, as measured by the Charlson index(147). This is derived from the primary care record. A higher score indicates more co-morbidities. The age and gender balance in this cohort are similar to those in the National Hip Fracture Database audit programme (7).

Table 3-5 Hip Fracture Cases: Baseline HES & CPRD

	Female (N=4738)	Male (n= 1501)
Mean Age (SD)	82 (9.58)	78 (12.24)
Gender proportion (%)	75.94	24.06
BMI (SD)	24 (4.67)	25 (4.11)

Summary data of hip fracture cases as defined in HES and CPRD only.

If we examine the demographics of the subset of patients for who there is a linked HES record. The same broad conclusions can be drawn. Specifically that there are more women than men and that the women are on average older. No co-morbidity index is presented for HES as for the purposes of this analysis the CCI is derived from the primary care (CPRD) record.

The basic demographic features of the hip fracture patients in this cohort appear to be similar to the nationally described datasets and literature (4) (148, 149). We can therefore be confident that this cohort is broadly representative of hip fracture patients.

3.4.3 Baseline Demographics: Hip Fracture Infection Cases

Table 3-6 Baseline CPRD Infection Cases (< 120 Days)

	Female (N=119)	Male (n=33)
Age (Mean, SD)	79.0(10.66)	73.0 (13.87)
Gender proportion (%)	78.3	21.7
BMI (Mean, SD)	25.4 (5.73)	25.4 (4.549)
Charlson Comorbidity Index		
0 (%)	*71 (54.6)*	*22 (45.9)*
1 (%)	*41 (31.5)*	*14 (31.1)*
2 (%)	*9 (6.9)*	*4 (8.9)*
3 (%)	*9 (6.9)*	*5 (11.1)*

Summary data of hip fracture cases with a code for Surgical Site Infection as defined in CPRD only.

A total of 152 cases had a code for SSI present up to 120 days after their index admission in CPRD (table 3-6).

The infected population had a slightly higher preponderance of females and were on average younger than the broader CPRD cohort. There were a higher proportion of patients with a Charlson index of 3 for both males and females compared to the cases. Although the absolute differences are small. This relationship is explored in the risk factors for infection analysis further on.

Table 3-7 Baseline Characteristic HES Infections No Time Limit

	Female (N=69)	Male (n= 22)
Mean Age (SD)	79.13 (10.16)	73.55 (13.15)
Gender proportion (%)	75.82	24.18
BMI (SD)	27.04 (6.20)	25.15 (4.18)

Summary of baseline characteristics in cases of SSI identified in HES only, with no time limit on timing of diagnosis

Table 3-8 Baseline Characteristic HES Infections Limited To 365 Days After Index

	Female (N=37)	Male (n= 11)
Mean Age (SD)	79 (9.49)	74 (15.75)
Gender proportion (%)	77	23
BMI (SD)	28.37 (7.21)	24.96 (4.96)

Summary of baseline characteristics in cases of SSI identified in HES only, with 365 day time limit on timing of diagnosis

Where the HES diagnostic codes were applied to the linked population, a total of 91 cases were identified. Similar to the CPRD diagnoses, the time of diagnosis was sometimes years after the index date. However the list of codes in ICD is much more specific for a periprosthetic infection. Therefore for the analyses both time limited and non limited diagnoses were used. Baseline features of each population are presented here. Although of the 91 diagnosed cases of SSI in HES, only 48 were dated within 365 days of index event. These two cohorts are described in tables 3-7 & 3-8.

3.4.4 Time To Diagnosis Wound Infection

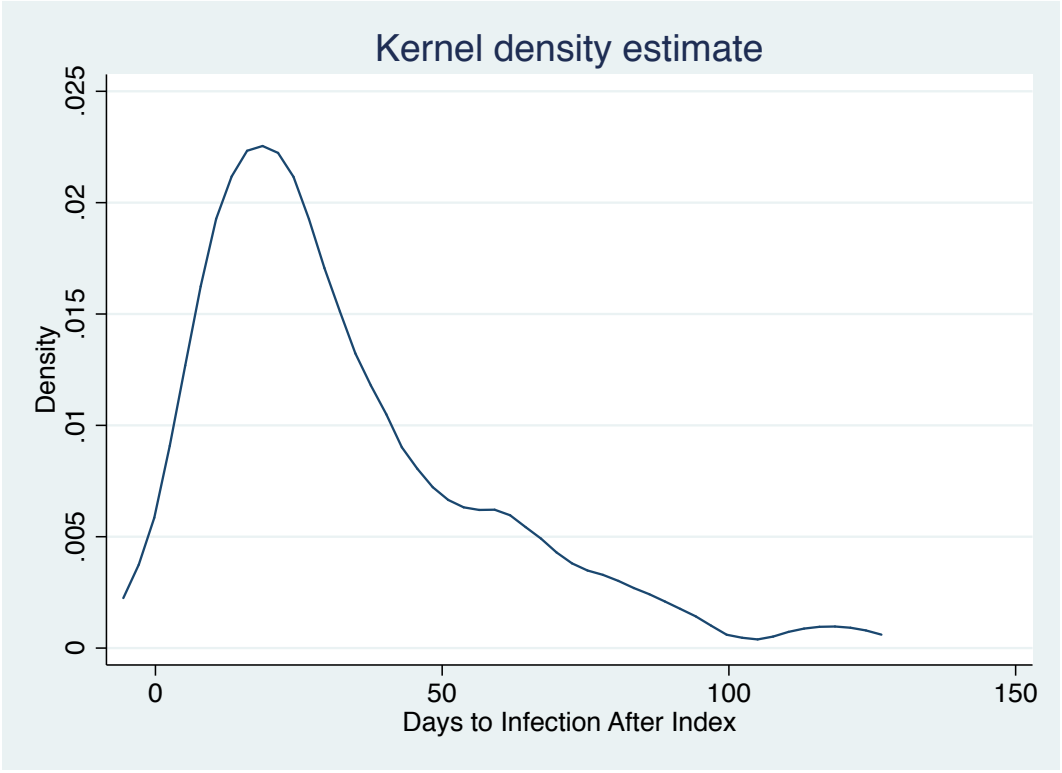
Table 3-9 Summary Of Time To Diagnosis Of Wound Infection Codes in each dataset

Time (days)	CPRD	HES
Median (Mean)	**119 (554.7)**	**186 (439.6)**
Total	**301**	**85***

*Median and mean number of days SSI codes were recorded after index date for each dataset. Total number of cases with SSI diagnostic codes in each dataset *6 cases removed as time to infection was **prior** to index date.*

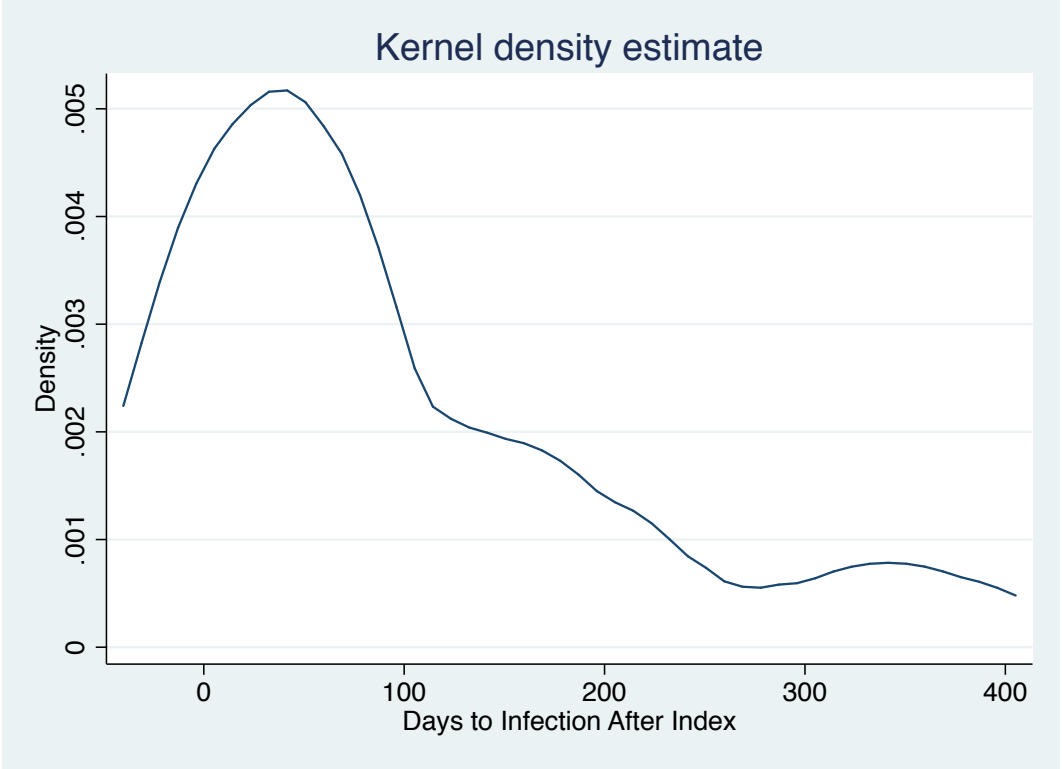
Table 3-9 outlines the days after index admission where the wound infection was coded. There are some extreme outliers of up to 5,000 days after index admission. Figures 3-1 & 3-2 outline the spread of cases by time in a Kernel density plot. This plot highlights that the majority of infections are diagnosed and recorded as such in the acute period.

Figure 3-1 Summary of Time To Diagnosis For CPRD Surgical Site Infections: Kernel Density Plot



Kernel density plot, demonstrating the frequency distribution of each time point after index that the SSI diagnostic codes were given for the CPRD dataset.

Figure 3-2 Summary of Time To Diagnosis For HES Surgical Site Infections: Kernel Density Plot



Kernel density plot, demonstrating the frequency distribution of each time point after index that the SSI diagnostic codes were given for the HES dataset.

3.4.5 Infection in HES and CPRD

Table 3-10 identifies a total number of surgical infections from each parent cohort, along with the respective numbers from each data set. Each proportion is presented with 95% confidence intervals. Cases of SSI were found in both CPRD and HES. These were accounted for in the total estimate. Both cases and outcomes (SSI) could be defined in CPRD and HES. Of the total number of hip fracture cases in CPRD, 152 had a code in CPRD for SSI within 120 days of admission. Of the total number of hip fracture cases in HES, 48 had SSI coded for in HES as well within 365 days.

These could then be combined in two ways: Where the HES identified SSI outcomes were added to the CPRD SSI outcomes for all the CPRD defined hip fractures. Alternatively the CPRD SSI outcomes could be added to the HES SSI outcomes for the HES defined hip fractures, provided the cases were still originally defined in HES. In each instance, overlap was removed and the original time constraint applied.

Table 3-10 Summary Of The Number Of Cases Of SSI In Each Cohort

	Infected cases	Total number of hip fracture cases	Percentage rate	Percentage 95% CI	Per 1000 case rate
CPRD	152	13,920	1.1%	0.9%-1.3%	11
HES	48	6,239	0.8 %	0.6%-1.1%	8
Total (CPRD)*	192	13,920	1.4%	1.2%-1.6%	14
Total (HES)**	104	6,239	1.7%	1.4%-2.0%	17

Summary of numbers of SSI codes in each dataset. SSI outcome captured in either HES or CPRD with CPRD defining case. . ** HES hip fracture cases that have SSI outcome captured in either HES or CPRD. Cases of overlap have been removed from each total.*

3.4.6 Wound Problems in CPRD and HES.

An additional set of codes was used to capture associated wound problems that were not specific for infection-see tables 3-1 & 3-2. The study dataset was then interrogated for these codes to consider a 'worst care scenario'.

In isolation these problems do not amount to a surgical infection, however they are related. In some circumstances they may progress to surgical infection. Indeed some wound problems are subsidiary parts of some surgical infection diagnostic criteria(150) e.g. dehiscence.

Firstly, each wound problem code list was compared to the relevant infection code list, and overlaps explored. In each of these analyses, time to problem was limited to 120 days after index date on the basis that they are not hip or hip fracture specific.

Only 4 cases of wound problem were found in the CPRD hip fracture cohort within 120 days of surgery, and only 1 of these cases also had a code for wound infection.

In HES there were 14 cases of patients with wound problem codes within 120 days of index. Of these 14 cases. 2 also had a code for infection.

A total of 15 new cases were added to the list of 104 cases of infection identified in either CPRD or HES to give a 'worst-case scenario'.

Table 3-11 Summary Of Possible Number Of Wound Problems/Outcomes In HES Defined Cohort

	'Infected' cases	Non-Infected cases	Percentage rate	Percentage 95% CI	Per 1000 case rate
CPRD+ HES combined*	119	6239	1.9%	1.6%-2.3%	19

Summary of cases with either SSI codes or wound problem codes. All cases and codes are defined in HES.

3.4.7 Length of Stay

Table 3-12 Outline Of Length Of Stay For Cases Of SSI And Non Infected Cases

Parameter (n)	Median (mean)	Interquartile range
CPRD&HES SSI (104)	11 (17.6)	9-18
No infection (6103)	16 (23.6)	10-28

Length of stay in days. Cases of hip fracture and SSI were defined in HES AND CPRD.

Having identified the surgical site infection cases in each data set, data around length of stay were explored. These findings are summarised in table 3-12. Data in this cohort show that those diagnosed with a surgical infection, have a paradoxically shorter than average stay. Patients who died as inpatients were excluded from this analysis.

3.4.8 Rate of Infection Over Time

The cohort presented here represents the years 1999 to 2013. The numbers of infected cases identified across the data were calculated against the index year to explore the stability in time.

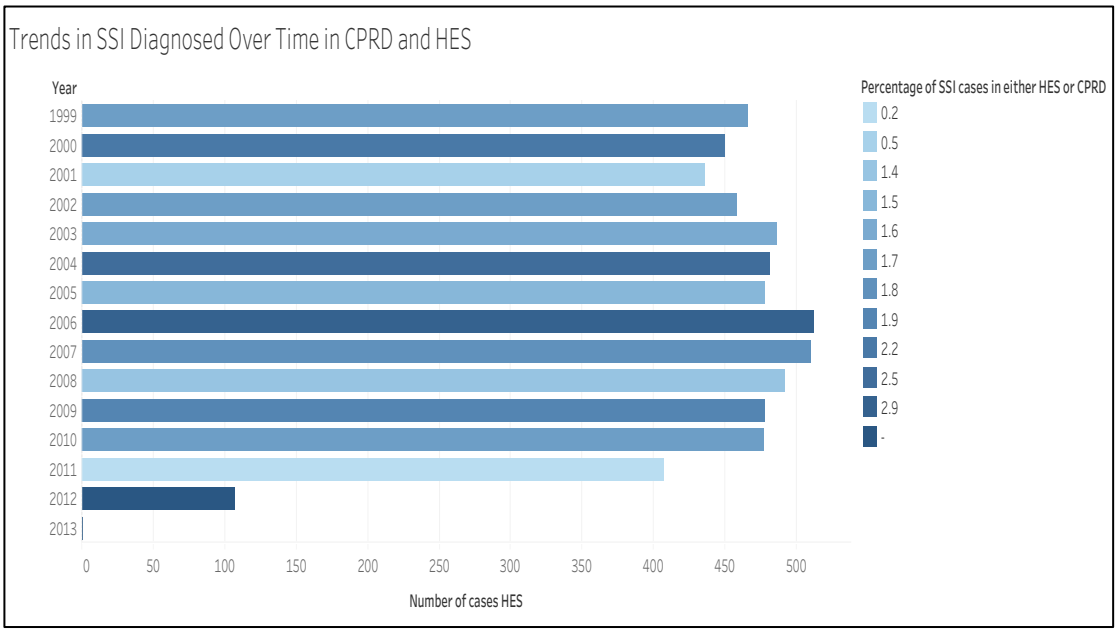
Table 3-13 Summary Of SSI Per Year In Each Of CPRD And HES As Well As In Combination

Year	Number of cases CPRD	Number of Infections (t limit 120 days-CPRD)	Number of cases HES	Number of Infections (t limit 365 days-HES)*	Number of Infections (total)**	Percentage total***
1999	1066	8 (0.8)	466	6 (1.3)	8	1.7
2000	1018	14 (1.4)	450	3 (0.7)	10	2.2
2001	981	7 (0.7)	436	1 (0.2)	2	0.5
2002	1029	12 (1.2)	458	4 (0.9)	8	1.7
2003	1048	11 (1.0)	486	4 (0.8)	8	1.6
2004	989	19 (1.9)	481	3 (0.6)	12	2.5
2005	943	11 (1.2)	478	3 (0.6)	7	1.5
2006	1043	14 (1.3)	512	7 (1.4)	15	2.9
2007	992	7 (0.7)	510	7 (1.4)	9	1.8
2008	962	11 (1.1)	492	4 (0.8)	7	1.4
2009	886	10 (1.1)	478	3 (0.6)	9	1.9
2010	893	11 (1.2)	477	2 (0.4)	8	1.7
2011	813	6 (0.7)	407	1 (0.2)	1	0.2
2012	776	8 (1.0)	107	0(-)	0	-
2013	490	3 (0.6)	1	0 (-)	0	-
Total	**13920**	**152 (1.1)**	**6239**	**48 (0.7)**	**104**	1.7

*Table outlining the stability of rate of infection by index year. CPRD infections were limited to those diagnosed within 120 days, HES infections were limited to those diagnosed within 365 days. *The HES cases of SSI have their overlapping CPRD case included. **Number of total infections defines its hip fracture cases in HES AND CPRD and defines its outcome (SSI) in EITHER CPRD or HES. *** 'Percentage total' is calculated using the number of HES cases of hip fracture as denominator and number of total infections as numerator.*

The number of infections diagnosed per year, is relatively stable. There appear to be consistent numbers of cases and infections across both the HES and CPRD data sources.

Figure 3-2 Trends In SSI Over Time (1999-2013)



Trends in time, cases of hip fracture were identified in HES and SSI identified in either CPRD or HES.

3.4.9 Risk Factors For Infection

One of the significant benefits of CPRD GOLD is the access to high quality data about the patients' medical background. This is particularly valuable for exploring risk factors for infection. The CPRD data were used to create a Cox regression model(151). The outcome of interest was time to surgical site infection. The outcome was defined in CPRD with the addition of SSI coded in HES, The parent cohort was the CPRD cohort. This was chosen, as the covariates of interest were primarily co-morbidity and lifestyle factors that are well coded

in primary care. This was also done to increase the number of outcomes available to the model.

Cox proportional hazards assumption was assessed using Schoenfeld's residuals. Each covariate was tested individually as well as a 'global test'. The global test gave a p value of 0.51 i.e. statistical significance was not reached when testing the hypothesis that the hazards were not proportional. A full breakdown of each covariate is presented in appendix 9.

Table 3-14 Multivariate Cox Regression model

Characteristic	Hazard Ratio (95% CI)	P value
Charlson Comorbidity Index		
0	1	-
1	1.18(0.72-1.92)	0.512
2	1.09(0.51-2.35)	0.819
3	**2.37 (1.14-4.93)**	**0.021***
Diagnosis of chest or urine infection in 90 days prior to index admission		
Yes	1.37 (0.60-3.19)	0.454
No	1	-
Gender		
Male	0.88 (0.51-1.41)	0.525
Female	1	-
Antibiotics prior to index admission		
Yes	1.22(0.79-1.90)	0.361
No	1	-
Age		
50-60	0.70 (0.21-2.30)	0.56
60-70	1.44 (0.77-2.69)	0.26
70-80	1.16 (0.72-1.86)	0.55
80-90	1	-
Smoking		
Yes	1.62 (0.90-2.92)	0.11
Former	0.94 (0.56-1.57)	0.80
No	1	-
Deprivation Index		
LEAST	1	-
LESS	0.65(0.34-1.25)	0.19
MID	1.13 (0.63-2.05)	0.68
MORE	0.80 (0.42-1.52)	0.49
MOST	0.94(0.47-1.85)	0.85
Body Mass Index		
<18.5 underweight	1.12 (0.39-3.20)	0.83
18.5-24.9 normal	1	-
25-29.9 overweight	1.24 (0.77-2.00)	0.86
30-34.9 Class 1 obesity	1.00 (0.50-2.00)	1.00
35-39.9 Class 2 obesity	1.42 (0.50-4.05)	0.51
> 40.0 Class 3 obesity	2.12 (0.50-9.01)	0.31

Cox regression model reporting hazard of SSI in hip fracture cases defined in CPRD. Cases of infection identified in both CPRD and HES. Covariates with their associated hazard ratios. Statistically significant covariates are in bold

Table 3-14 demonstrates the hazard ratios of widely assessed covariates that may affect risk of SSI. Most recognised risk factors such as obesity and smoking failed to demonstrate significantly higher risk in this model. All hazard ratios were associated with broad 95% confidence intervals. Only Charlson comorbidity index of 3 demonstrated statistical significance. This is congruent with the noted baseline features of the infected population table 3-6.

3.5 Discussion

3.5.1 Summary of Findings

Given the difficulties of understanding SSI from the literature, administrative data would seem to represent an important opportunity to look for events in the vast numbers of patients treated for hip fracture.

However as seen here, administrative data have significant limitations.

In isolation the CPRD GOLD and HES data showed a surgical infection rates of 1.10% (95% CI 0.92-1.28%) and 0.85% (95%CI 0.63%-1.10%) respectively. In combination, the rate seen was between 1.4% (95% 1.2%-1.6%) and 1.7% (95%CI 1.20%-1.40%) depending on whether the hip fracture cases were defined in CPRD or HES respectively. The patients with surgical infection were typically younger and had more co-morbidities as recorded using the Charlson index.

When the diagnostic codes were relaxed to include possible infections, the combined rate increased to 1.9 % (95% CI 1.6%-2.3%). Risk factor for SSI noted in the Cox model was a Charlson comorbidity index of 3. The relatively low number of outcomes limited the utility of this modelling.

The rates of infection seen in these two related cohorts are plausible, but possibly underestimate the truth. Studies considering the accuracy of hospital episode data have reported a median accuracy of 83.2% for diagnosis using ICD10 across a range of diseases(152). However it is worth noting that the majority of studies concern 'primary' diagnoses and not complications like SSI. There was also a significant spread of accuracy (IQR 67.3–92.1%). The mechanism for which data is completed and can flow through the two cohorts gives us insight into the limitations that may cause the underestimation. Specifically, diagnoses made in HES are returned to the primary care provider, where they 'should' be additionally recorded. However here we see a poor relationship between them. Only 11 patients had a diagnosis recorded in both datasets. This suggests relatively poor 'reciprocal coding'. Similarly usual clinical care upon diagnosis of SSI in hip fracture patients in primary care is to return the patient back to secondary care where formal diagnosis can be confirmed, and treatment commenced. Again the poor overlap suggests either that this process is not taking place or that it is not being captured adequately at the hospital end. Alternatively, it is possible that the cases of SSI are managed in the outpatient setting where coding accurately is more challenging, as coders are required to extract data from unstructured clinical notes.

The existence of a group of patients being diagnosed exclusively in primary care is not confirmed by the findings here. However, it is an interesting possibility. This would raise an issue of an unrecognised burden within primary care, as well as the consideration of how effective such management may be for the patients in question.

This finding also raises a consideration for surveillance practice which focuses currently on inpatient diagnoses and readmissions (40).

Considering these limitations, the rate of 1.40%-1.70% is well within the realms of plausibility when considered in the context of the literature and other data. Other studies that have explored the effectiveness of administrative data for identifying surgical site infection have principally focused on hospital data-specifically HES for England and Wales. Jen and colleagues compared HES to the Health Protection Agency (HPA-now known as PHE(40)) data in primary hip and knee and hemiarthroplasty surgery. Interestingly, this study found a surgical site infection rate of 3.3% in their HES cases. This study should have significant overlap with the data contained in this work, as their dates were 1996-2006, compared to 1999-2013 for this work. The discrepancy between cases detected in HES was disconcerting, and so the Jen and colleagues were contacted. Their study only used HES hemiarthroplasty cases and did not limit the coding of SSI by time. They had additional linkage that accounted for transfer between different hospitals. Of these reasons, the exclusive inclusion of hemiarthroplasty and no time limit on case definition would seem like the most likely explanation for the difference in SSI rate. The synthesis in chapter 2 identified hemiarthroplasty operations as having the higher event rate across the different types of operation between the main types of surgical treatment. This has been observed in other studies on this specific procedure(32)

The systematic review chapter has already discussed the study by Jettoo and colleagues(102). This piece of work looked only at HES data in patients with intracapsular hip fractures treated with sliding hip screw and cannulated screws. Their rates of SSI were comparable to the rate seen in the HES data in this study

(0.41%-Jettoo vs. 0.85% Chapter 3). Looking beyond the UK at administrative data is more challenging; particularly when dealing with relatively low frequency events as is seen in SSI. The process of data capture may just as readily explain the differences between systems as by true variation in event rate. The tendency to underestimate SSI identified in this chapter, has been seen in other studies of administrative data in hip fracture(141).

The data on length of stay for patients showed a paradoxically shorter length of stay for the patients with a diagnosis of infection. This is a particularly unexpected finding given the literature surrounding the effect of infection on this parameter(153, 154).

Given the treatment requirements for surgical infection, it seems highly improbable that there is a true reduction in length of stay for those with an infection. One must consider alternative explanations as being more likely. In this instance, inadequate SSI case capture would seem the most probable explanation. There may be a systematic bias in how particularly severe infections, or those requiring extensive treatment fail to additionally be recorded as surgical infections. This would mean that those who are coded as having this problem potentially only represent the patients who were discharged successfully after antibiotic only treatment, or were well enough to continue treatment as outpatients.

Surgical infection is not the only determinant of extended inpatient stay and hence within the non-infection coded cohort, there are significant numbers of patients with other reasons for extended stay such as medical complication and increased care requirements(155).

The use of two related data sets that may inform one another, allows some valuable insights into patterns of behaviour surrounding diagnosis and treatment of infection.

Taken in isolation each dataset identifies a relatively low rate of infection. In particular a rate of 0.85% in the HES linked cases is substantially fewer than would be expected. At an institutional level, there are compelling reasons to record the presence of complications such as surgical infection accurately. Not least due to the funding attracted by further intervention. However 'payment by results' only was introduced in 2004, 5 years in to this study. The effect of this administrative incentive in these two data sources is unknown for this outcome. The data under study here demonstrate a stable event rate over time. This would suggest that this incentive had little observable effect on SSI. In addition surgical site infection in hip fracture is a component of the mandatory surveillance in orthopaedics (40, 156). It remains however a 'second order' diagnosis. The limitations of administrative datasets as a source of data for determining prevalence of surgical complications more broadly is increasingly recognised(141).

The incorporation of codes suggestive of wound problems as a surrogate for a surgical infection increased the estimate to 1.9%. However the corresponding loss of confidence in accuracy of diagnosis would undermine this as a strategy for definitive work in the area. It does serve as a possible 'upper bound' of confidence as to what the detectable rate of infection in these two cohorts may be.

To my knowledge, this is the first study to use CPRD data to look at SSI. Therefore limited comparison can be made in this arm. However, other studies

have compared the utility of HES and CPRD in identifying cancers at a national level (157). Here too, CPRD was found to have fewer diagnoses compared to HES and the appropriate cancer registries. Their recommendation was to identify the cases from alternative sources to CPRD to avoid bias. Whilst clearly there are important differences in the respective disease processes, treatment pathways and patient demographics, the limitations in CPRD for diagnosis are not without precedent.

The cohort of patients examined here was taken from 1999 to 2013; although in 2013 very few cases of hip fracture were reported in HES. In percentage terms the rate of infection varied from 0.2% to 2.9% when hip fracture cases were defined in HES and SSI was taken from either CPRD or HES. In absolute terms this represents a minimum number of 1 case of SSI and 15 cases of SSI. With numbers this small, it is difficult to draw definitive conclusions about the behaviour of SSI diagnosis over time from these data. However it is of interest that in 2004 there was a change to the financial reward scheme within the NHS for all major medical and surgical conditions(158). In response to this, many trusts devoted increased resources to their coding activity. The downstream effect of this is unknown for SSI, however it would be plausible that any general effort to increase coding accuracy would improve the numbers of cases of SSI captured. However this trend is not observed in the data under consideration in this chapter. A specific payment for performance scheme for hip fracture was introduced to England and Wales in 2010. The so-called 'Best Practice Tariff' focused on six specific metrics for hip fracture care as captured within the NHFD(159). The first study to look at the effectiveness of these hip fracture

specific targets demonstrate a benefit in terms of mortality(159), but no other studies offer insight into any possible effect this process may have had on the datasets under study for this chapter. Further limitations in understanding this process relate to the very short period of overlap between the incentive scheme and the data under study-years 2010-2013.

One of the aspirations for the CPRD data set in particular was to more deeply interrogate the data for the patient risk factors for developing infection. The model selected was a Cox regression model. This form of survival analysis allows multiple covariates to be considered and assessed, and assesses the time to event. In this case SSI. The critical assumption of proportional hazards was tested and shown not to be violated. If this were not the case the alternative would have been a flexible parametric survival model as this requires no such assumption(160).

The Cox model has precedent in the orthopaedic literature when assessing risk factors for surgical site infection(161, 162).

Alternative models would include multiple logistic regression or Kaplan Meir survival.

The Cox model was preferred to these alternatives as both logistic regression and Kaplan Meir have significant limitations. Specifically, multiple logistic regression is unable to incorporate time at risk. This leaves patients who are lost to follow up or death before the end of the study lost to the analysis. The Cox model is able to deal with patients who are under study but do not have the outcome by censoring. Kaplan Meir plots are a similar survival type analysis to Cox regression, however they too are limited as they are unable to manage

multiple covariates. In a condition like SSI, consideration of multiple variables is highly important because of the many factors that interact in developing SSI.

Final considerations for the modelling of the data under study relate to competing risk. This describes whether an alternative outcome could prevent the outcome of interest from taking place. In this study the outcomes of interest is surgical site infection. The other outcome that could bear on SSI as an outcome is patient death. However death is not in and of itself informative of SSI. A patient could die without SSI, with SSI but not because of SSI but also they could die of sepsis secondary to SSI. Analysis taking this into account may be undertaken using Fine and Grey regression. This is an important consideration in any analysis of hip fracture data as mortality is significant. However no clear consensus exists on the way to deal with these uncertainties.

The principle limitation for the model used here is the relatively low number of outcomes. Our multivariate model identified high comorbidity index as a predictive covariate for SSI. The very broad 95% confidence intervals undermine the precision of number attributed to this risk. However this is a well-recognised risk for SSI(163). Other covariates such as social deprivation, smoking and obesity failed to demonstrate statistical significance. The most likely explanation is again the low number of outcomes available to the model, as there are a number of mutually supportive studies that identify these parameters as being risk factors for surgical infection(32, 163, 164) (165, 166).

Other exploratory covariates such as pre-index diagnosis of common infections and antibiotic treatment were also found to be non-significant as risk factors here. The final other possible consideration here is the reference hazard used for each covariate. The model built here used the subcategory with the most

observations as the reference hazard. Alternatives could have been used and included as a sensitivity analysis, however this would not have improved the model, and therefore was not undertaken.

3.6 Conclusions

Administrative data present both opportunity and challenge in seeking to understand SSI. The process of understanding a 'rare' event lends itself well to the vast numbers of patients that can be studied using such datasets. However, the complicated pathways, competing priorities and limitations of coding appear to compromise this process, particularly when used in isolation. Additional trends to early discharge for surgical patients in general and hip fracture patients in particular will further shift emphasis to case capture outside of hospital. The use of combined datasets as seen here offer an overview, albeit an imperfect one, of both primary and secondary care. Studies from other healthcare settings raise similar concerns about using administrative data to understand healthcare associated infections like SSI(167, 168).

The implications for clinical practice are that closer combined working with primary care givers with regards to wound care and concern is critical. Patients and their carers also need to be empowered to engage with secondary care as well as primary care if there are concerns about surgical site infection.

For researchers, policy makers and clinicians, UK administrative data would seem to be inadequate in isolation to understand burden of disease, variation between regions/centres and cost implications for surgical site infection.

4 Exploration Of Treatment For Surgical Site Infection In Administrative Data. A Study Of Primary And Secondary Care Datasets In Isolation And Combination.

Declarations

The 'Big Data' group within NDORMS, Oxford University, hold the data included in this study. The data were extracted by Dr Antonella Delmestri-database manager. Some code lists were generated in tandem with Dr D Metcalfe, and this is outlined in the manuscript. The candidate undertook all analysis.

Ethics Approval was granted under an ISAC amendment for the use of these data.

4.1 Introduction

Having considered diagnosis of SSI in administrative data, a complementary strand is to look at the use of treatment as a surrogate. As seen in chapter 2, there are many studies that take this approach. The two principle arms of treatment are antibiotics and surgery, which may be used in combination or less commonly in isolation.

No specific operation or antibiotic is specific for SSI, therefore each must be considered alongside the diagnostic codes used in chapter 3. Both CPRD and HES are potential sources of data for antibiotic prescriptions (CPRD) and further surgical treatment (HES). Therefore each of these data sources was interrogated for details around antibiotic treatment and further surgery.

4.2 Aims

- To explore prescription of antibiotics after hip fracture.
- To explore the proportion of these antibiotics which may be attributed to wound infection in the context of other medical infections.
- To describe the number of revision operations undertaken and what proportion of these have an associated diagnosis of infection

4.3 Method

4.3.1 Study Design

The source data and code libraries were identical as for chapter 3 but additional procedural codes were derived from the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4th edition) code library. Prescription data were described using the British National Formulary(142).

Both HES and CPRD were examined in isolation as cohorts of hip fracture patients and in combination according to the question being tackled. For some of the questions around antibiotic treatment, a case-control approach was used. The controls were age and gender matched patients with no diagnosis of hip fracture in CPRD.

The principle difference for this chapter compared to chapter 3 is the use of additional outcomes and their combination with the diagnostic outcomes described in chapter 3.

4.3.2 Data Source

Clinical Practice Research Datalink (CPRD) GOLD and Hospital Episode Statistics (HES) as described previously in chapter 2 were used. The same data cut was used and is described in chapter 3 table 3-3.

For part of the analysis undertaken here, a group of controls was selected. These patients were matched in age and gender. Selection of controls considered a number of possible control populations. Total hip replacement population

undergo anatomically related procedures. However there is good evidence to suggest that the total hip replacement population is significantly younger-the mean age being 72 for total hip replacement compared to 82 for hip fracture(7). A population like the THR population would likely have different baseline risk for the parameters under consideration in this chapter. This will be due to better surgical fitness and higher baseline function both of which are prerequisites for undergoing THR in the first place .

An alternative population for consideration might be a different fragility fracture group such as wrist fracture. This may more closely align with the 'frailty' of the hip fracture population, but the surgical differences and mobility implications of the different injuries also significantly limit the utility of comparison.

4.3.2.1 Code lists-Revision Surgery

The diagnosis of wound infection was as for chapter 3. The Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4th edition) code library was searched for codes which relate to revision arthroplasty, revision fixation or non-revision further surgery. A separate code list was used for each.

Previous work within the big data group had generated lists of codes for revision surgery in the hip arthroplasty group. This code list was reviewed and the OPCS4 code dictionary checked to look for additional hemiarthroplasty specific codes. None were found. No code list for 'revision fracture surgery', focussing on the revision of either the sliding hip screw, intramedullary nail and cannulated screws, existed. Therefore a new list was generated. Once again, this was undertaken by two independent reviewers (candidate & DM) and a third senior

reviewer (MC) resolved disagreement. A third code list of non-revision reoperation related to infection was generated in a similar manner. This focussed on procedures such as biopsy and wound washout. The code lists are included in full in the appendix 10.

The codes for revision are not specific for further surgery after hip fracture, therefore 'confirmation of laterality' was explored to increase confidence in accuracy of revision coding.

4.3.2.2 Primary Care Antibiotic prescription-CPRD

A code list to look at prescription of antibiotics was also generated. There is uncertainty around how many, if any, patients are treated for SSI in primary care independent of the hospital clinical team. However, no antibiotic is specific for SSI and no formal guidance exists to direct its treatment in primary care. The candidate and DM generated a new code list, with final review by a third senior reviewer (MC). This was informed by the national guidance on treatment for cellulitis in primary care that has a broadly similar microbiological profile (169). The effectiveness of this is explored in the results. The list of codes is extensive, but the list of antibiotics is presented in appendix 11. Preparations were limited to the oral route of administration.

4.3.3 Statistical Analysis

Summary descriptive statistics were used as the principal technique to explore the rate and consistency of infection and its relationship to treatment. Baseline features of patients were also analysed in this manner.

Where the results of different means of diagnosis were explored, Venn diagrams were created. None of the codes for revision surgery or antibiotics are specific for SSI. Therefore, inferring the reason for reoperation presents additional complexity. First and foremost this was done by combining diagnostic codes with prescription and reoperation data. Unlike revision surgery, additional comparisons can be made with the prescription data to the non-hip fracture controls. This was done as a 'difference-in-difference' to estimate any additional risk of having antibiotic prescription as a result of hip fracture.

This analysis was exploratory. Where deemed appropriate, tests of proportions were used to examine whether differences observed could be attributed to chance. The two-sample test of proportions was carried out with thresholds for significance set at the conventional 5% as two-tailed. Expressions of uncertainty were also included.

4.4 Results

4.4.1 Baseline Characteristics Of Population Under Study

The baseline characteristics of patients with hip fracture, the cases, in this data set are outlined in chapter 3 tables 3-4 & 3-5. The characteristics of the controls are presented here in table 4-1.

Table 4-1 Baseline Characteristics Controls And Cases

	Controls		Cases	
Gender	Female (N=20,133)	Male (n=6,619)	Female (N=10,461)	Male (n=3,459)
Mean Age (SD)	80.83 (10.0)	75.98(13.6)	81.319 (10.2)	76.71(13.8)
Gender proportion (%)	75.26	24.74	75.2	24.8
BMI (SD)	24.185 (4.8)	24.92 (4.2)	24.185 (4.8)	24.92 (4.2)
Charlson Comorbidity Index				
0 (%)	*12,225 (60.7)*	*4,045 (61.1)*	*5,635 (53.9)*	*1,730 (50.0)*
1 (%)	*5,574 (27.7)*	*1,669 (25.2)*	*3,306 (31.6)*	*1,066 (30.8)*
2 (%)	*1,644 (8.2)*	*596 (9.00)*	*1,042 (10.0)*	*411 (11.9)*
3 (%)	*690 (3.4)*	*309 (4.7)*	*478 (4.6)*	*252 (7.3)*

Baseline summary characteristics of case of hip fracture and controls-both defined in CPRD only.

It can be seen that the cases and controls are well matched. This is useful as any risk of antibiotic prescription and diagnosis of infection such as chest or urine should be relatively well balanced between the cases and controls. By extension any differences that may emerge can be more confidently, but not absolutely,

related to the hip fracture episode. Of course such comparisons are not possible with regards to SSI diagnosis, as the control population does not have the relevant exposure.

4.4.2 Prescription Of Antibiotics In Primary Care

Table 4-2 Summary Of Cases And Controls With Antibiotic Prescription

	Control (%)after Index date	**Case (%)- after index date**	**Total**	*Case – before index date*
No Antibiotics	**17,110 (64)**	**8,915 (64)**	**26,025**	*5,697 (40.9)*
Antibiotics	**9,642(36)**	**5,005 (36)**	**14,647**	*8,223 (59.1)*
Antibiotics - 120 days	***1,495 (5.6)****	***1,177 (8.5)****	***2,672***	*1,014* (7.3)*
Total	**26,752**	**13,920**	**40,672**	-

*Summary of rate of antibiotic prescription in CPRD between hip fracture cases and age/sex matched controls. *Test of proportions comparing antibiotic prescription within 120 days of index between cases and control. Risk difference 2.87% (95% CI 2.3%- 3.4%). p < 0.0001.*

A first look at the rate of antibiotic prescription shows that there is a high level of antibiotic prescription in both case and control populations (table 4-2). If we consider a time limit on when the antibiotics were prescribed, a difference emerges between the cases and the controls. The observed rate difference of three per cent (5.6 vs 8.5) in the hip fracture population (cases) is significant ($p < 0.0001$). This represents a risk difference of 2.87%.

The CPRD data allows reference to the number of antibiotic prescriptions issued prior to the index admission, which in turn acts as a further comparator to the observed rate after 120 days for the cases.

Primary Care Antibiotics And Wound Infection

Table 4-3 Summary Of Antibiotic Prescription In Relation To Diagnostic Codes For SSI

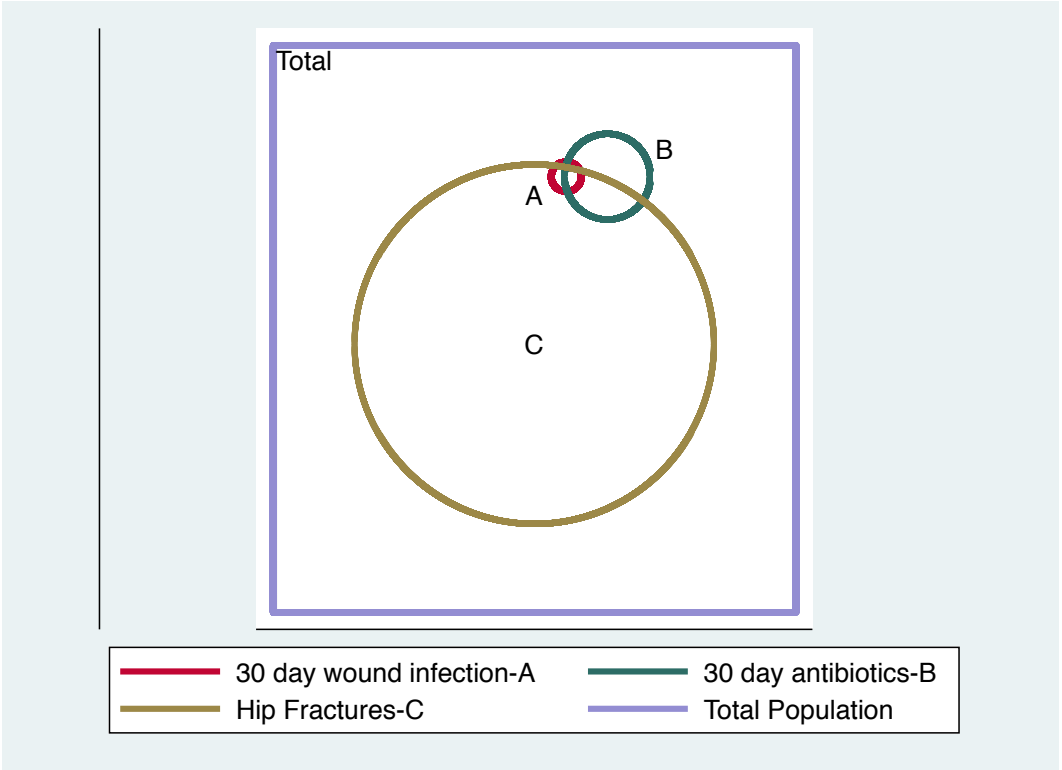
120 days after index	CPRD Surgical Site Infection	No CPRD Surgical Site Infection	Total
Abx Prescription	84	1,093	1,177
No Abx prescription	68	12,675	12,743
Total	152	13,768	13,920

Summary of the prescription rates of antibiotics combined with the diagnostic codes of SSI-all defined in CPRD. Similar limits on time after index date were used as for the previous chapter to try to increase relevance to the hip fracture episode.

Relatedness of diagnostic codes to prescription data for SSI is outlined in table 4-3. Eighty-four of the 1,177 cases with an antibiotic prescription had a concomitant diagnosis of SSI in CPRD (7.14%). Of more relevance are the 68 cases with a diagnosis of SSI but no recorded antibiotic prescription.

The relationship of the antibiotics to the hip fracture case and wound infection diagnoses are presented graphically in figure 4-1.

Figure 4-2 Venn Diagram Outlining Prescription Of Antibiotics, Hip Fracture Cases And Cases Of SSI



Venn diagram outlining the numbers of patients with a diagnosis of wound infection up to 30 days after index (A), a prescription of antibiotics up to 30 days after index date(B) and a diagnosis of hip fracture in CPRD (C). This is in the context of the total population (cases and controls) under study (Total).

4.4.4 Chest, Urine and Wound Infections

The data on prescription of antibiotics in isolation do not inform in any detail about drivers of treatment. By incorporating the codes for SSI, an approximation can be made about the number of cases where treatment is initiated in primary care. In order to contextualise the antibiotic prescription and SSI codes, they are presented alongside the diagnosis of chest infection and urine infection (table 4-4). There are higher proportions of chest, urine and wound infection for hip fracture patients at both 30 and 120 days. These differences are statistically and clinically significant ($p < 0.00001$) across each type of infection. No statistical comparison was made between wound infection codes in cases and controls.

Chest and urine infections were chosen, as they are common after hip fracture (170-172).

Table 4-4 Summary Of Codes For Medical Infection, SSI And Antibiotic Prescription In CPRD

	30 days				120 days			
	Chest Infection (% of Total)	Urine Infection (% of Total)	Wound Infection (% of Total)	Antibiotic Prescription (% of Total)	Chest Infection (% of Total)	Urine Infection (% of Total)	Wound Infection (% of Total)	Antibiotic Prescription (% of Total)
Cases	258 (1.9)	166 (1.1)	90 (0.6)	344 (2.5)	730 (5.2)	590 (4.2)	152 (1.1)	1177 (8.5)
Controls	251 (0.9)	171 (0.6)	7 (0.0*)	447 (1.7)	959 (3.6)	603 (2.3)	23 (0.1)	1495 (5.6)
Percentage Risk Difference	(1)**	(0.5)**	(0.6)	(0.8)**	(1.6)**	(1.9)**	(1)	(2.9)**

*A summary of diagnostic codes identified in CPRD in case and control populations for chest, urine and wound infection as well as antibiotics prescription. The percentage risk difference for between the observed number of each in the cases and controls is presented. For each observed group the difference was subjected to a statistical significance test. **Two tailed test of proportions was used. In each instance p <0.00001*

4.4.5 Rate Of Antibiotic Prescription Prior To Index Date

Table 4-5 Comparison Of Antibiotic Prescription In Cases And Controls Prior To Index Date

Patient Group	No antibiotics within 120 days pre index	Antibiotics within 120 days pre index (%)	Total
Control	12,796 (89.8%)	1,461 (10.2%)	14,257
Case	5,697 (84.9%)	1,014 (15.1%)	6,711

Summary of numbers of hip fracture cases and age/sex matched controls with a prescription for antibiotics in CPRD prior to index date.

The CPRD data also allow insight into the rate of antibiotic prescription prior to index admission. Despite close matching in baseline characteristics as seen in table 4-5, there is a clinically and statistically significant difference in preadmission antibiotic prescription.

4.4.6 Revision Surgery

As well as using antibiotics, further surgery is a mainstay of treating orthopaedic infection. This may be limited treatment to the soft tissues such as washout and debridement procedures. More commonly, further surgery may involve removal of some or all of the components implanted as part of primary treatment.

As can be seen from the systematic review chapter, reoperation for infection is frequently used to identify infection in retrospective studies. Usually in combination with microbiology results(153).

Therefore the HES data under study were interrogated for procedures coded for revision. Three code lists were used for this purpose. The two broadest categories for treatment for hip fracture are internal fixation (SHS, IM Nail,

cannulated screws) and arthroplasty (total hip replacement and hemiarthroplasty). Each of these families of procedure has a related set of revision procedures. Code lists to reflect these procedures were used to find cases of reoperation. One limitation is that there is scope for 'crossover'. By which I mean patients who originally receive arthroplasty, might undergo internal fixation as a revision procedure for example when a periprosthetic fracture occurs. Similarly the cohort treated initially with internal fixation may have revision surgery using arthroplasty. This means that revision was considered in the broadest possible sense.

In a similar vein to the antibiotic treatment component, revision is not specific to one indication. However the list of indications is relatively small.

The code lists for revision were combined with a third category of non-revision further surgery that aimed to capture some of the infection related procedures such as debridement and washout. This type of operation is often used in the hip fracture population who may not tolerate extensive revision surgery.

Table 4-6 Numbers Of Cases With Further Surgery Coded Alongside Diagnostic Codes For SSI.

Further surgery in HES	Number of cases (% of total) n= 6,239*	Number of cases (% of total) n= 6,239***	Number of revisions with infection diagnosis (HES)	Number of revisions with infection diagnosis (CPRD)	Overlap	% number of revisions with an SSI diagnosis (HES or CPRD)
Revision arthroplasty	151 (2.4)	95 (1.5)	16	8	2	14.6%
Non revision further surgery	20 (0.3)	7 (0.1)	9	1	1	45.0%
Revision Fixation	100 (1.6)	73 (1.2)	9	8	0	17.0%
All reoperation**	249	164	24	15	2	14.9%

*Cases of hip fracture with an associated code for revision surgery. *Cases were defined in HES AND CPRD. **All reoperation cases only include one reoperation per case i.e. if a patient had more than one reoperation that would still only be counted once. ***Laterality confirmed from primary procedure*

Table 4-6 outlines the absolute numbers of each code group, along with the number of patients who also had a code of infection in wither HES or CPRD. The revision codes were only looked for in the HES data set, as the procedural information in CPRD is limited. The ability to confirm 'laterality' of the procedures was an even smaller sub proportion of those with codes for revision surgery. The number of revisions in absolute terms is relatively small. The number of these revisions associated with a diagnosis of infection was even smaller. Given these limitations no modelling was attempted to explore the risk of revision and infection.

4.5 Discussion

This chapter has explored the ability of different codes for treatment to understand infection after hip fracture surgery. The two complementary arms of treatment are further surgery and antibiotics. Neither of these modalities are specific to surgical site infection.

The proportion of patients receiving antibiotics in general is very high. More than one in ten patients in both the cases and controls had received antibiotics in the 120 days prior to index admission. The patients who went on to have a hip fracture had an additional 5% risk of having had antibiotics prior to their index date. These rates are likely to be higher because the codes used to identify these antibiotics were selected in the context of SSI treatment and are therefore limited.

Post hip fracture, the rate of antibiotic prescription is also high, but interestingly not as high as pre index. This could be because the prescription data were looked at only in CPRD, and the typical hip fracture patients spends 23 days in secondary care(173), therefore they aren't 'available' to their primary care to receive antibiotics. It is entirely possible that antibiotic prescriptions were dispensed in secondary care and recorded only in HES. An important limitation in considering these data is the boundless scope of which antibiotics may have been prescribed for a multitude of indications.

Nonetheless the additional 2.9% burden of antibiotics within 120 days in the hip fracture cohort compared to the controls can be considered clinically as well as statistically significant.

The driver of these antibiotic treatments may be other 'medical' infections. Hip fracture patients are recognised as a particularly frail and vulnerable population. The admission to hospital, as well as the associated reduced mobility is all strong predictors for developing infection of any kind (174, 175).

The relationship of antibiotics to the primary question asked of these data, namely what is the rate of surgical site infection after hip fracture surgery, is complex. Specifically, we would expect all patients diagnosed with SSI to be treated with antibiotics, however the broad range of indications for antibiotics means the reverse inference cannot be made.

The data from CPRD show that surprisingly there is a significant group of patients with a diagnosis of SSI, but no corresponding prescription for antibiotics (68/152). This could be because the patients are being immediately referred on to secondary care when the diagnosis is made. This is the preferred course of action by the orthopaedic community, who frequently seek to take microbiology samples in hospital to confirm diagnosis and guide treatment. Alternative explanations include the use of antibiotics not captured in the code list generated for this study, or inadequate coding at the practices. Furthermore there may be antibiotic prescriptions given entirely in secondary care.

The prevailing paradigm for treating surgical site infections is almost entirely focussed around secondary care. In particular for orthopaedic surgery where confirmed cases of infection often need extensive courses of antibiotics and further surgery.

The evidence of antibiotic use in association with the SSI diagnostic codes possibly suggest a group of patients diagnosed and treated within the primary care setting. This is a particularly interesting possibility as almost all work

focussing on identifying cases of surgical site infection are focussed on in-hospital diagnosis and readmission.

The other major component of treating surgical site infection is further surgery. The type of surgery can be formal revision of implanted materials, excision of joint e.g. Girdlestone's procedure or debridement of the affected tissues. The numbers of patients undergoing further surgery for their hip fracture is very small (164-1.5%). Of these cases even fewer have a diagnostic code for SSI as well.

The explanation for these low rates of further surgery can be explained by clinical context as well as deficiencies in the process of data capture. As seen in the baseline characteristics, hip fracture patients are typically frail. Typically they represent high surgical risk, over 60% of hip fractures have an ASA grade 3 or above(176) . The threshold for offering a patient further surgery must be understood in this context. Death is also a competing risk for undergoing revision, and given that the 1 year mortality for all hip fracture is very high at 30% (100, 177), the risk of revision will be correspondingly low. The place of surgery in treating SSI, including debridement and full formal revision, is less well formulated in hip fracture compared to primary joint arthroplasty. For example the use of debridement compared to formal single stage revision or two-stage revision(178).

There are therefore numerous significant reasons why further surgery is an uncommon occurrence after hip fracture. Additionally examining further surgery in these datasets cannot improve upon the use of diagnostic codes for identifying SSI in hip fracture patients. The value in looking at further surgery in this chapter is that it highlights the potential limitations in using further surgery

as signal for SSI. This technique was seen in many of the studies discussed in chapter 2 (52).

4.6 Conclusion

Data on antibiotic prescription alone cannot improve upon the diagnostic coding explored in chapter 3, as they lack diagnostic specificity. However they provide useful context for understanding the 'general risk' for infection for hip fracture patients. The use of routine data to understand SSI must bear in mind the limitations noted here and elsewhere. Interventional studies aiming to use the administrative data to capture study outcome would need significant scale to be sufficiently powered.

There would appear to be value in combing both hospital and primary care data to capture cases of SSI as it would appear that there is relatively little reciprocal coding taking place in this study data set.

5 Randomised Controlled Feasibility Trial Of Standard Wound Management Versus Negative-Pressure Wound Therapy In The Treatment Of Adult Patients Having Surgical Incisions For Hip Fractures-A Protocol

Declarations

The candidate was the Chief Investigator for this study. He oversaw a full trial team based within Oxford Trauma. He held responsibility for the inception, design, delivery and reporting of the trial. The candidate, along with his supervising team, worked alongside the administrative team in the WHiTE cohort and the centres participating in the WHISH study. The sample size calculation was undertaken prior to formally starting the DPhil for the purposes of the grant applications relating to the project work.

Aspects of this work have been presented, and the formal study protocol has been published(179):

Masters JPM, Achten J, Cook J Dritsaki M, Sansom L & Costa ML
Randomised controlled feasibility trial of standard wound management versus negative-pressure wound therapy in the treatment of adult patients having surgical incisions for hip fractures
BMJ Open 2018; **8:e020632**. doi: 10.1136/bmjopen-2017-020632

This chapter has been modified from the published protocol to reflect more closely the specific aims of the thesis.

Study Sponsor

The study sponsor was Oxford University

Ethical Approval

Ethical approval was granted by Oxford C Research Ethics Committee, 28/04/2017, 17/SC/0207.

Study Registration

Trial registration number ISRCTN55305726.

Reporting

Both Chapters 5 & 6 are reported along the CONSORT guidelines and its feasibility extension: appendix 13(180).

5.1 Introduction

The first chapters have identified a possible rate of infection of between 1.40% and 2.08%. These methods are limited as outlined in their respective chapters. The use of a prospective study that formally seeks to identify infection in each patient may offer significant methodological improvement on the two studies undertaken so far. This study incorporated two overarching aims. Firstly, to capture SSI in hip fracture patients and secondly to explore the feasibility of comparing negative pressure dressings to standard care in a randomised controlled trial.

The nature of this prospective study needed to achieve several key objectives:

- Inform the event rate of surgical site infection
- Identify whether patients will participate in a study of negative pressure wound therapy
- Identify whether healthcare teams will participate in a study of negative pressure wound therapy
- Explore how capturing surgical site infection in this complex patient population functions in the setting of a study.

Within the United Kingdom, a prospective cohort study is run across 17 centres- the World Hip Trauma Evaluation study (WHiTE)(181). This prospective cohort is a vehicle for embedded randomised controlled trials of interventions for hip fractures.

Previous studies within the cohort highlight that the recruitment and clinician participation would likely be possible within this study vehicle(182, 183). However as has been highlighted in both the thesis introduction and the first

three chapters, there is important uncertainty around the true event rate of surgical site infection after surgery. One of the important limitations is around where and how the outcome data are reported and collected.

These limitations could be addressed by undertaking a piece of preparatory work to improve confidence in these areas of uncertainty. Furthermore given the interest in exploring the possibility of whether incisional negative pressure wound therapy can reduce the rate of surgical site infection, this prospective study could also consider the implementation of this intervention as part of the development work.

Development work in preparation for a full randomised controlled trial typically falls in to two categories: feasibility or pilot study. Pilot studies are frequently small-scale versions of the planned larger trial whereas feasibility studies try to answer whether a study can be done (184). Some conceptual frameworks classify pilot studies as a subset of feasibility(185).

The study described in this chapter and chapter 6-WHiTE 7-has elements of both pilot study and feasibility study. The process of recruitment, clinical team involvement and trial procedure is well established to be effective in the WHiTE studies undertaken to date. Therefore these elements of WHiTE 7 are more closely aligned to a pilot study. The only uncertainty in these areas was fine detail about this specific intervention.

However despite the experience with the previous WHiTE studies and there remained a critical feasibility question about the rate of SSI in this population. This is a reflection of the likely true event rate being between 1% and 5%. In turn this has implications for sample size calculations for any definitive randomised

controlled trial. As such this parameter represents a true threshold for feasibility.

A protocol was written and published as well as registration of the study within a trials registry. These steps are an important part of the scientific process, and make an important contribution to the transparency of studies.

A protocol is a critical document for any scientific study as it outlines the methodology and parameters by which the study will be conducted and analysed. It defines the conditions and procedure of the study which if repeated should yield the same result.

5.2 Aims and Objectives

A feasibility trial comparing NPWT to standard wound dressings following hip fracture surgery was undertaken. It was intended to obtain a reliable estimate of the rate of surgical site infections in the target population. Feasibility was also considered in terms of other aspects of the trial such as recruitment and randomisation.

5.2.1 Primary objective:

To quantify the rate of surgical site infection after hip fracture surgery in patients treated with standard dressing and NPWT. Patients were assessed at both 30 days and 4 months. We examined how many surgical site infections occur, and when the diagnosis was made.

Both 'how many infections' and 'when they are diagnosed' will inform the design of a full-scale trial. Each time point addresses the criteria of the CDC, and the

routine follow up of patients in the current England, Wales and Northern Ireland care pathway.

5.2.2 Secondary Objectives:

- To measure the number and nature of further surgical interventions to the hip.
- To determine rate of recruitment and willingness to take part in the trial
- To explore the collection of SSI data in the hip fracture population in the context of a large-scale clinical research setting.

5.3 Methods And Analysis

5.3.1 Study Design, Setting and Participants

This study was embedded within the WHiTE cohort(181). Five different centres participated in the trial across England. This included Major Trauma Centres and Trauma Units. The study considered patients undergoing surgery for hip fracture.

5.3.2 Eligibility

Patients were eligible for this study if:

· They were 65 years or older

· They had a hip fracture requiring surgical treatment.

Exclusion criteria: Patients having percutaneous fixation of an undisplaced intracapsular fracture of the hip. This small sub-group of patients (less than 5% on the National Hip Fracture Database, have very small surgical incisions,

typically 1-2cm(7). Where incisions are so small, it is unlikely that they will benefit from incisional Negative Pressure Wound Therapy.

5.3.3 Recruitment of participants, screening and eligibility assessment

5.3.3.1 Consent

Patients with a hip fracture are a clinical priority for urgent operative care. They will undergo surgery on the next available trauma operating list. All patients with a fracture of the hip are in pain and have received opiate analgesia. It is understandable that the majority of patients find the initial period of their treatment in hospital confusing and disorientating. Similarly, patients' next of kin, carers and friends are often anxious. Both patients and carers may have difficulty in weighing up the large amounts of information about the injury and treatment plan. In this emergency situation, the focus is on obtaining consent for surgery and informing the patient and any next of kin about immediate clinical care. This is supported by national guidance that recommends surgery should take place within 36 hours(12). It is often not possible for the patient or relative/carer (consultee) to review trial documentation, weigh the information and communicate an informed decision about whether they would wish to take part.

The consent procedure for this trial reflected that of the surgery. The clinical team assessed capacity before seeking consent for the surgical procedure. This capacity assessment then informed the best approach for consent to the study. A member of the research team then sought consent in line with the Mental Capacity Act. This was either from the patient themselves or an appropriate

consultee. A National Research Ethics Committee approved this consent procedure. Patient representatives from the WHiTE study steering group helped to develop this consent procedure.

The consent procedure was key to maximising the representativeness of the study population.

5.3.3.2 Randomisation

Randomisation was undertaken once the treating surgeon confirmed eligibility, and consent was given. In most cases there was certainty about which procedure would be performed and patients were randomised prior to going to theatre. If there was any doubt as to which procedure would be performed, then randomisation would be performed at the end of the operative procedure, before applying the wound dressing. Patients were enrolled into the study via a secure, remote online randomisation system.

Randomisation only took place after online registration to ensure concealment of the allocation sequence. The Oxford Clinical Trials Unit trial statistician (JC) generated the randomisation sequence. Randomisation was stratified by site using permuted blocks of varying sizes with 1:1 allocation ratio to secure, 24 hours, web-based randomisation system.

5.3.3.3 Blinding

As the wound dressings are clearly visible, the patients could not be blinded to their treatment. In addition, the treating surgeons were not blind to the treatment, but took no part in the post-operative research assessment of the patients. Independent research assistants who were blind to the treatment

allocation collected the clinical outcome data. Questionnaire data was entered onto the trial central database in the trial central office.

5.3.3.4 Interventions

5.3.3.4.1 Surgery

Patients with a hip fracture usually have surgery on the next available trauma operating list. Some patients may be delayed by medical factors such as anticoagulation, however surgery will proceed as soon as is determined safe by the treating team. This was reflected in this trial. All patients received a general or regional anaesthetic. Routine prophylactic antibiotics were given to all patients immediately before surgery and all patients were assessed for venous thromboembolism prophylaxis according to local policy. At the end of the operation, the study intervention was applied. This trial involved the application of two types of wound dressing; standard dressing and negative pressure wound therapy.

5.3.3.4.2 Standard Dressing.

The standard dressing for a surgical wound comprises a non-adhesive layer applied directly to the wound that is covered by a sealed dressing. The standard dressing does not use 'negative pressure'. The exact details of the dressing materials was left to the discretion of the treating surgeon as per their routine practice.

5.3.3.4.3 Incisional Negative Pressure Wound Therapy

The iNPWT dressing uses an absorbent layer that is placed onto the wound as an intrinsic part of a sealed dressing. A sealed tube connects the dressing to a built

in mini-pump that creates a partial vacuum over the wound. This can only be kept on for 7 days according to the manufacturer.

5.3.4 Outcome Measures

5.3.4.1 Primary outcome

The primary outcome measure for this study is surgical site infection; We used the Centre for Disease Control (CDC) and Prevention definition of a "deep surgical site infection", that is a wound infection involving the tissues deep to the skin that occurs within 30 or 90 days of surgery (150).

Infection was chosen to reflect both the broader aims of the thesis as well as the most clinically important metric for determining the effectiveness of wound dressings. The CDC criteria were used as they are the standard by which a number of public health organisations assess their SSI burden, as well as other related research studies(1, 2, 40). An alternative would have been the Public Health England definition which is based on the CDC definition but has a number of modifications around the inclusion of microbiology and the use of antibiotics. Given the greater use of the unmodified CDC definition in both the SSI literature, and the research literature for NPWT, this was preferred over the PHE definition. That said, the parameters used in PHE were considered in the analysis.

The time of diagnosis was also assessed; The CDC definition applies up to the 90 days after hip fracture surgery (144). However the national care pathway for hip fractures involves remote follow up at 4 months. Therefore to ensure that assessment meets the CDC criteria and is consistent with existing care practice, each patient will be assessed at 30 days and 4 months.

At 30 days the patients were assessed either as an inpatient or over the telephone if they had been discharged from the study site.

At 4 months patients were asked, via telephone interview, about any further symptoms of wound infection, which had emerged since the 30 day time point.

5.3.4.2 Determining Surgical Site Infection

The clinical reporting forms were constructed and worded such that the 30-day form asked about symptoms from 0-30 days, and the 4-month form asked about symptoms from 30 days to 4 months.

1. Fluid is leaking from the wound AND the fluid is pus

2. At least one criterion from each of criteria a AND b.

a. Either the wound is gaping open (dehisced) OR Surgeon has deliberately opened wound

b. Either the area around the wound is painful or tender OR any fever of 38°C since surgery

3. Any sign of abscess or infection on direct examination or imaging (e.g. ultrasound)

A patient was considered to have an infection if they reported positively to criteria 1, or 3. They were also considered to have an infection if the reported both a gaping or medically opened wound (criteria 2a) with symptoms indicating infection (criteria 2b).

Additional note on the use of microbiology in diagnosis

The January 2018 update changed the CDC criteria by merging the microbiology criterion with the 'open and symptomatic'-criterion 2 above. However it was not

put in as an absolute requirement, but only if samples were taken. That is to say if criterion 2 was met, and samples were taken which identified microorganisms then deep SSI can be diagnosed. Similarly if criterion 2 was met and no samples were taken then a deep SSI can be diagnosed. It is only if samples were taken, but did not come back positive that a deep SSI could not be diagnosed. The degree of intentionality now needed was very complicated to capture across sites, particularly in the middle of a study. In addition key reference data such as the Public Health England surveillance data does not use culture as part of this diagnostic criterion(40). To this end microbiology was not included as part of the study definition above. This was based on experience with other similar large scale trials capturing infection data using these criteria. An additional complexity in capturing and interpreting the microbiology data is the likely heterogeneity in practice of intraoperative sampling. There exist cultural silos in which different groups of surgeons practice. The Prosthetic Joint Infection (PJI) community have developed protocols for sampling and guidelines for interpretation of microbiology results(186). This is not in place for hip fracture care and suspected infection. There are also variable clinical thresholds for undertaking formal deep microbiology samples based on patient fitness for further surgery. This in turn can introduce an important bias. These variations in practice may skew the use of microbiology as a diagnostic criterion, particularly in the hip fracture population. Nonetheless microbiology data were captured to help guide this process for the definitive study. These data are reported in the results.

5.3.4.3 Secondary Outcome Measures

5.3.4.2.1 Recruitment rate

The rate of recruitment of potential participants, both in terms of eligibility and those who consent (or on whose behalf consent is provided) was recorded and reported.

5.3.4.2.2 Allied Infection Measures

As well as an assessment against the CDC criteria, other indicators of SSI were collected. This includes antibiotic treatment for wound infection, further surgery for wound infection and 'clinician diagnosis' of wound infection.

5.3.4.2.3 Core Outcome Set For Hip Fractures (187):

Mortality .

EuroQol EQ-5D-5L

Complications

Mobility

Retention rate (24).

5.3.5 Adverse Event Management

Adverse events (AE) are defined as any untoward medical occurrence in a clinical trial subject and which do not necessarily have a causal relationship with the treatment. All AEs were listed on a specific Case Report Form for routine return to the 'WHISH' central office.

Where adverse events are expected as part of the surgical interventions, and do not need to be reported immediately, they were recorded in the 'Complications' section of the Case Report Forms and/or Patient Questionnaires. These events are: complications of anaesthesia or surgery (bleeding or damage to adjacent structures such as nerves, tendons and blood vessels, delayed unions/non-

unions, further surgery to remove/replace metalwork, dislocation, wound dehiscence and thromboembolic events). Where a complication may be related to the primary outcome measure e.g. the formal infection outcome CRF questions were asked. The chief investigator reviewed all SAEs.

5.3.6 Follow-up

Each patient was assessed in the current UK national audit framework for hip fracture patients (7). This involved contact by telephone 4 months after surgery. As per the feasibility aims of this study, patients were also contacted 30 days post surgery. This was over the telephone if the patient had been discharged, or by the hospital research team if still an inpatient at that study site.

We investigated SSI at 4 month time point to ensure that each patient had been assessed by 90 days which is specified by the CDC.

At the 4 month time-point we collected the data required for the National Hip Fracture Database, health-related quality of life and the other components of the hip fracture core outcome set(187).

Details of any late complications were sent securely to the trial co-ordinating centre. Complications were recorded on the dedicated CRF by the site research associate and recorded on the CRFs at 30 days/discharge and at 4 months via telephone interview.

Personal consultees were asked for follow up data where the participant had permanent loss of capacity. Some patients or consultees did not wish to provide follow up data but agreed to the study team reviewing their medical records. In

this instance, clinical reporting forms were completed by the site and returned in the same manner. This is referred to as 'routine data only' option.

5.3.7 Source Data

This feasibility trial was undertaken in an embedded cohort(181). The additional follow up time point of 30 days was unique to the WHISH study. It was chosen to reflect the outcome criteria described under the primary outcome measure. There was uncertainty over what proportion of patients would be assessed in person, via their medical records or over the telephone at the 30 day time point. Of particular interest were those patients reporting by the telephone, where there was no independent assessment of their reported symptoms.
To understand the implications of this, all patients who reported an SSI at 30 days had their medical record reviewed to see whether there was evidence of the SSI recorded there. These cases of SSI were supplemented with a random 10% subset of patients who reported 'no SSI' by telephone.

5.3.8 Sample Size

The purpose of the study was to determine the rate of surgical site infection to inform the sample size for the definitive trial. The current estimates are based on passive methods of surveillance and are likely underestimates. Four hundred and sixty four participants, divided between two study arms, was based on the number of hip fractures treated at each of the recruiting centres and a conservative recruitment estimate of 50% of eligible patients at each centre. Wilson's confidence interval (CI) method at 2-sided 95% significance level with

20% loss to follow-up allowed us to estimate the overall 30 day deep infection rate to within 3-5% depending upon the actual rate.

5.3.9 Rehabilitation

Early full weight-bearing mobilisation is routine in all cases of hip fracture. Details of the rehabilitation were left to the discretion of the treating team as per usual clinical practice for the purposes of the study.

5.3.10 Data Management

The Case Report Forms were designed by the chief investigator in conjunction with the trial management team. All electronic patient-identifiable information was held on a secure, password-protected database at the Kadoorie Centre, University of Oxford accessible only to the research team. Paper forms with patient-identifiable information were held in secure, locked filing cabinets within a restricted area. Patients were identified by a code number only. Direct access to source data/documents was required for trial-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required. All paper and electronic data will be retained for at least five years after completion of the trial

5.3.11 Statistical Analysis

Standard statistical summaries (e.g. means, standard deviations, medians, IQR) are reported for all discrete and continuous outcome measures. Baseline data (e.g. age and gender) were summarised to check comparability between treatment arms. No formal hypothesis testing took place; as per the aim of this feasibility study, the analysis will report the SSI rates overall and in the two

treatment groups on an intention-to-treat basis at 30 days and 4 months post-recruitment. Analysis was exploratory, and done to explore the effectiveness of the feasibility study. Any between group differences are *'post hoc'* and were interpreted in this context. These differences were analysed using descriptive statistics, and with appropriate measures of uncertainty (e.g. 95% confidence intervals).

If a full -scale trial is feasible and funded, the data from this feasibility study will be included in the final analysis of the definitive trial. This is contingent on the future definitive trial being sufficiently similar to this feasibility study. Reporting of the study outcomes was done accordingly to enable use of the outcome data in a future definitive trial if such a study goes ahead. Feasibility was shown if the rate of SSI in the feasibility data was sufficiently high to that a clinically important difference could be shown, and that the number of patients needed to do this would be realistic. This was the basis on which to proceed, along with the other aims such as recruitment and retention.

Some data were not be available due to voluntary withdrawal of patients, lack of completion of individual data items or general loss to follow-up. In this hip fracture cohort there is significant mortality at 30 days; 6.7% (1). Where possible the reasons for missing data was ascertained and reported. The nature and pattern of the missing data is important to understand for the full study, so is carefully considered.

Reasons for ineligibility, non-compliance, withdrawal or other protocol violations are stated and any patterns summarized.

5.3.12 Trial Oversight

The day-to-day management of the trial was the responsibility of the Chief Investigator supported by the trial manager. This was overseen by the Trial Management Group, who met monthly to assess progress. It was also the responsibility of the Clinical Trial Manager and Chief Investigator to undertake training of the research associates at each of the trial centres. The Trial Statistician and Health Economist supported and approved the data capture systems, design of databases and clinical reporting forms.

A Study Oversight Committee (SOC) and a Data & Safety Monitoring Committee (DSMC) was already established for the WHiTE cohort and other embedded studies. The DSMC used a DAMOCLES charter that defined its terms of reference and operation in relation to oversight of the trial. There was no formal interim analyses of effectiveness. They did, however, see copies of data accrued to date, or summaries of that data by treatment group and assessed the screening algorithm against the eligibility criteria.

They also considered emerging evidence from other related trials or research and review related SAEs that had been reported. They were in a position to advise the chair of the Trial Steering Committee at any time if, in their view, the trial should have been stopped for ethical reasons, including concerns about participant safety. DSMC meetings were held at least annually during the recruitment phase of the study.

5.3.13 Quality Control

The study was monitored in accordance with the approved protocol, relevant regulations and standard operating procedures by the Host organization,

Sponsor and appropriate Regulatory Authorities. A Monitoring Plan was developed according to Oxford Clinical Trials Research Unit standard operating procedures which involves a risk assessment. The monitoring activities are based on the outcome of the risk assessment and may involve central monitoring and site monitoring.

5.3.14 Ethics

Ethical approval was granted by Oxford C Research Ethics Committee, 28/04/2017, 17/SC/0207

6 Randomised Controlled Feasibility Trial Of Standard Wound Management Versus Negative-Pressure Wound Therapy In The Treatment Of Adult Patients Having Surgical Incisions For Hip Fractures-Results

Declarations

The candidate was the Chief Investigator for this study. He oversaw a full trial team based within Oxford Trauma. He held responsibility for the inception, design, delivery and reporting of the trial.

The statistical analysis was undertaken by the candidate under the supervision of Dr B Shirkey and Professor J Cook, trial statisticians within Oxford Clinical Trials Research Unit.

Aspects of this work have been presented:

Wounds International Meeting UK, Harrogate November 2018 *Winner for Infection category.*

Duthie Day, Oxford November 2018

Study Sponsor

The study sponsor was Oxford University

Ethical Approval

Ethical approval was granted by Oxford C Research Ethics Committee, 28/04/2017, 17/SC/0207.

Study Registration

Trial registration number ISRCTN55305726.

Reporting

Both Chapters 5 & 6 are reported along the CONSORT guidelines and its feasibility extension-appendix 13(180).

6.1 Objectives

The objectives for this study were as outlined in the protocol

- To quantify the rate of SSI after hip fracture surgery in patients treated with standard dressing and NPWT.
- To measure the number and nature of further surgical interventions to the hip.
- To determine rate of recruitment and willingness to take part in the trial
- To explore the collection of SSI data in the hip fracture population in the context of a large-scale clinical research setting.

6.1.1 Recruitment

6.1.1.1 Screening

In order to identify participants at each site, a screening log was kept. This was populated by the local trauma and orthopaedic research team. The team consisted of research nurses, trainee PIs, and the site PI. The typical format would be for the screening log to be completed at the daily trauma meeting. This meeting would typically involve discussion of all cases admitted in the previous 24 hours combined with those undergoing surgery that day. This process has been effective in the WHiTE cohort and the preceding WHiTE trials.

At this meeting the research team would liaise with the clinical team in charge. It would be the responsibility of the clinical team to clarify eligibility and classify the fracture concerned. The clinical team in also give input into a patient's capacity. This system was in place for all sites.

Table 6-1 Screening Across WHISH study sites

WHiTE 7	Number of patients screened	Number of patients eligible	Number of patients inelligible	Ineligible: less than 65 Y/o	Ineligible: being managed non-operatively	Ineligible: P. Screw fixation of Undisplaced intercaps #	Ineligible patient Unlikely complete Questionnairs	Ineligible: Other
John Radcliffe Hospital	248	222	26	7	9	10	0	0
Norfolk & Norwich University Hospital	478	437	41	29	11	0	1	0
Queen's Medical Centre	356	294	62	34	9	19	0	0
Poole General Hospital	399	368	31	19	9	3	0	0
Southmead Hospital Bristol	269	233	36	24	5	3	3	1
Totals	1750	1554	196	113	43	35	4	1

Summary of numbers of patients screened at each centre, and reasons they were deemed ineligible.

The process of screening is outlined in table 6-1 and the flow of patients through the study screening process is outlined in figure 6-1.

6.1.1.2 Reasons for Ineligibility.

The principal reason for ineligibility was age (113/228). This study was limited to patients over the age of 65 to accommodate both the requirements of the National Hip Fracture Database, and other studies involving the same intervention(2). Forty three patients were treated non-operatively, and 35 were treated with percutaneous screw fixation. These were part of the exclusion criteria. Interestingly 35 patients as a proportion of the total number of people having hip fracture treatment is relatively small (2% vs 5% in NHFD).

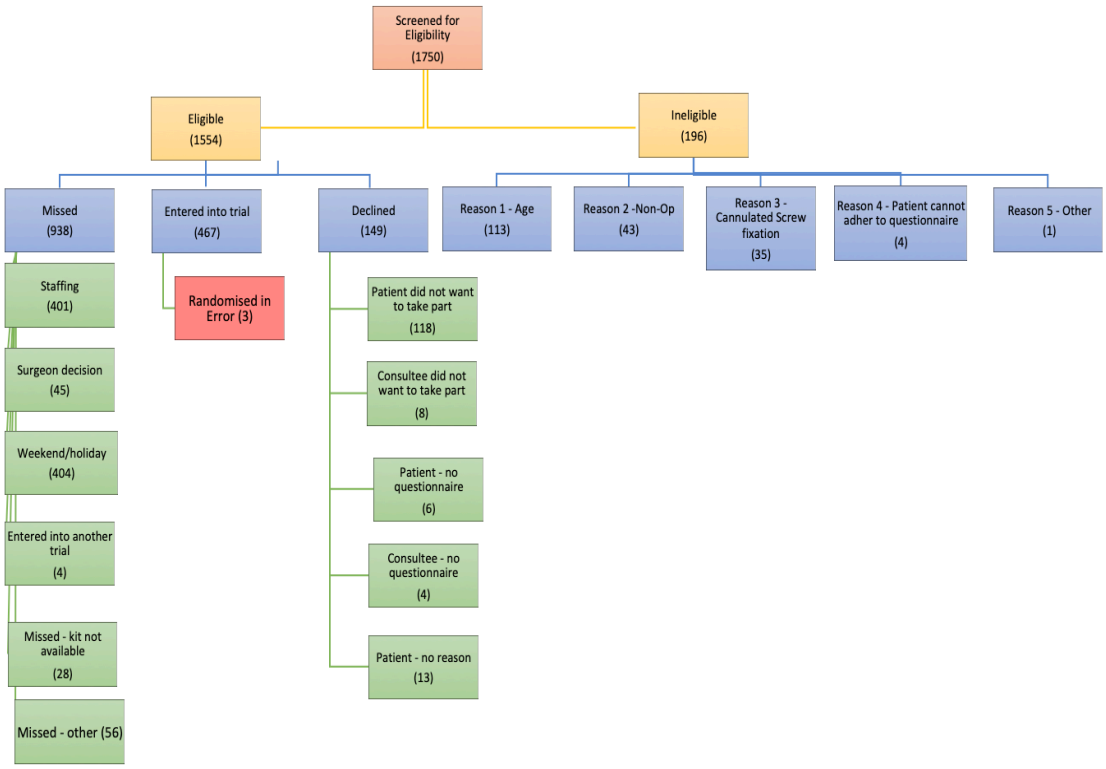
6.1.1.3 Reasons For Missing Patients

900 patients that were eligible at screening, were missed for inclusion in the study. This was due largely to staffing issues at each centre, and out of hours care being delivered, particularly at the weekend. This was not hugely surprising

given the huge numbers of potential patients who attend hospital seven days a week. Poole Hospital (PGH) is one of the highest volume hip fracture centres in the United Kingdom. The NHFD reports over 900 cases per year at this hospital alone(7). As a centre, PGH is relatively new to the WHiTE cohort, and only has one full-time research nurse. Norfolk and Norwich experienced similar difficulties with staffing during this study. In two centres (SMH & JRH) patients were eligible for both this study and WHiTE 4. WHiTE 4 was a randomised control trial comparing the effectiveness of an X Bolt with a sliding hip screw(188). Patients were eligible for both studies, and a significant proportion were included in both. However three patients across both sites were lost due to this co-enrolment activity.

Whilst there was no broad problem with clinical equipoise in this study, some of the surgeons, particularly at Bristol, felt that the incisions used for intramedullary nailing were too small to benefit from negative pressure wound therapy. This was discussed with the site PI, and an agreement reached to assess patients at the end of these procedures for eligibility. Where the incisions were bigger than the percutaneous size, they were still included in the study.

Figure 6-1 Screening and recruitment flow diagram WHISH study



Flow diagram highlighting the movement of patients from screening to inclusion or exclusion alongside reasoning for each.

Four hundred and sixty four patients were recruited successfully into the study between July 2017-February 2018. Three patients were randomised in error and withdrawn. This was due to the patient being randomised prior to consent being given by the patient or consultee.

Table 6-2 Recruitment Numbers Over Time Across Sites

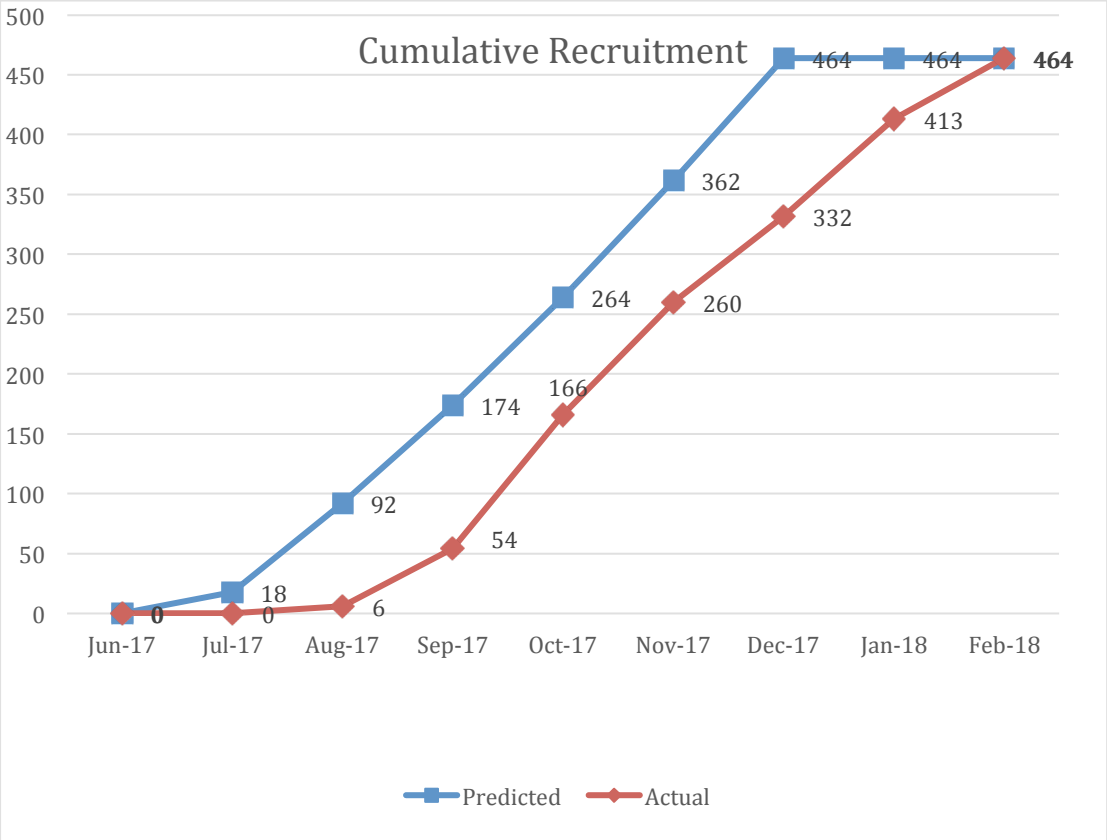
Recruitment Monthly Total									
Site	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	**Overall**
John Radcliffe Hospital	-	-	4	42	32	30	23	19	**150**
Norfolk & Norwich University Hospital	-	-	18	21	15	9	2	1	**66**
Queens Medical Centre	-	3	13	17	17	14	20	7	**91**
Poole General Hospital	0	3	7	12	15	6	14	6	**63**
Southmead Hospital	-	-	6	20	15	13	22	18	**94**
Total	0	6	48	112	94	72	81	51	**464**

Summary of numbers of patients recruited at each site over the total study period.

As outlined in protocol the study included patients with and without capacity. This was felt to be very important to ensure the best possible external validity of the patients included.

There was a staggered process of opening each site, starting with PGH, with the summer months showing slower recruitment. The John Radcliffe Hospital recruited the highest number of patients.

Figure 6-2 Cumulative recruitment over time WHISH study



Graphical representation of actual number of patients (y axis) recruitment over the study period (red line) compared to the predicted (blue).

Table 6-2 and figure 6-2 demonstrate recruitment as the trial proceeded. We had anticipated opening in June 2017 however the study didn't open until 31 July 2017. This explains why no patients were recruited on the day the study opened, and why in June and July there were no recruits.

Recruitment in the summer months was particularly affected by staffing, however once into autumn recruitment accelerated.

6.1.2 Consent And Included Patients

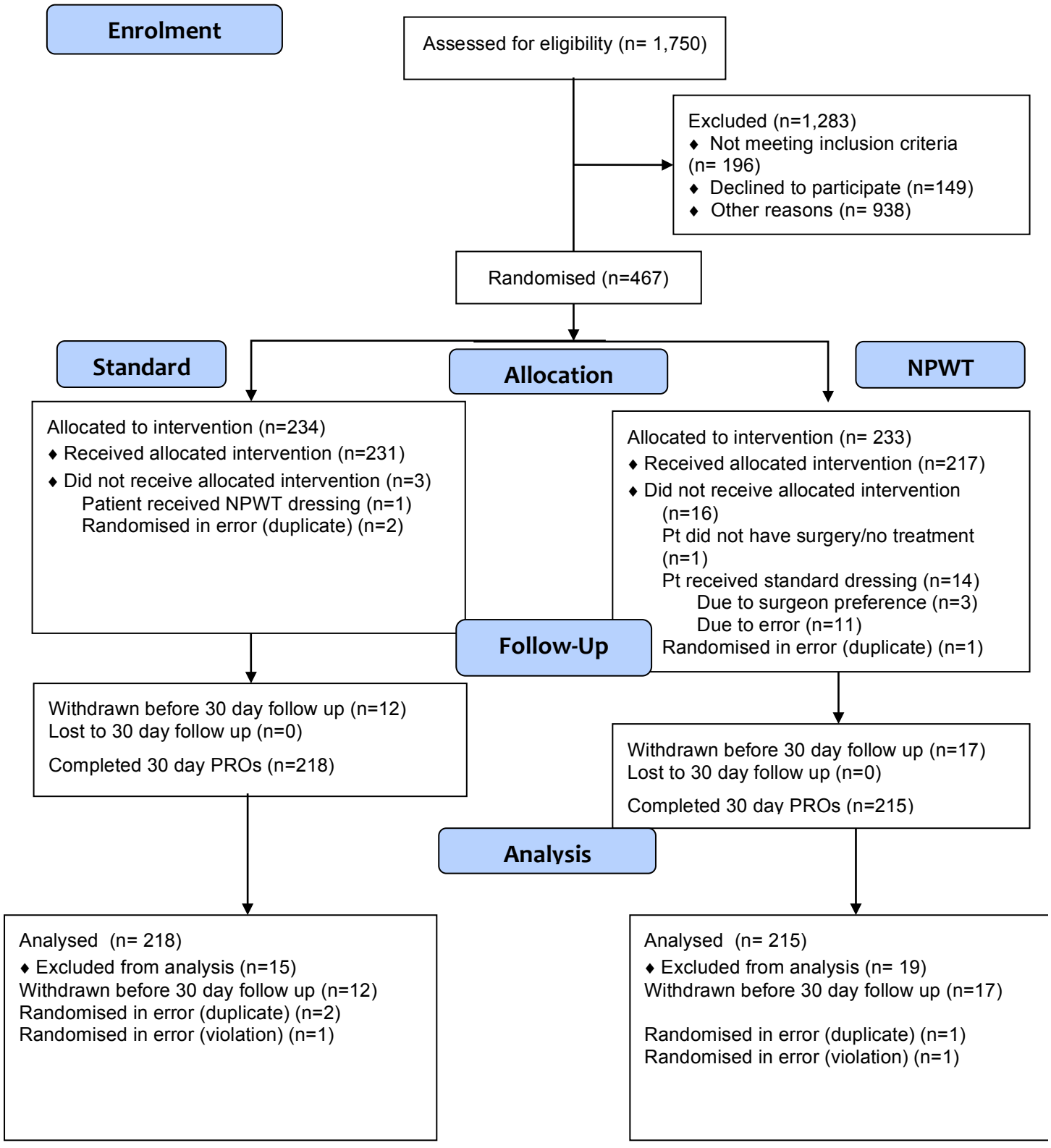
The majority of patients in the study gave prospective consent themselves (64.7%). A smaller but significant proportion entered the study on the advice of

a consultee. The consultee could have been either a friend or relative (personal) or a healthcare professional (nominated). Where patients entered on the advice of the consultee, they were assessed post-operatively to see whether they had regained capacity and wish to continue with the study. Eighteen patients withdrew at this stage, but the majority continued. When patients did not recover capacity, a personal consultee was approached.

6.1.3 End of recruitment

Screening and recruitment ended once the target number of patients was recruited. The overall aim of this study was to develop a more robust understanding of the true rate of infection. This necessitated follow up and analysis. There was no plan to continue the feasibility study into the definitive study.

6.1.4 Patient Flow Diagram-CONSORT



6.1.5 Trial Delivery

6.1.5.1 Allocation of treatment

Ten patients did not receive their study allocated dressing. In common with other studies of dressings in orthopaedic trauma this often reflected site logistics where a patient may 'roll over' from the end of one theatre list to another day and the instruction to use a study dressing is not passed on. There was a heavy preponderance of cross over from the iNPWT arm to standard care. Again on discussing these events with the sites, they reported principally a logistics challenge.

6.1.5.2 Trial Management and Oversight

The trial management meetings (TMGs) were held monthly by the central trial team. Initially these were stand-alone meetings for the WHISH study, however midway through the trial they were brought together with the other WHiTE study meetings. In addition the WHISH study was subject to the oversight of the Data Safety and Monitoring Committee and study oversight committee.

6.1.5.3 Withdrawals and Missing data

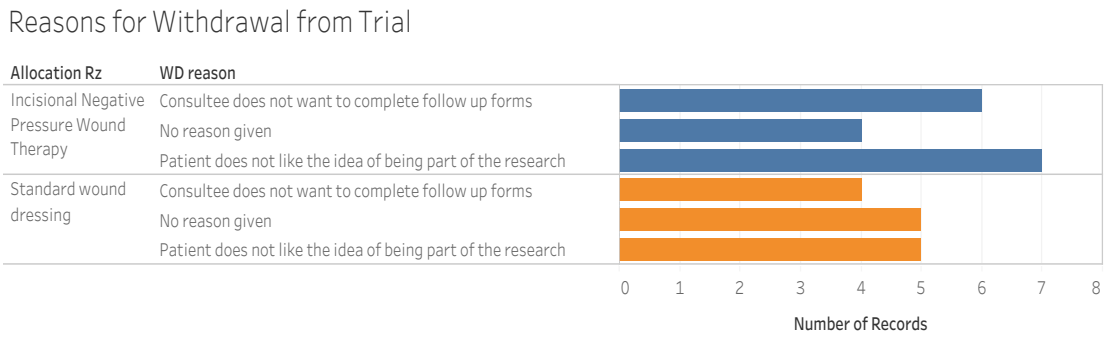


Figure 6-3 Reasons For Withdrawal From WHISH Study

The total number of withdrawals from the study is presented above in figure 6-3 with reasons. There was balance between the two treatment arms in both number and reason for withdrawal. The overwhelming majority (30/31) of withdrawals from the study came prior to the 30 day primary outcome collection.

Withdrawals were the principle reason for missing primary outcome data. Sites completed primary outcome data for patients who did die before 30 days. This was based on the data recorded in the medical record. One patient with SSI died before 30 days (12 days) and had their outcome recorded in this way. Each patient who died had a death notification form completed at sites where possible.

6.1.5.4 Protocol Deviations

Seven patients received percutaneous screws, despite this being an exclusion criterion for the study. This took place at one particular site (N&N), where the patients were entered into the study on the presumption that they would have one of the eligible operations for their hip fracture. However in these 7 patients, the treating clinical team changed the planned procedure in theatre.

6.1.5.5 Audit

The Oxford Clinical Research Trials Unit audited the study in May 2018. The WHISH study was found to have a good standard of documentation. Certification to this effect included in the appendix 12.

6.1.6 Baseline Data

Table 6-3 Baseline Patient Characteristics

Characteristic	Standard (n=230)	iNPWT (n=232)
Age (Median and IQR)	84.9(77-89)	85.2(77-90)
Gender (F:M)	73%: 27%	69%: 31%
ASA I	3 (1.4%)	5 (2.3%)
ASA II	54 (24.5%)	52 (23.4%)
ASA III	129 (58.6%)	125 (56.3%)
ASA IV	33(15.0%)	40 (18%)
ASA V	1 (0.5%)	0(0.0%)
Mean preop AMTS (SD)	8.0 (3.0%)	7.4 (3.5%)
Own home	185 (85.6%)	177 (82.3%)
Residential care	16 (7.4%)	17 (7.9%)
Nursing home	10 (4.6%)	19 (8.8%)
Other	5 (2.4%)	2(1.0%)
Regular Smoker		
Y	15 (7.0%)	21 (10.0%)
N	198 (93.0%)	190 (90.0%)
Diabetic		
Y	24 (12.6%)	34 (18.9%)
N	190 (87.4%)	179 (81.1%)

Summary characteristics of patients included in the WHISH trial by trial treatment. Absolute numbers and percentages are presented.

Table 6-3 outlines the baseline demographic characteristics for the patients randomised into the study. This is in line with what would be expected from this cohort of patients. It is worth noting that the median age is slightly higher on account of excluding the patients aged between 60 and 65. Table 6-4 outlines the fracture patterns seen in the trial. They are balanced by treatment arm. Table 6-5 outlines the surgical treatment received across both arms.

Table 6-4 Distribution Of Fracture Types Across Study

Fracture type	Standard	iNPWT	Total
A1	22 (9.6%)	26 (11.2%)	48 (10.4%)
A2	48 (20.9%)	41 (17.7%)	89 (19.3%)
A3	5 (2.2%)	6 (2.6%)	11 (2.4%)
B1	13 (5.7%)	15 (6.5%)	28 (6.1%)
B3	136 (59.1%)	136 (58.6%)	272 (58.9%)
ST	6 (2.6%)	8 (3.4%)	14 (3.0%)
Total	230	232	462

Summary of fracture classification reported across treatment arms. Fracture classifications are reported in line with the classification system used in the WHiTE cohort which is in turn based on the AO system(181).

Table 6-5 Baseline Patient Treatment Characteristics

Treatment Parameter	Standard	iNPWT	Total
Surgery <36 Hours	129 (56.1%)	143 (61.6%)	272 (58.9%)
Operation			
Hemiarthroplasty (Cemented)	113 (49.3%)	118 (51.1%)	231 (50.2%)
Hemiarthroplasty (Uncemented)	2 (0.9%)	3 (1.3%)	5 (1.1%)
Arthroplasty - THR (Cemented)	11 (4.8%)	9 (3.9%)	20 (4.3%)
Arthroplasty - THR (Uncemented)	0 (0%)	1 (0.4%)	1 (0.2%)
Arthroplasty - THR Hybrid	15 (6.6%)	13 (5.6%)	28 (6.1%)
Internal Fixation - Cannulated Screws	2 (0.9%)	5 (2.2%)	7 (1.5%)
Internal Fixation - IM Nail	15 (6.6%)	17 (7.4%)	32 (7.0%)
Internal Fixation - Sliding Hip Screw*	71 (31.0%)	65 (28.1%)	136 (29.6%)
Surgeon Grade			
Consultant	153 (66.5%)	156 (67.5%)	309 (67.0%)
ST3 +	66 (28.7%)	66 (28.6%)	132 (28.6%)
SAS	11 (4.8%)	9 (3.9%)	20 (4.3%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Wound Closure			
Interrupted Suture	26 (15.5%)	16 (9.8%)	42 (12.7%)
Skin Clips	25 (14.9%)	26 (16.0%)	51 (15.4%)
Subcuticular Suture	111 (66.1%)	117 (71.8%)	228 (68.9%)
Other	6 (3.6%)	4 (2.5%)	10 (3.0%)

*Summary of treatment characteristics according to study arm. *A proportion of the patients with sliding hip screw were treated with an 'X-bolt' device as part of the WHiTE 4 trial as outlined.*

The types of surgery performed are again balanced well across each treatment arm by the randomisation process. It is worth noting that there were 7 patients treated with cannulated screws, despite this being an exclusion criterion. This was because the patient was entered into the study and randomised prior to

going to theatre for treatment. Once in theatre the operative treatment plan was changed from hemiarthroplasty to internal fixation with cannulated screws. These patients have been retained in the analysis on an intention to treat basis.

6.1.7 Outcomes

6.1.7.1 Primary Outcome

Table 6-6 Primary Outcome Rate Of Surgical Site Infection Between Treatment Arms

Intervention	Standard		CDC SSI-30 days (95% CI)	iNPWT		CDC SSI-30 days (95% CI)	Total		CDC SSI-30 days (95% CI)	*Risk Difference (95%CI)*	*Relative Risk (95% CI)*
CDC SSI at 30 days /total	14	218	6.4% (3.9-9.7)	4	214	1.9% (0.05-3.7)	18	*432*	4.2% (2.5-6.5)	*-4.6 (-0.8--8.2)*	*0.29 (0.097-0.87)*

Between group differences for SSI in WHISH study presented as number and percentage. Risk difference and relative risk are also presented.

Table 6-6 outlines the number of patients who had diagnosis of surgical site infection at 30 days according to the criteria outlined by the Centre for Disease Control(150). The denominator for each group is the total number of patients randomised to each arm, with the randomisation errors and patients who declined consent removed. There was a total rate of 18 infections in 432 patients, giving an overall rate of 4.2% at 30 days.

As a feasibility study, these data are not powered to detect a difference between treatment groups and infer effectiveness of interventions. However the difference between groups was noted.

The numbers of patients reporting each set of symptoms is outlined in table 6-7. Each patient may report more than one criterion.

6.1.7.2 Exploring Capture of SSI in Hip Fracture Patients

6.1.7.2.1 Processing And Defining Surgical Site Infection

The protocol chapter outlines the CDC SSI criteria and its interpretation for this study. Table 6-7 outlines the number of cases that report each criterion. Each patient can report more than one 'set of symptoms'.

Table 6-7 Cases Of Surgical Site Infection By CDC criterion Met

Criteria 30 days	Standard (n=218)	iNPWT (n=214)	Total (432)
1. Pus	3	1	4
2a. Open	5	2	7
2b. Gap	5	2	7
3. Abscess	9	3	12

Distribution of patients with SSI according to the Centre for Disease Control definition criteria. Pus= purulent drainage from wound, open=active opening by clinical team of the relevant wound, gap = dehiscence or spontaneous 'gapping' of the wound, abscess=radiological or clinical diagnosis of abscess in the wound.

For those patients reporting across criterion 2, the presence or absence of microbiological samples was also investigated. A total of 9 cases reported relevant symptoms. Each case had their medical record reviewed to see if there was evidence of a microbiological sample being taken, and if this sample was positive. This is outlined in table 6-8. Eight of the 9 cases had both samples and a positive test; one patient had no sample taken.

Table 6-8 Results Of Microbiology For WHISH Study Patients with SSI diagnosis

SSID	Microbiology performed	Organism
S1004	Yes	Corynebacterium striatum
S1116	Yes	Enterococcus faecium
S1204	Yes	Proteus mirabilis, Escherichia coli, enterococcus faecalis & escerichia fergusonii
S1259	Yes	Enterococcus faecalis
S1264	Yes	Staphylococcus epidermidis
S1429	Yes	Pseudomonas
S1102	No evidence	N/A
S1013	Yes	Staphylococcus aureus
S1184	Yes	Proteus species

Outline of organisms identified by microbiological sampling in cases where the CRF identified SSI according to the CDC definition.

6.1.7.2.2 Source Data for Primary Outcome

The 30-day clinical reporting form was completed in different settings depending on where the patient was at the time.

Table 6-9 Source Data For 30 Day CRF

Method of CRF completion	All cases	30 day deep SSI	Total
Telephone	276	9	285 (66.1%)
Medical Review	63	1	64 (14.8%)
At Site	74	8	82 (19.0%)
Total	413	18	431

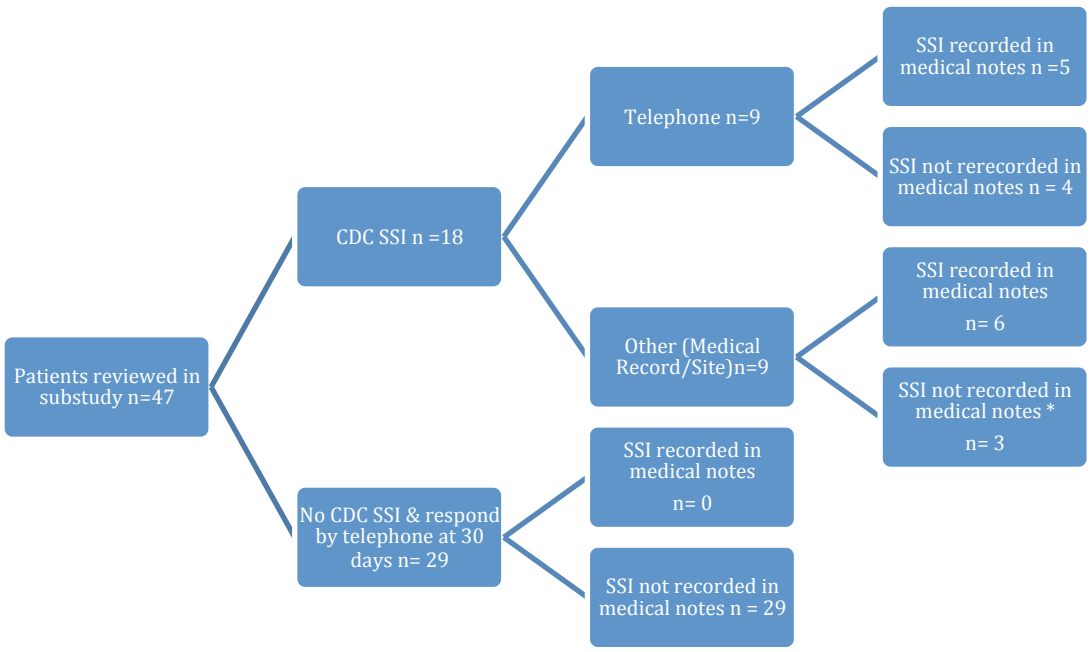
Summary of data sources for completion of 30 day CRF for all patients in WHISH study, exclusive of patients who withdrew prior to 30 days. Telephone=CRF completed after call with patient or carer over the telephone. Medical Review=CRF completed on the basis of information in the medical record. At Site=CRF completed using combination of medical record and in person review as patient still in study hospital at 30 day time point.

As a study population, the majority of patients were contacted by telephone. This is an unavoidable scenario as most patients are discharged before 30 days. At 30 days the hip fracture patients are often not settled in their final 'post injury'

destination. A significant number of these calls were made to patients in other institutions such as interim care placements. There was no formal research staff at these sites, so telephone calls were made to the patients and care placement staff. This was in addition to those who were in their own home.

This was explored with a supplementary data quality exercise where a random 10% of patients who reported by telephone had their medical records checked in addition to see whether the SSI was recorded there. This random sample was supplemented with all those who met the criteria of SSI at 30 days. This could give an indication as to how likely patients who report by telephone are to report symptoms that may not be recorded in the medical record.

Figure 6-4 Outcome Of Patients Who Underwent Additional Review Of Medical Record



Summary of patient numbers of those diagnosed with SSI on the basis of the CRF who had their records reviewed, alongside a random sample of patients without SSI.*Review of these three cases were completed in person at the site, using a combination of the record and the patient

There were no additional infections noted in the random subset of patients who responded by telephone. Of the 18 patients with a recorded SSI on the study 30-day CRF, 11 were noted in the site medical record.

6.1.7.3 Allied Outcomes

There are a number of important metrics associated with the primary outcome of surgical site infection. These relate to evidence of treatment for infection or other wound healing complications. These are outlined in table 6-10.

Table 6-10 Allied Infection Outcomes In WHISH

	Standard (%)	95% CI (%)	iNPWT (%)	95% CI (%)	Total (%)	95% CI (%)	*Risk Difference (95%CI*	*Relative Risk (95% CI)*
Doctor diagnosed wound infection	8/219 (3.7)	1.6-7.1	2/215 (0.9)	0.1-3.3	10/434 (2.3)	1.1-4.2	-2.7 (-0.7-5.5)	0.25 (0.05-1.19)
Antibiotic for wound infection	10/219 (4.6)	2.2-8.2	6/215 (2.8)	1.0-6.0	16/434 (3.7)	2.1-5.9	-1.8 (-5.3-1.7)	0.61 (0.22-1.65)
Further Surgery for infection-4m	2/161 (1.2)	0.2-4.4	1/152 (0.7)	0.01-3.6	3/313 (1.0)	0.1-2.8	-	-
Debridement for infection	5/155 (3.2)	1.1-7.4	2/150 (1.3)	0.2-4.7	7/305 (2.3)	0.9-4.7	-1.9 (-5.2-1.4)	0.41 (0.8-2.10)

Summary of parameters related to primary outcome (SSI). Each characteristic is presented by study arm as well as the risk difference/relative risk between each arm. Each outcome is reported at 30 days except for further surgery for infection which is reported at 4 months.

6.1.7.3.1 Further Surgery

The mainstay of surgical intervention in these patients was debridement (n =7). Three patients underwent further surgery within the 4 month follow up period e.g. revision. This is a relatively small proportion of patients undergoing surgery within 4 months relative to the number of cases of SSI.

6.1.7.3.2 Additional Infection beyond 30 days

Signs, symptoms and diagnoses of infection as outlined above were asked about at the 4-month follow up time point as well. These questions were framed to capture the features of surgical infection that may have developed between 30 days and 4 months. For the purposes of the study patients were only able to have a surgical infection 'once'. That is to say if they reported positive diagnosis before 30 days and at 4 months, then the outcome was recorded once.
Four patients reported infection between 30 days and 4 months, but only 1 of these had no previous diagnosis within the study of surgical infection i.e. follow up at 4 months identified 1 new surgical infection.

Table 6-11 Surgical Site Infection At 4 Months After Surgery

Intervention	Standard		CDC SSI-4 month (95% CI)	iNPWT		CDC SSI-4 month (95% CI)	Total		CDC SSI-30 days (95 % CI)	*Risk Difference (95%CI)*	*Relative Risk (95% CI)*
CDC SSI at 4 months	14	218	6.4% (3.9-9.7)	5	214	2.3% (0.8-5.4%)	19	*432*	4.4% (2.6-6.8)	*-3.7 (-0.1--7.3)*	*0.37 (0.13-1.03)*

Between group differences for SSI in WHISH study at 4 months presented as number and percentage. Risk difference and relative risk are also presented.

6.1.8 Complications and Safety Data

These data were collected in line with the remainder of the cohort as outlined in the protocol. If responses to clinical reporting forms suggested an adverse event or complication, then the respective additional forms would be completed for details. Additional information from the site was also requested if needed to help make determinations of relatedness.

6.1.8.1 Complications

Due to the elderly and frail nature of the hip fracture population, there is relatively high number of complications reported within the study. They were expected in this context. The complications are summarised in table 6-12.

Table 6-12 Complications reported by intervention

Complication	Standard	iNPWT	Total
Acute Kidney Injury	3	13	16
Cerebrovascular Event	7	2	9
Chest Infection/Pneumonia	38	54	92
Failure of fixation	2	0	2
Periprosthetic Fracture	1	0	1
Transfusion	22	27	49
Urinary Tract Infection	41	50	91
Myocardial Infarction	3	5	8
Venous Thromboembolic	5	2	7
No Complication	16	14	30
Other	4	4	8
Total	155	177	332

Complications reported using the embedded cohort complications reporting form. 'No complication' identifies cases which were identified as complications by the site but actually referred to adverse events or other trial infringement. .

The complications reporting operated side-by-side to the primary outcome data collection process.

6.1.9 Adverse Events

As with the complications, unrelated adverse events were relatively common, with 24 being reported in total. None were determined to be related to the trial intervention by either the site Principle Investigator or the Chief Investigator.

The adverse events are listed in appendix 14. There was no evidence to suggest a difference in adverse events between the two treatment arms.

6.1.9.1 Deaths

Table 6-13 Deaths In Study

	Standard	iNPWT	Total
Alive	189	194	383
Dead (n =death within 30 days)	43 (17)	36 (16)	79 (33)

Summary of deaths noted during the study period with sub reporting of the 30 day time point.

The 30-day mortality seen in this study was 33 patients out of a possible 432 (7.6%). There is no gross imbalance in the deaths between the two study treatment arms.

6.1.10 Secondary Outcomes

In line with the core outcome set for hip fractures, data were collected on health related quality of life, mobility walking status and death. These parameters were collected successfully and will be reported in any open publication of the results of this study. Mortality is reported in table 6-13. Mobility and Health Related Quality of Life are reported in appendix 15 in tables 8.15.1 and 8.15.2.

6.2 Discussion

6.2.1 Summary of Findings

The objectives for the WHISH study were to assess each patient against the CDC criteria for SSI, to explore the capture of this outcome in the hip fracture population, to understand recruitment and retention and the nature of further surgery for cases of SSI. There were 18 cases of SSI in 432 patients at 30 days-a rate of 4.2%. These 18 patients were assessed using a variety of data sources

against 4 criteria defined by the Centre for Disease Control. A smaller proportion of these 18 patients underwent further surgery in the study window (n=9). Patients, site study teams and clinical teams were able to recruit 464 patients over a 6 month period.

The feasibility objectives have been met and a fully powered study comparing incisional negative pressure wound therapy to standard care can be deemed feasible on the basis of these data.

These objectives were focussed on informing the true rate of SSI to power a definitive randomised controlled trial. The understanding of infection rates in the literature and administrative data in hip fracture patients was limited and is likely an underestimate.

6.2.2 Limitations

Whilst the 464 patients sample size can be considered large for a feasibility study, it was still relatively small to capture a 'rare' outcome. This is reflected in the broad confidence intervals for both the treatment groups and the total study population. The most important potential source of bias here is the lack of blinding to treatment arm. This is a well-recognised issue in studies in surgery(189). In this specific study, an open difference between treatments could influence care of the wound after surgery. In addition the ability of the patients who reported their symptoms to see and know that they had been treated with a new technology could have influenced their perception. Qualitative work from the WOLLF trial discussed patient perception around the use of open negative pressure wound therapy(190). This found that patients felt

very positive about a new technology(191). It would not be inconceivable to imagine a similar process at work here.

The five centres used to recruit patients to this study were chosen to be a mixture of Major Trauma Centres, and Trauma Units. However it is worth noting that the 3 major trauma centres (JRH, NUH & SMH) have been at the forefront of changing hip fracture care across the UK. It would be conceivable that these sites reflect the best level of hip fracture care by having long established dedicated care pathways for hip fracture patients being managed by an expert set of staff.

6.2.3 Strengths

The generalisability of this study is good. The baseline characteristics of the patients included in the study demonstrate that they are representative of both the broader WHiTE cohort as well as similar national data sets such as the National Hip Fracture Database(7).

Other important considerations for generalisability relate to the inclusion of patients who lack capacity. Forty per cent of hip fracture patients have some form of cognitive impairment(192). The inclusion of these patients here under provision of the Mental Capacity Act bolsters the external validity of the findings of this study. Indeed these patients may well be amongst the most vulnerable to wound problems within the hip fracture population.

The surgical treatment of patients in this study closely reflects the standard of care across the National Health Service.

The headline rate of infection diagnosed in this study is 4.2% at 30 days. This is higher than the rate seen in published literature in the United Kingdom, as well as the work earlier demonstrating how many infections can be identified using

administrative data. This study has used recognised criteria from the Centre for Disease Control to define its cases. We have robust data capture and engage with all the patients enrolled in the study at 30 days. This study offers methodological improvements when considered in the context of previous work discussed earlier in the thesis. One can therefore be increasingly confident that the rate of infection may well be as high as 4.2%, taking into account the 95 confidence intervals (2.5% – 6.5%).

If indeed this rate is true, then this could imply as many as 3,000 patients being affected by this complication every year.

It would appear that an important driver for this increased rate of infection detection relates to patient engagement after discharge. Almost all of the evidence reviewed in chapter 2 focused on hospital-based diagnosis. The discovery of these infections being treated in the community represent an important finding for surveillance, and any future studies which will seek to assess the effect of an intervention on infection. That said by virtue of the fact that surgical site infection is the primary outcome measure, it may have increased awareness of the diagnosis in the clinical and research teams.

The second objective in this study was to explore the diagnosis of SSI. This was considered in broad terms and considered the criteria responses for those with a diagnosis of SSI, the source data and the microbiology in relation to its use in CDC.

The collection of surgical site infection data was highly informative both when considering capture of infection, but also in terms of how a larger scale study would need to be resourced and designed.

The CDC definition is principally a tool for surveillance, but it is recognised for use in interventional studies(1, 2, 28). The definition has had modifications over time such as the inclusion and exclusion of certain criteria. The current definition reported by CDC was used for this study as outlined in the protocol and is based on previous experience with other large scale trials(2, 190). The responses across the 4 criteria outlined in the protocol were relatively balanced; that is to say no one criterion appeared to be driving the overall observed rate of SSI. Different organisations modify this definition; indeed the current published surveillance guidance from Public Health England uses additional parameters such as 'diagnosis by clinician'. It also reports surveillance up to 12 months where CDC had revised their time point to 90 days for implant-based surgery(40). The PHE case definition is of particular relevance as this is the benchmark by which SSI rates are noted across England and Wales (193).

The source data for this study were either telephone contact, in person review at the study site or using the medical record.

Broadly speaking, evidence around post-discharge surgical site infection capture is weak(194). The evidence is also heavily focussed on routine surveillance, and not the research setting for testing interventions. Additionally there is no formally recognised 'gold standard' against which different methods can be tested.

From the outset of the WHISH study, it was clear that an unknown proportion of patients would need to be assessed outside of the study centres at the 30 day mark over the telephone. This was largely pragmatic. The decision to assess over the telephone was based on the feedback from the patient and public members of the WHiTE cohort who indicated that additional hospital visits, for research

purposes only, would be highly unacceptable. In addition hip fracture patients, except those receiving total hip replacement, have no formal routine clinical follow up; recalling patients for formal healthcare professional review would also be prohibitively expensive.

The assessment of the medical records of patients who responded by telephone sought to gain an understanding of how accurate telephone contact was for identifying SSI relative to the alternative of using only the medical record. Those who reported SSI over the telephone were assumed to be correct. This is supported to a limited extent by studies that compared patient reported wound infection to either medical record or clinical review (195, 196).
Of similar concern was the possibility that telephone based follow up would miss cases of SSI. Our 10% sample of cases that had an additional review of medical records after 4 month follow up identified no further surgical site infections. Given the practical limitations of working with this population, telephonic follow up would seem to be of benefit in capturing cases of SSI above and beyond the review of site based medical records.

The study criteria for diagnosing SSI in WHISH did not require the use of microbiology as outlined in the CDC criteria(144). However when those who met the associated criteria (an open or opened wound with the pain, tenderness or fever -hereafter referred to as 'criterion 2') had their records interrogated, 8 of the 9 patients did have positive microbiological samples. The one patient with no positive microbiology result did not have any samples taken. Therefore these 9

cases would still meet the CDC criteria with the microbiology component retained.

However the use of microbiology for diagnosis is far from clear, particularly in the hip fracture cohort. The data from CPRD in chapter 4 highlight just how prevalent the use of antibiotics is in this population, even before their injury. The background level of antibiotic treatment in combination with the prophylactic measures taken such as induction antibiotics and antibiotic loaded cement in the arthroplasty cases still make the interpretation complex. Particularly at the scale required for a definitive trial using SSI as an outcome.

Of the patients with SSI, relatively few underwent further surgery. Of those who did, debridement was the most common procedure. This can be explained by the relatively short period of follow up in WHISH (4 months), and the likely high threshold for further surgery in hip fracture patients. This mirrors the findings in the NHFD. The 2017 NHFD report included 65,645 patients; they identified only 554 reoperations at 120 days (0.8%) (197). Although their data completeness at the 120 day time point was noted to be poor.

The data from WHISH, as well as chapters 2 & 4 would therefore suggest that reoperation in all forms is a poor means by which to capture and understand SSI. There were no untoward safety issues related to the incisional negative pressure wound therapy within the study.

A definitive RCT of this topic can be deemed feasible. The rate of SSI observed is higher than suggested in literature synthesis, administrative and routine

surveillance data. This has important downstream implications for sample size calculations for trials assessing SSI as a primary outcome measure.

It was unclear before beginning the study how well patients would be recruited and retained within the study. In this respect, the study appears to have functioned successfully. All five centres recruited well, there were few issues with clinical equipoise or study compliance. The only exception being the appropriateness of intramedullary nail devices for the iNPWT dressing.

The situation of the study within a broader cohort was a significant benefit. In particular the site expertise at identifying eligible patients, and recruiting them using the Mental Capacity Act was all based on their experience in the broader WHiTE cohort and previous related trials. This adds significantly to both the external validity of the trial results and the speed at which recruitment took place.

The capture of patient infection data was complicated and required significant resources at both the site and central trial study team. Given the typical length of stay for a hip fracture patient is 23 days, it was anticipated that 30 day follow up would be primarily at the site. In fact, the majority of patients were followed up over the telephone. This is further complicated by the fact that patients are often transitioning to alternative care arrangements at this thirty-day point. Despite these difficulties, the rate observed was plausible and all patients were assessed against recognised criteria for surgical site infection. Further discussions around implications for sample size are included in the conclusion chapter of the thesis.

7 Conclusions and Scope for Future Work

This concluding chapter will review the aims of the previous chapters of work, consider how the data from each study interact and discuss the considerations going forward for a full formal randomised trial comparing incisional negative pressure wound therapy to standard care.

7.1 Review of Objectives

- To systematically review and synthesise where appropriate the published evidence around SSI in hip fracture.
- To examine the diagnosis of SSI in large scale primary and secondary care administrative datasets of patients with hip fracture.
- To estimate the rate of SSI in a feasibility randomised controlled trial comparing iNPWT and standard care in hip fracture surgery.

7.2 Review of Findings

7.2.1 Systematic Review

From 5,926 unique papers, 20 studies were eligible for inclusion. These studies included reports of hip fracture surgery in general as well as specific subtypes such as hemiarthroplasty. A range of study designs and SSI outcomes were used. Overall pooled estimates for hip fracture surgery SSI rate was 2.08%. There was considerable heterogeneity between studies. There were considerable sources of bias that would suggest under reporting across the literature.

7.2.2 Administrative Data

Thirteen thousand cases of hip fracture in primary care were analysed alongside a subset of 6,239 patients from secondary care. This work used a range of code lists to define both SSI and related treatments. It also sought to explore the uncertainty around using administrative data by examining best and worst-case scenarios. The overall best estimate from this data set was between 1.4% and 1.7%.

7.2.3 Randomised Feasibility Trial

The final piece of work was a 464 patient feasibility randomised controlled trial. This study identified a higher rate of SSI than the other two streams of work- 4.2% at 30 days and 4.4% at 120 days. A number of feasibility outcomes were realised such as the willingness of patients and clinicians to engage with a study of this nature and intervention.

7.2.4 Strengths

Taken as a whole, this thesis addresses the existing understanding of the rate of SSI, in a holistic manner. It has attempted to use a range of tools available to the clinical researcher to triangulate an estimate to inform future studies, particularly of interventional studies.

The strengths of this work can focus on the use of large numbers of observations, and a UK focus. The sources of data are an additional strength in that each study considered data from multiple centres within the UK. The applicability of the results ought to be broad. This is particularly important for SSI as there is likely

to be variation in a wide range of factors that contribute to rates observed. This includes but is not limited to variation in nursing care, staffing ratios, wound care protocols, antibiotic prophylaxis regimens, surgical implant use and operating theatre management.

Future work must account for this, in order to avoid spurious inferences which may reflect practice variation.

7.2.5 Limitations

It was not possible to apply a consistent case definition across all 3 work packages. This was a function of external factors such as the code dictionaries used for administrative data, and the wide variation in the use of definitions across the UK literature. The effect of this limitation can be tentatively explored by considering the reported infection rates from the literature with formal case definition and comparing them to WHISH which used the CDC definition. This gives a rate of 1.29% and 4.4% respectively. This does not explain the significant difference observed. What seems much more likely is the quality and comprehensiveness of the follow up in WHISH contributes to the observed differences.

Study specific limitations have been discussed in their respective chapters, however none of these would seem to account definitively for the observed difference between the three work streams. In particular between the WHISH study and the other two studies.

7.3 Considerations For Further Studies In Hip Fracture SSI

The work undertaken has interesting implications for the on going monitoring of SSI in hip fracture. The current work by Public Health England already was understood to have limitations, which would appear to be reinforced by the findings presented here(44).

The WHISH study ran over a relatively short time period of 6 months. A longer duration of study may reveal variation in time, not seen here. Cases of SSI may cluster and not appear consistently over time. There are not enough events here to explore this possibility, so a larger scale observational study may reveal patterns in events. In turn this may offer insights into risk and suitable interventions.

7.3.1 Outcome Measures

The CDC definition and processes used in this feasibility study appeared to work effectively. The use of recognised and clinically relevant criteria gives the study important face validity. The difficulty is that the use of 30 day phone calls is highly labour intensive. Any full-scale study will need significantly more patients to improve confidence in any treatment effect seen. Undertaking the follow up calls at a later time point would retain the benefit of individual patient engagement, but when they are more settled in their post injury care setting e.g. residential care.

The use of 'prescription of antibiotics for wound infection' as an outcome is appealing as it is a very specific piece of data. Indeed this forms part of the PHE surveillance criteria (40). The benefits of this would be a very specific piece of

data that should be recorded in both primary and secondary care.

Conventionally most treatments for SSI routinely involve some course of antibiotics. However as seen in the CPRD data this may not be easy to determine from routinely collected data. The lack of condition specificity for antibiotics in SSI as well as the relatively high background rate of prescription means that indication for prescription would be a critical parameter to capture reliably.

As has been seen in the literature, some studies report infection on the basis that a patient required further surgery. On the one hand this would appear to be robust in that confidence in diagnosis can be high with robust reporting of operative findings and the possibility of taking samples. This also has its limitations.

Specifically, there are additional considerations, which are particularly pertinent for hip fracture patients. Often patients may be considered to be too unwell to tolerate further surgery. In this circumstance patients may be treated indefinitely with antibiotics. In a similar vein, patients may be treated with extensive courses of antibiotics until the fracture has healed (where treated with internal fixation) before further intervention is contemplated . This means any study seeking out further surgery must have extended periods of follow up. Long follow up periods add in additional complexity with withdrawals, loss to follow up and death. In turn this requires increasing reliance on statistical inferences generated using models and assumptions. This is inferior to directly observed data.

The rate of further surgery seen here in the 4-month window may well be higher if the study patients were followed up for an extended period of time. There are additional external factors such as shifting paradigms of care. Metsemakers and

colleagues suggest a low threshold for surgical exploration for suspected 'Fracture related infection' cases(198). Widespread adoption of this guidance may see rates of reoperation grow.

The low rate of revision surgery seen in WHISH and the synthesis of published literature would have significant implications on any power calculations undertaken for a definitive study. This is discussed more extensively below.
The primary outcome of this study was to determine the rate of deep SSI in the surgically treated hip fracture population. This was a critical parameter to define, as the rate of infection is a fundamental determinant of a definitive trial sample size. The role of sample size is to *a priori* establish how many patients would need to be included to detect a particular difference in treatment effect with statistical confidence. The process of undertaking sample size calculations for clinical effectiveness research can be informed by guidance such as DELTA 2(199). This framework identifies best practice in determining the assumptions and parameters that feed into a meaningful sample size calculation. In particular how to determine the 'target difference' also referred to as the Minimally Clinical Important Difference (MCID).
DELTA outlines several key steps to undertake for this process. Two important sources of determining what might be considered the MCID for any interventional study can be determined by the literature or the community affected by the condition.

Literature

Chapter 2 explored the rate of infection identified in the literature for patients undergoing surgery for hip fracture. The point estimate rate of infection across

the 11 studies was 2.08%. However there is heterogeneity, particularly within study design and outcome definition that makes this synthesis unsuitable in isolation to inform a definitive study.

Regarding iNPWT as the intervention, there is only one study that sought to study its efficacy in a randomised trial (78). In this case, only a surrogate outcome measure was used and therefore is limited in informing a trial that seeks to establish difference in rate of SSI.

Other studies of SSI in hip fracture have focussed on patients undergoing certain types of surgery e.g. hemiarthroplasty(103, 111). Hargrove and colleagues did not specify a sample size calculation for their study, but did demonstrate an absolute reduction of 10 % in all surgical site infections, and a reduction of 3.4% in deep SSI.

Sprowson and colleagues also showed a reduction in SSI in their quasirandomised study, although at lower rates (3.5% vs. 1.1%)(111). A larger study based on this work is being undertaken, in this they have speculated on a meaningful clinically important reduction in SSI being 1.5% i.e. a reduction from 3% to 1.5% WHiTE 8 (ISRCTN15606075).

The range of events and effect sizes seen here, in two studies with important limitations in their methods would not seem to offer sufficiently robust information on which to base a definitive sample size on.

Other studies in different types of orthopaedic trauma patients (e.g. open fracture) are limited in their applicability to the relatively low event rate seen in hip fracture.

Clearly the WHISH trial data present an insight into what might be an effect size for iNPWT. The primary outcome analysis for the feasibility study presented, although ancillary, did actually reach statistical and clinical significance. The principal limit on being able to use these data to recommend iNPWT is that there remains considerable uncertainty around each point estimate, and the effect of adding a single further case of infection was to nullify the statistical significance. The 'fragility' of the data to the addition of a single further case highlights the need for definitive study before recommendations can be made(200).

Clinical Stakeholders

An alternative, preferred approach, to powering a full study could use an effect size based on clinical importance and likelihood to change practice. Delta 2 guidance highlights several key areas regards to the determining the MCID in a study like WHISH. Firstly it is self evident that any reduction in adverse events, of which SSI can be considered an example, is important. Additionally where work is needed to determine the size of difference of importance opinion seeking or anchoring are to be preferred and the target difference specified in a particular study should be important to at least one stakeholder group. To address these considerations, the WHISH feasibility data were presented at the Orthopaedic Trauma Society (OTS) annual meeting in January 2019. This meeting represents the interests of the surgical community treating patients with hip fracture. A series of possible effects were presented to the members of this meeting and discussion undertaken. After considering reductions of 1%, 2% and 3% in the rate of SSI, it was determined that a reduction of over 1% in rate of SSI in a clinical trial would be sufficient to change practice. It is worth noting though that this is speculation as to whether a true change in practice would be achieved.

This insight from the clinical stakeholder can then be combined with the feasibility data to infer the sample size of a definitive study of incisional negative pressure wound therapy in hip fracture surgery.

In table 7-1 a 'thought experiment' is presented where possible rates of reduction are presented with the accompanying sample sizes. Power was set at 90% and two-sided significance at 5%. The hypothetical test of proportions was the Chi squared test.

The WHISH rate of SSI at 4 months was used for a baseline event rate round to the nearest whole number (4 %). An alternative event rate of 6% (based on the control arm only) is also presented. Reductions of 1.5%, 2% and 3% were calculated in turn to explore the implications for sample size.

Table 7-1 Sample Size Calculations For Definitive Trial

Outcome	Event rate	Inferred important effect reduction	Sample Size (Total)
CDC SSI	**4%**	**1.5%**	**5,870**
CDC SSI	4%	2%	3,054
CDC SSI	4%	3%	1,136
CDC SSI	6%	1.5%	9,288
CDC SSI	6%	2%	4,988
CDC SSI	6%	3%	2,004

Overview of possible sample size for full scale randomised controlled trial, based on an overall SSI event rate of 4% or control group event rate 6%.

Given the parameters outlined in table 7-1, the proposed sample size to take forward for this study would be 5,870 patients.

7.3.2 Withdrawals

Withdrawal patients present an additional consideration for sample size calculations and future study design. This is of particular interest due to the nature of the consent process used in the WHiTE cohort in general and WHISH in particular.

The cohort and its embedded trials use the Mental Capacity Act to enrol patients undergoing emergency surgery; the full process is outlined in the protocol chapter. The use of professional and nominated consultees gives scope for patients to decline consent and leave the study after randomisation and entry. This presents both methodological and practical considerations.

Methodological considerations relate to the loss of patients from the study that have been exposed to the intervention of interest. It is possible that there are systematic reasons why certain patients withdraw from studies e.g. dislike of intervention/complication. By virtue of withdrawing such observations cannot be made and misleading conclusions may be drawn. In the specific scenario of WHISH, the withdrawn patients may have had the outcome of interest, however this is unknown.

In full scale powered studies, patients who withdraw may undermine the sample size calculations. The typical approach to this is to add in more patients based on the anticipated withdrawal rate. This can restore power, but assumes a 'like-for like' replacement of additional patients for withdrawn patients. As the patients have withdrawn, it is impossible to determine the truth of this possibility.

Alternative approaches for dealing with withdrawn patients include imputation and 'best case -worst case scenario'. In imputation the observed rate of events is

extrapolated to the withdrawn population and included in the analysis. This restores the original study population(201). Sensitivity analyses can then explore the difference including these imputed data would make. This analytic technique is widespread, but still relies on an assumption that the withdrawn population are similar to the retained in study population.

The 'best case -worst case scenario' makes no such assumption and considers a range, allowing for uncertainty. However this too has limits and in the example of WHISH adding in a 'worst case scenario' would involve adding 33 additional cases of SSI. This is more than was observed across the retained population and would not be considered clinically plausible.

There would not appear to be a good solution to the withdrawn population issue here. The use of the MCA is a critical component of study external validity, particularly in emergency care and patients who lack capacity. The addition of patients to the sample sizes suggested above to take withdrawals into account allows meaningful inferences to be drawn from the study data collected. The remaining uncertainty around what happens to withdrawn patients should be explained in any resultant communication of results.

7.4 Conclusion

The work in this thesis had attempted to look at three different work streams to get a better understanding of the rate of surgical site infection after hip fracture surgery. In the process, the strengths and limitations of each approach have been considered, and an estimate obtained. The principle 'take home message' must be that the rate of SSI is highly influenced by how you look and how hard you look.

Within this overarching aim was the consideration about how to power an interventional study to examine the effects of treatments aiming to reduce SSI. In this instance, incisional negative pressure wound therapy was chosen. The final two chapters demonstrated feasibility both from an SSI event rate perspective, but other important feasibility measures like outcome capture and recruitment. Designing and implementing a definitive study which was able to answer the clinical effectiveness questions for incisional negative pressure wound therapy could have looked for emerging efficient study designs such as 'data enabled trials.'

Data enabled trials use routinely collected data in patients who have been randomly allocated to different interventions, typically at treating centre level. The advantages of this type of study include highly efficient recruitment and outcome collection. In particular the outcome collection typically uses administrative data such as the Hospital Episode Statistics (HES). Studies of infection would appear to be well suited to the large-scale data collection possible through this method. However the work undertaken in this thesis raises important questions around the suitability of such an approach. In particular the work undertaken in chapters 3 and 4 highlight the limitations of administrative data in capturing infection outcomes. In addition the poor reciprocal coding between the two data sources studied in these chapters would likely be an important limitation for any such study. This work when considered alongside the WHISH trial would suggest that a traditional study design would be most suitable for studying SSI in hip fracture patients. The work undertaken here may

be an important piece of preparatory work before selecting the exact study design and method for low event outcome such as SSI.

The importance of continued assessment and surveillance of SSI in general is only likely to grow. The impetus on reducing nosocomial infections is only likely to increase with the growing threat of antibiotic resistance.

Future Directions

Having completed this work, and shown the full scale trial to be feasible, my plan is to apply to the National Institute for Health Research Health Technology Assessment programme for funding. Alongside this, I will engage with industry to support the excess treatment costs.

No significant change to the methodology is planned, and therefore the data collected in the feasibility may be retained for inclusion in the definitive trial. Approval from the ethics committee has been granted for the use of these data for this purpose.

8 Appendices

8.1 Appendix 1a Rerun search string from Hyldig et al in MEDLINE(77)

(incisions[All Fields] OR incision[All Fields] OR (("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgical"[All Fields]) AND incisions[All Fields]) OR incisional[All Fields]) AND (("negative-pressure wound therapy"[MeSH Terms] OR ("negative-pressure"[All Fields] AND "wound"[All Fields] AND "therapy"[All Fields]) OR "negative-pressure wound therapy"[All Fields] OR ("negative"[All Fields] AND "pressure"[All Fields] AND "wound"[All Fields] AND "therapy"[All Fields]) OR "negative pressure wound therapy"[All Fields]) OR ((("surgical procedure! s, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgical"[All Fields]) AND ("injuries"[Subheading] OR "injuries"[All Fields] OR "wounds"[All Fields] OR "wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields])) AND (subatmospheric[All Fields] OR "sub atmospheric"[All Fields] OR (negative[All Fields] AND ("pressure"[MeSH Terms] OR "pressure"[All Fields])) OR ("vacuum"[MeSH Terms] OR "vacuum"[All Fields]) OR "negative suction drainage"[All Fields] OR "vacuum assisted closure"[All Fields])))

Appendix 1b Rerun search string from Hyldig et al in Embase

1 ((incisions or incision or surgical incisions or incisional) and (negative pressure wound therapy or (surgical wounds and (subatmospheric or "sub atmospheric" or negative pressure or vacuum or "negative suction drainage")))).mp.
2 vacuum assisted closure.mp. or exp vacuum assisted closure/ 649
3 exp skin incision/ or surgical incisions.mp. 711
4 2 and 3 18
5 1 or 4 62
6 limit 5 to yr="2015 -Current" 57
7 limit 6 to updaterange="emedx(20190122160128-20190123161855],emexb(20190122160128-20190118084145]"

8.2 Appendix 2 PROSPERO registration document for Chapter 2

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

A systematic review of studies reporting the rate of surgical site infection after hip fracture surgery in the united kingdom

James Masters

Citation

James Masters. A systematic review of studies reporting the rate of surgical site infection after hip fracture surgery in the united kingdom. PROSPERO 2017 CRD42017050685 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017050685

Review question

What is the rate of surgical site infection in hip fracture surgery in patients treated in the United Kingdom?

Searches

MEDLINE
Embase
English Language only
Inception to May 2018 for search
Only studies published after 2000 included.

Types of study to be included

Any original study which seeks to identify surgical site infection as a specific outcome measure after hip fracture surgery of greater than 100 patients published on patients treated in the United Kingdom.

Condition or domain being studied

Surgical Site Infection in Hip Fracture Surgery

Participants/population

Adults having surgical treatment for hip fracture in the United Kingdom.

Intervention(s), exposure(s)

Exposure: any surgical treatment of hip fracture excluding external fixation

Comparator(s)/control

Not applicable.

Context

Studies must focus on the 'typical hip fracture cohort' i.e. not extremes of age or injury mechanism.

Main outcome(s)

Surgical Site infection (SSI) as defined by study.

Timing and effect measures

Minimum follow up of 30 days after surgery.

Additional outcome(s)

Reoperation.

Other adverse outcome.

Data extraction (selection and coding)

Name of study
Date of study
Country of origin
Study period
Retrospective or prospective

Study type
Definition of SSI
Number of hip fracture operations
Types of hip fracture surgery
Number of SSI diagnoses made
Number of reoperations for infection
Gender ratio of patients
Average age

Risk of bias (quality) assessment
Newcastle-Ottowa scale-modified

Strategy for data synthesis
An assessment of study heterogeneity will be made by analysing the data extracted and characteristics. Where there is sufficient clinical homogeneity in respect to population characteristics, a meta-analysis will be undertaken for those specific outcomes. Due to anticipated heterogeneity in study design, definition and follow up procedure, a random effects model will be used with an appropriate expression of uncertainty.

Analysis of subgroups or subsets
If possible, subgroup analysis will be undertaken to look at any differences in infection between patients undergoing fixation or arthroplasty-the two broadest categories for hip fracture treatment. Sensitivity analysis will examine study definition of outcome (SSI) and study size.

Contact details for further information
James Masters
james.masters@ndorms.ox.ac.uk

Organisational affiliation of the review
Oxford Trauma

Review team members and their organisational affiliations
Mr James Masters.

Collaborators
David Metcalfe. NDORMS
Matt Costa. NDORMS

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English

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England

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PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Subject indexing assigned by CRD

Subject index terms
Hip Fractures; Humans; Pelvic Bones; Surgical Wound Infection

Date of registration in PROSPERO
28 February 2017

Date of publication of this version
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Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Versions
28 February 2017
09 January 2018
15 March 2019

PROSPERO
This information has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites.

8.3 Appendix 3 PRISMA statement for chapter 2

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	42
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A no chapter specific abstract included in thesis
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	43-45 as well as introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	47
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	46 & appendix
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language,	47

		publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	46 & 47
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	48 & figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	50-51
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	50 & Appendix 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	51-52 & appendix 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	51

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	51

8.4 Appendix 4 MOOSE checklist for Chapter 2

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	45
2	Hypothesis statement	-
3	Description of study outcome(s)	45
4	Type of exposure or intervention used	47
5	Type of study designs used	49
6	Study population	45 & 47
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	42 & 48
8	Search strategy, including time period included in the synthesis and key words	Appendix 3, 46
9	Effort to include all available studies, including contact with authors	48 & 50
10	Databases and registries searched	46
11	Search software used, name and version, including special features used (eg, explosion)	46
12	Use of hand searching (eg, reference lists of obtained articles)	48
13	List of citations located and those excluded, including justification	Fig 1 & 54
14	Method of addressing articles published in languages other than English	47
15	Method of handling abstracts and unpublished studies	47
16	Description of any contact with authors	50
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	55
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	50
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	50
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	-
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	51-52

22	Assessment of heterogeneity	51
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	51
24	Provision of appropriate tables and graphics	Tables 1-3, Figures 1-8
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 2-3 & 2-4
26	Table giving descriptive information for each study included	Table 2-2
27	Results of sensitivity testing (eg, subgroup analysis)	71-73 Fig 2,3 & 8
28	Indication of statistical uncertainty of findings	Figures 2-4 to 2-8

8.5 Appendix 5 Search string run in both MEDLINE and Embase for study identification chapter 2

1. hip fracture/ or exp femur intertrochanteric fracture/ or exp femur neck fracture/ or exp femur pertrochanteric fracture/ or exp femur subtrochanteric fracture/ or exp femur trochanteric fracture/

2. *hip fracture/ or exp *femur intertrochanteric fracture/ or exp *femur neck fracture/ or exp *femur pertrochanteric fracture/ or exp *femur subtrochanteric fracture/ or exp *femur trochanteric fracture/

3. (hip* adj9 fractu*).ti,ab.

4. (hip* adj9 break*).ti,ab.

5. (proximal femur* adj9 fractur*).ti,ab.

6. (proximal femur* adj9 break*).ti,ab.

7. 2 or 3 or 4 or 5 or 6

8. 1 or 3 or 4 or 5 or 6

9. hip surgery/

10. *hip surgery/

11. surg*.ti,ab.

12. operat*.ti,ab.

13. proced*.ti,ab.

14. replacement arthroplasty/ or hip replacement/ or total arthroplasty/

15. *replacement arthroplasty/ or *hemiarthroplasty/ or *total arthroplasty/

16. fracture fixation/ or intramedullary nailing/ or plate fixation/

17. *fracture fixation/ or *intramedullary nailing/ or *plate fixation/

18. orthopedic fixation device/ or bone plate/ or femoral fixation device/

19. *orthopedic fixation device/ or *bone plate/ or *femoral fixation device/

20. fixation*.ti,ab.

21. 10 or 11 or 12 or 13 or 15 or 17 or 19 or 20

22. 9 or 11 or 12 or 13 or 14 or 16 or 18 or 20

23. infection rate/

24. *infection rate/

25. (rate* adj3 infection*).ti,ab.

26. infect*.ti,ab.

27. *infection/ or *"bone and joint infections"/ or *device infection/ or *healthcare associated infection/ or *infection complication/ or *infection rate/

28. infection/ or "bone and joint infections"/ or device infection/ or healthcare associated infection/ or infection complication/ or infection rate/

29. surgical infection/ or "infections associated with other infections or conditions"/ or infectious complication/ or postoperative complication/

30. *surgical infection/ or *"infections associated with other infections or conditions"/ or *infectious complication/ or *postoperative complication/

31. 23 or 25 or 26 or 28 or 29

32. 24 or 26 or 27 or 30

33. 8 and 22 and 31

8.6 Appendix 6 Data Fields Extracted Chapter 2

Study Author
Year of publication
Journal
Site of study
Years of study
Prospective or retrospective study
Patient cohort i.e all types of hip fracture or certain subsets of surgical care
Number of patients
Follow up
Criteria for diagnosing surgical site infection
Total number of infections
Superficial infections
Deep Infections
Reoperation for infection
Number of Total Hip Replacements
Number of Total Hip Replacements with SSI
Number of hemiarthroplasty
Number of hemiarthroplasty with SSI
Number of intramedullary nail
Number of intramedullary nail with SSI
Number of cannulated screws
Number of cannulated screws with SSI
Number of sliding hip screw
Number of sliding hip screw with SSI
Mean age of cohort in study
Gender ratio of cohort

8.7 Appendix 7 Newcastle-Ottawa scale for assessing quality of non-randomised studies as modified for chapter 2.

A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

~~2) Selection of the non exposed cohort~~
   ~~a) drawn from the same community as the exposed cohort ✸~~
   ~~b) drawn from a different source~~
   ~~c) no description of the derivation of the non exposed cohort~~

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

~~4) Demonstration that outcome of interest was not present at start of study~~
   ~~a) yes ✸~~
   ~~b) no~~

~~Comparability~~

~~1) Comparability of cohorts on the basis of the design or analysis~~
   ~~a) study controls for _____ (select the most important factor) ✸~~
   ~~b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)~~

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

The sections with lines struck through were not used to assess the quality of the included studies

8.8 Appendix 8 Reasons For Exclusion For Chapter 2

Wrong study design 5	Agarwal(202), Bell(203), Hossain(204), Manoharan (205), Wijerantna(206),
Wrong population 11	Bridle(207), Chan(208), Dawe(209), Grammatopoulos(210), Johnston(211), Hahnel(212), Hapuarache(213), Hay(214), Shukla(215), Shukla(216), Tai(217)
Not in UK 2	Henderson(218), Hunter(219)
Too few patients 3	Dawson(220), Mabrouk(221), Middleton(222),
Wrong outcome 5	Fox(223), Jennings(224), Jonas(225), Wood(226), Wordsworth(227),
Inadequate follow up 3	Sanchez-Ballester(228), Umarji(229), Yassa (138)

8.9 Appendix 9 Schoenfeld Residuals

Covariate	rho	chi2	Degrees of freedom	Prob>chi2
Charlson Comorbidity Index				
0	.	.	1	.
1	-0.042	0.14	1	0.71
2	-012	1.16	1	0.28
3	0.04	0.14	1	0.71
Diagnosis of chest or urine infection in 90 days prior to index admission				
No	.	.	1	.
Yes	0.01	0	1	0.96
Gender				
Female	.	.	1	.
Male	0.11	1.08	1	0.30
Age				
50-60	.	.	1	.
60-70	0.09	0.68	1	0.41
70-80	0.18	2.87	1	0.09
80-90	0.15	2.14	1	0.14
Antibiotics prior to index admission				
Yes	0.04	0.14	1	0.71
Smoking				
No	.	.	1	.
Yes	-0.14	1.75	1	0.19
Former	0.03	0.06	1	0.71
Deprivation Index				
LEAST	.	.	1	.
LESS	-0.03	0.10	1	0.75
MID	-0.07	0.50	1	0.48
MORE	-0.17	2.59	1	0.11
MOST	-0.03	0.07	1	0.79
Body Mass Index				
<18.5 underweight	.	.	1	.
18.5-24.9 normal	0.01	0.00	1	0.95
25-29.9 overweight	0.06	0.30	1	0.58
30-34.9 Class 1 obesity	0.06	0.39	1	0.53
35-39.9 Class 2 obesity	-0.02	0.04	1	0.85
> 40.0 Class 3 obesity	0.24	5.28	1	0.02
Global test		18.90	20	0.52

8.10 Appendix 10 Code Lists For Identifying Procedures

OPCS codes for Revision-Arthroplasty (4th Edition)	Description
W370	Conversion from previous cemented total prosthetic replacement of hip joint
W372	Conversion to total prosthetic replacement of hip joint using cement
W373	Revision of total prosthetic replacement of hip joint using cement
W374	Revision of one component of total prosthetic replacement of hip joint using cement
W380	Conversion from previous uncemented total prosthetic replacement of hip joint
W382	Conversion to total prosthetic replacement of hip joint not using cement
W383	Revision of total prosthetic replacement of hip joint not using cement
W384	Revision of one component of total prosthetic replacement of hip joint not using cement
W390	Conversion from previous total prosthetic replacement of hip joint NEC
W392	Conversion to total prosthetic replacement of hip joint NEC
W393	Revision of total prosthetic replacement of hip joint NEC
W395	Revision of one component of total prosthetic replacement of hip joint NEC
W430	**Conversion from previous cemented total prosthetic replacement of joint NEC**
W432	**Conversion to total prosthetic replacement of joint using cement NEC**
W433	**Revision of total prosthetic replacement of joint using cement NEC**
W434	**Revision of one component of total prosthetic replacement of joint using cement NEC**
W440	**Conversion from previous uncemented total prosthetic replacement of joint NEC**
W442	**Conversion to total prosthetic replacement of joint not using cement NEC**
W443	**Revision of total prosthetic replacement of joint not using cement NEC**
W444	**Revision of one component of total prosthetic replacement of joint not using cement NEC**
W450	**Conversion from previous total prosthetic replacement of joint NEC**
W452	**Conversion to total prosthetic replacement of joint NEC**
W453	**Revision of total prosthetic replacement of joint NEC**
W455	**Revision of one component of total prosthetic replacement of joint NEC**
W462	Conversion to prosthetic replacement of head of femur using cement
W463	Revision of prosthetic replacement of head of femur using cement
W472	Conversion to prosthetic replacement of head of femur not using cement
W473	Revision of prosthetic replacement of head of femur not using cement
W482	Conversion to prosthetic replacement of head of femur NEC
W483	Revision of prosthetic replacement of head of femur NEC
W520	**Conversion from previous cemented prosthetic replacement of articulation of bone NEC**
W522	**Conversion to prosthetic replacement of articulation of bone using cement NEC**
W523	**Revision of prosthetic replacement of articulation of bone using cement NEC**
W533	**Revision of prosthetic replacement of articulation of bone not using cement NEC**
W540	**Conversion from previous prosthetic replacement of articulation of bone NEC**
W542	**Conversion to prosthetic replacement of articulation of bone NEC**
W543	**Revision of prosthetic replacement of articulation of bone NEC**
W572	**Primary excision arthroplasty of joint NEC**
W574	**Conversion to excision arthroplasty of joint**
W580	**Conversion from previous resurfacing arthroplasty of joint**
W582	**Revision of resurfacing arthroplasty of joint**
W930	Conversion from previous hybrid prosthetic replacement of hip joint using cemented acetabular component
W932	Conversion to hybrid prosthetic replacement of hip joint using cemented acetabular component
W933	Revision of hybrid prosthetic replacement of hip joint using cemented acetabular component
W940	Conversion from previous hybrid prosthetic replacement of hip joint using cemented femoral component
W942	Conversion to hybrid prosthetic replacement of hip joint using cemented femoral component
W943	Revision of hybrid prosthetic replacement of hip joint using cemented femoral component
W950	Conversion from previous hybrid prosthetic replacement of hip joint using cement NEC
W952	Conversion to hybrid prosthetic replacement of hip joint using cement NEC
W953	Revision of hybrid prosthetic replacement of hip joint using cement NEC

Codes in bold were combined with anatomical specifiers for the hip Z761, Z756 & Z834	
OPCS codes for Revision-Fixation	Description
O17.1	Remanipulation of intracapsular fracture of neck of femur and fixation using nail or screw
W26.3	**Remanipulation of fracture of bone and skeletal traction NEC**
W26.4	**Remanipulation of fracture of bone NEC**
W28.3	**Removal of internal fixation from bone NEC**
O17.2	**Remanipulation of fracture of long bone and rigid internal fixation NEC**
O17.3	**Remanipulation of fracture of long bone and flexible internal fixation HFQ**
O17.5	**Remanipulation of fragment of bone and fixation using screw**
O17.6	**Remanipulation of fracture of bone and fixation using plate**
O17.8	**Other specified secondary closed reduction of fracture of bone and internal fixation**
O17.9	**Unspecified secondary closed reduction of fracture of bone and internal fixation**
W26.8	**Other specified other closed reduction of fracture of bone**
W26.9	**Unspecified other closed reduction of fracture of bone**
W25.3	**Fixation Bone External & Remanipulation Fracture**
W23.1	**Secondary open reduction of fracture of bone and intramedullary fixation**
W23.2	**Secondary open reduction of fracture of bone and extramedullary fixation HFQ**
W23.3	**Secondary open reduction of intra-articular fracture of bone**
W23.4	**Secondary open reduction of fracture of bone and skeletal traction HFQ**
W23.5	**Secondary open reduction of fracture of bone and external fixation HFQ**
W23.6	**Secondary open reduction of fracture of bone and internal fixation HFQ**
W23.8	**Other specified secondary open reduction of fracture of bone**
W23.9	**Unspecified secondary open reduction of fracture of bone**
W67.1	**Secondary open reduction of fracture dislocation of joint and skeletal traction HFQ**
W67.2	**Secondary open reduction of traumatic dislocation of joint and skeletal traction NEC**
W67.4	**Secondary open reduction of traumatic dislocation of joint NEC**
W67.6	**Remanipulation of traumatic dislocation of joint**
W67.7	**Secondary open reduction of fracture dislocation of joint and internal fixation NEC**
W67.8	**ther specified secondary reduction of traumatic dislocation of joint**
W67.9	**Unspecified secondary reduction of traumatic dislocation of joint**
W62.1	**Primary arthrodesis and internal fixation of joint NEC**
W62.2	**Primary arthrodesis and external fixation of joint NEC**
W62.8	**Other specified other primary fusion of other joint**
W62.9	**Unspecified other primary fusion of other joint**
Codes in bold were combined with anatomical specifiers for the hip Z761, Z756 & Z834 as appropriate	

OPCS codes for Revision-Attention to hip joint	Description
W394	Attention to total prosthetic replacement of hip joint NEC
W454	**Attention to total prosthetic replacement of joint NEC**
W544	**Attention to prosthetic replacement of articulation of bone NEC**
W954	**Attention to hybrid prosthetic replacement of hip joint using cement NEC**
Codes in bold were combined with anatomical specifiers for the hip Z761, Z756 & Z834 as appropriate	

8.11 Appendix 11 List Of Antibiotics Used In CPRD-Identified In BNF

Clindamycin
Amoxicillin
Flucloxacllin
Clarithromycin
Co-amoxiclav
Ampicillin

8.12 Appendix 12 Certificate for the completion of OCTRU audit

OCTRU
Oxford Clinical Trials Research Unit

Audit Completion Certificate

This is to confirm that the CAPA for Audit Reference OA-054 for the WHISH Trial is complete and the audit is closed

Audit reference: OA-054
Lead Auditor: Joanna Black
Date of Audit report: 23May2018
Date of Audit response: 06Jun2018
Date audit confirmed closed by the auditee: 09Aug2018

UKCRC Registered Clinical Trials Units

Signature of Lead Auditor:
Date: 22Aug2018



8.13 Appendix 13 CONSORT checklist for WHISH trial (Feasibility Extension)

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	132
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	No dedicated abstract for trial within thesis
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	27-38
	2b	Specific objectives or research questions for pilot trial	118
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	121
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	119-120
	4b	Settings and locations where the data were collected	119
	4c	How participants were identified and consented	119-120
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	122
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	123-125, 126
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	129-130
Sample size	7a	Rationale for numbers in the pilot trial	128
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	121

	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	121
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	121
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	121
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	121-122
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	129
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	Table 23, figure 12, table 24, figure 13
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 12 & 142
Recruitment	14a	Dates defining the periods of recruitment and follow-up	139 & figure 13
	14b	Why the pilot trial ended or was stopped	141
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Tables 25,26 & 27. 145-146.
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	142
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	147-149, 152 Table 28 & 33
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	Figure 15 Table 32 150-151
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	152-154, Appendix 8
	19a	If relevant, other important unintended	n/a

		consequences	
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	155
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	156
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	157-161
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	Conclusion chapter
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	117
Protocol	24	Where the pilot trial protocol can be accessed, if available	116
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	132-133
	26	Ethical approval or approval by research review committee, confirmed with reference number	132-133

8.14 Appendix 14 Table of Significant Adverse Events (SAE) for WHISH trial

Patient ID	Site	Date of Receipt	Diagnosis	Causality	Expectedness
S1062	OUH	26/10/2017	Patient given multiple bags of fluid. This led to a drop in oxygenation requiring nasal cannula and 2L of oxygen	Not related	Unexpected
S1244	SMH	04/12/2017	Patient died - patient deteriorated post op- with hospital acquired pneumonia. Was placed on end of life care 30/11/2017	Not related	Unexpected
S1208	OUH	11/01/2017	Lung cancer	Not related	Unexpected
S1325	OUH	25/01/2018	Infective Diarrhoea	Not related	Unexpected
S1184	PGH	25/01/2018	Wound Infection	Definitely related	Expected
S1383	SMH	27/01/2018	Chest Sepsis - Death	Not related	Unexpected
S1396	OUH	08/02/2018	Pneumothorax during pacemaker insertion	Not related	Unexpected
S1413	SMH	06/02/2018	Death	Not related	Unexpected
S1198	SMH	06/02/2018	Fall resulting in Fractured right neck of femur (contralateral to trial fracture)	Not related	Unexpected
S1304	OUH	08/02/2018	Investigations whilst inpatient for colorectal cancer	Not related	Unexpected
S1382	SMH	20/02/2018	Death - ? Due to aspiration Pneumonia	Not related	Unexpected
S1356	SMH	20/02/2018	Death	Not related	Unexpected
S1364	OUH	21/02/2018	Pubic Rami fracture and right sided pneumonia	Not related	Unexpected
S1396	OUH	21/02/2018	Small Bowel Obstruction	Not related	Unexpected
S1121	SMH	28/02/2018	Death	Unlikely to be related	Expected
S1278	SMH	04/04/2018	Admitted to hospital	Not related	Unexpected
S1280	OUH	08-Jun-18	Gastroenteritis +/- C. Difficile	Not related	Unexpected
S1255	UHN	25-Jul-18	Proximal Humeral fracture and LRTI	Not related	Unexpected
S1364	OUH	09-Aug-18	Fracture of contralateral neck of femur	Not related	Unexpected
S1428	OUH	11-Aug-18	Left hip pain	Not related	Unexpected
S1428	OUH	11-Aug-18	Left intra-capsular NOF#	Not related	Unexpected
S1094	OUH	11-Aug-18	Small Bowel Obstruction	Not related	Unexpected
S1337	PGH	24-Aug-18	Proximal Humerus Fracture (Right)	Not related	Unexpected

8.15 Appendix 15 Secondary Outcome Measures

Table 8.15.1 Gross Euroquol 5d-5l score by treatment arm WHISH study

Domain	Standard Dressings						Incisional Negative Pressure Wound Therapy					
Level	1	2	3	4	5	Total	1	2	3	4	5	Total
Mobility n (%)	23 (18)	43 (33)	39 (30)	15 (11)	11 (8)	131	32 (26)	29 (24)	33 (27)	14 (12)	13 (11)	121
Self care n (%)	76 (58)	23 (18)	13 (10)	5 (4)	14 (11)	131	63 (52)	17 (14)	16 (13)	5 (4)	20 (17)	121
Usual Activities n (%)	42 (32)	24 (18)	37 (28)	3 (2)	25 (19)	131	46 (38)	26 (21)	13 (11)	10 (8)	26 (21)	121
Pain n (%)	58 (44)	39 (30)	27 (21)	6 (5)	1 (1)	131	60 (50)	36 (30)	22 (18)	2 (2)	1 (1)	121
Anxiety n (%)	91 (69)	25 (19)	12 (9)	1 (1)	1 (1)	131	82 (68)	16 (13)	19 (16)	3 (2)	0 (0)	121

Summary of health related quality of life scores by intervention arm. Levels of health represented range from 1 (best outcome) to 5 (worst outcome).

Table 8.15.2 Summary of patient mobility at 4 months after injury by treatment arm in WHISH study.

	Standard Dressings n(%)	Incisional Negative Pressure Wound Therapy n(%)	Total
Freely mobile without aids	27 (20)	25 (20)	52 (21)
Mobile Outdoors with one aid	27 (20)	27 (22)	54 (21)
Mobile Outdoors with two aids or frame	36 (27)	30 (25)	66 (26)
Some indoor mobility but never outdoors without help	7 (5)	87(7)	15 (6)
No functional mobility with lower limbs	34 (28)	32 (26)	66 (26)
Total	131	122	253

Summary of patient mobility at 4 months by study treatment arm.

8.16 Appendix 16 Published Papers Associated With Thesis



■ EDITORIAL

Negative pressure wound therapy and orthopaedic trauma

WHERE ARE WE NOW?

J. P. M. Masters, J. Nanchahal, M. L. Costa

From The Kadoorie Centre, Oxford, United Kingdom

Negative pressure wound therapy (NPWT) has become a common form of treatment for both open and closed wounds. The use of this sophisticated dressing has increased dramatically over the last decade in many fields of surgical practice.

It was originally used in complex open wounds such as pressure ulcers and diabetic feet. However, there has been an expansion of the indications and it is now also used for incisional wounds, where there is concern about wound discharge and healing potential.

This article considers NPWT in orthopaedic trauma. The evidence from trauma is also informing elective practice, particularly in high-risk wounds such as those used in arthroplasty[1] and spinal surgery.[2] What these areas of practice have in common is a surgical wound, where wound breakdown and subsequent infection would have catastrophic consequences for the patient.

Open wounds

The initial use of NPWT in orthopaedic trauma was in wounds associated with open fractures. Stannard et al[3] performed a randomised controlled trial (RCT) involving 59 patients with 63 fractures and showed a significantly lower rate of infection in those treated with NPWT. This important finding has not yet been replicated in further randomised trials. However, other authors have reported corroborating clinical metrics, such as the rate of wound healing.[4] Téot et al[5] studied 257 trauma patients as part of a large multicentre non-randomised study examining outcome measures including definitive closure, complete re-epithelialisation or improvement in the wound. They found that NPWT resulted in an improved healing time in different types of wound. They did not assess the rate of infection in those treated with 'standard' non-NPWT dressings.

A systematic review of the literature on the use of NPWT in open fractures identified 13 studies.[6] The report was of a reduced rate of infection in patients treated with NPWT compared with gauze dressings. However, the study by Stannard et al,[3] described above, was the only randomised trial. Stannard et al[3] also suggested that NPWT may allow definitive soft-tissue coverage to be deferred beyond 72 hours without an increase in infection. However, this is in contradiction to the current National Institute for Health and Care Excellence guidelines.[7]

Incisional wounds

The application of NPWT to closed incisions is a recent occurence. There are fewer studies in this area but there is growing use of NPWT for this indication. In orthopaedics, the scope for this is huge, with 'high-risk' closed incisions making up much of the work done in trauma as well as in areas of elective surgery. High-risk wounds in young patients are usually associated with high-energy injuries, such as road traffic accidents and falls from a height where there is significant damage to the soft tissues, as well as to bone. In older patients, even wounds associated with low-energy fractures may be considered a high risk as the soft tissues are more fragile and the patients have more comorbidities.[8-10]

The largest study in closed wounds in orthopaedic trauma was also conducted by Stannard et al.[11] They randomised 249 patients with fractures of the tibial plateau, pilon or os calcis to receive either NPWT or standard wound dressings. They found a significant reduction in the rate of infection and wound dehiscence in the NPWT group. This is the most recent work from these authors pointing towards a beneficial effect in the 'high-risk' trauma group.[3,12]

Hyldig et al[13] attempted to synthesise those RCTs which looked at NPWT in closed incisional wounds, not only in orthopaedics but in thoracic, abdominal and plastic surgery. They concluded that whilst NPWT appeared to reduce the rate of wound infection and complications, the heterogeneity of the patients limited the strength of recommendations that could be made.

■ J. P. M. Masters, BSc, MRCS, Clinical Research Fellow
The Kadoorie Centre, Orthopaedic Trauma, John Radcliffe Hospital Oxford OX3 9DU, UK.

■ J. Nanchahal, PhD FRCS (Plast), Professor of Hand, Plastic and Reconstructive Surgery, NDORMs
University of Oxford, Kennedy Institute of Rheumatology, Roosevelt Drive, Headington, Oxford, UK.

■ M. L. Costa, PhD, FRCS(Tr&Orth), Professor, Orthopaedic Trauma
The Kadoorie Centre, John Radcliffe Hospital, Oxford, OX3 9DU, UK.

Correspondence should be sent to Mr J. P. M. Masters; e-mail: jpmm1986@gmail.com

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NPWT has particular relevance in orthopaedic trauma surgery when the management of the soft tissues may be the key to the successful management of any associated fracture.

Application of subatmospheric pressure to the dressing results in positive pressure to the wound. For wounds with closed incisions, NPWT distributes the tension at the wound margins and helps obliterate the dead space in the underlying tissues.[14,15]

The mechanisms of action of negative pressure therapy has been explored using human samples and cells and animal models in a wide range of types of wound.[16] NPWT on open wounds leads to local hypoxia, which in turn leads to increased expression of vascular endothelial growth factor, platelet derived growth factor and fibroblast growth factor 2; important mediators of neovascularisation. NPWT also leads to reduced local inflammation, including reduced macrophage infiltration, down regulation of tumour necrosis factor, interleukin-1β and upregulation of interleukin-10. Additionally, there is reduced expression of the matrix metalloproteinases, whilst the levels of tissue inhibitors of metalloproteinases remain unchanged.[16] An important mode of action is through microdeformation of mechanically sensitive cells, leading to enhanced cellular proliferation, migration and differentiation.[17]

The current situation

NPWT shows great promise in reducing the complications associated with high-risk wounds, both for the management of open and closed wounds. However, as in many areas of orthopaedic practice, our ability to interpret the evidence is limited by low numbers of underpowered trials and the use of heterogenous outcome measures.[18]

As with any new technology, the issue of cost effectiveness inevitably rears its head. Even if using NPWT dressings can reduce the rate of wound complications, can the significant difference in price justify its widespread adoption? A study comparing NPWT with standard dressings found that whilst the inpatient costs of NPWT were approximately four times higher, this was offset by a shorter inpatient stay and 'time to outcome'.[5] However, a Cochrane review of NPWT on closed incisions failed to identify studies evaluating the economics of NPWT that would be suitable for inclusion.[18]

We need to develop a stronger evidence base of the use of NPWT. There are four key outstanding issues:

- The development of a core set of outcomes for wound healing to be used in all clinical research in this area;
- Larger trials to confirm the clinical effectiveness of NPWT in both open and incisional wounds;
- Robust health economic evaluations to assess the cost effectiveness of NPWT;
- Detailed understanding of the mechanisms of action of NPWT both in open and closed incisions, which may lead to improved use of the technique.

There is some progress in each of these areas. At this year's inaugural Wound Research Network Meeting, delegates promoted the concept of a generic core set of outcomes to be used in research in the area of wound healing. This may take some time. However, some advances have been made in developing sets of outcomes which might be used for specific wounds, for example a United Kingdom-wide consensus for a set of outcomes for open fractures.

Two large-scale National Institute for Health Research Health Technology Assessment (HTA) trials to investigate both clinical and cost effectiveness are currently underway. The Wound in Open Lower Limb Fractures (WOLLF) trial[19] has finished recruitment in 22 trauma centres throughout the United Kingdom, and is due to report early in 2017. This RCT involving 460 patients compares the use of NPWT with routine dressings in open fractures where the wound has not been primarily closed after initial debridement. In order to reflect the expanding use of NPWT in the management of closed incisional wounds, HTA have also funded the Wound Healing in Surgical Trauma (WHiST) trial. This has recently started to recruit patients in the United Kingdom in order to assess the effect of NPWT on wound infection at 30 days compared with standard dressings on closed incisions in major trauma patients with limb fractures. This trial will recruit 1540 patients from the United Kingdom's major trauma research network.[20] WHiST will also facilitate further laboratory studies to elucidate the mechanism of action of NPWT in trauma surgery.

The use of large-scale trials gives an unparalleled insight into the effectiveness of an intervention in a health service. This in turn can inform clinical practice at a national and international level. However, the timing of such trials in the lifecycle of the development and implementation of a technology is critical. The Normalisation Process Theory attempts to describe how new technologies and behaviours are implemented in health care.[21] However, it is not clear at which stage of the process it is best to undertake large pragmatic trials. The IDEAL framework, seeks to provide guidance on the matter, but this is still a controversial area;[22] too early, and the multimillion pound trial is an expensive way to test unproven technologies; too late, and behaviour relating to new technologies is entrenched. This, in turn, may make equipoise difficult and interfere with recruitment,[23] although there is evidence that even where behaviour is well established, trials can influence practice.[24]

We hope that WHiST and WOLLF will offer answers about the optimal application of NPWT in orthopaedic trauma, before indiscriminate usage becomes normal practice.

References

1. **Pachowsky M, Gusinde J, Klein A, et al.** Negative pressure wound therapy to prevent seromas and treat surgical incisions after total hip arthroplasty. *Int Orthop* 2012;36:719–722.
2. **Nordmeyer M, Pauser J, Biber R, et al.** Negative pressure wound therapy for seroma prevention and surgical incision treatment in spinal fracture care. *Int Wound J* 2015. (Epub ahead of print).
3. **Stannard JP, Volgas DA, Stewart R, McGwin G Jr, Alonso JE.** Negative pressure wound therapy after severe open fractures: a prospective randomized study. *J Orthop Trauma* 2009;23:552–557.

4. **Arti H, Khorami M, Ebrahimi-Nejad V.** Comparison of negative pressure wound therapy (NPWT) &conventional wound dressings in the open fracture wounds. *Pak J Med Sci* 2016;32:65–69.
5. **Téot L, Guillot-Masanovic M, Miquel P, et al.** Clinical impact of negative-pressure wound therapy: a 1,126-patient observational prospective study. *Wound Repair Regen* 2014;22:341–350.
6. **Schlatterer DR, Hirschfeld AG, Webb LX.** Negative pressure wound therapy in grade IIIB tibial fractures: fewer infections and fewer flap procedures? *Clin Orthop Relat Res* 2015;473:1802–1811.
7. **No authors listed.** NICE. Fractures (Complex): Assessment and Management.: https://http://www.nice.org.uk/guidance/ng37/chapter/Recommendations (date last accessed 16 May 2016).
8. **Namba RS, Paxton L, Fithian DC, Stone ML.** Obesity and perioperative morbidity in total hip and total knee arthroplasty patients. *J Arthroplasty* 2005;20(Suppl 3):46–50.
9. **Dowsey MM, Choong PF.** Early outcomes and complications following joint arthroplasty in obese patients: a review of the published reports. *ANZ J Surg* 2008;78:439–444.
10. **Golden SH, Peart-Vigilance C, Kao WH, Brancati FL.** Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* 1999;22:1408–1414.
11. **Stannard JP, Volgas DA, McGwin G III, et al.** Incisional negative pressure wound therapy after high-risk lower extremity fractures. *J Orthop Trauma* 2012;26:37–42.
12. **Stannard J.** Complex orthopaedic wounds: prevention and treatment with negative pressure wound therapy. *Orthop Nurs* 2004;23(Suppl 1):3–10.
13. **Hyldig N, Birke-Sorensen H, Kruse M, et al.** Meta-analysis of negative-pressure wound therapy for closed surgical incisions. *Br J Surg* 2016;103:477–486.
14. **Huang C, Leavitt T, Bayer LR, Orgill DP.** Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014;51:301–331.
15. **Suh H, Lee AY, Park EJ, Hong JP.** Negative Pressure Wound Therapy on Closed Surgical Wounds With Dead Space: Animal Study Using a Swine Model. *Ann Plast Surg* 2016;76:717–722.
16. **Glass GE, Murphy GF, Esmaeili A, Lai LM, Nanchahal J.** Systematic review of molecular mechanism of action of negative-pressure wound therapy. *Br J Surg* 2014;101:1627–1636.
17. **Huang C, Leavitt T, Bayer LR, Orgill DP.** Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014;51:301–331.
18. **Webster J, Scuffham P, Stankiewicz M, Chaboyer WP.** Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention. *Cochrane Database Syst Rev* 2014;10:CD009261.
19. **Achten J, Parsons NR, Bruce J, et al.** Protocol for a randomised controlled trial of standard wound management versus negative pressure wound therapy in the treatment of adult patients with an open fracture of the lower limb: UK Wound management of Open Lower Limb Fractures (UK WOLFF). *BMJ Open* 2015;5:009087.
20. **No authors listed.** WHist. http://www.ndorms.ox.ac.uk/clinical-trials/current-trials-and-studies/whist (date last accessed 16 May 2016).
21. **May CR, Mair F, Finch T, et al.** Development of a theory of implementation and integration: Normalization Process Theory. *Implement Sci* 2009;4:29.
22. **Ergina PL, Barkun JS, McCulloch P, et al.** IDEAL framework for surgical innovation 2: observational studies in the exploration and assessment stages. *BMJ* 2013;346:3011.
23. **Potter S, Mills N, Cawthorn SJ, Donovan J, Blazeby JM.** Time to be BRAVE: is educating surgeons the key to unlocking the potential of randomised clinical trials in surgery? A qualitative study. *Trials* 2014;15:80.
24. **Costa ML, Jameson SS, Reed MR.** Do large pragmatic randomised trials change clinical practice?: assessing the impact of the Distal Radius Acute Fracture Fixation Trial (DRAFFT). *Bone Joint J* 2016;98-B:410–413.

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Randomised controlled feasibility trial of standard wound management versus negative-pressure wound therapy in the treatment of adult patients having surgical incisions for hip fractures

James P M Masters,[1] Juul Achten,[1] Jonathan Cook,[2] Melina Dritsaki,[3] Lucy Sansom,[1] Matthew L Costa[1]

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[1]Oxford Trauma, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK
[2]Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK
[3]Oxford Clinical Trial Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK

Correspondence to
Dr James P M Masters; james.masters@ndorms.ox.ac.uk

ABSTRACT

Introduction Deep wound infection is a catastrophic complication after hip fracture surgery. However, current understanding of infection rates in this population is limited. Many technologies such as incisional negative-pressure wound therapy (NPWT) show promise in reducing the rate of infection. This trial is a feasibility study looking to establish a value estimated with a greater precision of the rate of deep infection after hip fracture treatment in patients treated with NPWT versus standard dressing following hip fracture surgery.

Methods and analysis A randomised controlled trial of 464 patients will be run across multiple centres. It is embedded in the World Hip Trauma Evaluation cohort study. Any patient over the age of 65 years having surgery for hip fracture is eligible unless they are being treated with percutaneous screw fixation. A web-based randomisation sequence will stratify patients by centre. Patients will be allocated to either NPWT or standard care on a 1:1 basis. The primary outcome measure is the Centre for Disease Control definition of deep infection at 30 days. Follow-up at 4 months will also assess deep infection and the core outcome dataset for hip fractures. This includes health-related quality of life (EQ-5D-5L), mobility, mortality and late complications such as further surgery. The primary analysis will be intention to treat.

Ethics and dissemination Oxford C Research Ethics Committee granted ethical approval on 28/04/2017, 17/SC/0207. The results of this study will be reported in a peer-reviewed publication and inform the design of a future full-scale trial.

Trial registration number ISRCTN55305726.

Strengths and limitations of this study

- This prospective trial will estimate the true rate of infection according to nationally recognised criteria.
- Robust data collection systems will be used to determine the rate of deep infection.
- This study will include the full range of hip fracture patients including those without capacity, across multiple centres ensuring good external validity to our findings.
- The potential limitation will be to accurately capture those cases of infection where patients move through different institutions and care pathways.

INTRODUCTION

Hip fracture is one of the biggest challenges facing patients and healthcare systems at present. Worldwide, there are 1.3 million hip fractures with more than 65 000 hip fractures in England, Wales and Northern Ireland every year.[1] These figures are projected to rise to >100 000 by 2020 in the UK[2] and more than 6 million by 2050 worldwide.[3] The global cost of this clinical problem is estimated at 1.75 million disability-adjusted life years lost and represents 1.4% of the total healthcare burden in established market economies.[4]

The overwhelming majority of hip fractures are treated surgically. The principal objective of surgical treatment is to enable patients to return to weight-bearing mobilisation as soon as possible.

As with all surgical treatments, one of the most important potential complications is surgical site infection (SSI). Hip fracture patients are particularly vulnerable to SSI. The reasons for this vulnerability are multifactorial. For instance, 60% of hip fracture patients have at least one major medical comorbidity such as steroid or other immunosuppressive medication use, malignancy and diabetes.[5] These comorbidities sit alongside age-related deterioration of immune function.

SSI can be either superficial or deep. Superficial infections only involve the skin and subcutaneous tissue, whereas 'deep' infections involve the deeper layers and the metalwork implanted in the hip. Deep infection

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has profound consequences for hip fracture patients including a significantly increased hospital stay and they are 4.5 times less likely to survive to discharge.[6] Of those that do survive, patients with deep infection have been found to be three times less likely to return to their original residence.[6] These findings have been found in other large cohort studies.[7]

Due to the severe consequences of deep infections in this patient group, a number of interventions are undertaken to try and reduce the risk of infection such as perioperative antibiotics, vigorous skin preparation and wound dressing. Wound dressing is one of the most important interventions to address the risk of postoperative infection. The role of a postoperative wound dressing is to minimise bacterial ingress into the wound, manage exudate from the wound site and protect the soft-tissues while they heal.

Traditionally, the surgical incision is covered with an adhesive dressing or gauze to protect the wound from contamination from the outside environment. These 'standard dressings' have been used throughout the National Health Service (NHS) for many years. Negative-pressure wound therapy (NPWT) is an alternative form of dressing which may be applied to closed surgical incisions. In this treatment, an 'open-cell', solid foam overlies the incision and is covered with a semipermeable membrane which is only permeable to gas. A sealed tube is used to connect the foam to a pump, which creates a partial vacuum over the wound. This negative-pressure therapy provides a sealed environment, preventing bacterial ingress and removes blood and serous fluid exuding the wound. The application of negative pressure to the foam leads to the application of positive pressure to the wound bed and has been shown to reduce the incidence of wound haematoma.[8] Recent laboratory studies suggest that NPWT shifts the cytokine profile to being less inflammatory, promotes the production of proangiogenic growth factors and enzymes responsible for matrix remodelling, leading to improved wound healing.[9–13]

However, a recent Cochrane review for surgical wounds concluded, 'it is still not clear whether NPWT promotes faster healing and reduces complications associated with clean surgery'. 'Given the cost and widespread use of NPWT, there is an urgent need for suitably powered, high-quality trials to evaluate the effects of the newer NPWT products that are designed for use on clean, closed surgical incisions. Such trials should focus initially on wounds that may be difficult to heal'.[14]

The current feasibility trial will assess the feasibility of performing a randomised controlled trial (RCT) on wound dressings in this challenging population, and it will aim to estimate the current infection rates for hip fracture patients. Capture of SSI rates falls under the remit of Public Health England's Surgical Site Infection Surveillance Programme.[15] Their report from 2015 reports a SSI incidence of 1.3% (95% CI 1.3% to 1.5%).[15] However, infection rates reported in the literature for this patient group are often higher, with some reports stating rates as high as 7%.[16 17] There is growing evidence that the surveillance system from Public Health England is providing a significant underestimate of the true incidence.[18–20] This is borne out by local audit of hip fracture patients at two large teaching hospitals in the England, that have found infection rates between 5% and 8%, respectively (unpublished data). A reliable estimation of infection will be required to inform the sample size for a large RCT.

AIMS AND OBJECTIVES

We aim to conduct a feasibility trial of NPWT versus standard dressing following hip fracture surgery. It is intended to obtain a reliable estimate of the rate of SSIs in the target population. In addition, feasibility will be considered in terms of other aspects of the trial such as recruiting and randomising large numbers from individual sites within a relatively short time frame.

The primary objective is:

To quantify differences in the rate of 'deep infection'—as defined by the Centre for Disease Control (CDC)—after hip fracture surgery in standard dressing and NPWT. Patients will be assessed at 30 days and 4 months. We will examine how many deep infections occur, and when the diagnosis is made.

Both 'how many deep infections' and 'when they are diagnosed' will be crucial to inform the design of a full-scale trial. Each time point addresses the requirements of the CDC, and the routine follow-up of patients in the current UK care pathway.

The secondary objectives are:

1. To determine the number and nature of further surgical interventions related to the injury, in the first 4 months after the index procedure.
2. To investigate which outcomes will be required to assess cost-effectiveness, of NPWT versus standard dressing for wounds associated with hip fracture surgery in a definitive trial.
3. To determine recruitment rate and willingness to participate in the trial.
4. To capture the core outcome set for hip fracture studies.

METHODS AND ANALYSIS

Study design

This is a multicentre two arm non-blinded randomised feasibility study embedded within a prospective cohort.

Setting and participants

This feasibility study is embedded within the World Hip Trauma Evaluation cohort.[21] It will be run in five different centres across England including Major Trauma Centres and Trauma Units. All patients being surgically treated for hip fracture will be considered for enrolment.

Eligibility

Patients will be eligible for this study if

- They are aged 65 years or older.

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► They have a hip fracture requiring surgical treatment.

Exclusion criteria: Patients having percutaneous screw fixation of an undisplaced intracapsular fracture of the hip. This small subgroup of patients (less than 5% on the National Hip Fracture Database (NHFD)) have very small surgical incisions—typically 1–2 cm. Where incisions are so small, it is unlikely that they will benefit from an advanced dressing like NPWT.

Recruitment of participants, screening and eligibility assessment

Consent

Patients with a hip fracture are a clinical priority for urgent operative care. They will undergo surgery on the next available trauma operating list. All patients with a fracture of the hip are in pain and have received opiate analgesia. It is therefore understandable that the majority of patients find the initial period of their treatment in hospital confusing and disorientating. Similarly, patients' next of kin, carers and friends are often anxious at this time and may have difficulty in weighing the large amounts of information that they are given about the injury and plan for treatment. In this emergency situation, the focus is on obtaining consent for surgery (where possible) and informing the patient and any next of kin about immediate clinical care. This is supported by national guidance that recommends surgery should take place within 36 hours.[22] It is often not possible for the patient or relative/carer (consultee) to review trial documentation, weigh the information and communicate an informed decision about whether they would wish to participate. The consent procedure for this trial will reflect that of the surgery, with the clinical team assessing capacity before taking consent for the surgical procedure and this capacity assessment then being used to decide on the proper approach to consenting to the research. An appropriate method, in line with the mental capacity act and approved by a National Research Ethics Committee, will then be used to gain either prospective or retrospective consent from the patient or appropriate consultee by a Good Clinical Practice (GCP)-trained, appropriately delegated member of the research team.

Randomisation

The treating surgeon will confirm eligibility at the end of the operative procedure, but before the wound dressing is applied. Eligible patients will be enrolled into the study via a secure, remote online randomisation system. To ensure concealment of the allocation sequence, patients will only be randomised after they have been registered on the online system. The allocation sequence will be generated by the trial statistician at the Oxford Clinical Trials Unit. Randomisation will be on a 1:1 basis, stratified by trial centre. All modern operating theatres include a computer with web access, so a secure, 24 hours, web-based randomisation system will be used to generate the treatment allocation intraoperatively.

Postrandomisation withdrawals/exclusions

Participants may decline to continue to take part in the trial at any time without prejudice. A decision to decline consent or withdraw will not affect the standard of care the patient receives.

Blinding

As the wound dressings are clearly visible, the patients cannot be blind to their treatment. In addition, the treating surgeons will also not be blind to the treatment, but will take no part in the postoperative research assessment of the patients. The clinical outcome data will be collected by independent research assistants who will not be blind to the treatment allocation. Questionnaire data will be entered onto the trial central database by a data clerk in the trial central office.

Interventions

Patients with a hip fracture usually have surgery on the next available trauma operating list. Some patients may be delayed by medical factors such as anticoagulation, however, surgery will proceed as soon as is determined safe by the treating team. All patients will receive a general or regional anaesthetic. Routine prophylactic antibiotics will be given to all patients immediately before surgery and all patients will be assessed for venous thromboembolism prophylaxis according to local policy. At the end of the operation, a dressing is applied to the surgical wound. This trial will involve two types of wound dressing: standard dressing and NPWT.

Standard dressing

The standard dressing for a surgical wound comprises a non-adhesive layer applied directly to the wound that is covered by a sealed dressing. The standard dressing does not use 'negative pressure'. The exact details of the dressing materials and duration will be left to the discretion of the treating surgeon as per their routine practice, but the details of each dressing applied in the trial will be recorded.

Negative-pressure wound therapy

The NPWT dressing uses an 'open-cell', solid foam layer which is laid onto the wound as an intrinsic part of a sealed dressing. A sealed tube connects the dressing to a built in mini-pump that creates a partial vacuum over the wound. This can only be kept on for 7 days according to the manufacturer that will be reflected in this study.

Any further wound dressing after the initial dressing will be recorded and will follow the allocated treatment unless otherwise clinically indicated.

Outcome measures

Primary outcome

The primary outcome measure for this study is deep infection; We will use the CDC and Prevention definition of a 'deep SSI', that is a wound infection involving the tissues deep to the skin that occurs within 30 or 90 days of injury.[23]

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The treating clinical team will make the diagnosis of 'deep infection', as per routine clinical practice. The treating clinicians will not be part of the research team. Since the prompt diagnosis and treatment of infection is fundamental to the patient's routine clinical care, the treating surgeon/clinician will always document such a change in management in the patient's medical record.

In addition to the rate of infection, time of diagnosis will be assessed; The CDC definition applies up to the 90 days after hip fracture surgery.[23] However, the national care pathway for hip fractures involves remote follow-up at 4 months. Therefore, to ensure that assessment meets the CDC criteria and is consistent with existing care practice, each patient will be assessed at 30 days and 4 months.

At 30 days, the patient will be assessed either as an inpatient or over the telephone according to the relevant clinical parameters.

At 4 months patients will be asked, via telephone interview, about any further symptoms of infection which may have emerged since the 30-day time point. Of the infections that are identified, we will establish when the diagnosis was made in the course of recovery.

Secondary outcome measures in this trial

Mortality

Qualitative work with patients who sustain hip fractures identified mortality as an important metric.[24]

EuroQol EQ-5D-5L

The EuroQol EQ-5D is a validated measure of health-related quality of life, consisting of a five-dimension health status classification system and a separate Visual Analogue Scale.[25] Responses to the health status classification system will be converted into multiattribute utility (MAU) scores using tariffs currently under development for England.[26] These MAU scores will be combined with survival data to generate Quality Adjusted Life Year (QALY) profiles for the purposes of the economic evaluation. The EQ-5D has been validated to be completed by a patient's proxy in case of continues impaired capacity.

Complications

All complications and surgical interventions related to the index wound will be recorded.

Resource use

Will be monitored to help inform the economic analysis plan in the subsequent definitive trial. Cost data will be obtained from national databases or will be estimated in consultation with the hospital finance department. The cost consequences following discharge, including NHS costs and patients' out-of-pocket expenses will be recorded via a short questionnaire, which will be administered at 4 months postinjury. This will be either by patient or consultee.[27]

Mobility

The ability to walk indoors and outdoors is rated very highly by patients. It has been included in a recommended 'core outcome set' for trials assessing interventions in hip fractures.

Residential status

Also captured on case report form (CRF). The residential status is also part of the core outcome set for hip fractures and NHFD dataset.[24] It will be captured at baseline and at 4 months.

Recruitment rate

The rate of recruitment of potential participants, both in terms of eligibility and those who consent (or on whose behalf consent is provided) will be recorded.

Retention rate

The rate of retention through the study visits of participants will be recorded.

Adverse event management

Adverse events (AEs) are defined as any untoward medical occurrence in a clinical trial subject and which do not necessarily have a causal relationship with the treatment. All AEs will be listed on the appropriate CRF for routine return to the 'WHISH' central office.

Some AEs are expected as part of the surgical interventions, and do not need to be reported immediately, provided they are recorded in the 'Complications' section of the CRFs and/or patient questionnaires. These events are: complications of anaesthesia or surgery (bleeding or damage to adjacent structures such as nerves, tendons and blood vessels, delayed unions/non-unions, further surgery to remove/replace metalwork, dislocation, wound dehiscence and thromboembolic events). All participants experiencing Significant Adverse Events (SAEs) will be followed up as per protocol until the end of the trial.

Follow-up

Each patient will be assessed in the current UK national audit framework for hip fracture patients. This means they will contact by telephone 4 months after surgery. As per the feasibility aims of this study, we will also assess each patient at 30 days. This may be in person as an inpatient or over the telephone is the patient has been discharged.

The 4-month time point will collect the data required for the NHFD, health-related quality of life and the other components of the hip fracture core outcome set.[24] We will also investigate deep infection at the 4-month time point to ensure that each patient has been assessed by 90 days which is required by the CDC.

Details of any late complications will be sent securely to the trial coordinating centre. Complications will be captured on the CRF by the site research associate and recorded on the CRFs at 30 days/discharge and at 4 months via telephone interview.

Where a personal consultee has agreed to the patient's involvement, we will ask them for the follow-up data if the participant has permanently lost capacity to consent. Those patients or consultees who do not wish to provide follow-up data but agree to the study team reviewing

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their medical records, clinical reporting forms will be completed by the site and returned in the same manner. This is referred to as 'routine data only' option.

Sample size

The purpose of the proposed feasibility study is to determine the rate of deep SSI which in turn will inform the sample size for the definitive trial. We will recruit a sample of 464 participants; divided equally in each of the two study arms. This is based on the number of hip fractures treated at each of the recruiting centres and assuming a conservative recruitment of 50% of eligible patients. Four hundred and sixty-four is based on Wilson's CI method at two-sided 95% significance level with 20% loss to follow-up). This will allow us to estimate the overall 30-day deep infection rate within 3%–5% depending on the actual rate.

Rehabilitation

Early full weight-bearing mobilisation is routine in all cases of hip fracture. Further details of the rehabilitation will be left to the discretion of the treating team as per usual clinical practice.

Data management

The CRFs will be designed by the trial manager in conjunction with the trial management team. All electronic patient-identifiable information will be held on a secure, password-protected database at the Kadoorie Centre, accessible only to the research team. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area. Patients will be identified by a code number only. Direct access to source data/documents will be required for trial-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required. All paper and electronic data will be retained for at least 5 years after completion of the trial.

Statistical analysis

Standard statistical summaries (eg, means, SDs, medians, IQR) will be reported for all discrete and continuous outcome measures. Baseline data (eg, age and gender) will be summarised to check comparability between treatment arms. This will only be shared with the Data Management Committee (DMC) in the first instance at the end of the feasibility study. No formal hypothesis testing will take place; as per the aim of this feasibility study, the analysis will report the deep infection rates overall and in the two treatment groups on an intention-to-treat basis at 30 days and 4 months postrecruitment.

Should this study demonstrate that a full-scale trial is feasible, the data from this feasibility study will be included in the final analysis of the definitive trial. This is contingent on the future definitive trial being sufficiently similar to this feasibility study. Baseline and follow-up outcome data will therefore not be released to the trial team unless the lack of feasibility is determined based on observed infection rate at the end of the feasibility study, or the definitive study cannot be conducted for other reasons (eg, lack of funding). Reporting of the study outcomes will be done accordingly to enable to use of the outcome data in a future definitive trial if such a study goes ahead.

Recruitment and retention rates will be reported through a consort diagram and so will inform the planning of a definitive trial with respects to sample size and the time points of measurements.

It seems likely that some data may not be available due to voluntary withdrawal of patients, lack of completion of individual data items or general loss to follow-up. In this hip fracture cohort, there is significant mortality at 30 days—6.7%.[1] Where possible the reasons for missing data will be ascertained and reported. Although missing data is not expected to be a problem for this study, the nature and pattern of the missing data is important to understand for the full study, so will be carefully considered.

Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarised.

Economic evaluation

An economic evaluation will not be the primary focus of the trial as it is a feasibility study. However, we will seek to collect relevant health economic data to explore how well this data can be reported in this group and whether any adaptations need to be undertaken to facilitate this. Given the sizeable financial difference between the two proposed interventions, a clear understanding of the health economics will be imperative in any subsequent larger trial.

Trial oversight

The day-to-day management of the trial will be the responsibility of the Clinical Trial Manager, based at Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences and supported by the Oxford Clinical Trials Research Unit (OCTRU) staff. This will be overseen by the Trial Management Group, who will meet monthly to assess progress. It will also be the responsibility of the Clinical Trial Manager to undertake training of the research associates at each of the trial centres. The Trial Statistician and Health Economist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

A Trial Steering Committee (TSC) and a Data and Safety Monitoring Committee (DSMC) will be set up. The study DSMC will adopt a (DA ta MO nitoring C ommittees: L essons, E thics, S tatistics) DAMOCLES charter which outlines its responsibilities. They will not perform any formal interim analyses of effectiveness. They will see copies of data accrued to date, or summaries of that data by treatment group. They will also assess the screening algorithm against the eligibility criteria. Emerging evidence from other related trials or research will be considered. Significant AEs will be reviewed. The DSMC

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may tell the chair of the TSC at any time if, in their view, the trial should stop for ethical reasons. This includes concerns about participant safety. The DSMC will meet at least once per year during the recruitment phase of the study.

Quality control

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures by the Host organisation, Sponsor or appropriate Regulatory Authorities. A Monitoring Plan will be developed according to OCTRU standard operating procedures which involves a risk assessment. The monitoring activities are based on the outcome of the risk assessment and may involve central monitoring and site monitoring.

Ethics and dissemination

Results of this study will be disseminated through peer-reviewed publication and presentation at conferences.

Contributors JPM, MLC and JA wrote the background section and developed the research question. JPM, MLC, JA and LS were responsible for the research methodology and management sections of the protocol. JC wrote the sample size and statistical analysis sections of the protocol. MD wrote the health economic evaluation section of the protocol. All authors reviewed and agreed the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Oxford C Research Ethics Committee granted ethical approval on 28/04/2017, 17/SC/0207.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1. The Royal College of Physicians. *National Hip Fracture Database (NHFD) Annual Report 2017*. London: The Royal College of Physicians, 2017.
2. The Royal College of Physicians. *National Hip Fracture Database (NHFD) Annual Report 2015*. London: The Royal College of Physicians, 2015.
3. Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–9.
4. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int* 2004;15:897–902.
5. Roche JJ, Wenn RT, Sahota O, *et al*. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. *BMJ* 2005;331:1374.
6. Pollard TC, Newman JE, Barlow NJ, *et al*. Deep wound infection after proximal femoral fracture: consequences and costs. *J Hosp Infect* 2006;63:133–9.
7. Theodorides AA, Pollard TC, Fishlock A, *et al*. Treatment of post-operative infections following proximal femoral fractures: our institutional experience. *Injury* 2011;42 Suppl 5(Suppl 5):S28–S34.
8. Stannard JP, Volgas DA, Stewart R, *et al*. Negative pressure wound therapy after severe open fractures: a prospective randomized study. *J Orthop Trauma* 2009;23:552–7.
9. Shweiki D, Itin A, Soffer D, *et al*. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature* 1992;359:843–5.
10. Saxena V, Hwang CW, Huang S, *et al*. Vacuum-assisted closure: microdeformations of wounds and cell proliferation. *Plast Reconstr Surg* 2004;114:1086–96. discussion 97-8.
11. Pietramaggiori G, Liu P, Scherer SS, *et al*. Tensile forces stimulate vascular remodeling and epidermal cell proliferation in living skin. *Ann Surg* 2007;246:896–902.
12. Morykwas MJ, Argenta LC, Shelton-Brown EI, *et al*. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. *Ann Plast Surg* 1997;38:553–62.
13. Pollak AN. Use of negative pressure wound therapy with reticulated open cell foam for lower extremity trauma. *J Orthop Trauma* 2008;22(10 Suppl):S142–S145.
14. Webster J, Scuffham P, Stankiewicz M, *et al*. Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention. *Cochrane Database Syst Rev* 2014;10:Cd009261.
15. Public Health England. *Surveillance of surgical site infections in NHS hospitals in England: 2014 to 2015*, 2015.
16. Noailles T, Brulefert K, Chalopin A, *et al*. What are the risk factors for post-operative infection after hip hemiarthroplasty? Systematic review of literature. *Int Orthop* 2016;40.
17. Edwards C, Counsell A, Boulton C, *et al*. Early infection after hip fracture surgery: risk factors, costs and outcome. *J Bone Joint Surg Br* 2008;90:770–7.
18. Wilson J, Charlett A, Leong G, *et al*. Rates of surgical site infection after hip replacement as a hospital performance indicator: analysis of data from the English mandatory surveillance system. *Infect Control Hosp Epidemiol* 2008;29:219–26.
19. Singh S, Davies J, Sabou S, *et al*. Challenges in reporting surgical site infections to the national surgical site infection surveillance and suggestions for improvement. *Ann R Coll Surg Engl* 2015;97:460–5.
20. Tanner J, Padley W, Kiernan M, *et al*. A benchmark too far: findings from a national survey of surgical site infection surveillance. *J Hosp Infect* 2013;83:87–91.
21. Costa ML, Griffin XL, Achten J, *et al*. World Hip Trauma Evaluation (WHiTE): framework for embedded comprehensive cohort studies. *BMJ Open* 2016;6:6.
22. NICE. *The Management of Hip Fracture in Adults*, 2014.
23. Centre for Disease Control. Surgical Site Infection (SSI) Event. 2018 http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf (cited 19 Jan 2018).
24. Haywood KL, Griffin XL, Achten J, *et al*. Developing a core outcome set for hip fracture trials. *Bone Joint J* 2014;96-B:1016–23.
25. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53–72.
26. Oppe M, Devlin NJ, van Hout B, *et al*. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. *Value Health* 2014;17:445–53.
27. *Self-reports of health care utilisation: can a questionnaire replace a diary? 16th Annual meeting of the international society for health technology assessment in health care*. The Hague, The Netherlands, 2000.

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9 References

1. Achten J, Parsons NR, Bruce J, Petrou S, Tutton E, Willett K, et al. Protocol for a randomised controlled trial of standard wound management versus negative pressure wound therapy in the treatment of adult patients with an open fracture of the lower limb: UK Wound management of Open Lower Limb Fractures (UK WOLLF). BMJ Open. 2015;5:e009087

2. Achten J, Vadher K, Bruce J, Nanchahal J, Spoors L, Masters JP, et al. Standard wound management versus negative-pressure wound therapy in the treatment of adult patients having surgical incisions for major trauma to the lower limb—a two-arm parallel group superiority randomised controlled trial: protocol for Wound Healing in Surgery for Trauma (WHIST). BMJ Open. 2018;8(6):e022115.

3. Costa ML, Achten J, Hennings S, Boota N, Griffin J, Petrou S, et al. Intramedullary nail fixation versus locking plate fixation for adults with a fracture of the distal tibia: the UK FixDT RCT. Health Technol Assess. 2018;22(25):1-148.

4. National Hip Fracture Database (NHFD) Annual Report 2015 [Available from: https://www.nhfd.co.uk/20/hipfractureR.nsf/docs/reports2015]

5. Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. Osteoporos Int. 1992;2(6):285-9.

6. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporos Int. 2004;15(11):897-902.

7. National Hip Fracture Database Annual Report 2018 [Available from: https://www.nhfd.co.uk/20/hipfractureR.nsf/docs/reports2018]

8. Parker M, Johansen A. Hip fracture. BMJ. 2006;333(7557):27-30.

9. Griffin XL, Parsons N, Achten J, Fernandez M, Costa ML. Recovery of health-related quality of life in a United Kingdom hip fracture population. Bone Joint J. 2015;97-B(3):372-82.

10. Segev-Jacubovski O, Magen H, Maeir A. Functional Ability, Participation, and Health-Related Quality of Life After Hip Fracture. OTJR: Occupation, Participation and Health. 2018;39(1):41-7.

11. Chaudhry H, Devereaux P & Bhandari M. Cognitive dysfunction in hip fracture patients. Orthop Clin North Am. 2013 Apr;44(2):153-62

12. NICE. The Management of Hip Fracture in Adults. NICE Guideline CG124. 2017.

13. Griffiths F, Mason V, Boardman F, Dennick K, Haywood K, Achten J, et al. Evaluating recovery following hip fracture: a qualitative interview study of what is important to patients. BMJ Open. 2015;5(1):e005406.

14. Roche JJ, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. BMJ. 2005;331.

15. No Authors. Femur. J Orthop Trauma. 2018;32:S33-S44.

16. Dreinhofer KE, Mitchell PJ, Begue T, Cooper C, Costa ML, Falaschi P, et al. A global call to action to improve the care of people with fragility fractures. Injury. 2018;49(8):1393-7.

17. Kjorholt KE, Kristensen NR, Prieto-Alhambra D, Johnsen SP, Pedersen AB. Increased risk of mortality after postoperative infection in hip fracture patients. Bone. 2019.

18. Lawrence VA, Hilsenbeck SG, Noveck H, Poses RM, Carson JL. Medical complications and outcomes after hip fracture repair. Arch Intern Med. 2002;162(18):2053-7.

20. McNamara I, Sharma A, Prevost T, Parker M. Symptomatic venous thromboembolism following a hip fracture. Acta Orthop. 2009;80(6):687-92.

21. Knudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. Ann Surg. 2004;240(3):490-8.

22. Guay J, Parker MJ, Gajendragadkar PR, Kopp S. Anaesthesia for hip fracture surgery in adults. Cochrane Database Syst Rev. 2016;2:Cd000521.

23. Potter LJ, Doleman B, Moppett IK. A systematic review of pre-operative anaemia and blood transfusion in patients with fractured hips. Anaesthesia. 2015;70(4):483-500.

24. Brunskill SJ, Millette SL, Shokoohi A, Pulford EC, Doree C, Murphy MF, et al. Red blood cell transfusion for people undergoing hip fracture surgery. Cochrane Database Syst Rev. 2015(4):Cd009699.

25. Shokoohi A, Stanworth S, Mistry D, Lamb S, Staves J, Murphy MF. The risks of red cell transfusion for hip fracture surgery in the elderly. Vox sanguinis. 2012;103(3):223-30.

26. Salem KMI, Shannak OA, Scammell BE, Moran CG. Predictors and outcomes of treatment in hip hemiarthroplasty dislocation. Ann R Coll Surg Engl. 2014;96(6):446-51.

27. Jiang D, Yu X, An H, Liang Y, Liang A. Hip and pelvic fractures and sciatic nerve injury. Chin J Traumatol. 2002;5(6):333-7.

28. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC Definitions of Nosocomial Surgical Site Infections, 1992: A Modification of CDC Definitions of Surgical Wound Infections. Infect Control Hosp Epidemiol. 1992;13(10):606-8.

29. Lister J. On the Antiseptic Principle in the Practice of Surgery. BMJ. 1867;2(351):246-8.

30. Tan SY, Tatsumura Y. Alexander Fleming (1881-1955): Discoverer of penicillin. Singapore Med J. 2015;56(7):366-7.

31. Alvarez-Nebreda M, Maranon E, Gonzalez de Villaumbrosia C, Barrera R, Gracia Y, Serra J. Surgical site infection following hip fracture surgery in the elderly: A frequent complication in orthogeriatric units. J Am Geriatr Soc. 2011;59:S159.

32. Noailles T, Brulefert K, Chalopin A, Longis PM, Gouin F. What are the risk factors for post-operative infection after hip hemiarthroplasty? Systematic review of literature. Int Orthop. 2016. Sep;40(9):1843-8

33. Jenks PJ, Laurent M, McQuarry S, Watkins R. Clinical and economic burden of surgical site infection (SSI) and predicted financial consequences of elimination of SSI from an English hospital. J Hosp Infect. 2014;86(1):24-33.

34. Astagneau P, Rioux C, Golliot F, Brücker G. Morbidity and mortality associated withsurgical site infections: results from the 1997–1999 INCISO surveillance. J Hosp Infect. 2001;48(4):267-74.

35. Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis. 2002;8(9):881-90.

36. Anderson DJ, Kirkland K, Kaye K, Thacker PA, 2nd, Kanafani ZA, Auten G, Auten G Sexton DJ, et al. Underresourced hospital infection control and prevention programs: penny wise, pound foolish? Infect Control Hosp Epidemiol. 2007 Jul;28(7):767-73

37. Trybou J, Spaepen E, Vermeulen B, Porrez L, Annemans L Hospital-acquired infections in Belgian acute-care hospitals: financial burden of disease and potential cost savings. Acta Clin Belg. 2013 May-Jun;68(3):199-205.

38. Stone PW, Braccia D, Larson E. Systematic review of economic analyses of health care-associated infections. Am J Infect Control. 2005;33(9):501-9.

39. Scott D. The Direct Costs of Healthcare-Associated Infections in US Hospitals and the Benefits of Prevention. Centers for Disease Control and Prevention Report 2009.

40. Protocol for the Surveillance of Surgical Site Infection. Public Health England 2013.

41. Public Health England. Surveillance of surgical site infections in NHS hospitals in England: 2017 to 2018. 2018

42. Wilson J, Charlett A, Leong G, McDougall C, Duckworth G. Rates of surgical site infection after hip replacement as a hospital performance indicator: analysis of data from the English mandatory surveillance system. Infect Control Hosp Epidemiol. 2008;29(3):219-26.

43. Singh S, Davies J, Sabou S, Shrivastava R, Reddy S. Challenges in reporting surgical site infections to the national surgical site infection surveillance and suggestions for improvement. Ann R Coll Surg Engl. 2015;97(6):460-5.

44. Tanner J, Padley W, Kiernan M, Leaper D, Norrie P, Baggott R. A benchmark too far: findings from a national survey of surgical site infection surveillance. J Hosp Infect. 2013;83(2):87-91.

45. Edwards C, Counsell A, Boulton C, Moran CG. Early infection after hip fracture surgery: risk factors, costs and outcome. J Bone Joint Surg, Br. 2008;90(6):770-7.

46. Roche JJW, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. BMJ. 2005;331(7529):1374.

47. Cruz E, Cano JR, Benitez-Parejo N, Rivas-Ruiz F, Perea-Milla E, Guerado E. Age as a risk factor of nosocomial infection after hip fracture surgery. Hip Int. 2010;20 Suppl 7:S19-25.

48. Montecino-Rodriguez E, Berent-Maoz B, Dorshkind K. Causes, consequences, and reversal of immune system aging. Journal Clin invest. 2013;123(3):958-65.

49. Wang Z, Anderson FA, Jr., Ward M, Bhattacharyya T. Surgical Site Infections and Other Postoperative Complications following Prophylactic Anticoagulation in Total Joint Arthroplasty. PLOS ONE. 2014;9(4):e91755.

50. NICE. Venous thromboembolism: reducing the risk for patients in hospital. NICE Guideline CG92.

51. Pollard TC, Newman JE, Barlow NJ, Price JD, Willett KM. Deep wound infection after proximal femoral fracture: consequences and costs. J Hosp Infect. 2006;63(2):133-9.

52. Theodorides AA, Pollard TC, Fishlock A, Mataliotakis GI, Kelley T, Thakar C, et al. Treatment of post-operative infections following proximal femoral fractures: our institutional experience. Injury. 2011;42 Suppl 5:S28-34.

53. Moore AJ, Blom AW, Whitehouse MR, Gooberman-Hill R. Deep prosthetic joint infection: a qualitative study of the impact on patients and their experiences of revision surgery. BMJ Open. 2015;5(12):e009495.

54. Tanner J, Padley W, Davey S, Murphy K, Brown B. Patients' experiences of surgical site infection. J Infect Prev. 2012;13(5):164-8.

55. Resistance and Healthcare Associated Infections (ARHAI) healthcare associated infection surveillance review subgroup. Final report and recommendations of the ARHAI healthcare associated infection (HCAI) surveillance review sub-group. 2012.

56. Troughton R, Birgand G, Johnson AP, Naylor N, Gharbi M, Aylin P, et al. Mapping national surveillance of surgical site infections in England: needs and priorities. J Hosp Infect. 2018;100(4):378-85.

57. Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016;16(12):e288-e303.

58. Allegranzi B, Bischoff P, de Jonge S, Kubilay NZ, Zayed B, Gomes SM, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016;16(12):e276-e87.

59. Lidwell OM, Elson RA, Lowbury EJ, Whyte W, Blowers R, Stanley SJ, et al. Ultraclean air and antibiotics for prevention of postoperative infection. A multicenter study of 8,052 joint replacement operations. Acta Orthop Scand. 1987;58(1):4-13.

60. WHO Surgical Safety Checklist [Available from: https://www.who.int/patientsafety/safesurgery/checklist/en/]

61. Blazeby J. Do dressings prevent infection of closed primary wounds after surgery? BMJ. 2016;353:i2270.

62. McHugh SM, Hill AD, Humphreys H. Laminar airflow and the prevention of surgical site infection. More harm than good? Surgeon. 2015 Feb;13(1):52-8

63. Ranhoff AH, Holvik K, Martinsen MI, Domaas K, Solheim LF. Older hip fracture patients: three groups with different needs. BMC Geriatr. 2010;10:65.

64. Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. Nature. 1992;359(6398):843-5.

65. Saxena V, Hwang CW, Huang S, Eichbaum Q, Ingber D, Orgill DP. Vacuum-assisted closure: microdeformations of wounds and cell proliferation. Plast Reconstr Surg. 2004;114(5):1086-96; 97-8.

66. Pietramaggiori G, Liu P, Scherer SS, Kaipainen A, Prsa MJ, Mayer H, et al. Tensile forces stimulate vascular remodeling and epidermal cell proliferation in living skin. Ann Surg. 2007;246(5):896-902.

67. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg. 1997;38(6):553-62.

68. Pollak AN. Use of negative pressure wound therapy with reticulated open cell foam for lower extremity trauma. J Orthop Trauma. 2008;22(10 Suppl):S142-5.

69. NICE. Wound Management Key Therapeutic Topic 2018 [Available from: https://www.nice.org.uk/advice/ktt14.]

70. Dumville JC, Gray TA, Walter CJ, Sharp CA, Page T, Macefield R, et al. Dressings for the prevention of surgical site infection. Cochrane Database Syst Rev. 2016(12). CD003091

71. Pachowsky M, Gusinde J, Klein A, Lehrl S, Schulz-Drost S, Schlechtweg P, et al. Negative pressure wound therapy to prevent seromas and treat surgical incisions after total hip arthroplasty. Int Orthop. 2012;36(4):719-22.

72. Hansen E, Durinka JB, Costanzo JA, Austin MS, Deirmengian GK. Negative pressure wound therapy is associated with resolution of incisional drainage in most wounds after hip arthroplasty. Clin Orthop Relat Res. 2013;471(10):3230-6.

73. Stannard J. Complex orthopaedic wounds: prevention and treatment with negative pressure wound therapy. Advances in Skin & Wound Care 2004;23 Suppl 1:3-cover.

74. Atkins BZ, Tetterton JK, Petersen RP, Hurley K, Wolfe WG. Laser Doppler flowmetry assessment of peristernal perfusion after cardiac surgery: beneficial effect of negative pressure therapy. Int Wound J. 2011;8(1):56-62.

75. Karlakki S, Brem M, Giannini S, Khanduja V, Stannard J, Martin R. Negative pressure wound therapy for managementof the surgical incision in orthopaedic surgery: A review of evidence and mechanisms for an emerging indication. Bone Joint Res. 2013;2(12):276-84.

76. Webster J, Scuffham P, Stankiewicz M, Chaboyer WP. Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention. Cochrane Database Syst Rev. 2014(10):CD009261.

77. Hyldig N, Birke-Sorensen H, Kruse M, Vinter C, Joergensen JS, Sorensen JA, et al. Meta-analysis of negative-pressure wound therapy for closed surgical incisions. Br J Surg. 2016;103(5):477-86.

78. Pauser J, Nordmeyer M, Biber R, Jantsch J, Kopschina C, Bail HJ, et al. Incisional negative pressure wound therapy after hemiarthroplasty for femoral neck fractures - reduction of wound complications. Int Wound J. 2016;13(5):663-7.

79. Craig P, Dieppe P Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008; 337 :a1655

80. Webster J, Scuffham P, Sherriff KL, Stankiewicz M, Chaboyer WP. Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention. Cochrane Database Syst Rev. 2012 (4):CD009261.

81. Munafò MR, Nosek BA, Bishop DVM, Button KS, Chambers CD, Percie du Sert N, et al. A manifesto for reproducible science. Nat Hum Behav. 2017;1:0021.

82. Munafò M, Smith GD. Robust research needs many lines of evidence. Nature. 2018(553):399-401.

83. Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration; 2011.

84. Bruce AJ, Ritchie CW, Blizard R, Lai R, Raven P. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. Int Psychogeriatr. 2007;19(2):197-214.

85. Henkelmann R, Frosch K-H, Glaab R, Lill H, Schoepp C, Seybold D, et al. Infection following fractures of the proximal tibia - a systematic review of incidence and outcome. BMC Musculoskelet Disord. 2017;18(1):481-.

86. Shao J, Chang H, Zhu Y, Chen W, Zheng Z, Zhang H, et al. Incidence and risk factors for surgical site infection after open reduction and internal fixation of tibial plateau fracture: A systematic review and meta-analysis. Int J Surg. 2017;41:176-82.

87. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine. 2009;6(7):e1000097.

88. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283:2008 - 12.

89. Mourad Ouzzani HH, Zbys Fedorowicz, and Ahmed Elmagarmid. Rayyan — a web and mobile app for systematic reviews. Syst Rev. 2016;5(210).

90. StataCorp. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC 2017.

91. Tableau (version. 9.1). Journal of the Medical Library Association : JMLA. 2016;104(2):182-3.

92. Fernandez MA, Griffin XL, Costa ML. Management of hip fracture. Br Med Bull. 2015;115(1):165-72.

93. Wells GS, B O'Connell, D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp]

94. Ahmed I, Khan MA, Allgar V, Mohsen A. The effectiveness and safety of two prophylactic antibiotic regimes in hip-fracture surgery. Eur J Orthop Surg Traumatol. 2016;26(5):483-92.

95. Barr LV, Vindlacheruvu M, Gooding CR. The effect of becoming a major trauma centre on outcomes for elderly hip fracture patients. Injury. 2015;46(2):384-7.

96. Chandran P, Azzabi M, Burton DJC, Andrews M, Bradley JG. Mid term results of Furlong LOL uncemented hip hemiarthroplasty for fractures of the femoral neck. Acta Orthop Belg. 2006;72(4):428-33.

97. Chapman G, Holton J, Chapman A. A threshold for concern? C-reactive protein levels following operatively managed neck of femur fractures can detect infectious complications with a simple formula. Clin Biochem. 2016;49(3):219-24.

98. Chaplin VK, Matharu GS, Knebel RW. Complications following hemiarthroplasty for displaced intracapsular femoral neck fractures in the absence of routine follow-up. Ann R Coll Surg Engl. 2013;95(4):271-4.

99. Duckworth AD, Phillips S-A, Stone O, Moran M, Breusch SJ, Biant LC. Deep infection after hip fracture surgery: predictors of early mortality. Injury. 2012;43(7):1182-6.

100. Findlay JM, Keogh MJ, Boulton C, Forward DP, Moran CG. Ward-based rather than team-based junior surgical doctors reduce mortality for patients with a fracture of the proximal femur: results from a two-year observational study. J Bone Joint Surg Br. 2011;93(3):393-8.

101. Jettoo P, James P. Dynamic hip screw fixation versus multiple screw fixation for intracapsular hip fracture. J Orthop Surg. 2016;24(2):146-9.

102. Hargrove R, Ridgeway S, Russell R, Norris M, Packham I, Levy B. Does pulse lavage reduce hip hemiarthroplasty infection rates? J Hosp Infect. 2006;62(4):446-9.

103. Harrison T, Robinson P, Cook A, Parker MJ. Factors affecting the incidence of deep wound infection after hip fracture surgery. J Bone Joint Surg Br. 2012;94(2):237-40.

104. Mackay DC, Harrison WJ, Bates JHJ, Dickenson D. Audit of deep wound infection following hip fracture surgery. J R Coll Surg Edinb. 2000;45(1):56-9.

105. Mamarelis G, Key S, Snook J, Aldam C. Outcomes after early return to theatre following hip hemiarthroplasty for intracapsular fracture of the femoral neck. Bone Joint J. 2017;99-b(7):958-63.

106. Morgan M, Black J, Bone F, Fry C, Harris S, Hogg S, et al. Clinician-led surgical site infection surveillance of orthopaedic procedures: a UK multi-centre pilot study. J Hosp Infect. 2005;60(3):201-12.

107. Reilly J, Allardice G, Bruce J, Hill R, McCoubrey J. Procedure-specific surgical site infection rates and postdischarge surveillance in Scotland. Infect Contr Hospl Epidemiol. 2006;27(12):1318-23.

108. Robinson CM, Houshian S, Khan LAK. Trochanteric-entry long cephalomedullary nailing of subtrochanteric fractures caused by low-energy trauma. J Bone Joint Surg Am. 2005;87(10):2217-26.

109. Shewale SB, Pandit HG, Latham JM. Hemiarthroplasty: To cement or not to cement? A preliminary report. Hip Int. 2004;14(3):189-92.

110. Sprowson AP, Jensen C, Chambers S, Parsons NR, Aradhyula NM, Carluke I, et al. The use of high-dose dual-impregnated antibiotic-laden cement with hemiarthroplasty for the treatment of a fracture of the hip: The Fractured Hip Infection trial. Bone Joint J. 2016;98-b(11):1534-41.

111. Wright DM, Blanckley S, Stewart GJ, Copeland GP. The use of orthopaedic POSSUM as an audit tool for fractured neck of femur. Injury. 2008;39(4):430-5.

112. Adams CI, Robinson CM, Court-Brown CM, McQueen MM. Prospective randomized controlled trial of an intramedullary nail versus dynamic screw and plate for intertrochanteric fractures of the femur. J Orthop Trauma. 2001;15(6):394-400.

113. Anakwe RE, Middleton SD, Jenkins PJ, Butler AP, Aitken SA, Keating JF, et al. Total hip replacement in patients with hip fracture: a matched cohort study. J Trauma Acute Care Surg. 2012;73(3):738-42.

114. Tsang STJ, Aitken SA, Golay SK, Silverwood RK, Biant LC. When does hip fracture surgery fail? Injury. 2014;45(7):1059-65.

115. Bidwai ASC, Willett KM. Comparison of the exeter trauma stem and the thompson hemiarthroplasty for intracapsular hip fractures. Hip Int. 2012;22(6):655-60.

116. Thakar C, Alsousou J, Hamilton TW, Willett K. The cost and consequences of proximal femoral fractures which require further surgery following initial fixation. J Bone Joint Surg Br. 2010;92(12):1669-77.

117. Cumming D, Parker MJ. Urinary catheterisation and deep wound infection after hip fracture surgery. Int Orthop. 2007;31(4):483-5.

118. Johnston P, Wynn-Jones H, Chakravarty D, Boyle A, Parker MJ. Is perioperative blood transfusion a risk factor for mortality or infection after hip fracture? J Orthop Trauma. 2006;20(10):675-9.

119. Palmer SJ, Parker MJ, Hollingworth W. The cost and implications of reoperation after surgery for fracture of the hip. J Bone Joint Surg Br. 2000;82(6):864-6.

120. Parker MJ, Pryor GA. Internal fixation or arthroplasty for displaced cervical hip fractures in the elderly: a randomised controlled trial of 208 patients. Acta Orthop Scand. 2000;71(5):440-6.

121. Khan AZ, Parker MJ. Minimally invasive sliding hip screw insertion technique. Hip Int. 2012;22(2):214-7.

122. Raut S, Parker MJ. Medium to long term follow up of a consecutive series of 604 Exeter Trauma Stem Hemiarthroplasties (ETS) for the treatment of displaced intracapsular femoral neck fractures. Injury. 2016;47(3):721-4

123. Khan SK, Jameson SS, Sims A, A'Court J, Reed MR, Rangan A, et al. Cemented Thompson's hemiarthroplasty in patients with intracapsular neck of femur fractures: survival analysis of 1,670 procedures. Eur J Orthop Surg Traumatol. 2015;25(4):655-60

124. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. Infect Control Hosp Epidemiol. 2008;29(11):996-1011.

125. Chandran P, Azzabi M, Burton DJC, Andrews M, Bradley JG. Mid term results of Furlong LOL uncemented hip hemiarthroplasty for fractures of the femoral neck. Acta Orthop Belg. 2006;72(4):428-33.

126. Emori TG, Culver D, Horan TC, Jarvis WR, JWhite JW, Olson DR, Banerjee S, et al. National nosocomial infections surveillance system (NNIS): description of surveillance methods. Am J Infect Control. 1991;19(1):19-35.

127. Peel AL, Taylor EW. Proposed definitions for the audit of postoperative infection: a discussion paper. Surgical Infection Study Group. Ann R Coll Surg Engl. 1991; 73(6): 385–388.

128. Christie J, Howie CR, Armour PC. Fixation of displaced subcapital femoral fractures. Compression screw fixation versus double divergent pins. J Bone Joint Surg Br. 1988;70(2):199-201.

129. D'Arcy J, Devas M. Treatment of fractures of the femoral neck by replacement with the Thompson prosthesis. J Bone Joint Surg Br. 1976;58(3):279-86.

130. Hunter GA. A comparison of the use of internal fixation and prosthetic replacement for fresh fractures of the neck of the femur. BJS. 1969;56(3):229-32.

131. Keene GS, Parker MJ. Hemiarthroplasty of the hip--the anterior or posterior approach? A comparison of surgical approaches. Injury. 1993;24(9):611-3.

132. McQueen MM, LittleJohn MA, Miles RS, Hughes SP. Antibiotic prophylaxis in proximal femoral fracture. Injury. 1990;21(2):104-6.

133. Parker MJ, Pryor GA, Myles JW. The value of a special surgical team in preventing complications in the treatment of hip fractures. Int Orthop 1994;18(3):184-8.

134. Robinson CM, Saran D, Annan IH. Intracapsular hip fractures: Results of management adopting a treatment protocol. Clinical Orthopaedics and Related Research. 1994(302):83-91.

135. Skinner PW, Powles D. Compression screw fixation for displaced subcapital fracture of the femur. Success or failure? J Bone Joint Surg Br 1986;68(1):78-82.

136. Wood MR. Femoral head replacement following fracture: an analysis of the surgical approach. Injury. 1980;11(4):317-20.

137. Yassa RR, Khalfaoui MY, Veravalli K, Evans DA. Pre-operative urinary tract infection: is it a risk factor for early surgical site infection with hip fracture surgery? A retrospective analysis. JRSM Open. 2017;8(3):2054270416675083.

138. Debray TPA, Moons KGM, Riley RD. Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: A comparison of new and existing tests. Res Synth Methods. 2018;9(1):41-50.

139. Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. Genome Med. 2016;8(1):39.

140. Sheehan KJ, Sobolev B, Guy P, Tang M, Kuramoto L, Belmont P, et al. Feasibility of administrative data for studying complications after hip fracture surgery. BMJ Open. 2017;7(4).

141. Joint Formulary Committee . British National Formulary (online): BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> 2017

142. Jen MH, Holmes AH, Bottle A, Aylin P. Descriptive study of selected healthcare-associated infections using national Hospital Episode Statistics data 1996–2006 and comparison with mandatory reporting systems. J Hosp Infect. 2008;70(4):321-7.

143. Centre for Disease Control Definition. Available from [https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf 2018]

144. Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. J Clin Epidemiol. 1995;48(12):1495-501.

145. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol. 1995;48(12):1503-10.

146. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

147. Baker PN, Salar O, Ollivere BJ, Forward DP, Weerasuriya N, Moppett IK, et al. Evolution of the hip fracture population: time to consider the future? A retrospective observational analysis. BMJ Open. 2014;4(4).

148. Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: A world-wide projection. Osteoporos Internat. 1992;2(6):285-9.

149. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36(5):309-32.

150. Cox D. Regression Models and Life-Tables (with Discussion). J Royal Stat Soc: Series B (Statistical Methodology). 1972;34:187-220.

151. Burns EM, Rigby E Mamidanna R, Bottle A, Aylin P, Ziprin P, Faiz OD. Systematic review of discharge coding accuracy. J Public Health (Oxf). 2012;34(1):138-48.

152. Theodorides AA, Pollard TCB, Fishlock A, Mataliotakis GI, Kelley T, Thakar C, et al. Treatment of post-operative infections following proximal femoral fractures: our institutional experience. Injury. 2011;42 Suppl 5:S28-34.

153. Kirkland KB, Briggs J, Trivette SL, Wilkinson WE, Sexton DJ. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol. 1999;20(11):725-30.

154. Castelli A, Daidone S, Jacobs R, Kasteridis P, Street AD. The Determinants of Costs and Length of Stay for Hip Fracture Patients. PLOS ONE. 2015;10(7):e0133545.

155. Public Health England. Surveillance of surgical site infections in NHS hospitals in England: 2014 to 2015. 2015.

156. Arhi CS, Bottle A, Burns EM, Clarke JM, Aylin P, Ziprin P, et al. Comparison of cancer diagnosis recording between the Clinical Practice Research Datalink, Cancer Registry and Hospital Episodes Statistics. Cancer Epidemiol. 2018;57:148-157

157. Dixon J. Payment by results—new financial flows in the NHS. BMJ. 2004;328(7446):969.

158. Metcalfe D, Zogg CK, Judge A, Perry DC, Gabbe B, Willett K, et al. Pay for performance and hip fracture outcomes. Bone Joint J. 2019;101-B(8):1015-23.

159. P Royston. Flexible parametric survival analysis using Stata: beyond the Cox model. STATA Press. Texas 2011.

160. Namba RS, Inacio MCS, Paxton EW. Risk Factors Associated with Deep Surgical Site Infections After Primary Total Knee Arthroplasty: An Analysis of 56,216 Knees. J Bone Joint Surg Am. 2013 1;95(9):775-82

161. Kurtz SM, Ong KL, Lau E, Bozic KJ, Berry D, Parvizi J. Prosthetic Joint Infection Risk after TKA in the Medicare Population. Clin Orthop Relat Res. 2010;468(1):52-6.

162. Everhart JS, Altneu E, Calhoun JH. Medical comorbidities are independent preoperative risk factors for surgical infection after total joint arthroplasty. Clin Orthop Relat Res. 2013;471(10):3112-9

163. Durand F, Berthelot P, Cazorla C, Farizon F, Lucht F. Smoking is a risk factor of organ/space surgical site infection in orthopaedic surgery with implant materials. Int Orthop. 2013;37(4):723-7

164. Yuan K, Chen HL. Obesity and surgical site infections risk in orthopedics: a meta-analysis. Int J Surg 2013; 11(5): 383-388

165. Meijs AP, de Greeff SC, Vos MC, Geerlings SE, Koek MB. The effect of body mass index on the risk of surgical site infection. Antimicrob Resist Infect Control. 2015;4(Suppl 1):O29-O

166. Stevenson KB, Khan Y Dickman J, Gillenwater T, Kulich P, Myers C, Taylor D, et al. Administrative coding data, compared with CDC/NHSN criteria, are poor indicators of health care-associated infections. Am J Infect Control. 2008 Apr;36(3):155-64

167. Jhung MA, Banerjee SN. Administrative coding data and health care-associated infections. Clin Infect Dis. 2009 15;49(6):949-55

168. Public Health England. Managing common infections: guidance for primary care. [Available from: https://www.gov.uk/]

169. French DD, Bass E, Bradham DD, Campbell RR, Rubenstein LZ. Rehospitalization after hip fracture: predictors and prognosis from a national veterans study. J Am Geriatr Soc. 2008;56(4):705-10

170. Boockvar KS, Halm EA, Litke A, Silberzweig SB, McLaughlin M, Penrod JD, et al. Hospital readmissions after hospital discharge for hip fracture: Surgical and nonsurgical causes and effect on outcomes. J Am Geriatr Soc. 2003;51(3):399-403

171. Hahnel J, Burdekin H, Anand S. Re-admissions following hip fracture surgery. Ann R Coll Surg Engl. 2009;91(7):591-5

172. Fragility Fracture Network. [Available from: https://www.fragilityfracturenetwork.org/]

173. Dong ZM, Chidi AP, Goswami J, Han K, Simmons RL, Rosengart MR, et al. Prior inpatient admission increases the risk of post-operative infection in hepatobiliary and pancreatic surgery. HPB (Oxford). 2015;17(12):1105-12

174. Wu X, Li Z, Cao J, Jiao J, Wang Y, Liu G, et al. The association between major complications of immobility during hospitalization and quality of life among

bedridden patients: A 3 month prospective multi-center study. PLOS One. 2018;13(10):e0205729-e.

175. Johansen A, Tsang C, Boulton C, Wakeman R, Moppett I. Understanding mortality rates after hip fracture repair using ASA physical status in the National Hip Fracture Database. Anaesthesia. 2017;72(8):961-6.

176. Lin JC-F, Liang W-M. Mortality, readmission, and reoperation after hip fracture in nonagenarians. BMC Musculoskelet Disord. 2017;18(1):144.

177. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004;351:1645 - 54.

178. Masters JPM, Achten J, Cook J, Dritsaki M, Sansom L, Costa ML. Randomised controlled feasibility trial of standard wound management versus negative-pressure wound therapy in the treatment of adult patients having surgical incisions for hip fractures. BMJ Open. 2018;8(4):e020632.

179. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016; 24;355:i5239

180. Costa ML, Griffin XL, Achten J, Metcalfe D, Judge A, Pinedo-Villanueva R, et al. World Hip Trauma Evaluation (WHiTE): framework for embedded comprehensive cohort studies. BMJ Open. 2016;6(10).

181. Griffin XL, Parsons N, Achten J, Costa ML. Warwick Hip Trauma Study: a randomised clinical trial comparing interventions to improve outcomes in internally fixed intracapsular fractures of the proximal femur. Protocol for the WHiT Study. BMC Musculoskelet Disord. 2010;11:184.

182. Griffin XL, Parsons N, Achten J, Costa ML. The Targon Femoral Neck hip screw versus cannulated screws for internal fixation of intracapsular fractures of the hip: A randomised controlled trial. Bone Joint J. 2014;96 B(5):652-7.

183. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. PLOS ONE. 2016;11(3):e0150205-e.

184. Whitehead AL, Sully BG, Campbell MJ. Pilot and feasibility studies: is there a difference from each other and from a randomised controlled trial? Contemp Clin Trials. 2014;38(1):130-3.

185. Atkins BL, Athanasou N, Deeks JJ, Crook DW, Simpson H, Peto TE, et al. Prospective evaluation of criteria for microbiological diagnosis of prosthetic-

joint infection at revision arthroplasty. The OSIRIS Collaborative Study Group. J Clin Microbiol. 1998;36(10):2932-9.

186. Haywood KL, Griffin XL, Achten J, Costa ML. Developing a core outcome set for hip fracture trials. Bone Joint J. 2014;96-b(8):1016-23.

187. Griffin XL, Achten J, Sones W, Cook J, Costa ML. Randomised controlled trial of the sliding hip screw versus X-Bolt Dynamic Hip Plating System for the fixation of trochanteric fractures of the hip in adults: a protocol study for WHiTE 4. BMJ Open. 2018;8(1):e019944.

188. Karanicolas PJ, Farrokhyar F, Bhandari M. Practical tips for surgical research: blinding: who, what, when, why, how? Can J Surg 2010;53(5):345-8.

189. Costa ML, Achten J, Bruce J, et al. Effect of negative pressure wound therapy vs standard wound management on 12-month disability among adults with severe open fracture of the lower limb: The WOLLF randomized clinical trial. JAMA. 2018;319(22):2280-8.

190. Tutton EA-OhooX, Achten J, Lamb SE, Willett K, Costa ML. Participation in a trial in the emergency situation: a qualitative study of patient experience in the UK WOLLF trial. Trials. 2018 25;19(1):328.

191. Seitz DP, Gill SS, Gruneir A, Austin PC, Anderson GM, Bell CM, et al. Effects of dementia on postoperative outcomes of older adults with hip fractures: a population-based study. J Am Med Dir Assoc. 2014;15(5):334-41.

192. Tissingh EK, Sudlow A, Jones A, Nolan JF. Orthopaedic surgical site infection surveillance in NHS England. national audit of current practice. Bone Joint J. 2017;99-B(2):171-4.

193. Petherick ES, Dalton JE, Moore PJ, Cullum N. Methods for identifying surgical wound infection after discharge from hospital: a systematic review. BMC Infect Dis. 2006;6:170.

194. Mitchell DH, Swift G Gilbert GL. Surgical wound infection surveillance: the importance of infections that develop after hospital discharge. Aust N Z J Surg. 1999;69(2):117-20

195. Alazzawi S, Bardakos N, Hadfield SG, Butt U, Beer ZH, Field RE. Patient-reported complications after elective joint replacement surgery: are they correct? J Bone Joint Surg Br. 2012;94(8):1120-5

196. National Hip Fracture Database Annual Report 2017 [Available from: https://nhfd.co.uk/files/2017ReportFiles/NHFD-AnnualReport2017.pdf]

197. Metsemakers WJ, Morgenstern M, McNally MA, Moriarty TF, McFadyen I, Scarborough M, et al. Fracture-related infection: A consensus on definition from an international expert group. Injury. 2018;49(3):505-10.

198. Cook JA, Julious SA, Sones W, Hampson LV, Hewitt C, Berlin JA, et al. DELTA 2 guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial. BMJ. 2018;363:k3750.

199. Walsh M, Srinathan SK, McAuley DF, Mrkobrada M, Levine O, Ribic C, et al. The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index. J Clin Epidemiol. 2014;67(6):622-8.

200. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.

201. Agarwal SK, Khan AA, Solan M, Lemon M. Hip fracture surgery in mixed-use emergency theatres: is the infection risk increased? A retrospective matched cohort study. Ann R Coll Surg Eng. 2017;99(8):641-4.

202. Bell KR, Clement ND, Jenkins PJ, Keating JF. A comparison of the use of uncemented hydroxyapatite-coated bipolar and cemented femoral stems in the treatment of femoral neck fractures: a case-control study. Bone Joint J. 2014;96-B(3):299-305.

203. Hossain FS, Rambani R, Ribee H, Koch L. Is discontinuation of clopidogrel necessary for intracapsular hip fracture surgery? Analysis of 102 hemiarthroplasties. J Orthop Traumatol. 2013;14(3):171-7.

204. Manoharan G, Chatterton BD, Moores TS, Roberts PJ. Uncemented Thompson's hemiarthroplasty: safe, palliative and cost-effective surgery in the infirm patient-a consecutive series of 1445 cases. Eur J Orthop Surg Traumatol. 2018;28(6):1103-9.

205. Wijeratna MD, McRoberts J, Porteous MJ. Cost of infection after surgery for intracapsular fracture of the femoral neck. Ann R Coll Surg Engl. 2015;97(4):283-6.

206. Bridle SH, Patel AD, Bircher M, Calvert PT. Fixation of intertrochanteric fractures of the femur. A randomised prospective comparison of the gamma nail and the dynamic hip screw. J Bone Joint Surg Br. 1991;73(2):330-4.

207. Chan RN, Hoskinson J. Thompson prosthesis for fractured neck of femur. A comparison of surgical approaches. J Bone Joint Surg Br. 1975;57(4):437-43.

208. Dawe EJC, Lindisfarne EAO, Nicol S, White SM, Stott PM. Does using a modular variable offset hemiarthroplasty reduce length of stay after hip fracture? Early experience with the Exeter Unipolar hemiarthroplasty. Europ Orthop Traumatol. 2014;5(1):49-55.

209. Grammatopoulos G, Wilson HA, Kendrick BJL, Pulford EC, Lippett J, Deakin M, et al. Hemiarthroplasty using cemented or uncemented stems of proven design: a comparative study. Bone Joint J. 2015;97-B(1):94-9.

210. Johnston LE, Parker MJ. Hip fractures and chronic alcohol excess: A series of 7,023 cases. Hip Int. 2014;24(6):644-9.

211. Hahnel J, Burdekin H, Anand S. Re-admissions following hip fracture surgery. Ann R Coll Surg Engl. 2009;91(7):591-5.

212. Hapuarachchi KS, Ahluwalia RS, Bowditch MG. Neck of femur fractures in the over 90s: a select group of patients who require prompt surgical intervention for optimal results. J Orthop Traumatol. 2014;15(1):13-9.

213. Hay D, Parker MJ. Hip fracture in the immobile patient. J Bone Joint Surg Br. 2003;85(7):1037-9.

214. Shukla S, Johnston P, Ahmad MA, Wynn-Jones H, Patel AD, Walton NP. Outcome of traumatic subtrochanteric femoral fractures fixed using cephalo-medullary nails. Injury. 2007;38(11):1286-93.

215. Shukla S, Nixon M, Acharya M, Korim MT, Pandey R. Incidence of MRSA surgical-site infection in MRSA carriers in an orthopaedic trauma unit. J Bone Joint Surg Br. 2009;91(2):225-8.

216. Tai CC, Nirvani AA, Holmes A, Hughes SPF. Methicillin-resistant Staphylococcus aureus in orthopaedic surgery. Int Orthop. 2004;28(1):32-5.

217. Henderson CY, Ryan JP. Predicting mortality following hip fracture: an analysis of comorbidities and complications. Ir J Medi Sci. 2015;184(3):667-71.

218. Hunter GA. A further comparison of the use of internal fixation and prosthetic replacement for fresh fractures of the neck of the femur. BJS 1974;61(5):382-4.

219. Dawson D, Milligan D, Callachand F, Cusick L. Hip Hemi-Arthroplasty vs Total Hip Replacement for Displaced Intra-Capsular Hip Fractures: Retrospective Age and Sex Matched Cohort Study. Ulster Med J. 2018;87(1):17-21.

220. Mabrouk A, Madhusudan M, Waseem M, Kershaw S, Fischer J. Outcomes of geriatric hip fractures treated with AFFIXUS hip fracture nail. Adv Orthop;2014:509592

221. Middleton SD, McNiven N, Anakwe RE, Jenkins PJ, Aitken SA, Keating JF, et al. Medium-term patient-reported outcomes after total hip replacement for displaced hip fractures. Eur J Orthop Surg Traumatol. 2017;27(7):917-21.

222. Fox HJ, Pooler J, Prothero D, Bannister GC. Factors affecting the outcome after proximal femoral fractures. Injury. 1994;25(5):297-300.

223. Jennings AG, De Boer P. Should we operate on nonagenarians with hip fractures? Injury. 1999;30(3):169-72.

224. Jonas SC, Shah R, Al-Hadithy N, Norton MR, Sexton SA, Middleton RG. Displaced intracapsular neck of femur fractures in the elderly: Bipolar hemiarthroplasty may be the treatment of choice; A case control study. Injury. 2015;46(10):1988-91.

225. Wood DJ, Ions GK, Quinby JM, Gale DW, Stevens J. Factors which influence mortality after subcapital hip fracture. J Bone Joint Surg Br. 1992;74(2):199-202.

226. Wordsworth DR, Halsey T, Griffiths R, Parker MJ. Clopidogrel has no effect on mortality from hip fracture. Injury. 2013;44(6):743-6.

227. Sanchez-Ballester J, Smith M, Hassan K, Kershaw S, Elsworth CS, Jacobs L. Wound infection in the management of hip fractures: A comparison between low-molecular weight heparin and mechanical prophylaxis. Acta Orthop Belg. 2005;71(1):55-9.

228. Umarji SIM, Lankester BJA, Prothero D, Bannister GC. Recovery after hip fracture. Injury. 2006;37(8):712-7.