Predicting inhaled steroid responsiveness using blood eosinophil counts: personalising long-term management of COPD in primary care

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A thesis submitted for the degree of Doctor of Philosophy

Michaelmas Term 2019

This thesis is dedicated to my parents

Paul and Valerie Davis

for placing so much value on my education, teaching me that there is no limit to achievements and encouraging persistence and grit in all endeavours

Abstract

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Background

Management of chronic obstructive pulmonary disease (COPD), including initiation of inhaled corticosteroids (ICS), has thus far generally been based on a 'one-size-fits-all' approach. However, benefits of ICS are unclear, and they may harm some patients. Blood eosinophils have been identified as a readily available biomarker to guide decisions about ICS treatment in COPD, but they have not been studied in an ICS-naïve, primary care population. A device for estimating blood eosinophil counts at the point of care is now available. This doctoral project aimed to characterise blood eosinophils and ICS responsiveness in people with COPD in primary care, as well as assess agreement between near-patient vs. laboratory testing for blood eosinophils.

Methods

This project comprises two major studies, each with several constituent parts. First, a study of 30,378 routinely-collected primary care records were used for descriptive and hypothesis-testing components. Second, a prospective cohort study recruited 96

participants to obtain laboratory and near-patient blood eosinophil data at multiple visits over a six-month period.

Results

Approximately half of patients fell into a 'medium' category of eosinophils in the range 0.15 to 0.34 x10*9/L. Repeatability of eosinophil counts was either 'good' or 'excellent' in the two cohorts. There was a lower risk of acute exacerbations in patients with higher eosinophil counts who were prescribed an ICS, with a clear 'dose-response' by eosinophil count. There was no clinically important difference between near-patient and laboratory eosinophil values.

Conclusions

Patients with higher blood eosinophils are more likely to benefit from ICS. Blood eosinophil counts are generally repeatable and are applicable for guiding ICS treatment decisions in primary care. Blood eosinophil categories in combination with other clinical features such as acute exacerbation frequency could provide a more personalised approach to pharmacological management of COPD. Near-patient eosinophil count testing could support rapid decisions about ICS treatment in primary care.

Acknowledgements

First and foremost, I must thank my supervisors – Chris Butler, Mona Bafadhel, Emily McFadden and Margaret Smith – for their support and encouragement. I am particularly grateful for the fact that they have trusted me to get on with it and to ask for help when needed, and that they have been extremely speedy with reviewing thesis chapters given my rapidly impending Expected Date of Delivery. Emily and Margaret have also been admirably patient with my statistical foibles and ignorance, and I have learned so much from them which I will use in the future.

Many others have provided input and advice at various stages of funding application, study design, analysis and write-up: thanks to Richard Stevens, for statistical input into the funding application; Ben Feakins, for initial help with working out the CPRD and getting to grips with Stata; Debbie Hay and Catherine Garnett, for haematology advice; David McCartney for providing a second clinical opinion on CPRD code lists and keeping an eye on COMET during my maternity leave; my cousin Jessie Davis for helping with flow chart design; Jason Oke for statistical input into repeatability analysis; Tim Harries at KCL for sharing insight into his unpublished systematic review findings; and colleagues (too many to name individually) met through PCRS, conferences and elsewhere, for critical comment and clinical grounding, as well as inspiration. I must also thank other DPhil students in the department for sharing of their wisdom at the various stages of the DPhil process, and particularly Constantinos Koshiaris for dealing with my Stata queries so willingly. I thank the NIHR for providing me with funding, my PPI representative, the CTU nursing team (Heather Rutter, Karen Madronal, Pippa Whitbread and Bernie Mundy), and all the patients who have participated in the COMET study.

I have been fortunate to have had amazing office companions during my doctoral studies, for shared cups of tea, lunch breaks and gossip – Gail Hayward, David McCartney, Ben Feakins, Becks Fisher and Rachel Brettell – leading to friendships which I hope will long continue. In the last six months I have been based in college, and I thank Daniel Anthony for so readily letting me take over the Maitland room, and Somerville SCR for frequent provision of (decaf) coffee to break up the writing. More generally, I thank my colleagues in my other roles (Daniel and Suzie Anthony, and Damian Tyler at Somerville, and all my colleagues at 19 Beaumont Street surgery) for their patience, good humour and support when I've been trying to juggle several different things.

Three senior primary care academics – Dan Lasserson, Anthony Harnden and Susan Jebb – have provided me with inspiration and unofficial mentorship over the last five or more years. I have been extremely grateful for their wise counsel when I have been at risk of losing motivation with the whole endeavour, and for their role in helping to make sure I could see beyond the thesis.

Lastly, I thank my family and friends, for both practical and emotional support. My husband, Michael, has provided endless love, support and encouragement and has always believed in me. And our daughter Lizzie (currently aged two and a half) puts it all in perspective.

November 2019

Baby Rowan was born on 20th November 2019 and we had a rather difficult first year together, compounded by the Covid-19 pandemic (nursery closure, isolation, etc.). I am therefore only submitting my thesis corrections in March 2021. I thank my examiners for their helpful feedback at my viva in January 2020, and for their patience since then. My supervisors have also provided prompt and helpful comments for me when undertaking corrections.

I am extremely fortunate to have friends who have provided incredibly valued emotional and practical support at various points and who I thank for my survival of the last year – particularly Kate Bailey, Eleanor Smith, Sarah McCartney, Meriel Cowan, Gail Hayward and Elle Hawkes – as well as my GP, Jonathan Williams, my cousin Jessie Davis, and my sister Christina Easton. Susan Jebb has also been enormously kind in reducing pressure of deadlines and sorting out administrative things in the department for me. Rebecca Fortescue's friendship and company during our first year with our baby boys, and encouraging me to believe in myself and in the novelty of my thesis content, has been hugely valuable.

It has been a year for reflection and focusing on the important things in life, and I have decided to take a more relaxed approach to my career over the next few years whilst my children are small. I hope this thesis will serve to remind me of my achievements when I return in the future.

March 2021

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List of abbreviations

ACF	Academic Clinical Fellow
BDP	Beclomethasone dipropionate
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
CI	Confidence interval
COMET	Near-patient testing to guide COPD MaintenancE Treatment in primary care: observational study to determine variability and accuracy of inflammatory biomarkers in stable state
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CTU	Clinical Trials Unit
CRF	Case Report Form
CRN	Clinical Research Network
CRP	C-reactive protein
CV	Co-efficient of variation
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints study
FBC	Full blood count
FeNO	Fraction of exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practice/General Practitioner
HES	Hospital Episode Statistics
HR	Hazard ratio
HRA	Health Research Authority
ICC	Intra-class correlation co-efficient
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICS	Inhaled corticosteroid

IL-5	Interleukin-5
IMD	Index of Multiple Deprivation
IQR	Interquartile range
ISAC	Independent Scientific Advisory Committee
LABA	Long-acting beta-2 agonist
LAMA	Long-acting muscarinic antagonist
LR	Likelihood ratio
LRTI	Lower respiratory tract infection
MHRA	Medicines and Healthcare Products Regulatory Agency
MRC	Medical Research Council
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NPV	Negative predictive value
ONS	Office for National Statistics
OPCRD	Optimum Patient Care Research Database
OUH	Oxford University Hospitals
PCRS	Primary Care Respiratory Society
PIS	Patient Information Sheet
POC	Point-of-care
PPV	Positive predictive value
PPI	Patient and public involvement
PROSPERO	Prospective Register of Systematic Reviews
QOF	Quality and Outcomes Framework
RCT	Randomised controlled trial
RISP	Research Information Sheet for Practices
SABA	Short-acting beta-2 agonist
SAMA	Short-acting muscarinic antagonist
SD	Standard deviation
VAS	Visual Analogue Scale
WBC	White blood cell count

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Preface: A personal journey

In this preface I discuss my reasons for embarking on this doctoral project and how I came to undertake the studies included within it, my choice of supervisors, the changes I have made to the thesis I originally planned (and why), and my other primary care, respiratory and clinical academic roles.

From 2010-2014 I undertook an Academic Clinical Fellowship (ACF) in Primary Care, based in the Nuffield Department of Primary Care, University of Oxford. During this time I completed my clinical training in General Practice, and led or was involved in research studies across a range of fields including diagnostic technology, child health, infection and antibiotic prescribing, and I developed skills in study designs including systematic reviews, diagnostic accuracy and qualitative studies, running clinical studies in a secondary care and non-NHS setting, and completed a Postgraduate Diploma in Healthcare Research.

I was clear after my ACF that I wanted to continue long-term as a clinical academic, and I therefore applied for doctoral research funding from the National Institute for Health Research (NIHR). I wanted a project which linked my interest in diagnostic technology, with my longstanding clinical interest in respiratory medicine, and particularly in chronic obstructive pulmonary disease (COPD). I was also keen to use a doctoral program to fill in gaps in my research knowledge, specifically to become familiar with using a large primary care database such as the Clinical Practice Research Database (CPRD), to improve my statistical knowledge and ability with statistical programming, and to gain experience of running a clinical study in a primary care setting through an established Clinical Trials Unit (CTU).

I was fortunate to be introduced to Mona Bafadhel and Ian Pavord (both respiratory consultants and researchers at the Oxford University Hospitals (OUH) NHS Trust) by my GP ACF mentor, Dan Lasserson. Mona had recently completed studies on phenotyping COPD exacerbations[1] and blood eosinophil-guided treatment of COPD exacerbations in secondary care,[2] which had identified blood eosinophils as a biomarker of eosinophilic exacerbations and as a potential guide to directing oral steroid treatment in exacerbations, and was shortly to commence studies recruiting in primary care to address the same question, using point-of-care testing to provide an immediate eosinophil count. Several studies[3-8] (discussed in Chapter 1) published a decade previously had indicated that sputum eosinophils could be used to guide oral or inhaled corticosteroid treatment in long-term COPD management, but this had not been studied for peripheral blood eosinophils or in a primary care population, which seemed an obvious literature gap, and next step for research, given Mona's new findings in the context of COPD exacerbations. As such, blood eosinophils could be a potential easy-to-measure biomarker (as they are obtained automatically as part of the full blood count), highly applicable for use in a primary care setting, which could be used to direct inhaled corticosteroid (ICS) treatment – the use of which had become more controversial due to concerns about harms, particularly pneumonia, associated with its use (see Chapter 1).

Together with Dan, Mona, Ian, and Chris Butler (Professor of Primary Care, who had recently moved to Oxford from Cardiff and was commencing a study on CRP-guided antibiotic treatment of COPD exacerbations), I designed a research proposal that would address this hypothesis and included a systematic review, CPRD study and prospective observational cohort study recruiting in primary care (the 'COMET' study). I also planned

to investigate other putative biomarkers of eosinophilic inflammation which might be applicable to a primary care setting, including fraction of exhaled nitric oxide (FeNO, which had recently attracted interest in asthma diagnosis and management), and periostin.

I consulted with patients living with COPD via local patient groups, who found managing multiple inhalers burdensome and welcomed research which might help better target inhalers to those who would most benefit (full details of patient and public involvement are in Section 3.2.10).

I was fortunate to obtain NIHR funding and I commenced my doctorate in October 2014. Due to the complexities of the epidemiological analysis, the NIHR requested that I appoint a specific statistical supervisor: this was initially Richard Stevens, followed for most of my doctorate by Emily McFadden and Margaret Smith. I have undertaken specific training courses (described in the epilogue) to improve my skills in statistical methods.

Published work in the field of blood eosinophils in COPD was relatively sparse at the time I commenced my doctorate. However, over the last five years this has expanded greatly, from only a handful to several hundred or more papers, particularly in terms of post-hoc analysis of previously published trials of ICS, and studies using routinely-collected data. In this thesis I have tried to make clear the logical progression of my work over time, in the context of work being done by others. I have therefore generally presented the background literature in the introduction and methods chapters as it was at the time of planning the studies and developing the protocols, as this formed the basis for undertaking the studies. However, I have considered the most recent work up to the present, and have incorporated these more recently published studies and guidelines, in the discussion elements of the

results chapters and the overall conclusions chapter, in order to give a complete picture of where my work fits into the present state of scientific knowledge.

Although my studies have largely taken place as set out in my NIHR and doctoral study application, there have been a couple of changes which are important to mention. First, I designed and published[9] a detailed protocol for a systematic review, and undertook the literature search for this. However, I became aware that a very similar systematic review was being undertaken by a primary care group at Kings College London (to be published shortly), and at the same time it became clear that the methodology and analysis required for the CPRD study would be far more complex and greater than anticipated, and I decided (in conjunction with my supervisors) that focusing on this would be more useful in terms of my personal training and development than undertaking a systematic review which would be duplicative of others' work. Second, due to the vastness of the analysis on blood eosinophils (from both the CPRD and COMET studies), as well as the expanding field, I decided to narrow the focus of this thesis, to be concerned specifically with blood eosinophils (and I changed the thesis title to reflect this). Therefore although I mention other inflammatory biomarkers (FeNO, periostin, C-reactive protein (CRP)) in passing where relevant, they are not discussed in detail here. I plan to publish results in relation to these other biomarkers in due course (and results for periostin are not yet available at the time of writing).

I undertook my doctoral research on a part-time basis, and alongside it I have continued in other roles and led or contributed to other research projects (both respiratory and non-respiratory-related) in my department and elsewhere. A list of publications obtained during my doctorate (fifteen in total) is listed in Appendix A. Other related studies (not yet

submitted for publication) include CPRD studies on statins in COPD (as part of a successfully awarded NIHR grant on which I am co-applicant), and ICS withdrawal in COPD using the CPRD.

The other roles I have undertaken during my doctorate have included: working as a locum GP around Oxfordshire and then subsequently as a salaried GP at 19 Beaumont Street surgery, Oxford, where I am Respiratory Lead and responsible for Clinical Research within the practice; Research Lead for the Primary Care Respiratory Society, where I am the lead for research activities within the organisation, Chair of the Research Committee, and member of Executive and Conference committees, and also sit as the primary care representative on the UK Respiratory Research Council and Member of the National Asthma and COPD Audit Programme Research Committee; Janet Vaughan Tutor in Clinical Medicine at Somerville College, where I am Organising Tutor for Clinical Medicine and lead admissions and give tutorials (including in respiratory basic science); and Integrated Respiratory Team GP in Oxford, contributing to the assessment and management of patients with COPD in the community. I have also been a member of the Board of Examiners for Part II Graduate Entry Medicine, sit on several Trial Steering Committees, participate in regular peer review, was Chair of the Society for Academic Primary Care South West region conference 2017, and in 2015 was awarded an Ig Nobel Prize in Diagnostic Medicine for previous work on speed bumps in appendicitis, and regularly give public engagement in science talks on this topic. All of these roles have, in one form or other, positively contributed to and enhanced my understanding and undertaking of this doctoral project, as well as contributing to my personal development as a clinical academic.

During the period of my doctorate I have also had my first child (followed by 12 months' maternity leave), and am shortly expecting my second child, in fact I am submitting this thesis on the eve of my due date. Thanks to this biological deadline and the time needed to get my head back into analysis after a period of chronic sleep deprivation, I have focused in the last eight months on completing analysis and writing this thesis, and therefore I have not yet published any of the work directly related to my doctoral studies. I have however presented it widely at regional, national and international meetings, as detailed in Appendix A, and used feedback received in refining the analysis and conclusions.

I do hope you enjoy reading it.

Chapter 1: Introduction: potential role of eosinophils in the management of COPD

This chapter summarises the state of the evidence current at the time of planning the thesis (both obtaining the funding and planning the methods for the component studies), generation of the overall hypothesis for the thesis and related objectives, and a summary of how I have organised the thesis to answer these objectives.

1.1 Data sources and searches

Relevant published studies were identified through a search strategy incorporating keywords and search terms for COPD and blood eosinophils, and their variants (e.g. 'chronic bronchitis', 'emphysema', 'biomarkers') and including Medline, EMBASE[a], Web of Science and CENTRAL[b] databases and other trial registries (an example search strategy is given as Appendix B, originally planned to be used as part of a systematic review). Searches of the Prospective Register of Systematic Reviews (PROSPERO) database did not identify any further relevant systematic reviews, although as discussed in the Preface, I was aware of one being undertaken at Kings College London. Throughout the duration of my thesis, I received weekly Pubmed notifications for papers in which the abstract included 'COPD' or 'eosinophil' terms, and published by key authors in the field. I also reviewed the reference lists of any relevant articles.

[a] EMBASE: Excerpta Medica databse
[b] CENTRAL: Cochrane Central Register of Controlled Trials

1.2 Background

1.2.1 COPD and its management in primary care

COPD is a chronic respiratory condition affecting 1 million people in the UK, predominantly caused by smoking.[10] It is characterised by airflow obstruction which is not fully reversible, and symptoms include breathlessness, cough and increased sputum. It accounts for more than £800 million in direct healthcare costs and causes an estimated 24 million lost working days per annum in the UK.[10] Exacerbations are acute worsening of symptoms which may result in a hospitalisation or death, and contribute to progressive decline in COPD;[11] exacerbations are rated by patients as the most important outcome measure in COPD.[12]

COPD diagnosis is by a combination of clinical findings (history and examination), together with post-bronchodilator spirometry confirming airflow obstruction (forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.7). National Institute for Health and Clinical Excellence (NICE) guidance defines severity by degree of airflow obstruction using percentage of predicted FEV_1 (giving severity categories of mild, moderate, severe and very severe),[10] but COPD severity can also be classified by degree of breathlessness (for example using the MRC breathlessness (Medical Research Council) or CAT (COPD Assessment Test) scores) and frequency of exacerbations, such as in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[13] Reversibility (change in airflow limitation in response to salbutamol) is not recommended as part of routine diagnosis, but can be helpful where there is suspicion of asthma.[10]

COPD management can be divided into non-pharmacological (e.g. smoking cessation and pulmonary rehabilitation) and pharmacological measures (predominantly inhaled therapies), with therapies added when patients experience frequent exacerbations or

persistent breathlessness, and should ideally be co-ordinated by a multi-disciplinary team.[10] NICE guidelines recommend a short-acting bronchodilator (beta-2 agonist, SABA, or muscarinic antagonist, SAMA), followed by long-acting bronchodilator (beta-2 agonist, LABA, or muscarinic antagonist, LAMA). Inhaled corticosteroids (ICS) are recommended in combination with LAMA or LABA for worsening symptoms or moderate or severe COPD (FEV_1 <50% predicted).[10] All three agents (LABA, LAMA and ICS) can now be prescribed as monotherapy or as combination inhalers; a useful summary of currently available inhaled drugs for airways disease can be found at https://www.pcrs-uk.org/resource/table-inhaled-drugs).

In reality, the majority of long-term COPD management takes place entirely in primary care (in many practices by a single practice nurse with varying amounts of specific training) and there is low understanding and adherence to guidelines.[14,15] Furthermore, guidelines are in general based on large pharmaceutically-sponsored studies which have been conducted in a secondary care and/or trial setting which are poorly reflective of the primary care COPD population; less than a fifth of 'real-life' COPD patients are eligible for COPD clinical study inclusion criteria, and in general are older, with better lung function, quality of life and fewer exacerbations.[16,17]

1.2.2 Evidence for ICS use, potential harms and current prescribing practice

Trials of long-term use of ICS for COPD have demonstrated some reduction in exacerbations (particularly in frequent exacerbators with more severe COPD), and some symptomatic benefit, but their effects on rate of lung function decline and mortality are unclear.[18-22] However, their use can be associated with adverse effects, particularly pneumonia,[23-25] but also tuberculosis,[26] diabetes,[27] cataracts,[28] and osteoporotic

fractures,[29] contributing to the guideline recommendation that the risk-benefit ratio favours ICS use in those with moderate-severe, but not mild COPD.[30] They are also expensive to the NHS: the total cost of LABA/ICS combination therapy is more than any other drug and in 2010 almost £500 million was spent on them.[31]

Adherence to guidelines in primary care is particularly poor in this respect, and ICS are widely used in the management of COPD. LABA/ICS is the most commonly prescribed maintenance therapy at the point of COPD diagnosis,[32] and patients tend to drift towards triple therapy (LABA, LAMA and ICS) in the years following COPD diagnosis.[33] 38% COPD patients are over-treated with ICS (did not meet criteria for being prescribed ICS) and this resulted in an estimated cost of over £250,000 per year.[31] There is therefore a need to improve clarity around when ICS should be prescribed in primary care.

1.2.3 Eosinophils and COPD

Biomarkers are biological parameters that can be objectively measured and evaluated, and in COPD can potentially be used to define populations (or phenotypes) that will derive most benefit from a drug, and predict disease course or clinical outcomes.[34] The peripheral blood eosinophil count is a potential biomarker in COPD which could be used in primary care because it is easily available (unlikely sputum eosinophils) and already provided automatically when a 'full blood count' is requested, which is done commonly in routine practice. In fact, NICE recommends that patients with COPD have a full blood count at the time of diagnosis to identify anaemia or polycythaemia.[10]

Eosinophil biology in health and disease

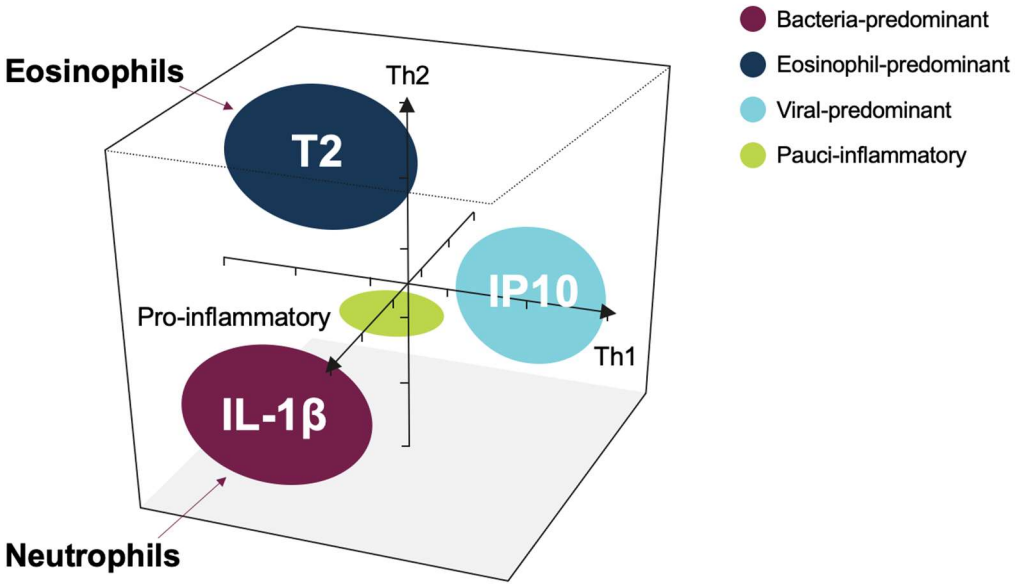
Eosinophils are part of the innate immune system and are produced in the bone marrow, then migrate to and reside in the thymus or gastrointestinal tract until they are recruited to tissues in response to inflammatory stimuli. This is particularly under the direction of interleukin-5 (IL-5), a cytokine which is predominately produced by T-helper-2 cells. Mature eosinophils make up less than 5% of total peripheral blood leucocytes and have a mean blood transit time of 26 hours.[35-37] In response to external stimuli, eosinophils release cytotoxic granule proteins, type 2 cytokines, enzymes and growth factors.[35] The immunological eosinophil response is complex including their role in promoting host defence against helminthic, bacterial and viral infection.[36]

Despite the role of the eosinophil in immune defence, promotion of disease pathology (such as allergic disease) can be caused by dysregulated eosinophil recruitment and/or activity. This is particularly well understood for asthma, and to a lesser extent in COPD, but is also important in the pathophysiology of eosinophilic oesophagitis, eosinophilic myopathies, and hypereosinophilic syndromes.[36]

In asthma, activation of eosinophils contributes directly to mucous production, bronchoconstriction, and airway dysfunction and remodelling. Elevated eosinophils have been found in blood sputum and tissue of patients with asthma, and correlate with asthma severity,[38] which can be reduced by corticosteroid treatment which reduces airway eosinophils. Efficacy of monoclonal antibody treatment towards IL-5 in patients with eosinophilic asthma provides evidence that eosinophils are a key effector cell in asthma pathogenesis, and not merely a bystander.[35]

Less is known about the role of eosinophils in the pathophysiology of COPD, however there is increasing evidence that it also has an important role in COPD.[39] There is clear overlap with asthma in that eosinophils have been detected in sputum, bronchoalveolar lavage and bronchial biopsy samples of patients with COPD, and there is a similar pattern of type-2 mediators in the airways.[35] Additionally, as with asthma, patients fall into eosinophilic and non-eosinophilic groups. Biological modelling has found that there is a subset of COPD patients (28%) who have increased airway eosinophil count in stable state and at exacerbation (Bafadhel *et al,* Figure 1.1),[1] and this fits with the potential role of the eosinophil in host defence against bacteria and viruses, which are well established triggers for exacerbation.[11] Patients with COPD also vary in terms of their general inflammatory biomarker phenotype, both in type and quantity of inflammation. Furthermore the differential expression of airway and systemic biomarkers of inflammation, including airway and blood granulocytes including eosinophils and neutrophils, and serum CRP, are associated with poorer outcomes in COPD, including more exacerbations,[40] faster decline in lung function,[41] hospitalisations,[42] and mortality.[42,43] Higher sputum eosinophils are also associated with poor outcomes in patients with COPD, including faster decline in lung function.[41]

Figure 1.1: Proportional representation of COPD exacerbation clusters



Eosinophil-predominant cluster is outlined in dark blue (top left). Figure reproduced from reference.[1]

Blood eosinophil distribution and repeatability in COPD

Bafadhel[31] was the first to describe the relevance of the peripheral blood eosinophil count in COPD exacerbations, determining, as per Figure 1.1,[1] that the peripheral (blood) eosinophil count correlates with airway eosinophil count, and determined this to be the best predictor of an eosinophilic exacerbation.[a] Subsequent to this work, investigators have sought to understand further the utility of the eosinophil in COPD. Median blood eosinophil level in patients with COPD is around 0.20 x10*9/L.[b]. Observational studies also show that that there seems to be little variation between clinical characteristics in patients with COPD above or below this level, nor their association with co-morbidities including

[a] More recently conducted studies, discussed in Section 5.4.3, have found conflicting findings about the relationship and correlation between sputum and blood eosinophils.
[b] Throughout the thesis I have given blood eosinophil counts in x10*9/L units, to two decimal places, as this is how they are most commonly provided in UK primary care. 100 cells/µL equates to 0.10 x10*9/L.

asthma and helminth infection.[44,45] Blood eosinophil counts appear to be higher in those with atopy (0.19 vs.0.15 x10*9/L).[46] However, these studies have been conducted in highly selective secondary care populations and are relatively small, thus variation of eosinophil counts due to co-morbidity may be particularly relevant given that the COPD population is elderly and often with multiple co-morbidities.

A biomarker will only be useful if it remains relatively stable within an individual, when other variables remain constant. Secondary analysis of data from the Bafadhel study[1] showed good within-patient stability of blood eosinophils at 3-month intervals over one year (intra-class correlation co-efficient 0.79), with 35% of patients having counts that varied above or below a threshold of 0.40 x10*9/L.[35] In another study over a 3-year period, 49% patients had an eosinophil count which varied above and below a cut-off of blood eosinophils ≥2% total leucocyte count, with 37% persistently above and 14% persistently below this threshold.[47]

It should be noted that these proposed thresholds are all within what has been traditionally denoted as 'normal range' for blood eosinophils (reference range for Oxford University Hospitals NHS Trust is 0.0-0.5 x10*9/L), validated on healthy individuals, but which notably would include volunteers with atopy, as the general population incidence of atopy is approximately 40%.[48]

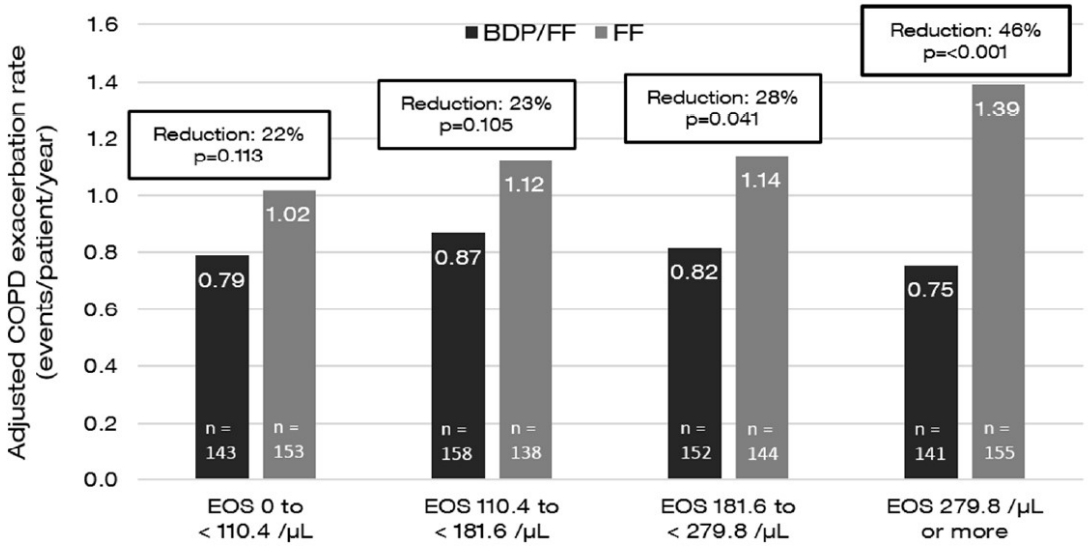
Early population-based cohort studies have shown that higher blood eosinophils are associated with poor outcomes in patients with COPD, including mortality,[49,50] but there is minimal data on the association of blood eosinophils with disease prognosis.

Eosinophils as a biomarker of corticosteroid responsiveness

Early studies showed that in patients with higher sputum eosinophil counts, treatment in stable state with both oral and inhaled steroids improved FEV_1, dyspnoea and quality of life,[3-6] and management by sputum eosinophil count resulted in a reduction in severe exacerbations.[7] Patients who responded to oral steroids in terms of improvements in FEV_1 had a raised blood eosinophil count at baseline; but this was not commented on by the authors at the time.[8] In the first of its kind, a randomised placebo-controlled biomarker interventional study of blood eosinophil-directed treatment of exacerbations of COPD found a higher rate of treatment failure when COPD patients with lower blood eosinophils were treated with oral steroids.[2]

Following the increasing interest in blood eosinophils as a biomarker in COPD, many retrospective post-hoc analyses of randomised controlled trials of ICS, incorporating stratification by blood eosinophil count at baseline, were commenced in 2014 which have since been published.[51-60] Various cut-offs for eosinophil count have been used in these analyses (including 0.15, 0.30 x10*9/L, and 2% total leucocyte count, as well as continuous analysis). Although statistical significance varies between different analyses, different study populations, and different inhaled corticosteroids, the findings are similar; namely that there is a greater response to ICS-containing preparations in patients with a higher baseline eosinophil count, and there is a dose-response relationship of both rate of exacerbations and ICS-responsiveness according to degree of eosinophilic inflammation in the blood (see Figure 1.2).

Figure 1.2: Adjusted COPD exacerbation rate (events/patient/year) with LABA/ICS (BDP/FF, black) and LABA alone (FF, grey) stratified by baseline blood eosinophil quartile



BDP, beclomethasone dipropionate. FF, formoterol fumarate. Figure reproduced from reference.[60]

Other markers of eosinophilic inflammation[a]

Fraction of exhaled nitric oxide (FeNO) is a breath test which correlates with eosinophilic airway inflammation, and is becoming of increasing importance in management of asthma, particularly in targeting and adjusting ICS treatment.[61-63] It has not been so widely studied in the COPD population, however some studies have shown that it can be used to predict response to both oral and inhaled steroids.[64-66]

Periostin is an extracellular matrix protein which has been shown to be a potential blood biomarker for eosinophilic airway inflammation in asthma[67] and some correlation with blood eosinophil count and FeNO.[68] In patients with COPD, it remains stable over time

[a] I mention these only briefly as the focus of my thesis has narrowed to blood eosinophils only.

irrespective of disease severity and ICS use, and is correlated with blood eosinophil count, particularly in ex-smokers.[69]

1.2.4 Point-of-care testing

Point-of-care, or near-patient, testing, refers to any test taken at the time of consultation which produces results which can be used to make immediate decisions about patient treatment, and is associated with increased patient and GP satisfaction.[70,71] It is increasingly used in primary care, particularly in Scandinavia, where, for example, CRP-guided treatment for acute respiratory infections is common.[72] There is now a commercially available device for measuring blood eosinophils in a near-patient setting (the HemoCue® WBC DIFF), which uses blood from a finger prick sample placed on a microcuvette with analysis by a photo microscope to detect stained white blood cells. These are identified and counted using mathematical algorithms and image recognition technology, providing a white cell count differential in several minutes (information from manufacturer).

1.3 Unanswered uncertainties

Although there appears to be utility of the peripheral blood eosinophil count in COPD and in particular in the potential response to inhaled corticosteroids, it is worth noting that the majority of the studies discussed have been conducted in a secondary care and/or trial setting. This is a limitation to generalisability as we know these types of studies are poorly representative of the primary care COPD population.[16,17] Furthermore, many patients referred to secondary care will already have been using ICS, which reduces airway eosinophilic inflammation,[3,4] so findings from these studies may not be applicable to those patients in primary care who will be ICS-naïve at the point when step-up treatment might

be being considered. Finally, a variety of eosinophil cut-offs have been proposed, whilst the proportion of patients with an elevated eosinophil count varies widely, again making interpretation or extrapolation of the current literature in patients in primary care difficult.

Stability (or repeatability) of eosinophil count is also important for utility in clinical practice, and whether primary care clinicians can look at just one value in decision-making (vs. needing to establish a mean over time from more than one blood test, which is more laborious). Additionally, while binary thresholds are easier to use practically in every day clinical practice, they are less useful for assessing overall associations, when continuous measures are more useful, particularly for a biomarker which appears to fluctuate around the threshold value[47] (e.g. a relatively stable eosinophil count of 0.14 and 0.16 x10*9/L on two occasions would be variably categorised as 'low' and 'high' using a 0.15 x10*9/L threshold). However, there is little information on repeatability of blood eosinophils in a primary care population. Finally, there has been no attempt to characterise the blood eosinophils in the primary care ICS-naïve population in relation to their distribution, stability, nor association with disease outcomes (prognosis) or response to ICS treatment.

These unanswered uncertainties appropriately raise concern about the application of the blood eosinophils to a primary care environment where the majority of patients with COPD are seen, and when results are not immediately available.[73] This clinical gap could potentially be filled by point-of-care testing of eosinophils. However, there are no published studies assessing the accuracy of the HemoCue® WBC DIFF in the primary care COPD population; no evaluation in patients with steroid-naïve COPD; nor patients' views of this test. My DPhil thesis will aim to address this evidence gap and is described as below.

1.4 Overall hypothesis and clinical context

The hypothesis of this doctoral thesis is that an eosinophilic phenotype of COPD exists within the ICS-naïve primary care COPD population, and that this represents a group of patients who are likely to do better on ICS treatment (i.e. will remain more stable for longer compared to patients without an eosinophilic phenotype). That is, that ICS may only be effective in a subset of patients with COPD, which might explain their only modest effectiveness across the whole COPD population. This ICS-responsive phenotype could be identified using blood eosinophils, including near-patient testing at the point of care. In practice, this would involve a test at the point at which ICS treatment were being considered to determine whether the patient is likely to be a responder or not.

Using individual characteristics to tailor treatment more effectively to patients with COPD, including using near-patient testing, could lead to targeted ICS treatment of those who would most benefit, and focused alternative treatment strategies in those unlikely to benefit, while avoiding unnecessary prescriptions which may cause harm. This has the potential to provide a more personalised approach to maximising individual benefit to treatment rather than the current 'one-size-fits-all' approach, which would reduce disease and treatment burden for patients, and reduce health care costs.

If evidence were generated in support of the main hypothesis, along with additional information on eosinophil distribution, repeatability and near-patient testing in primary care, it is envisaged that this work could potentially inform the development of an eosinophil-guided ICS treatment strategy, which could then be evaluated in a subsequent clinical trial.

1.5 Thesis objectives, overview of projects and outline structure

Key thesis objectives are summarised in Box 1.1.

Box 1.1: Key thesis objectives

- To describe existing practice of blood eosinophil testing in ICS-naïve primary care patients with COPD in the period before starting a new inhaled maintenance treatment
- To assess blood eosinophil distribution in the primary care COPD population
- To assess the association between higher blood eosinophil counts and clinical characteristics
- To assess within-person variation and stability over time of blood eosinophil counts, to decide whether the most recent value can be used in decision-making
- To investigate whether baseline blood eosinophil count predicts disease outcomes over time, in the population starting a new inhaled maintenance treatment
- To test whether baseline blood eosinophil count predicts inhaled steroid responsiveness and whether there is a dose-response (by eosinophil count and ICS dose) for this effect
- To investigate use of near-patient eosinophils compared to laboratory eosinophils, and feasibility and acceptability of undertaking such measurements in a primary care setting

Important subsidiary questions within these objectives include whether there is an association of patients who have a history of asthma or atopy (which are more likely to produce an eosinophilic phenotype[74,75]), higher exacerbation frequency, and assessing different eosinophil thresholds for the above questions. I have elected to use a primary binary threshold using absolute (rather than percentage) eosinophils of 0.15 x10*9/L as this was being used increasingly in other published studies at the time[51] and following advice of experts. As emerging evidence became more available, I have performed more detailed sensitivity and subgroup analysis with different eosinophil counts and this is discussed within individual chapters.

My work has focused on the Clinical Practice Research Database (CPRD) which is a primary care database of routinely-collected data, which can provide an efficient way of answering many of the above objectives using epidemiological methods, particularly as one can look retrospectively at blood eosinophil counts at the time before a patient started an ICS therapy, using a large existing dataset. However, there are limitations associated with large database research, particularly confounding reasons why patients may have had their full blood count measured which might introduce bias. Furthermore, near-patient testing for blood eosinophils is not currently available in routine clinical practice, so there would be no information on this in the CPRD. Therefore, a prospectively observational study is also need to characterise blood eosinophils, including near-patient testing, and their repeatability, in a more controlled study setting.

Studies conducted as part of my thesis therefore include:

1) CPRD study

   Database cohort study using retrospective analysis of routinely-collected primary care data of ICS-naïve COPD patients – including three sub-studies with a progressively narrowing study cohort, for addressing the different overall objectives as above

2) COMET[a] study

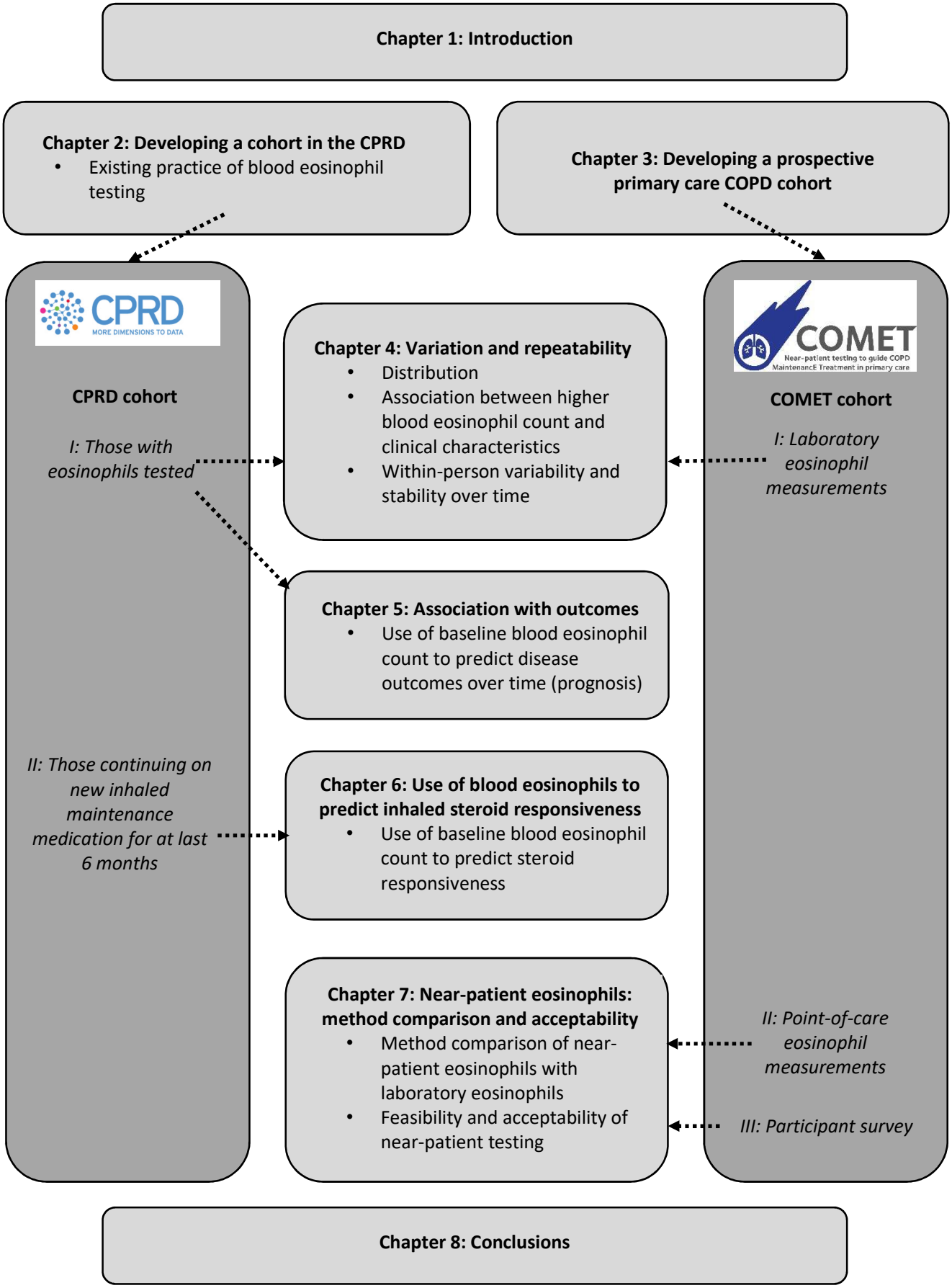
   Prospective observational cohort study of ICS-naïve patients in primary care with clinically stable COPD with monitoring of blood and airway biomarkers at multiple

[a] COMET: Near-patient testing to guide COPD MaintenancE Treatment in primary care: observational study to determine variability and accuracy of inflammatory biomarkers in stable state

time-points, including method comparison of near-patient blood eosinophil testing and its acceptability to patients

Because of the overlapping methods and objectives addressed in different ways by the two studies, I have chosen to organise my thesis by its objectives rather than component studies, which provides a more logical progression through the objectives in question. The thesis structure is summarised in Figure 1.3. Chapters 2 and 3 provide general information on methods for developing the two cohorts (CPRD and COMET respectively), with baseline characteristics and some discussion of the cohorts in comparison to each other, and in relation to existing studies. Chapters 4 to 7 cover detailed statistical methods, results and discussion relating to the thesis objectives as described above, with CPRD and COMET findings presented in parallel where objectives are overlapping (Chapter 4), to enable easier comparison. Chapter 8 brings together all the findings in overall conclusions, reflections and future directions (including implications for practice and research, which are discussed at the end rather than in individual chapters).

Figure 1.1: Summary of thesis structure (bullet points denote objectives, as detailed in Box 1.1)



Chapter 2: Developing a cohort in the Clinical Practice Research Datalink: baseline characteristics and overall outcomes

This chapter sets out the methods and data management for the Clinical Practice Research Datalink (CPRD) study, as well as presenting baseline characteristics and outcomes for the whole CPRD cohort before further division to answer specific thesis objectives in later chapters. Statistical analysis methods and results for specific study objectives are presented separately later, and integrated with results from the COMET study where relevant, as part of Chapter 4 (CPRD Part Ia), Chapter 5 (CPRD Part Ib) and Chapter 6 (CPRD Part II).

2.1 Introduction

2.1.1 Clinical Practice Research Datalink data

The CPRD is a primary care database of anonymised medical records from GPs, with 14.5 million patients included (CPRD August 2016 release). In the UK, 98% of the population are registered with a National Health Service (NHS) general practitioner (GP); information is recorded routinely on computers using a coding system (Read codes, which correspond to medical codes within the CPRD) combined with free text, and using a unique NHS number, which remains with the patient if they move GPs.[76] The CPRD is therefore a rich source of routinely collected health data for research, including data on demographics, symptoms, tests, diagnoses and therapies prescribed, and has been well-validated.[77] Patients in the CPRD are broadly representative of the UK general population in terms of age, sex and ethnicity.[76] Approximately half of the data is individually linked with other national datasets, enabling integration with secondary care via Hospital Episode Statistics (HES),

socio-economic markers of deprivation, and Office for National Statistics data on causes of death.

2.1.2 Aims and objectives

The CPRD provides an efficient way of answering the question of whether primary care clinicians can use the most recent blood eosinophil count in the medical record at the point of initiating a new inhaled maintenance medication, to guide the most appropriate choice of treatment (whether an ICS therapy would beneficial), because the data available to a GP making this decision in practice is the same as what can be accessed via the CPRD.

Aim I (descriptive component)

Ia: To describe existing practice of blood eosinophil testing in ICS-naïve primary care patients with COPD in the period before starting a new inhaled maintenance treatment

Specific objectives:

- To assess the number of routinely-collected blood eosinophil tests and to compare baseline characteristics of those who have an eosinophil count in their clinical record with those who have not, to assess validity of CPRD study findings
- To assess blood eosinophil distribution in the primary care COPD population
- To assess the association between higher blood eosinophil counts and clinical characteristics
- To assess within-person variation and stability over time of blood eosinophil counts, to decide whether the most recent value can be used in decision-making

Ib: To investigate whether baseline blood eosinophil count predicts disease outcomes over time, in the population starting a new inhaled maintenance treatment

Specific objectives:

- To assess disease outcomes in the time period following starting the new inhaled maintenance treatment
- To assess the contribution of baseline blood eosinophil counts to disease outcomes

Aim II (hypothesis-testing component)

II: To test whether baseline blood eosinophil count predicts inhaled steroid responsiveness

Specific objectives:

- To compare disease outcomes over time between patients starting treatment with ICS and those starting treatment with a non-ICS inhaled maintenance treatment
- To stratify the above by baseline blood eosinophil count to assess whether this modifies effectiveness of treatment (whether disease outcomes differ between treatment exposure in different blood eosinophil groups)
- To investigate whether there is dose-response for this effect, by different cut-offs of eosinophil count and different doses of ICS treatment

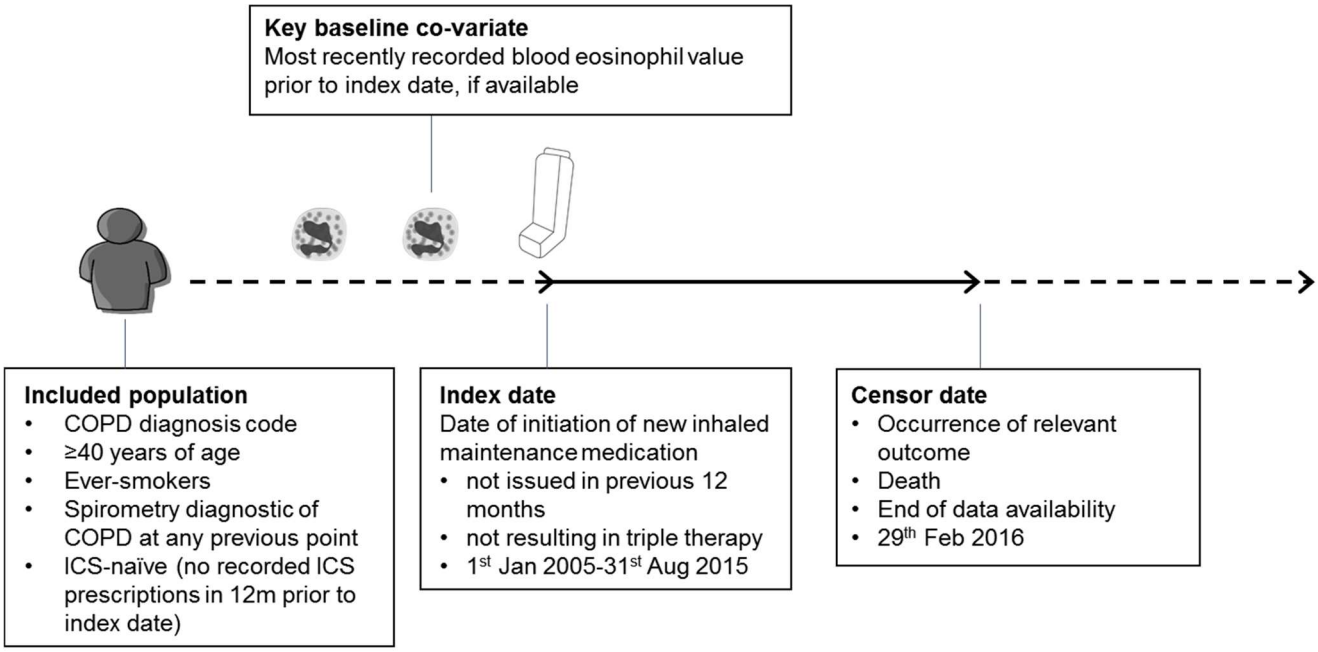
2.2 Methods

2.2.1 Study design

As the principal thesis question is to answer Aim II, the cohort was planned to address this question primarily, and aim I objectives relate to this population. A detailed search and review of existing published studies over the last two decades which had used the CPRD or other health care routine clinical databases to investigate outcomes under ICS treatment was conducted in order to establish the most appropriate study design to minimise bias.[78-83] Of particular relevance was how other researchers had defined their population and outcomes, addressed issues such as diagnostic and exposure misclassification, and designed methods to reduce confounding by indication and immortal time bias in comparing outcomes under treatments in an observational non-randomised study. Various

strategies for addressing these problems have been discussed at length in pharmaco-epidemiological literature;[84,85] for this study I chose a new-user active comparator design, comparing outcomes of those commencing inhaled maintenance medication containing an ICS (ICS group) with those not containing an ICS (non-ICS group), looking for effect modification by baseline blood eosinophil count. Through this design, the drug of interest is compared with another drug used for the same indication rather than with a no treatment group, which ensures that the groups have similar treatment indications and attempts to reduce differences in patient characteristics (both measured and unmeasured), and includes the cohort of patients from the time of treatment initiation, rather than prevalent users.[86] Due to the potential association of higher eosinophils with poorer prognosis,[49] high and low eosinophil groups initiating an ICS could not be compared directly, so it was planned to incorporate this into the model looking for an interaction effect of eosinophils with treatment group, as well as to stratify by eosinophil groups. The study cohort is summarised in Figure 2.1 and the approved study protocol is included as Appendix C. Potential weaknesses in this study design will be discussed in the Discussion section of the chapter relating to Aim II (hypothesis-testing component, Chapter 6).

Figure 2.1: Summary of study cohort



2.2.2 Code list development

I developed code lists to determine diagnoses, therapies, tests and outcomes, for which specific details are given in the relevant sections below; code lists are included as Appendix D. I developed a search strategy and used the CPRD Code Browser[a] to identify relevant codes (see Table 2.1 for example), and combined these with existing code lists published for other studies,[87-89] code lists previously used for CPRD studies in my department (smoking status), and Quality and Outcomes Framework (QOF) Read code lists where applicable (available from https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/1/codelist/copd/). For test values (e.g. eosinophil counts, spirometry, etc.), numerical values attached to "entity types" were used (listed as part of Appendix D). Development of drug codes lists used

[a] The CPRD Code Browser refers to two browser dictionaries, which are graphical user interfaces to databases of medical codes and product codes. Medical codes are mapped to Read codes entered by primary care clinicians as diagnoses or the reasons for consultations. The databases are compiled by the Health and Social Care Information Centre, and updated every six months.

search terms for drug substance names and product names (both generic and proprietary), as well as by British National Formulary drug group e.g. "Selective Beta 2 Agonists/Corticosteroids (for Respiratory Conditions)". Included codes were then independently selected from potential lists by me and another GP (David McCartney), and any disagreements discussed and adjudicated by a third clinician (Mona Bafadhel, respiratory consultant). Hospital Episode Statistics (HES) used ICD-10 (International Classification of Diseases) codes; "Basic" rather than "Integrated" HES were used as this provided details on whether the ICD-10 code was the primary cause of the hospitalisation, or an unrelated co-morbidity, based on my clinical experience of hospital discharge summaries.

Table 2.1: Example of potential code list development using CPRD Code Browser searches

Search term	Numbers identified
copd	24
*chronic*obstr*	58
*obstr*pulm*	47
emphys	31
*obstr*air*	11
coad	6
*smok*asth*	1
*chronic*bronch*	19
*obstr*bronch*	2
*chronic*pulm*	58
cobd	0
*obstr*resp*	20
*chronic*resp*	14
aecb	0
*obstr*lung*	3
*chronic*lung*	1
Total identified through search	295
Total after removal of duplicates	190

2.2.3 Included population

Included patients were those ≥40 years of age with a COPD diagnosis code, a history of smoking, and spirometry diagnostic of COPD (FEV_1/FVC ratio <0.7) at any point, who were

starting a new inhaled maintenance medication for COPD in the period 1st January 2005-31st August 2015 (defined as the index date). A new inhaled maintenance medication was defined as a prescription for LABA, LAMA, ICS or combination, where a prescription for that drug category had not been issued in the previous 12 months. The criteria for diagnosing COPD were based on a validation study using the CPRD which had tested various algorithms;[87] although this study concluded that the presence of a Read code alone was sufficient to identify COPD, I selected the algorithm which had the highest specificity, even though this would reduce sample size. This validation study only included ever-smokers and I followed the same approach. The range of index dates were chosen to be after the introduction of QOF targets in UK primary care which improved electronic coding of COPD and spirometry,[90] but before blood eosinophils were promoted as a potential biomarker in COPD, which might have influenced prescribing choices.

Excluded patients were those with a diagnosis of bronchiectasis, alpha-1 anti-trypsin deficiency, interstitial lung disease and cystic fibrosis. As I wanted to focus on the steroid-naïve COPD population, patients were excluded if they had an ICS prescription, or 3 or more oral steroid prescriptions, in the previous 12 months. Those commencing triple therapy were also excluded to enable a better comparison between ICS and non-ICS therapies, and because this would be unlikely to reflect a prescriber's initial choice of inhaled maintenance treatment. However, I did not exclude prescriptions for ICS monotherapy even though that is outside of guidelines, because this has been shown to be a common initial treatment for COPD in other database studies[33] and I wanted to study what occurs in real-life practice. I also did not exclude patients with co-existent diagnosis or history of asthma, which applies to many real-life COPD patients (approximately one quarter),[87] but whom are usually

excluded from trials,[20] because I wanted the findings to be more relevant to real-life practice.

Eligible patients were required to have continuous data for a minimum of 24 months prior to and 6 months following the index date, to ensure adequate recording of baseline covariates and outcomes. Only patients with linked data were included: linkage was to Hospital Episode Statistics (HES) which gives information on hospitalisations and diagnoses, Index of Multiple Deprivation (IMD) (socio-economic deprivation score) and Office for National Statistics data on causes of death. Censoring occurred due to end of data availability (29th February 2016 if not before), death, or occurrence of the relevant outcome (see later).

2.2.4 Covariates

Covariates which were assessed and considered for inclusion are listed in Box 2.1. These were selected as demographic, disease and general health characteristics which might be potential risk factors for severe disease and poor outcomes or which might confound the association of eosinophils with prognosis (Aim I), or the selection of maintenance therapy (Aim II), and which had been assessed in other studies.[89,91,92]

Box 2.1: Covariates assessed for inclusion in models

Sex
Age[a]
Smoking status (ex-smoker vs. current smoker)[a]
Socio-economic status (IMD quintile)[a]
Atopy (presence of codes for allergy, eczema or hay fever) [b]
Asthma history (none vs. active[d] vs. historical[b])
Airflow limitation severity (NICE severity classification)[10] [a]
MRC breathlessness scale[a]
Baseline exacerbation frequency[c]
Baseline pneumonia episode frequency[c]
Baseline exposure to oral steroids (number of courses)[c]
Baseline reliever inhaler frequency (short-acting bronchodilator prescriptions)[c]
Theophylline used[d]
Oxygen use[b]
Nebulised therapies[d]
Non-elective hospitalisations[c]
GP attendances[c]
Charlson comorbidity index (comorbidities recorded in addition to COPD)[93] [a]
Influenza vaccination[c]
Pneumococcal vaccination[e]
Blood eosinophil count[a] (see Section 2.2.5 below for further discussion)
Season of blood eosinophil count (see Section 2.3.3 below for further discussion)

Aim II only:
Calendar year of index prescription

[a] at or most recently coded prior to index date
[b] at any time prior to index date
[c] in year prior to index date
[d] in two years prior to index date
[e] in five years prior to index date

2.2.5 Blood eosinophil count

Blood eosinophil count is provided automatically as part of a request for a full blood count, which is requested frequently in primary care. Assessment of a full blood count is NICE recommended as part of the work-up of COPD diagnosis, to look for anaemia or polycythaemia.[10] For my primary analysis, I used the most recently recorded blood eosinophil count in the two years prior to the index date; this decision was based on simplicity of use for primary care clinicians to be able to access and look at the most recent result. Eosinophil values within two weeks of an exacerbation, pneumonia episode or elevated C-reactive protein (CRP) (>100mg/L) were excluded (for the primary analysis) as

eosinophil values change at the time of acute event and might therefore not reflect baseline state.[2] A primary cut-off of ≥0.15 x10*9/L was used to categorise patients into high and low eosinophil groups. This cut-point was chosen in response to advice from an external expert (Prof Ian Pavord) in response to unpublished work at the time of study set up.[94] Supplementary secondary cut-offs of ≥0.34 x10*9/L and the eosinophils as a continuous variable were used following the emergence of additional literature.[74,95]

Blood eosinophil readings were transformed from other units or percentage values to x10*9/L, as done in other database studies looking at eosinophils.[38] Values of zero or ≥1.5 x10*9/L, or where the total white cell count was outside of the range 3-15 x10*9/L, were excluded, as they were felt more likely to be a data error (missing values may be entered as zero), or a haematopoietic problem and not truly representative of baseline state, following discussion with haematology colleagues. In case of variation of values throughout the year with possible higher values in hay fever season, an analysis of season of eosinophil test was conducted as part of data management, with a plan to include this in the model if relevant. Results are generally presented rounded to the nearest 0.01x10*9/L as this is the most detail given by most analysers (i.e. to two decimal places).

2.2.6 *Outcomes*

The primary outcome was time-to-first COPD exacerbation following the index date, which was selected as an outcome of most relevance to patients.[12] COPD exacerbations were defined as any of the following: code for exacerbation of COPD; code for lower respiratory tract infection (LRTI); prescription of exacerbation-specific antibiotic e.g. amoxicillin/macrolide/doxycycline and oral steroid for 5-14 days; symptom of exacerbation (cough, breathlessness or sputum) plus prescription of exacerbation-specific antibiotic or

oral steroid; hospital admission with COPD or an acute respiratory code as the primary cause of the hospitalisation, or a COPD exacerbation code as any diagnosis within the hospitalisation episode. Any exacerbation within two weeks of a previous exacerbation was counted as the same episode. Exacerbation events defined by prescriptions alone and occurring on the same date as spirometry, or a code implying rescue pack administration (see Appendix D), were excluded as this suggested a visit for annual COPD review with provision of a rescue pack, rather than an exacerbation. This was partly based on a published validation study.[88]

Secondary outcomes analysed were pneumonia episodes, and hospitalisations and death due to COPD, pneumonia or any cause (all time-to-event following index date). A pneumonia episode was defined as a CPRD code for pneumonia, hospital admission with an ICD-10 pneumonia code, or a death certificate with pneumonia listed as a cause. A pneumonia episode or hospitalisation occurring within two weeks of a previous event was counted as the same episode.

2.2.7 Exposure and comparator (Aim II only)

Patients were categorised into ICS (exposure) or non-ICS (comparator) groups according to the type of new inhaled drug (ICS group: ICS, ICS/LABA, or ICS/LAMA; Non-ICS group: LABA, LAMA, or LAMA/LABA).

For the primary analysis, prescriptions had to be continued for a minimum of 6 months after the index date: other database studies have shown that approximately one quarter of patients are not prescribed the therapy again in the subsequent 6 months,[32] and I wanted to study actual treatment effects rather than intention-to-treat. Continuous use

was defined as duration of treatment (usually 30 days) plus an additional 90 days' grace period between scripts and scripts totalling at least 90 days' supply, similar to methods used in a previous new user cohort study of ICS in COPD.[89]

Many patients drift towards triple therapy over time[33] and so the date of first prescription of drug from alternative class (in order to be as similar as possible between the two groups) was recorded. Where patients added another drug within the first month after index date which would have resulted in a change of group, they were excluded as it could not be established whether this was a change or an addition (post-hoc decision, discussed further in Chapter 6). Sensitivity analyses explored the effect on results of managing medication adherence and change of drug class in different ways (discussed further in Chapter 6).

To examine a potential dose-response relationship in ICS-containing medications, the strength of ICS prescribed on the index date was stratified into low, medium and high daily-dose of ICS (corresponding to estimated equivalent daily doses of beclomethasone dipropionate (BDP) of ≤500µg, >500-1000µg and >1000µg respectively), as in a previous CPRD ICS study.[89]

2.2.8 Statistical analysis

For all analysis, I used Stata (Release SE13 64-bit). In general, data are presented as mean with standard deviation (SD), median with interquartile range (IQR) or hazard ratios (HR) with 95% confidence intervals (CI). Division of variables into categories for non-binary variables was based on what seemed clinically sensible, or to achieve approximately equal groups (for example, number of GP consultations in year prior to index date I divided into 0-3, 4-7, and 8 or more to reflect low, medium or high consultation rates; exacerbations in

previous year; a history of frequent exacerbations was defined as ≥2 in previous year and less frequent exacerbations defined as <2 in previous year). Baseline characteristics were compared between groups using logistic regression (or linear regression when assessing eosinophils as a continuous variable, appropriately transformed as applicable). Characteristics were included in regression models as covariates if significant ($p<0.10$) in univariate analysis, or thought to be of potential clinical importance.

A Cox proportional hazards model was used to assess disease outcomes in the period following starting the new inhaled maintenance treatment (index date). I excluded patients with events in the first 30 days following index date to reduce protopathic bias (when treatment appears to cause the outcome due to lag time from first symptoms and start of treatment before diagnosis), as in other studies.[89] For the main models, the proportional hazards assumption was assessed both graphically and using a formal statistical test; for those variables where it was not met ($p<0.05$), the model was re-run using the time-dependent variable command for these variables to check that it did not make any difference to the outcomes of interest.

Further details of statistical methods relating to specific study objectives, and sensitivity and subgroup analyses, are presented, in conjunction with COMET statistical methods where relevant, adjacent to the relevant results sections (Chapters 4, 5 and 6), due to significant overlap in methods and to enable easier reading.

2.2.9 Missing data

For the assessment of clinical diagnosis and outcomes, I assumed that absence of any relevant medical code meant true absence of disease. I expected age, sex and prescriptions

to be well recorded in the cohort and so planned a complete case analysis. Spirometry was poorly coded and so I used standard formulae[96] to calculate percentage predicted FEV_1 from data available. Where height was missing, I used the mean height of that sex and 10-year age category in the cohort. Nonetheless, FEV_1 percentage predicted remained missing for a quarter of the population and therefore I did not include this in the main analysis, but conducted a sensitivity analysis to assess the effect of incorporating it into the model. The same was true for MRC breathlessness scale, which was missing for approximately half of patients. I did not perform multiple imputation because the assumption that the missing data were missing completely at random or missing at random may not be realistic[97] (discussed further in Section 2.4.1 below).

2.2.10 Sample size

Study power was estimated for the hypothesis-testing part of the study (Aim II) based on counts available via CPRD Gold fob holders. A random sample of 25 practices (577,928 records of 11,192,535 records, ~5.16% of the linked English practices in CPRD), gave 843 records fulfilling the criteria. Of these, 466 were getting a new ICS treatment and 377 were getting a new non-ICS treatment at the index date, of whom only 600 had an eosinophil record within 2 years of index date. Within each treatment group, we would expect approximately 25% of patients to have high eosinophil levels, and 75% to have low levels (estimate based on previous studies,[53,91,94,98,99] but allowing for a lower eosinophil threshold and milder disease in our study). Table 2.2 gives estimated numbers expected, by eosinophil count, within the CPRD (only those with linked data).

Table 2.2: Random sample of CPRD to check sample size for feasibility assessment

Exposure group	Random sample of 5.16%	Estimated numbers with an eosinophil record	Scaled up to all CPRD practices (100%)	Estimated numbers by eosinophil count	
				High eosinophil (25%)	Low eosinophil (75%)
ICS	466	332	6434	1609	4826
Non-ICS	377	268	5194	1299	3896
TOTAL	843	600	11628	2908	8722
Expected HR (ICS vs. non-ICS)				0.72	0.90

We expected HR for time-to-first exacerbation in the ICS vs. non-ICS groups to be about 0.90 in the low eosinophil group and about 0.72 in the high eosinophil group (based on data from secondary analysis of ICS trials[99]). In the low eosinophil group, a HR of 0.90 could be estimated with a standard error of less than 0.01 with approximately 3800 events (power 90%, alpha 0.05). In the high eosinophil group, a HR of about 0.72 could be estimated with a standard error of 0.01 with approximately 1100 events (power 90%, alpha 0.05). Thus, our expected patient numbers (8700 in the low eosinophil group and 2900 patients in the high eosinophil group) should give more than adequate power. Sensitivity analyses changing key parameters (estimated HR/n/SD) were consistent with this.

2.2.11 Ethical approval

The protocol was reviewed and approval for access to the data was obtained from the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency (protocol number 16_094) (Appendix C). Ethical approval for observational research using the CPRD with approval from ISAC has been granted by a National Research Ethics Service committee (Trent MultiResearch Ethics Committee, REC reference number 05/MRE04/87).

2.3 Data management

The initial data cleaning and management was performed by Margaret Smith according to pre-defined instructions in the ISAC protocol and data management plan. I then undertook cleaning and management of spirometry, outcomes, and laboratory data (leucocytes, neutrophils, eosinophils and CRP). Although summarised in turn below, focusing on the major and most interesting steps, in practice they occurred in parallel as several aspects were inter-dependent. Data management in relation to post-hoc sensitivity analyses to account for changes of treatment group during follow-up are discussed in Chapter 6.

2.3.1 Spirometry data management

For inclusion in the study, participants required an FEV_1/FVC ratio <0.7 at any time point (including after index date). However, I needed to look at this further in order to establish the date it had taken place (as this was part of the outcome definition for exacerbations; see Sections 2.2.6 above and Section 2.3.2 below), and to establish the degree of airflow limitation (FEV_1 percentage predicted) at or most recently coded prior to index date (NICE severity classification[10]).

Spirometry data was available on or before the index date for 23,436/30,378 (77.1%) patients (48,760 readings in total). In order to calculate percentage predicted FEV_1 using standard formulae[96] from absolute FEV_1 in litres where no percentage predicted was provided (n=6,263), I inputted age (estimated at date of test, based on year of birth), sex and height (imputed for those readings with this missing (n=1,838) based on mean values for 10-year age category and sex in the whole cohort). I dropped those where there was no percentage predicted or absolute FEV_1 available (n=5,046). For those with both absolute and percentage predicted FEV_1 available, I compared results from my calculation with the

results in the database, and manually inspected those where the difference was >25%. As it was not clear which was the correct value, and awareness from my own clinical practice that there is confusion over which are the correct figures to input, I dropped these (n=175). I manually inspected results from patients with readings where FEV_1 % predicted was <20 (n=20) or >120 (n=16), and made a clinical judgement whether it was in keeping with other results or likely to be a data entry error, as I did not want to just exclude very low or high readings as this might bias the overall results. Single readings <5 or >140% were dropped as I thought these were more likely an error than a true reading. I also manually inspected those readings within 2 weeks of each other and found that generally the higher reading was implausible, so used the lower reading. Finally, I kept only the most recent reading, in the two years before index date (as earlier than this was unlikely to be representative of airflow limitation severity at the time of initiating the new inhaled maintenance medication). This resulted in 20,331/30,378 (66.9%) patients having valid spirometry data for use as a covariate for airflow limitation severity.

2.3.2 Outcomes data management

I classed codes for exacerbation (n=26,531), LRTI (n=108,072), COPD-related hospitalisations (n=23,556), and symptom codes plus prescription of either antibiotics or steroids (n=85,607), as potential exacerbation events. For double prescriptions (antibiotics and steroids) (n=48,540), I excluded those which occurred on the same day as a rescue

pack code (n=1,395) or spirometry code (any, not just valid, n=1,833) (n=2,996 excluded in total).[a]

I divided data into events into those occurring in the year before, and any time after the index date (for calculation of baseline exacerbation frequency variable and exacerbation outcome variables, respectively). Events occurring within 2 weeks of another were dropped. I flagged events occurring in the first 30 days after index date, to exclude later as part of outcomes analysis (Section 2.2.8). I calculated the time to exacerbation after index date, for use in the Cox model.

I followed a similar approach for defining pneumonia episodes and other secondary outcomes.

2.3.3 Laboratory data management

I looked at the online supplements of recently published CPRD studies[95,100] but could not find any detail on data management of eosinophils or other laboratory data. For each biomarker result, I looked at the different variables provided (medical code, entity type, measurement code, and operator code) and when this was non-standard e.g. unconventional units, I inspected the results and decided whether to include the results or not. As an example, Table 2.3 shows the variation in unit type given for blood eosinophil; for all of these, with the exception of '%', discussed below, the results appeared within

[a] While exploring the data, I found that n=2,599 spirometry results were coded on the same day as an exacerbation, and n=414 had spirometry coded on the same as a hospital admission. This concerned me, as in clinical practice it would be unusual to perform spirometry whilst the patient was unstable, and so hypothesised that it might be due to using the same code after the patient had recovered from their acute illness, and adding spirometry performed during recovery in hospital which was retrospectively added by practice coders to be the same date as the original hospital admission. I decided that as it was not clear what had happened, and I had not pre-specified to exclude these, nor had they been excluded in CPRD exacerbation validation studies,[88] I would keep them in.

normal range for x10*9/L, so I assumed it was only the units which had been miscoded/missing.

Table 2.3: Measurement codes associated with blood eosinophil count in the CPRD

Specimen Unit of Measure	Frequency	Percent
%	4,337	8.89
/L	157	0.32
1	5	0.01
10*12/L	41	0.08
10*3/mL	2	0.00
10*9	389	0.80
10*9/L	43,170	88.5
10*9/mL	5	0.01
L	71	0.15
No Data Entered	547	1.12
g/L	43	0.09
pH	1	0.00
Total	**48,768**	**100.0**

I removed duplicates, inspected the remainder and made individual decisions. For percentage neutrophils and eosinophils, I converted to absolute values based on absolute leucocytes on the same day. I dropped results which were significantly outside of normal range, on the grounds that these would be not representative of baseline state and more likely suggestive of an acute or haematopoietic problem: this was outside of 3-15 x10*9/L for leucocytes (n=777/46,691), 1-13 x10*9/L for neutrophils (n=264/44,917), and 0.01-1.5 x10*9/L for eosinophils (n=1,202/43,684).[a] I also excluded neutrophil and eosinophil

[a] I had originally planned to use 0-1.5 x10*9/L as the inclusive range for eosinophils, but during assessment of residuals in linear regression, and the fact that there was a spike at the lower end of the data spectrum even after logarithmic transformation of eosinophils, I became concerned that the zeros may not be true values. I consulted with a laboratory haematologist (Deborah Hay) who in turn spoke to a Senior Biomedical Scientist (Kate Cubbage) at the OUH Trust, who informed me of a field safety notice issued in August 2018 about eosinophil counts reported as zero by automatic analysers but which were actually greater than this on blood film examination. I therefore decided to re-analyse the data excluding the zeros.

results where the leucocyte count on the same day was absent or significantly outside of normal range.

I divided into groupings based on various cut-points as planned for the different analyses (see detailed statistical analysis methods sections of subsequent analyses). CRP presented a particular challenge in this respect due to test qualifiers (<, =, >, etc.), as many results, especially 5, were actually '<5', due to the lower limit of laboratory detection. I decided to only divide CRP into binary categories, of 5 or less and more than 5, excluding those with a test qualifier of '<' or '≤' above this (n=275/10,321 values).

Eosinophil counts close to acute events

I flagged results which were within two weeks of an acute event (exacerbation, pneumonia episode or elevated CRP >100mg/L), as I had planned to exclude these from main analysis on the grounds that this might not be representative of baseline values. Although a study published during my protocol development, which used another primary care database to investigate association between blood eosinophils and exacerbations, found that results were not relevantly different after excluding the patients (17%) with blood eosinophil counts measured at exacerbation,[75] I wanted to validate this myself in my cohort. I also planned to exclude the results, rather than the entire patient. Table 2.4 compares eosinophil counts close to acute events with those at least two weeks away from one; only raised CRP was associated with a significant reduction in eosinophil count, which may relate to low eosinophils being a poor prognostic marker in severe hospitalised exacerbations.[101] Sensitivity analysis excluding counts close to acute events resulted in no significant difference in eosinophil counts (p=0.95, 0.94, 0.80 and 0.87 for exacerbations, pneumonia, CRP and all events respectively). I concluded to exclude these results from the

main analyses as planned, but conduct sensitivity analyses to ensure that inclusion did not affect overall results.

Table 2.4: Comparison of eosinophil counts close to acute events

	Geometric mean (x10*9/L) (n)		Geometric mean difference (x10*9/L)	p-value
	Within 14 days of event	**>14 days from event**		
Exacerbation event	0.20 n=3,199	0.20 n=38,766	0.001	0.77
Pneumonia event	0.20 n=1,217	0.20 n=40,748	-0.002	0.52
CRP >100	0.16 n=211	0.20 n=41,754	-0.04	<0.001
Any of above	0.20 n=3,395	0.20 n=38,570	-0.002	0.42

Geometric mean was used due to non-normal distribution of eosinophils (see later). Student's t-test was used to calculate p-value.

Variation of eosinophil count due to season

It was suggested to me during protocol development that eosinophils may be higher during the summer months, due to atopy and hay fever, and therefore season of eosinophil test was something I should consider incorporating into the model. I divided all eosinophil counts (after data cleaning) into seasons and compared the groups (Table 2.5). Eosinophil counts were statistically but not clinically different compared to reference. I therefore did not include season of eosinophil test in the main model, but conducted a sensitivity analysis incorporating this.

Table 2.5: Eosinophil counts by season of test

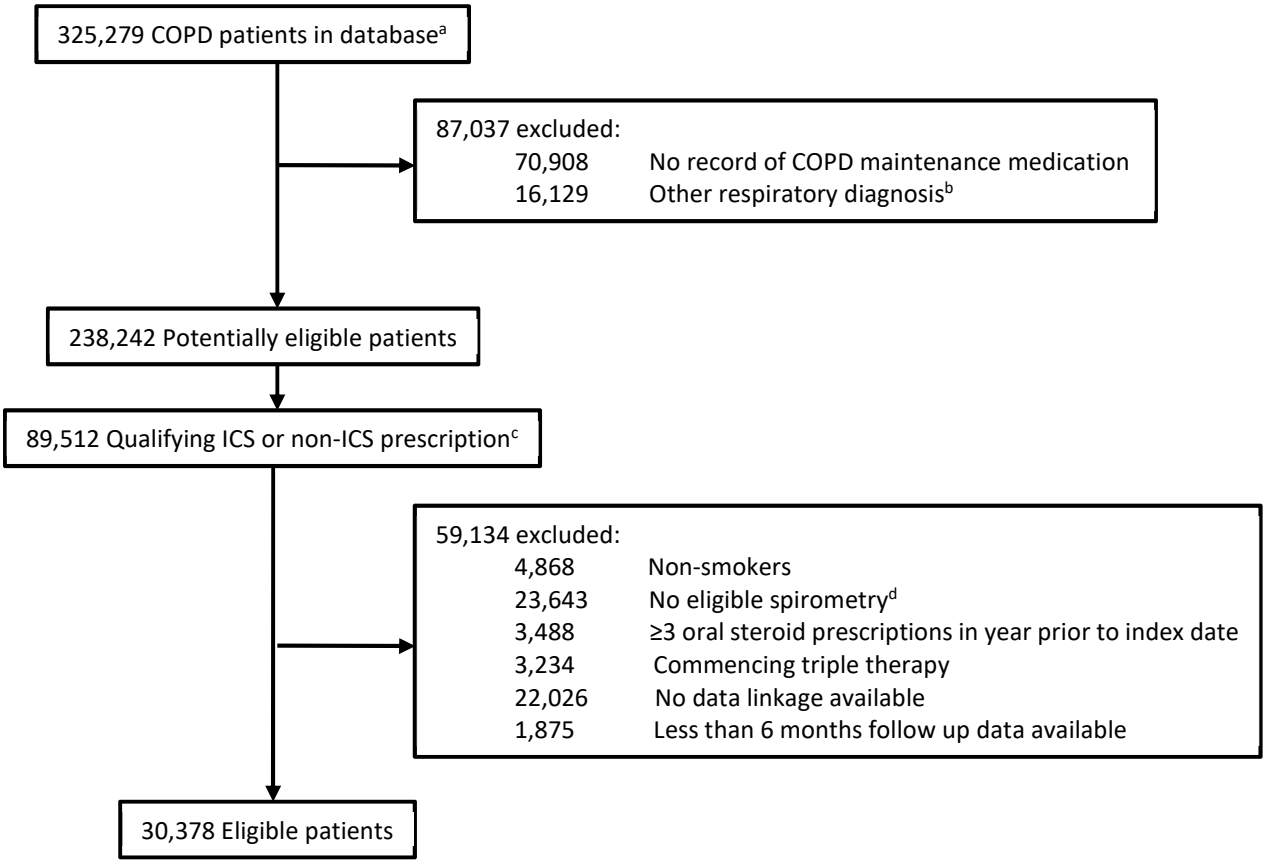
	Season	Geometric mean (x10*9/L) (n)	p-value (vs. reference group)	p-value (overall)
Including counts close to acute events (n=41,965)	**Spring (March-May)***	0.20 n=10,716	Reference	0.04
	Summer (June-August)	0.20 n=10,714	0.07	
	Autumn (September-November)	0.20 n=10,696	0.75	
	Winter (December-February	0.20 n=9,839	0.01	
Excluding counts close to acute events (n=38,570)	**Spring (March-May)**	0.20 n=9,818	Reference	0.02
	Summer (June-August)	0.20 n=10,069	0.11	
	Autumn (September-November)	0.20 n=9,872	0.85	
	Winter (December-February)	0.20 n=8,811	0.01	

Geometric mean was used due to non-normal distribution of eosinophils (see later). Linear regression was used to generate p-values; assumptions were tested and met. Number of tests may be reduced in winter months due to practice closures over Christmas and New Year. Eosinophil counts were significantly higher in winter, by 0.004 to 0.005 x10*9/L compared to reference groups. However results are rounded to two decimal places given as this is the maximum provided to UK primary care and this difference is not clinically significant.

2.4 Overall cohort demographics

Figure 2.2 shows the flow chart of steps to arrive at the final 30,378 patients included in the overall study cohort.

Figure 2.2: Study flow chart



[a] CPRD August 2016 release.
[b] Other respiratory diagnoses excluded were bronchiectasis, cystic fibrosis and pulmonary fibrosis.
[c] Qualifying prescription required patients be ICS-naïve (no previous ICS in the preceding 12 months), have at least 2 years of data, 1st January 2005 or later, and be aged 40 or older on the date of the prescription, which was the first prescription for that drug in at least 12 months.
[d] Eligible spirometry was spirometry diagnostic for COPD (FEV_1/FVC ratio <0.7) at any time point.

Total follow-up time was 144,217 years, mean 4.75 years (SD 2.8, range 0.5 to 11.2 years).

Table 2.6 summarises baseline characteristics of the study cohort.

Table 2.6: Baseline characteristics of overall CPRD study cohort

Characteristic (n=30,378)	**n (%)**
Demographic characteristics	
Age (mean, SD)	67.6 (10.8)
Age group in years	
40-49	1,748 (5.8)
50-59	5,273 (17.4)
60-69	9,889 (32.6)
70-79	9,071 (29.7)
80-89	4,136 (13.6)
>=90	261 (0.9)
Female sex	13,288 (43.7)
Socio-economic status (IMD quintile) (n=30,362)	
1 (least deprived)	4,394 (14.5)
2	6,167 (20.3)
3	6,010 (19.8)
4	7,433 (24.5)
5 (most deprived)	6,358 (20.9)
Respiratory disease characteristics	
Smoking status (n=30,223)	
Ex-smoker	16,313 (54.0)
Current smoker	13,910 (46.0)
Asthma history	
No asthma history	24,453 (80.5)
Past asthma (last coded >2 years before index date)	4,678 (15.4)
Current asthma (coded within 2 years of index date)	1,247 (4.1)
History of atopy	7,945 (26.2)
Airflow limitation severity (most recent FEV_1 % predicted) (n=20,331)	
Mild (≥80%)	2,737 (13.5)
Moderate (50-80%)	11,219 (55.2)
Severe (30-50%)	5,468 (26.9)
Very severe (<30%)	907 (4.5)
MRC breathlessness scale (n=11,715)	
1 (least severe)	1,901 (16.2)
2	5,122 (43.7)
3	3,143 (26.8)
4	1,367 (11.7)
5 (most severe)	182 (1.6)
Exacerbations in previous year	
0	15,126 (49.8)
1	9,430 (31.0)
2	3,886 (12.8)
3 or more	1,936 (6.4)
Pneumonia episodes in previous year	
0	24,019 (79.1)
1	4,925 (16.2)
2 or more	1,434 (4.7)

Characteristic (n=30,378)	n (%)
Oral steroid prescriptions in previous year[a]	
0	23,826 (78.4)
1	4,912 (16.2)
2	1,640 (5.4)
Salbutamol inhaler prescriptions in previous year	
0	10,202 (33.6)
1	6,503 (21.4)
2	3,172 (10.4)
3-5	4,282 (14.1)
6 or more	6,219 (20.5)
Theophylline in two previous years	344 (1.1)
Oxygen use ever	130 (0.4)
Nebulisers in two previous years	553 (1.8)
General health characteristics	
Non-elective hospitalisations in previous year	
0	25,667 (84.5)
1	3,590 (11.8)
2 or more	1,121 (3.7)
GP consultations in previous year	
0-3	11,138 (36.7)
4-7	10,216 (33.6)
8 or more	9.024 (29.7)
Charlson comorbidity index[b]	
0	18,835 (62.0)
1	4,524 (14.9)
2 or more	7,019 (23.1)
Influenza vaccination in previous year	19,057 (62.7)
Pneumococcal vaccination in previous 5 years	10,119 (33.3)
Baseline laboratory markers (most recent before index date) (geometric mean, range)	
Total white cell count (x10*9/L) (n=19,025)	7.44 (3.00-14.90)
Neutrophil count (x10*9/L) (n=18,508)	4.39 (1.00-12.80)
Eosinophil count (x10*9/L) (n=18,235)	0.20 (0.01-1.48)
Low eosinophils (<0.15) (n,%)	5,615 (30.8)
High eosinophils (≥0.15) (n,%)	12,620 (69.2)
Low eosinophils (<0.34) (n,%)	14,692 (80.6)
High eosinophils (≥0.34) (n,%)	3,543 (19.4)
Eosinophil count (% white cell count) (n=18,210)	2.70 (0.07-23.91)
C-reactive protein (mg/L) (n=4,833)	
Low CRP (≤5mg/L) (n,%)	2,920 (60.4)
High CRP (>5mg/L) (n,%)	1,913 (39.6)

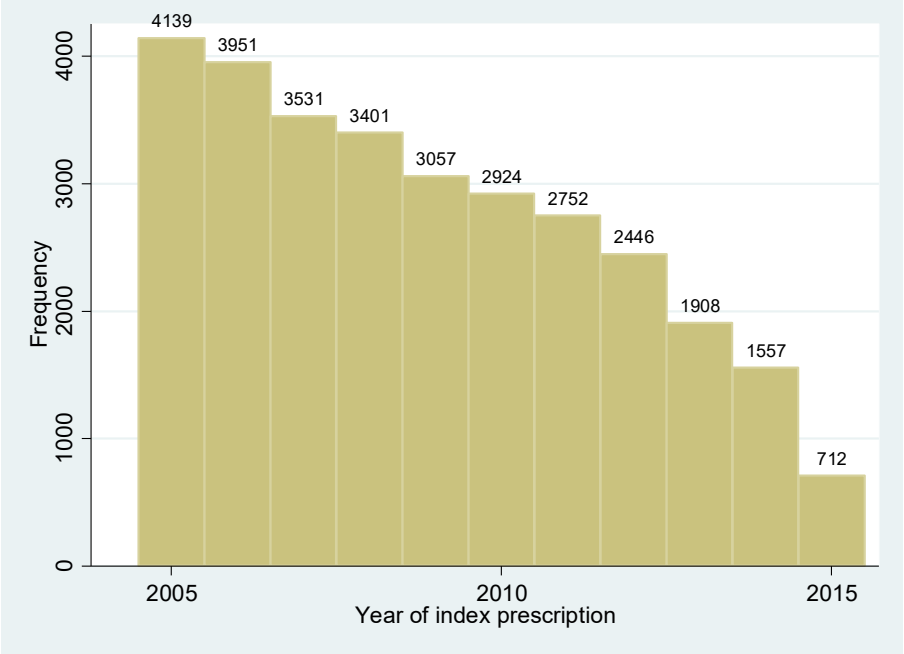
IMD, Index of Multiple Deprivation. For binary characteristics, only the affirmative is presented.

[a] 3 or more oral steroid prescriptions in previous year was an exclusion criterion

[b] Charlson comorbidity index refers to number of comorbidities recorded in addition to COPD[93]

The number of patients starting a new maintenance medication decreased with increasing calendar year (i.e. more patients entered the study cohort earlier in the study period, Figure 2.3). This may be due to a reducing number of patients eligible to start a new maintenance medication out of the available pool, as time progressed.

Figure 2.3: Frequency of patients by calendar year of index prescription (index date)



2.4.1 Missing data assessment

Small amounts of data were missing for smoking status (n=155) and socio-economic status (n=16). Given the small numbers (particularly once sample would be reduced for later analyses), I included these variables but conducted complete-case analysis in the models. However, a much larger amount of data was missing for NICE severity classification (n=10,047, 33.1%) and for MRC breathlessness scale (n=11,715, 38.6%) (65.4% missing one or the other). The former was due to issues with coding of spirometry data (Section 2.3.1 above) and both probably related to a slow increase in coding over the study period 2005 to 2015 as these became part of the QOF.[90]

I compared the population of those with data present and absent, for both of these variables, using logistic regression, in relation to baseline characteristics (Table 2.7). Those with missing data were more likely to be younger, female, less deprived, with asthma, more exacerbations but less salbutamol inhaler use, and more hospitalisations but fewer GP consultations. We hypothesised that, even amongst groups of patients with similar values for these covariates (age, female, deprivation, etc.), the likelihood of having spirometry or MRC breathlessness scale assessment may have been related to its value; or in other words GPs or nurses would tend to test people who they thought might have a problem. This would mean that the Missing at Random Assumption would be broken and multiple imputation should not be used.[97,102] Particularly as FEV_1 is not a good patient-related outcome measure,[12] I concluded that I would leave these variables out of the main models, but conduct sensitivity analysis including them.

Similar results were found when those with current asthma were dropped (data not shown). Missing data was also associated with worse outcomes (time-to-first exacerbation HR 1.05 (1.02 to 1.08, p=0.001) for missing severity, and HR 1.07 (1.04 to 1.10, p<0.001) for missing MRC scale.

Table 2.7: Logistic regression comparing those with missing severity and MRC variables

Characteristic	Odds ratio for missing severity (95% CI), p-value	Odds ratio for missing MRC scale (95% CI), p-value
Demographic characteristics		
Age group in years		
40-49	1.63 (1.45-1.83), p<0.001	1.43 (1.26-1.62), p<0.001
50-59	1.15 (1.06-1.24), p=0.001	1.10 (1.02-1.19), p=0.02
60-69	0.97 (0.91-1.04), p=0.43	0.95 (0.90-1.01), p=0.13
70-79	1.00 (ref)	1.00 (ref)
80-89	1.00 (0.92-1.04), p=0.91	0.93 (0.86-1.01), p=0.08
>=90	1.16 (0.89-1.52), p=0.28	0.94 (0.73-1.22), p=0.66
Female sex	1.14 (1.08-1.20), p<0.001	1.08 (1.03-1.14), p=0.002
Socio-economic status		
1 (least deprived)	1.00 (ref)	1.00 (ref)
2	0.87 (0.80-0.94), p=0.001	0.86 (0.80-0.94), p=0.001
3	0.81 (0.74-0.88), p<0.001	0.87 (0.80-0.95), p=0.001
4	0.84 (0.77-0.91), p<0.001	0.89 (0.82-0.97), p=0.006
5 (most deprived)	0.73 (0.67-0.79), p<0.001	0.79 (0.72-0.85), p<0.001
Respiratory disease characteristics		
Smoking status		
Ex-smoker	1.00 (ref)	1.00 (ref)
Current smoker	1.05 (1.00-1.11), p=0.06	0.91 (0.86-0.95), p<0.001
Asthma history		
No asthma history	1.00 (ref)	1.00 (ref)
Past asthma	2.12 (1.98-2.27), p<0.001	1.72 (1.60-1.84), p<0.001
Current asthma	1.85 (1.63-2.08), p<0.001	2.58 (2.24-2.97), p<0.001
History of atopy	0.99 (0.94-1.05), p=0.85	1.07 (1.01-1.13), p=0.02
Exacerbations		
0	1.00 (ref)	1.00 (ref)
1	1.27 (1.19-1.35), p<0.001	1.14 (1.07-1.21), p<0.001
2	1.31 (1.20-1.44), p<0.001	1.19 (1.09-1.30), p<0.001
3 or more	1.42 (1.25-1.61), p<0.001	1.32 (1.16-1.50), p<0.001
Pneumonia episodes		
0	1.00 (ref)	1.00 (ref)
1	1.03 (0.95-1.11), p=0.48	1.14 (1.06-1.23), p=0.001
2 or more	0.92 (0.80-1.05), p=0.22	1.11 (0.97-1.27), p=0.15
Oral steroid prescriptions		
0	1.00 (ref)	1.00 (ref)
1	0.98 (0.91-1.05), p=0.51	0.96 (0.90-1.03), p=0.29
2	1.01 (0.90-1.13), p=0.88	0.82 (0.73-0.91), p<0.001
Salbutamol inhalers		
0	1.00 (ref)	1.00 (ref)
1	0.70 (0.65-0.75), p<0.001	0.66 (0.61-0.70), p<0.001
2	0.61 (0.56-0.67), p<0.001	0.59 (0.54-0.65), p<0.001
3-5	0.54 (0.49-0.58), p<0.001	0.56 (0.52-0.61), p<0.001
6 or more	0.47 (0.43-0.50), p<0.001	0.54 (0.50-0.58), p<0.001
Theophylline use	0.99 (0.78-1.26), p=0.93	1.47 (1.15-1.87), p=0.002
Oxygen use	0.84 (0.56-1.25), p=0.38	0.70 (0.49-1.00), p=0.05
Nebuliser use	0.91 (0.75-1.10), p=0.32	1.14 (0.95-1.38), p=0.16

Characteristic	Odds ratio for missing severity (95% CI), p-value	Odds ratio for missing MRC scale (95% CI), p-value
General health characteristics		
Non-elective hospitalisations		
0	1.00 (ref)	1.00 (ref)
1	1.46 (1.36-1.58), p<0.001	1.45 (1.34-1.57), p<0.001
2 or more	1.65 (1.45-1.88), p<0.001	1.57 (1.37-1.80), p<0.001
GP consultations		
0-3	1.00 (ref)	1.00 (ref)
4-7	0.91 (0.85-0.96), p=0.001	1.04 (0.98-1.10), p=0.18
8 or more	0.89 (0.83-0.95), p<0.001	1.10 (1.04-1.17), p=0.002
Charlson comorbidity index		
0	1.00 (ref)	1.00 (ref)
1	0.93 (0.86-1.00), p=0.05	0.94 (0.87-1.01), p=0.07
2 or more	0.95 (0.88-1.01), p=0.10	0.77 (0.73-0.82), p<0.001
Influenza vaccination	0.72 (0.68-0.76), p<0.001	0.70 (0.66-0.74), p<0.001
Pneumococcal vaccination	0.92 (0.87-0.97), p=0.004	1.29 (1.23-1.37), p<0.001

Odds ratios are adjusted for all variables listed. Details and time periods for variables are listed in Table 2.6 above. n=30,207 due to missing data for smoking status and socio-economic deprivation.
(ref), reference group

2.5 Overall cohort outcomes

22,864/30,378 (75.3%) patients experienced an exacerbation during their follow-up period (mean 0.80/year (SD 0.97)). 1,635 (5.4%) died from COPD during follow-up, and 6,143 (20.2%) died from any cause.

After those with an exacerbation in the first month after index date (n=1,598) had been dropped as planned, 21,266/28,760 (73.9%) experienced an exacerbation during their follow-up period (mean 0.76/year (SD 0.92)) (Figure 2.4). Median time-to-first exacerbation was 599 days (95% CI 586 to 609).

Figure 2.4: Kaplan-Meier curve showing time-to-first exacerbation

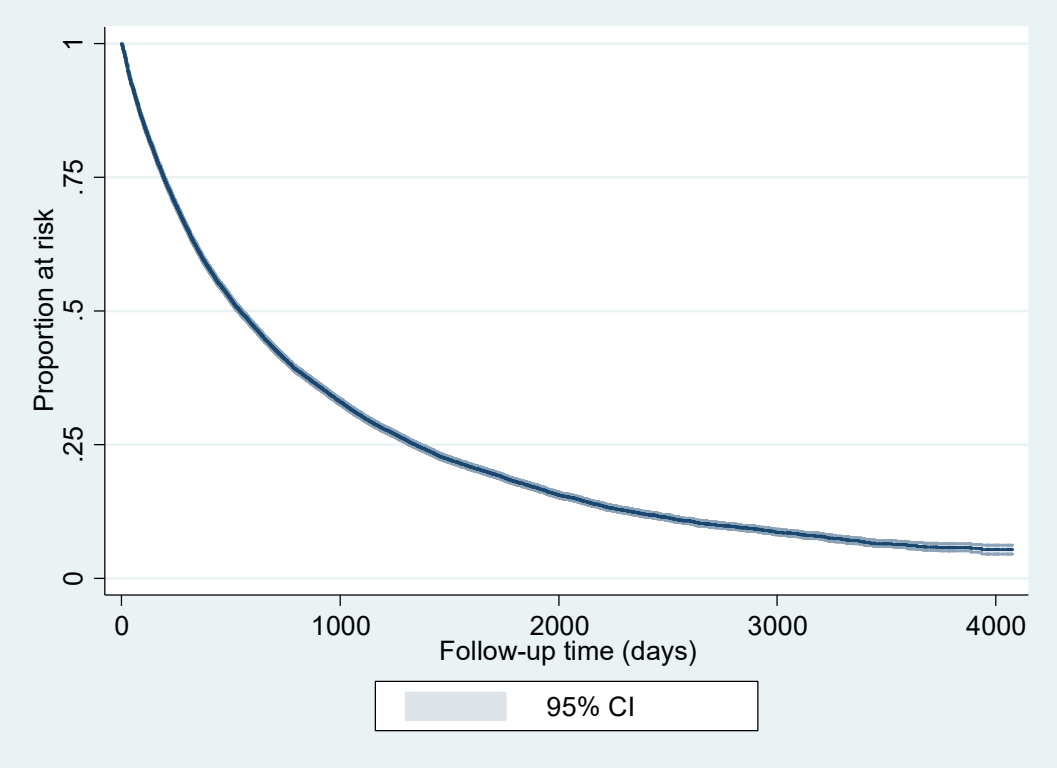


Table 2.8 shows hazard ratios for time-to-first exacerbation of each variable, both unadjusted and adjusted.

Table 2.8: Time-to-first exacerbation for baseline characteristics

Characteristic	Unadjusted hazard ratio (95% CI), p-value	Adjusted hazard ratio (95% CI), p-value
Demographic characteristics		
Age (continuous)	1.01 (1.01-1.01), p<0.001	N/a
Age group in years		
40-49	0.88 (0.83-0.93), p<0.001	0.93 (0.87-1.00), p=0.05
50-59	0.93 (0.89-0.97), p<0.001	0.98 (0.93-1.02), p=0.29
60-69	0.94 (0.91-0.98), p=0.001	0.97 (0.94-1.01), p=0.15
70-79	1.00 (ref)	1.00 (ref)
80-89	1.14 (1.09-1.19), p<0.001	1.14 (1.09-1.19), p<0.001
>=90	1.39 (1.20-1.61), p<0.001	1.34 (1.15-1.55), p<0.001
Female sex	1.10 (1.07-1.13), p<0.001	1.06 (1.03-1.09), p<0.001
Socio-economic status		
1 (least deprived)	1.00 (ref)	1.00 (ref)
2	1.05 (1.01-1.10), p=0.03	1.05 (1.01-1.10), p=0.03
3	1.01 (0.96-1.06), p=0.72	1.01 (0.96-1.06), p=0.69
4	1.08 (1.04-1.13), p=0.001	1.08 (1.03-1.13), p=0.001
5 (most deprived)	1.11 (1.06-1.16), p<0.001	1.10 (1.05-1.15), p<0.001
Year of index prescription (continuous)	0.98 (0.98-0.99), p<0.001	N/a
Respiratory disease characteristics		
Smoking status		
Ex-smoker	1.00 (ref)	1.00 (ref)
Current smoker	1.04 (1.01-1.06), p=0.01	1.09 (1.06-1.12), p<0.001
Asthma history		
No asthma history	1.00 (ref)	1.00 (ref)
Past asthma	0.99 (0.95-1.02), p=0.44	1.05 (1.01-1.09), p=0.01
Current asthma	1.08 (1.01-1.15), p=0.02	1.06 (1.00-1.14), p=0.07
History of atopy	1.11 (1.08-1.15), p<0.001	1.07 (1.04-1.10), p<0.001
Airflow limitation severity		N/a
Mild (≥80%)	1.00 (ref)	
Moderate (50-80%)	1.12 (1.06-1.18), p<0.001	
Severe (30-50%)	1.29 (1.22-1.37), p<0.001	
Very severe (<30%)	1.49 (1.36-1.63), p<0.001	
MRC breathlessness scale		N/a
1 (least severe)	1.00 (ref)	
2	1.06 (0.99-1.14), p=0.077	
3	1.16 (1.08-1.25), p<0.001	
4	1.18 (1.08-1.29), p<0.001	
5 (most severe)	1.47 (1.22-1.77), p<0.001	
Exacerbations		
0	1.00 (ref)	1.00 (ref)
1	1.49 (1.45-1.54), p<0.001	1.41 (1.36-1.46), p<0.001
2	2.01 (1.93-2.09), p<0.001	1.80 (1.72-1.89), p<0.001
3 or more	2.94 (2.79-3.10), p<0.001	2.51 (2.34-2.68), p<0.001
Pneumonia episodes		
0	1.00 (ref)	1.00 (ref)
1	1.55 (1.50-1.61), p<0.001	1.10 (1.06-1.15), p<0.001
2 or more	2.05 (1.93-2.18), p<0.001	1.05 (0.98-1.13), p=0.18

Characteristic	Unadjusted hazard ratio (95% CI), p-value	Adjusted hazard ratio (95% CI), p-value
Oral steroid prescriptions		
0	1.00 (ref)	1.00 (ref)
1	1.37 (1.32-1.42), p<0.001	1.07 (1.03-1.11), p=0.001
2	1.71 (1.62-1.82), p<0.001	1.14 (1.07-1.21), p<0.001
Salbutamol inhalers		
0	1.00 (ref)	1.00 (ref)
1	1.07 (1.03-1.12), p<0.001	0.99 (0.96-1.03), p=0.79
2	1.18 (1.12-1.23), p<0.001	1.03 (0.98-1.08), p=0.26
3-5	1.18 (1.13-1.23), p<0.001	1.06 (1.01-1.10), p=0.02
6 or more	1.26 (1.22-1.31), p<0.001	1.16 (1.12-1.21), p<0.001
Theophylline use	1.31 (1.16-1.47), p<0.001	1.11 (0.99-1.26), p=0.09
Oxygen use	1.42 (1.16-1.73), p=0.001	1.21 (0.98-1.48), p=0.07
Nebuliser use	1.45 (1.32-1.60), p<0.001	1.17 (1.06-1.29), p=0.002
General health characteristics		
Non-elective hospitalisations		
0	1.00 (ref)	1.00 (ref)
1	1.21 (1.16-1.26), p<0.001	1.05 (1.00-1.09), p=0.03
2 or more	1.45 (1.35-1.55), p<0.001	1.12 (1.04-1.20), p=0.002
GP consultations		
0-3	1.00 (ref)	1.00 (ref)
4-7	1.23 (1.19-1.27), p<0.001	1.10 (1.07-1.14), p<0.001
8 or more	1.43 (1.38-1.48), p<0.001	1.21 (1.16-1.25), p<0.001
Charlson comorbidity index		
0	1.00 (ref)	1.00 (ref)
1	1.08 (1.03-1.12), p<0.001	1.02 (0.98-1.06), p=0.37
2 or more	1.15 (1.12-1.19), p<0.001	1.07 (1.03-1.11), p<0.001
Influenza vaccination	1.16 (1.12-1.19), p<0.001	1.10 (1.07-1.14), p<0.001
Pneumococcal vaccination	1.04 (1.01-1.07), p<0.001	0.99 (0.96-1.02), p=0.50

(ref), reference group

Adjusted hazard ratio calculated using Cox regression, including all variables listed (categorical variable used for age and index year, as discussed in main text). Details and time periods for variables are listed in Table 2.6 above. n=28,780 for unadjusted analysis (except n=28,629 for smoking status, n=28,765 for socio-economic deprivation, n=19,343 for airflow limitation severity and n=11,135 for MRC breathlessness scale) and n=28,614 for adjusted analysis (which excluded airflow limitation severity and MRC breathlessness scale).

For age and index year, I explored whether including these as a categorical rather than continuous variable would improve the model, using a likelihood ratio test, and found that they did (p<0.001 for age and p=0.02 for index year), so I used categorical variables for analyses going forwards.[a] Including severity and MRC breathlessness scale did improve the

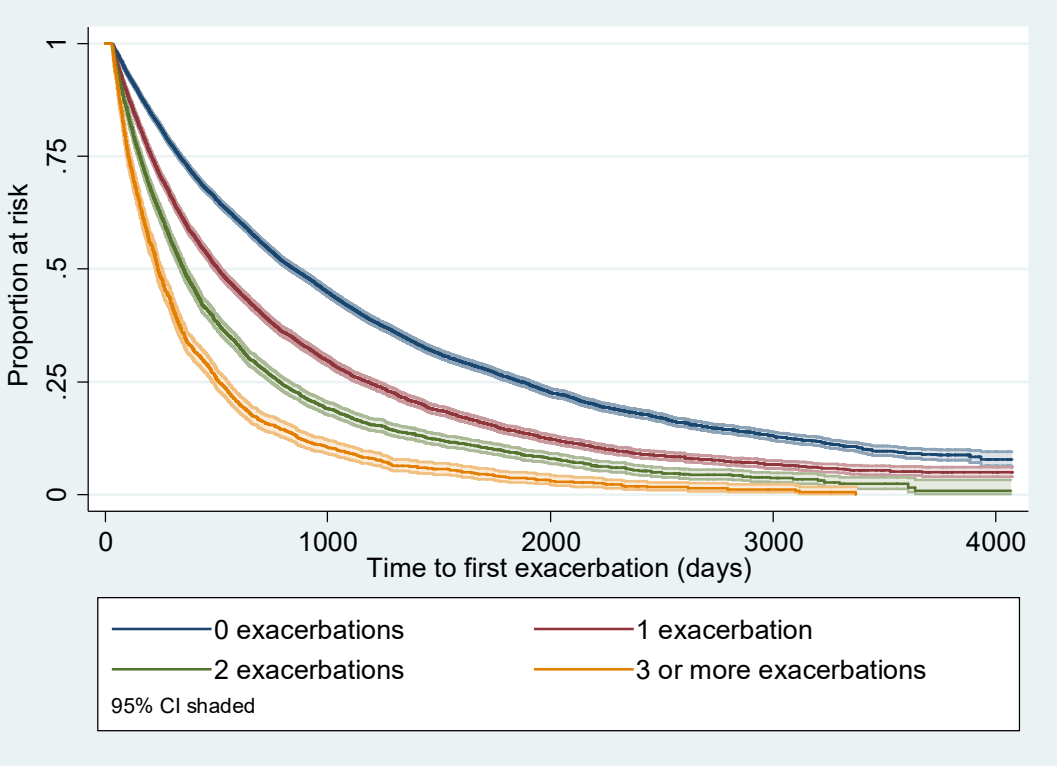
[a] N.B. I used the 70-79 age category as the reference group in the model because this was the largest group in my main (Aim II) analysis.

model ($p<0.001$) but did not change the hazard ratios for other variables by any important amount (data not shown).

As with all studies of datasets with a large sample size, where small effect sizes can appear statistically significant, one must be cautious in interpretation, as the effect may not be clinically significant. However, a worse outcome in terms of exacerbations appears to be particularly associated with increasing age, smoking, baseline exacerbation frequency (see Figure 2.5), oral steroid, nebuliser and high reliever inhaler use, and increasing hospitalisations, GP consultations and comorbidities.

I was surprised by the association of influenza vaccination with worse outcomes; I explored potential causes for this, particularly reasons a patient might visit the surgery more often, but found no significant interaction with baseline exacerbations, hospital admissions, GP consultations, Charlson category or inhaler use.

Figure 2.5: Kaplan-Meier curve showing time-to-first exacerbation, by baseline exacerbation frequency



2.6 Discussion

This discussion relates purely to the development of the overall cohort in terms of baseline demographics and the comparison of these with other published cohort studies. More detailed discussion of strengths and limitations, and comparison with other literature, in relation to answering specific thesis objectives, can be found in the results chapters.

2.6.1 Summary of findings

This chapter has described the overall methods of the CPRD study, leading to establishing a main ICS-naïve cohort for answering specific thesis objectives in subsequent chapters, and baseline characteristics and association of these with the primary outcome of time-to-first-exacerbation have been presented. All baseline covariates examined, except

pneumococcal vaccination, were significantly associated with the outcome, with the strongest predictor being baseline exacerbation frequency.

2.6.1 Strengths and limitations

Strengths of this cohort are inclusion of a large number (>30,000) real-world patients as managed in everyday clinical practice, which is high quality and representative of the UK population;[76] in contrast to many published trials or longitudinal cohort studies which are a highly selected population often recruiting from specialist tertiary clinics, and therefore not representative of primary care.[16,17] However, these large numbers also bring difficulties in that any tiny association will be statistically significant, even if differences are small or associations weak, and this may not be clinically significant; as such, it is not surprising that almost every covariate was associated with the primary outcome.

I included only those patients starting a new inhaled maintenance medication in order to effectively address Aim II. This meant that the cohort under study was consequently limited, so might not be representative of the whole COPD population. This limitation should be taken into account particularly when considering applicability to the general population living with COPD, and in terms of potential bias for the thesis questions regarding association between eosinophils and baseline characteristics, repeatability and variability, and association with prognosis. Furthermore, including those patients initiating ICS monotherapy, which is not included in COPD guidelines but reflective of current practice,[33] may result in the inclusion of more patients with asthma (for which ICS monotherapy is a more conventional treatment), rather than true COPD. This might affect applicability of findings to those with isolated, true COPD; however, proportions of patients

with coded asthma do not appear to be higher than in other studies (see Section 2.6.2 below).

Data management was a challenge in relation to spirometry where results could vary widely even within individual patients and with many extreme values, and there were considerable missing data for both spirometry and MRC breathlessness scale. A previous study validating spirometry in the CPRD found that recording quality was good,[103] and other studies have found that FEV_1 percentage predicted can be ascertained for approximately 75% patients in the CPRD.[104] Another CPRD study assessing predictors of exacerbations only had missing values of 2 and 12% for percentage predicted FEV_1 and MRC breathlessness scale, respectively,[92] so there may have been differences in our data management methods to account for this, but this is beyond the scope of what is reported in publications. Sensitivity analyses are planned of main analyses including these covariates to assess whether inclusion has any effect on overall results.

As the primary focus of my work was to investigate the utility of peripheral blood eosinophil count in primary care, it was important that this was assigned, managed and interpreted proportionally. In my work, I standardised the units of the peripheral eosinophil count in order to be able to deliver key messages in a uniform way. I also selected eosinophil counts that were closest to the index event. Although this was selected for ease of detection from a clinical point of view, sensitivity analysis as presented in Table 2.4 demonstrated that my selection of which eosinophil count to record would not affect the results, nor be affected if I excluded those close to exacerbations. I also investigated the seasonal effect on eosinophils (Table 2.5) and determined this was not clinically different. This is an important aspect of my work, as exacerbations of COPD are usually much higher in the winter.[10]

2.6.2 Comparison with other literature

Results comparisons will be discussed in more detail under the relevant study objectives. However, baseline characteristics of this study cohort are broadly similar to those found in other studies which will be discussed later, particularly in comparison to other studies which have used the CPRD or other primary care databases.[74,75,91,95,100,105-108] Differences arising are usually explained by differing methods or inclusion criteria creating a slightly different population; for example, including only those with at least one exacerbation in the baseline year,[74] exclusion of those with any history of asthma,[95,106] or no requirement for the patient to have been ICS-naïve during the baseline period.[100,107] For example, in a database study using the National Health And Nutrition Examination Survey (NHANES) data[a] to investigate relationship between blood eosinophils and clinical characteristics in those with spirometry-defined COPD (albeit mostly pre-bronchodilator), 18.5% any asthma history and 11.7% had current asthma, compared to 19.5% and 4.1% in my CPRD cohort. This may reflect the use of participant survey vs. clinician-coded data, and perhaps those with COPD self-identifying as having asthma as the cause of their respiratory symptoms rather than COPD.[91]

In this study cohort, half of patients had experienced no exacerbation in their baseline year, which is higher than that found in the post-hoc analyses of trials (as we would expect, as they tended to recruit a more severe population),[109] but lower than that in database cohort studies which did not require the patient to be initiating a new maintenance medication[75,100,107] (as in my CPRD study patients are presumably stepping up their medication due to worsening symptoms or exacerbations).

[a] The NHANES database is a cross-sectional clinical patient survey programme based in the United States

My finding that baseline exacerbation frequency is the strongest predictor of exacerbation outcome, with increasing hazard ratio as number of baseline exacerbations increased, is in keeping with other studies. A CPRD study found that prior exacerbations, increasing MRC breathlessness scale, increasing airflow limitation, females and co-morbidities were all risk factors for exacerbation frequency, which my findings replicate, and there was also a similar rate of exacerbations during follow-up of 0.89 per person per year (compared to 0.76 in my cohort).[92] Large prospective cohort studies, such as ECLIPSE[a], have also found that the single best predictor of exacerbations, across all severity stages, is a history of exacerbations.[110] A CPRD study covering a similar time period to my study assessing exacerbation frequency and multiple exacerbations in follow-up (rather than just time-to-first exacerbation) found that exacerbation frequency in a single year does predict long-term exacerbation rates, as well as similar baseline characteristics as risk factors for exacerbation frequency.[111] These associations have also been replicated in the OPCRD[b], another primary care database, in a study by Kerkhof *et al* which assessed risk factors for frequent COPD exacerbations.[75]

2.6.3 Conclusions

This is the first database cohort study looking at a cohort of ICS-naïve patients with COPD in primary care, at the time of commencing a new inhaled maintenance medication. Characteristics and outcomes of the overall cohort are similar to those in published literature, and as such later findings from specific study objectives are likely to be generalisable to the primary care population.

[a] Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints study
[b] Optimum Patient Care Research Database

Chapter 3: Developing a prospective primary care COPD cohort

This chapter covers the methods for the COMET[a] study, as well as baseline characteristics for the whole COMET cohort. Statistical analysis methods and results for specific study objectives will be presented integrated with results from the CPRD study in Chapter 4 (COMET Part I), and in Chapter 7 (COMET Parts II and III).

My thesis focuses on potential use of blood eosinophil count to guide decisions about ICS prescription and so I am focusing on these aspects of the study. I also collected data on fraction of exhaled nitric oxide (FeNO) and periostin, but results are not presented in this thesis.

3.1 Introduction

The rationale for this study is that there is limited evidence on repeatability and variability of blood eosinophils in the primary care COPD population, and no evidence on near-patient testing of blood eosinophils in stable state COPD management (as discussed earlier in Chapter 1).

3.1.1 Aims and objectives

I: To describe biomarker levels including repeatability and variability in a prospective study

Including specific objectives:

- To assess blood eosinophil distribution in the primary care COPD population

[a] Near-patient testing to guide COPD MaintenancE Treatment in primary care: observational study to determine variability and accuracy of inflammatory biomarkers in stable state

- To assess the association between higher blood eosinophil counts and clinical characteristics
- To assess within-person variation and stability over time of blood eosinophil counts, to decide whether the most recent value can be used in decision-making

II: To investigate use of near-patient eosinophils compared to laboratory eosinophils

Including specific objectives:

- *To assess method comparison of near-patient eosinophils compared to laboratory eosinophils*
- *To compare capillary blood testing with venous blood testing*

III: To assess the feasibility and acceptability of undertaking such measurements in a primary care setting

- Including acceptability of both laboratory and near-patient blood tests, testing at the COPD annual review, and being part of the research study

3.2 Methods

The approved protocol for the COMET study is included as Appendix E.

3.2.1 Study design

The design was a prospective observational cohort study with a nested method comparison study and feasibility assessment. Figure 3.1 shows the study procedures flow chart and Table 3.1 the schedule of study procedures. In summary, I planned to recruit approximately 100 ICS-naïve patients with COPD, identified from their primary care records and invited by post to take part in the study, followed by a screening telephone call to check eligibility. Participants attended for a baseline visit at their GP surgery, at which information was obtained on demographic and disease/medication characteristics, in conjunction with the

participant's health record. Measurements were taken including spirometry, FeNO, finger-prick blood test, and venous blood test (serum for periostin and saved serum, full blood count (FBC) and C-reactive protein (CRP)). Near-patient eosinophils were tested immediately using the Hemocue® WBC DIFF point-of-care (POC) machine, using both venous and capillary blood. Questionnaires on respiratory-related symptoms and quality of life were completed.

A further three visits took place over a six-month period, at approximately two-month intervals. At each of these visits, the same measurements were taken, and any exacerbations and changes to baseline characteristics were recorded.

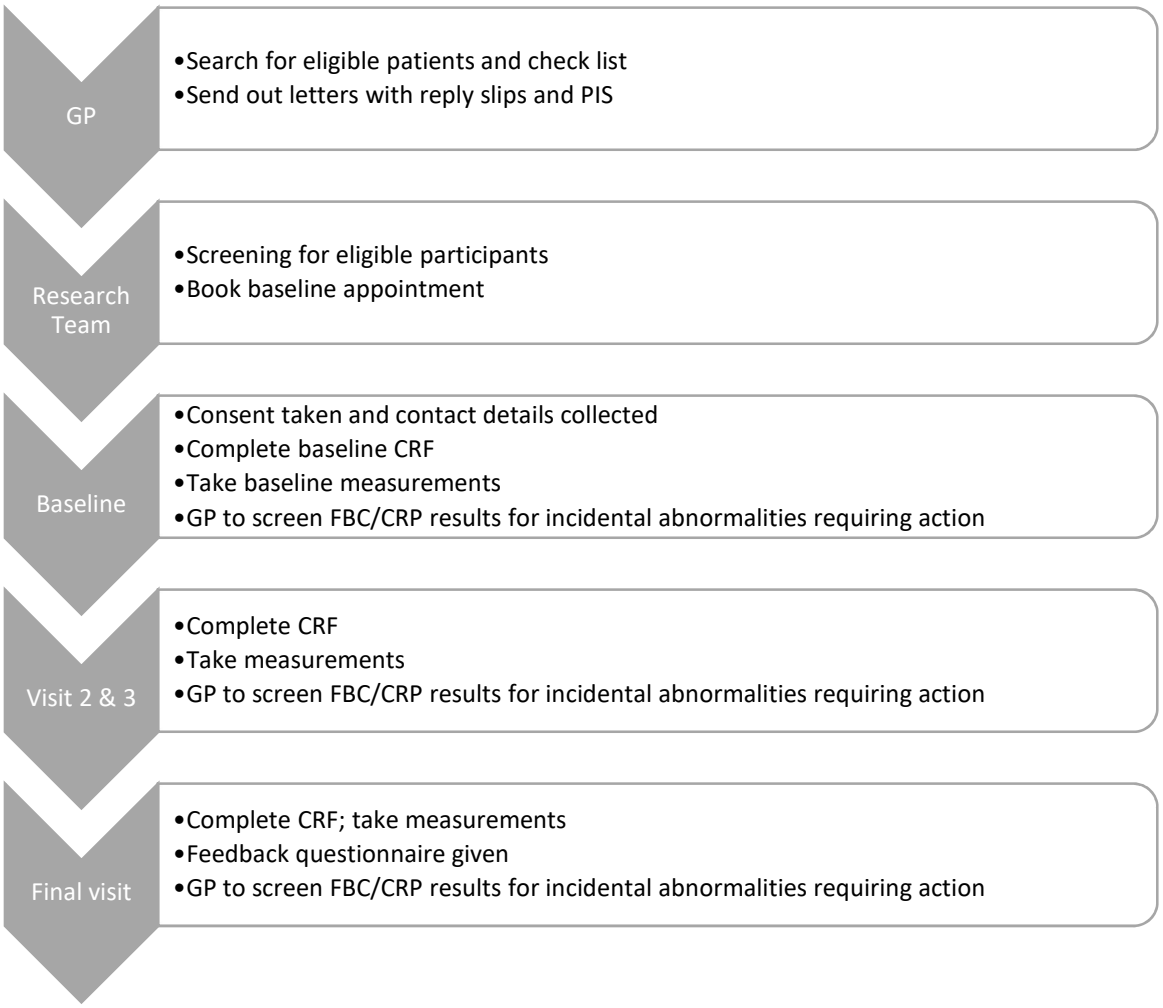
At the final visit, participants were given a survey to complete about the acceptability of such tests as part of their annual COPD review and their experience of being part of a research study.

The study did not mandate any changes to usual care. As part of the study design, additional tests were performed some of which are part of usual care, including spirometry and oxygen saturations, which were recorded in the notes so that they could then be used for clinical purposes by the usual care team.

I personally undertook the majority of study set-up, site recruitment and set-up, telephone eligibility screening, and appointment scheduling and organisation (i.e. trial management tasks). I led baseline appointments at the first two practices (seven participants) at which I

refined the working instructions for study nurses; after this, study procedures were undertaken by the Clinical Trials Unit research nurse team.[a]

Figure 3.1: Study procedures flow chart



PIS, patient information sheet; CRF, case report form; FBC, full blood count; CRP, C-reactive protein

[a] It is normal practice for studies recruiting in primary care for recruitment to be undertaken by a study nurse, from the Clinical Trials Unit or Clinical Research Network, or a practice nurse trained in study procedures. For the COMET study, due to only one set of devices, it was simplest to have this provided by the Primary Care Clinical Trials Unit nurse team.

Table 3.1: Schedule of study procedures

	Visit timing	Week 0	Week 8	Week 16	Week 24
	Screening and telephone contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Health record searches and recruitment letter	X				
Eligibility assessment	X	X			
Informed consent		X			
Demographics	X	X			
Contact Details		X	Check no changes	Check no changes	Check no changes
Medical history, smoking and medication history		X	Check no changes	Check no changes	Check no changes
Respiratory questionnaires		X	X	X	X
Physical examination (oxygen saturation only)		X	X	X	X
Fraction of exhaled nitric oxide (FeNO)		X	X	X	X
Spirometry including reversibility		X	X	X	X
Venous blood tests (FBC, CRP, periostin) – laboratory (all) and POC machine (FBC only)		X	X	X	X
Finger-prick blood test (POC machine)		X	X	X	X
Survey about acceptability of tests					X

3.2.2 Participant identification

Participants were recruited from primary care practices across Oxfordshire, with assistance of the Clinical Research Network (CRN). I produced a Research Information Sheet for Practices (RISP) (Appendix F) which described the study and encouraged practices to take part, with reimbursements provided for research activity (both Research Costs and Service Support Costs) as standard. I produced a Site Initiation Plan (Appendix G) to guide practices

through the study processes, and visited each practice to go through further details and provide them with the Investigator Site Folder.[a]

Inclusion and exclusion criteria

Inclusion and exclusion criteria are shown in Box 3.1. These were selected to mirror those in the CPRD study (Section 2.2.3), with the exception that I decided to include never-smokers following feedback at Patient and Public Involvement (PPI) meetings that this group of patients with COPD feels excluded from COPD studies but yet are managed the same as the current/ex-smoker COPD population.

Box 3.1: Inclusion and exclusion criteria for COMET study

Inclusion criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 40 years or above.
- Have a diagnosis of COPD meeting spirometric criteria for diagnosis of COPD (FEV_1/FVC ratio <0.7) (as recorded in their primary care records)

Exclusion criteria

- Any previous diagnosis of bronchiectasis, cystic fibrosis, interstitial lung disease, lung cancer, alpha-1 anti-trypsin deficiency or other chronic respiratory disease not related to COPD or asthma.
- Co-existent active diagnosis of asthma (reviewed in the last 2 years)
- Currently prescribed an ICS, or had a prescription for ICS in the last 2 years.
- Regularly takes oral steroids, or has been regularly taking oral steroids in the last 2 years. Regular use of oral steroids will in general be defined as a longer than 2 week course, although discrete short courses with tapering are acceptable for inclusion.
- Prior inclusion in a clinical trial of an investigational medicinal product for airways disease in the last 90 days or which may involve administration of oral or inhaled steroid treatment.

Screening for participants

I provided GP practices with an electronic search I had built in EMIS Web[b] (Appendix H). Because of the issues with spirometry coding that I was aware of through preliminary work

[a] With the exception of two practices who came on board while I was on maternity leave, where these visits were undertaken by an interim trial manager.

[b] EMIS Web is the patient operating system used by all Oxfordshire GP practices.

on the CPRD study, and my own clinical experience, I did not want to include spirometry in the search and exclude potentially eligible participants, and so I asked practices to conduct a further manual check of eligibility to include whether patients had eligible spirometry, and whether there were any other reasons they should not be invited for a research study, such as receiving end-of-life care or having severe dementia. However, this manual check was not performed by all practices, and some sent postal invitations to all patients identified by the electronic search. I asked practices to complete a screening log to record any patients excluded and with reasons, as well as to provide the total number of patients on their COPD register, however the former was so variably completed or missing that I was not able to use the data, and the latter I could obtain from publicly available data (see Table 3.2 legend).

Practice administrative staff then sent a letter out to eligible patients, which contained a cover letter personalised with GP practice details (Appendix I), Participant Information Sheet (Appendix J), a reply slip to provide contact details, and a prepaid envelope (to return the reply slip to the Nuffield Department of Primary Care Health Sciences, University of Oxford).

I had originally planned for GPs to follow up the postal invitation with a short telephone call to participants to remind them about participation, but the ethics committee requested that I remove this from the protocol on the grounds that it was potentially coercive. Having gained experience in running clinical research studies in my own GP practice since this time, this is actually a commonly used technique for increasing recruitment rates to studies, but is practically difficult to do given GP workload, so I think

not having this recruitment strategy is unlikely to have affected recruitment rates significantly.

Following receipt of the reply slip, I contacted the patient by telephone[a] and confirmed eligibility using standardised questions in the online Case Report Form (CRF) (discussed in Section 3.2.3 below). I then invited them to attend a research clinic held at their GP practice (which I had previously arranged with the research nursing team and practice administrative staff). I planned to arrange home visits in situations where the patient could not travel to their surgery, but this was not in fact necessary.

At the baseline appointment, I aimed for a further check of eligibility to take place in conjunction with the electronic health record, to include spirometry results which participants would be unlikely to know themselves. However, the eligibility check was not performed for all participants, but this did not come to light until most participants were nearing or had completed follow-up. When it was completed in retrospect, there were issues with confirming eligible spirometry, in that previous results were not easily visible or available. With hindsight, this was a difficult inclusion criterion and also not very pragmatic for the way in which these patients are managed in primary care; I concluded that I would keep all patients in the study, but perform a sensitivity analysis just including those who had eligible spirometry recorded at the baseline appointment for the key analyses.

[a] This was done by Clinical Trials Unit staff whilst I was on maternity leave.

Informed consent

The member of the study team who conducted the baseline appointment was responsible for taking informed consent, and needed to have Good Clinical Practice training for this purpose. Participants were given opportunity to ask questions and then were asked to complete an Informed Consent Form (ICF) for participation in the study (Appendix K).

3.2.3 Baseline characteristics

Box 3.2 summarises demographic, general health and disease-related characteristics which were recorded for all participants at the baseline appointment. This was predominantly recorded from the participant but using corroboration with the medical record for details which might be hard to remember or in the case of queries. It has been shown that patients can accurately remember the number of exacerbations they have in a year, with a high concordance between recall and those recorded on diary card (agreement 93.3%, Kappa=0.6146),[112] suggesting it is appropriate to use patient-reported information.

The detailed CRFs for the study can be found in Appendix L. These were designed iteratively with feedback from study nurses and a data manager. I aimed to collect sufficient data for useful analysis while trying to minimise quantity of information needed, to reduce appointment time for participants and study nurses. Data were inputted into the CRFs at the time of the appointment using a secure online platform (OpenClinica). Data arriving on paper e.g. blood results print-outs, respiratory questionnaires, were entered in duplicate by CTU staff to reduce error rates. Any queries were raised by the Clinical Data Manager and addressed usually by the person who had inputted the data.

Box 3.2: Baseline characteristics gathered for COMET study participants

Sex		
Age		
Smoking status		
Medical history	-	including specific questions on asthma, heart failure, hypertension, cancer, hay fever, eczema, autoimmune condition, any other chronic condition, and previous steroid use
COPD history	-	including date of COPD diagnosis, date and details of eligible spirometry, date of last exacerbation, number in previous year (and for each, whether treated at home/hospital and with steroids, antibiotics, nebulisers and/or respiratory support), and number in previous two years
Smoking history	-	including (for smokers or ex-smokers), start and quit dates, number of years, what smoked, and number smoked per day
Respiratory medication	-	all (including non-current), with start date and stop date, and last time inhalers had been taken if current
Other concomitant medication	-	only those current and considered medically relevant e.g. oral, nasal sprays (to avoid study nurses needing to type lots of unnecessary details about stoma bags, topical preparations etc.)

At subsequent appointments, fields were pre-populated with information given at the baseline appointment and the study nurse just had to confirm whether there had been any changes to medication, medical or COPD history e.g. exacerbations in the interim period.

3.2.4 Respiratory questionnaires

At each appointment, participants were asked their MRC breathlessness scale and to complete the COPD Assessment Test (CAT) and Clinical COPD Questionnaire (CCQ) (Appendix M). These are both self-administered COPD-specific questionnaires which take 1-3 minutes to complete, containing 8 or 10 items on a 5 or 7-point Likert scale, respectively.[113-115] I selected these because they are both well-validated for assessing symptoms and disease-related quality of life; the CAT is widely used, and the CCQ is most relevant to primary care.[115] I sought and was granted permission from the author for use of the CCQ.

3.2.5 Study measurements

These included physical examination, FeNO, spirometry, laboratory blood tests and near-patient blood tests, which are discussed in turn. I received training in use of spirometry, FeNO and point-of-care machines, from respiratory nurses or the manufacturer's representative as appropriate, and used these, along with my existing clinical experience, to produce a set of working instructions for the study nurses (Appendix N), to ensure standardisation of practice between individuals, and the first appointments were done jointly with study nurses so that we could discuss techniques, and iteratively revise the working instructions. Details which would be useful for the routine clinical care of patients and particularly those which would be useful for fulfilling Quality and Outcomes Framework criteria e.g. spirometry results, were entered into the practice health record.

Physical examination

Height and weight of participants were recorded (for use in spirometry calculations), and oxygen saturations using pulse oximetry. The pulse oximeter was carried in the study kit; weighing scales and height measurers relied on equipment already present in the GP practice.

Fraction of exhaled nitric oxide (FeNO)

I selected to use the NIOX VERO® machine (Aerocrine/Circassia, UK) (Figure 3.2) which is a portable device and widely used in the field. I purchased the machine and it was used in accordance with the manufacturer's instructions (incorporated into working instructions, Appendix N).

Figure 3.2: NIOX VERO® machine used to measure FeNO

The test was done before spirometry and before administration of salbutamol inhaler. The demo mode was used first to explain to the participant what they needed to do. The participant was allowed up to three attempts using the standard 10-second measurement and then proceeded to try for up to three attempts with the 6-second measurement, in accordance with advice from the manufacturer.

Spirometry

We used the Microlab Mk8 Spirometer, which is widely used in existing clinical practice in Oxfordshire (personal communication with local practice nurses), in accordance with standardised spirometry guidelines.[116] A calibration syringe was used to check the machine before each use, and annual re-calibration also took place. A checklist of contra-indications to spirometry was checked before performing spirometry, as part of the CRF (see Appendix L), and we also recorded time of last smoking and inhalers, as applicable. Participants were asked to avoid smoking, drinking alcohol, doing vigorous exercise, having a heavy meal or using their salbutamol inhaler for the few hours before the appointment.

Pre- and post-bronchodilator spirometry was undertaken, in order to establish reversibility and to measure post-bronchodilator spirometry in accordance to gold standard for testing

in COPD.[10] A 20-minute gap was allowed between administration of salbutamol inhaler and post-bronchodilator spirometry being performed. If the patient had not remembered to bring their inhaler, spirometry was still counted as post-bronchodilator if they had used a long-acting bronchodilator in the last 12-24 hours. Significant reversibility was defined as an increase in FEV_1 of ≥12% or ≥200ml;[117] this was recorded because it has been associated with eosinophilia[118] however it is no longer routinely recommended by guidelines as part of COPD diagnosis due to concerns about repeatability.[10,13,119]

Laboratory blood tests

A venous blood sample was taken using standard phlebotomy techniques, into serum, lithium-heparin and EDTA[a] tubes.

The lithium-heparin and EDTA tubes were for full blood count and CRP, and were requested, transported to the Oxford University Hospitals NHS Trust (OUH) laboratory, and subsequently processed via the routine pathway from GP practices. For these tests, results were transferred back to the practice using the routine system for notifying laboratory results to practices, and were checked in the normal way (coming into the GP's electronic 'lab reports' in-tray on EMIS Web). Research staff then extracted this data when returning to the practice for subsequent clinics, and/or at the end of the study. This ensured that any unexpected abnormalities e.g. severe anaemia, could be dealt with promptly by the participant's usual clinician in conjunction with the full background information, and meant that results were available in the participant's notes for future use.

[a] EDTA: Ethylene-diamine-tetra-acetic acid (standard tube for taking full blood count samples)

The serum sample was also transported to the OUH using routine transport from practices. It was then centrifuged, transferred to 2ml aliquots and stored in OUH freezers. Aliquots of serum were transported as a frozen batch to Viapath Ltd, a laboratory based in Kings College London, for testing for periostin – this used manual ELISA (enzyme-linked immunosorbent assay). The remaining aliquots were stored long-term in OUH freezers for use in future ethically-approved studies.

I produced a special COMET study label for use on serum samples in conjunction with the head of the OUH Biochemistry laboratory, for identification to laboratory staff so that the samples were processed correctly. This also featured instructions for study and practice staff on how to keep the sample if it could not be transported to the laboratory the same day (to refrigerate the serum sample and keep the others at room temperature, centrifuging the lithium-heparin sample if possible). However, in setting up research appointments, I planned these so that they were timed before the last laboratory transport of the day.

Near-patient blood tests

To test the accuracy of near-patient eosinophils compared to laboratory eosinophils, we used the Hemocue® WBC-DIFF machine (HemoCue AB, Ängelholm, Sweden) (Figure 3.3) which was the only point-of-care machine available in the UK for measuring eosinophil counts, which was provided on loan by the company for the purpose of the study. The HemoCue® device complies with the In-Vitro Diagnostic Medical Device Directive 98/79/EC and carries the European Community (EC) mark. The device works by using a disposable microcuvette pre-loaded with reagent, which haemolyses the red cells and then stains the

nuclei of white cells with methylene blue, which can then be analysed using image analysis technology (photomicroscopy).[120]

A finger prick sample was obtained using a lancet and the machine used in accordance with the manufacturer's instructions (incorporated into working instructions, Appendix N), for example using a large bore lancet, avoiding squeezing the finger, and wiping away the first drop of blood obtained.

Figure 3.3: Hemocue® WBC-DIFF machine used for measuring near-patient eosinophils

As any difference in results between near-patient and laboratory eosinophils might plausibly be due to the difference between capillary and venous eosinophils[a] we tested both a capillary and venous sample from each patient on the point-of-care machine. Other aspects of the white cell count differential outputted by the Hemocue® machine were also recorded (total white cell count, neutrophils and lymphocytes). Blood was transferred from the EDTA tube using a DiffSafe® blood dispenser device, as recommended by the OUH laboratory and in accordance with the manufacturers' instructions.

[a] Discussion on this with a consultant laboratory haematology suggested that there might be higher values in capillary samples as this would be more reflective of tissue contents where eosinophils are higher,[37] and leucocyte counts have been found to be significantly higher in finger prick samples compared to venous blood ($p<0.001$), particularly granulocytes.[121]

I had also initially planned to validate the machine measurements using manual blood films (capillary and venous, made at the time of taking the sample and then at the time of laboratory processing, from twenty consecutive samples), to try to explain any difference in results which might relate to eosinophil morphology or delay in processing of sample, and as manual blood films are the gold standard in full blood measurements compared to automated machines.[122] I underwent training in making manual blood films, but it was not straightforward and was going to be difficult to train study nurses in the technique. I therefore conducted a brief interim analysis of results halfway through the study (March 2018) to see whether it was likely to be necessary. The mean difference between laboratory and POC venous results (n=121) was 0.01x10*9/L (SD 0.05, p=0.14) and between POC capillary and POC venous results (n=164) was 0.01x10*9/L (SD 0.07, p=0.08). Along with further discussion with haematology specialist colleagues, I concluded that this small difference (unlikely to be clinically significant even with more data to increase power), was not sufficient to justify the large practical difficulty of assessing manual blood films, and so submitted a protocol amendment to remove this part of the study plan.

3.2.6 Follow-up and discontinuation/withdrawal

I chose four measurements over six-months as a pragmatic period to assess, during which eosinophils would vary if they were going to (half-life is approximately 18 hours and they have a mean blood transit time of 26 hours)[37] but where this was unlikely to be due to underlying progression of disease state; as well as the considerations of not having too lengthy a follow-up within the time constraints of a doctoral project, and based on PPI feedback (see Section 3.2.10 below). Follow-up appointments were arranged where possible at the previous appointment, or if not by telephone in the interim period. Where

participants did not attend follow-up appointments, I contacted them by phone several times and left messages, but stopped if no response after several attempts as I did not want to be intrusive, and they were then counted as lost to follow-up.

Criteria for discontinuation and withdrawal were as follows:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening). N.B. Starting an ICS during the study did not result in withdrawal.
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of consent
- Loss to follow up

If withdrawal from the study was due to loss to follow up, data already collected were used in analysis (and their health records were checked to establish any reason for loss to follow up e.g. death). If a participant stated a wish to withdraw, they were asked whether they wished their existing data to be excluded. Details were recorded in the CRF (Appendix L). The end of the study was defined as the last visit of the last participant.

3.2.7 Participant survey

At the final visit, participants were given a survey to complete and place in a sealed envelope, which asked for feedback on the acceptability of tests being incorporated into the routine COPD annual review, as process evaluation.

There was no existing questionnaire instrument available for these novel tests or validated on this specific population, so I designed a survey for this purpose using published recommendations for questionnaire development.[123,124] I therefore developed the survey

using examples from the literature (i.e. other surveys which had been designed to assess acceptability of POC tests compared to standard laboratory measurements).[70,125,126] Questions aimed to assess attitudes and beliefs in relation to testing in COPD, the annual review and the specific tests used in the study. These were a mixture of closed and open questions, to enable rapid answers which could be easily compared between participants, but also to enable a richer assessment of opinions giving participants the opportunity to respond in as much detail as they chose.[123]

Box 3.3 summarises the questions asked by the survey and the whole survey is shown in Appendix O. Questions were a combination of Visual Analogue Scale (VAS) responses and free text boxes. VAS was used for closed questions as it enabled more detailed assessment on a continuous scale.[70]

Studies have shown the low response rates are often due to participants being unable to easily read or follow the questionnaire,[127] which is relevant even where the sample is pre-selected. I therefore spent considerable time focusing on the design and layout of the survey, so that it was accessible with large font, colour pictures, and an uncramped style with short, easy to understand questions. It contained an example page with instructions, and descriptions and colour photographs of the different tests, which served as a reminder to participants. I used a mixture of positively and negatively framed questions in order to avoid a positive skew towards the responses which might be perceived as pleasing the research staff (social desirability bias).

It is important that pilot respondents of the questionnaire should be as similar as possible to those to whom the survey is aimed,[123] so after piloting with academic colleagues for feedback on the question format and structure, I asked my PPI representative who is a

patient with COPD, to complete it. He had no further feedback and thought it was clear and well-presented.

In addition to the main questionnaire, the survey also asked participants whether they would be willing to be contacted in future to discuss their opinions in more detail, which would form the basis of a future qualitative study. This was on a separate perforated page so that it could be detached and kept separately to the CRF material.

After completing the survey, participants were given a £30 gift voucher to thank them for their time in participating and to cover any incidental travel expenses. They were asked to sign a form to confirm that they had received the voucher, for financial administration purposes.

The VAS was a ten-centimetre scale recorded to the nearest one centimetre. Two data entry staff made measurements independently, and any discrepancies were checked. Quantitative survey questions were analysed descriptively, with the VAS assessed on a continuous scale (1-10) and presented as mean and SD. Free text comments were analysed using thematic analysis, by grouping into themes and presenting the richer responses in full.

Box 3.3: Questions featured in participant survey (Visual Analogue Scale except where stated as free text)

About the blood tests

- I found the blood test from my arm uncomfortable
- I found the blood test from my finger uncomfortable
- I don't mind putting up with the discomfort of a blood test if it helps with managing my COPD
- I would be happy to have a finger prick blood test as part of my COPD annual review
- I would be happy to have a blood test from my arm as part of my COPD annual review
- Any thoughts or comments about the blood tests and the process of getting the blood tests (free text)

About the breathing tests

- I find spirometry is easy to perform
- I find FeNO is easy to perform
- The visual display made it easier for me to understand how to use the FeNO machine
- I would be happy to have FeNO as part of my COPD annual review
- Any thoughts or comments about the breathing tests and the process of doing this (free text)

About the COPD annual review

- I find the annual review helpful
- In general, I feel happier if I have had a lot of tests
- I would like to have instant feedback on my results (rather than having to wait for a result of a test)
- I would be more motivated to look after my COPD because of additional testing
- Having these tests regularly would strengthen my relationship with my GP or nurse
- Any thoughts or comments about the COPD annual review and extra testing in general (free text)

About being in this study

- I have enjoyed being part of this study
- What did you find worked well? (free text)
- What did you find made it difficult? (free text)
- What would have made it easier for you? (free text)
- Any additional comments about the study (free text)

3.2.8 Statistical analysis

I used Stata (Release SE13 64-bit) for all analysis. In general, data are presented as mean with standard deviation (SD), median with interquartile range (IQR) or hazard ratios (HR) with 95% confidence intervals (CI). Division of baseline characteristics into categories for non-binary variables was based on what seemed clinically sensible, or to achieve

approximately equal groups, and based on what has been used in other primary care COPD studies.[128] The Charlson comorbidity index was used to categorise comorbidities recorded in addition to COPD.[93] Participants were also divided into those with or without atopy; with or without history of asthma; those on no, single, or dual bronchodilator therapy; exacerbation frequency (0, 1 or ≥2 in year prior); NICE airflow limitation classification;[10] and MRC breathlessness scale. Respiratory symptom questionnaire scores were analysed on a continuous scale as used in other studies.[128] Further specific details of categorisations are given as footnotes to the baseline characteristics table (Table 3.3).

For description of baseline characteristics which were repeated during the study, I used the first value for each participant.[a] Exacerbations during follow-up were described descriptively because the study was neither powered nor sufficient duration to robustly assess outcomes.

Further details of statistical methods relating to specific study objectives, and sensitivity and subgroup analyses, are presented (in conjunction with CPRD statistical methods where relevant) adjacent to the relevant results sections (Chapters 4 and 7), due to significant overlap in methods and to enable easier reading.

Missing data

I expected data to be well-recorded by study nurses, so I planned complete case analysis, using however many eosinophil counts were available. For methodological validation, I planned to perform a descriptive comparison of baseline characteristics by those who had

[a] I considered whether to use the last eosinophil value, to enable better comparison with the CPRD cohort, but decided against as it would be overly complex to transfer baseline characteristics to the final value, and this is both non-intuitive and there are already more important differences between the two cohorts of patients.

full eosinophil data and those who had incomplete (fewer than four) values. However, as numbers of missing data were small we subsequently concluded that this was likely to be meaningless.

For respiratory questionnaires where missing responses were likely, I followed recommendations for calculating the score as detailed in the validation studies for these questionnaires.[113,114]

Sample size

This was a preliminary study designed to gather further information on biomarkers of interest in a primary care population, where very little data currently exist, which made it hard to find information on which to base a detailed sample size calculation. 100 participants with four appointments per participant was selected as a pragmatic number which would also be acceptable to patients, based on PPI feedback.

3.2.9 Ethical approval

I submitted the application to ethics and it was approved (South East Scotland Research Ethics Committee 02 (reference 16/SS/0135)); this was after clarification was provided for the committee about various points and the PIS had been changed to be less 'coercive' and the phone call to potential participants by the GP had been removed from the protocol. I also received feedback and approval at various stages from the University of Oxford Clinical Trials and Research Governance team, Health Research Authority (HRA), and NIHR Clinical

Research Network (Thames Valley and South Midlands). The study is registered on the ISRCTN[a] primary clinical trial registry (registration number 12181464).

3.2.10 Patient and public involvement

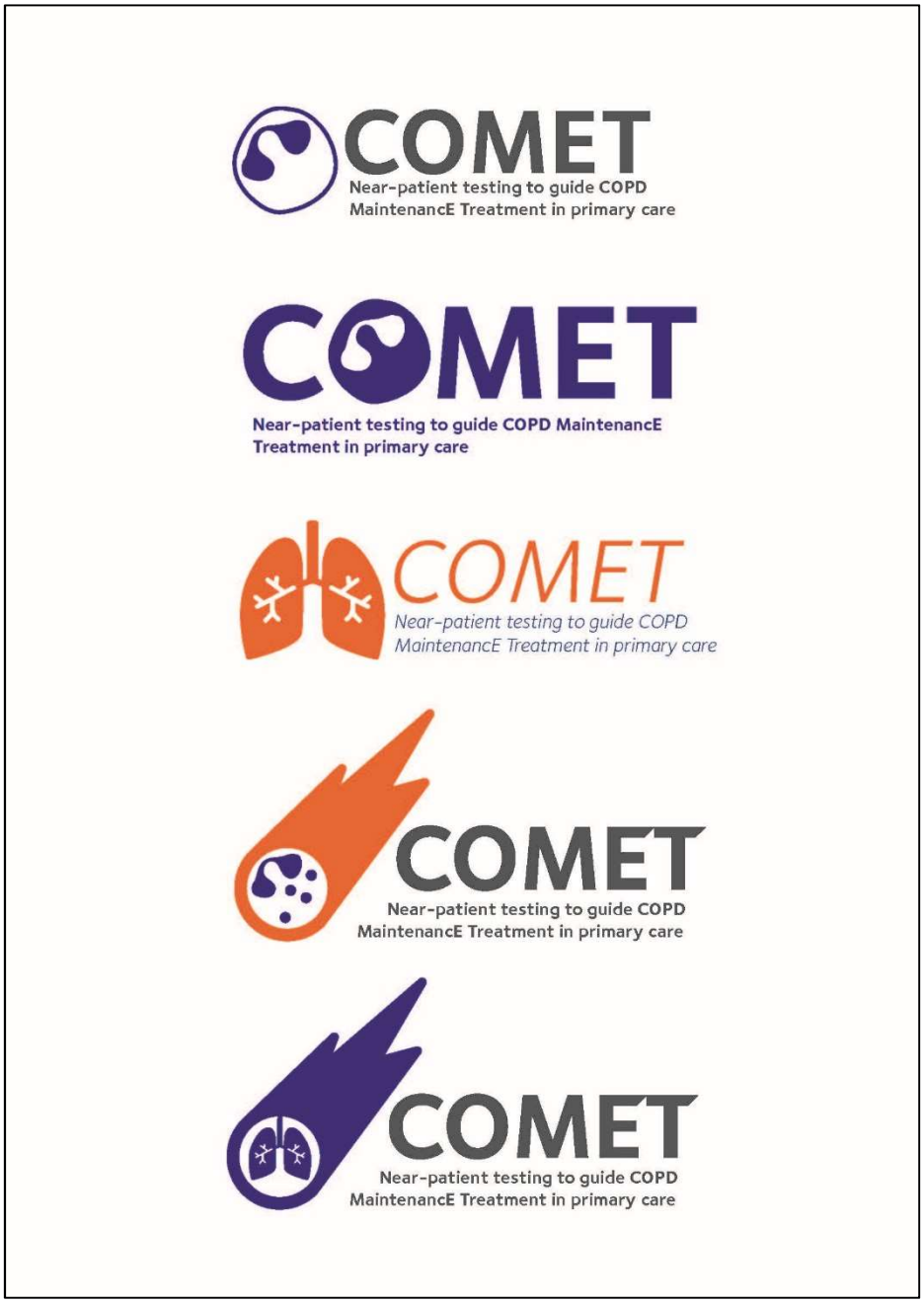
I have given presentations and received feedback from the Banbury 'Breathe Easy group'[b] on three occasions, at the time of submitted the funding application, developing the project ideas, and for further refinement of the protocol methods. Particularly, they gave feedback on the inclusion of non-smokers in the study, reducing the number of appointments from six to four, and the display mode to use as standard when using the FeNO machine.

I subsequently appointed a patient representative (a man in his seventies living with COPD), who inputted into the study protocol and reviewed study documents, giving critical feedback (for example, making it clearer the duration of appointment visits on the cover letter), and he helped with selection of the COMET study logo (Figure 3.4). He specifically suggested that GPs should contact potential participants alongside the mail invitation, to provide a personal touch and enhance recruitment, but this was subsequently removed following ethics committee feedback that this was overly coercive.

[a] ISRCTN: International Standard Randomised Controlled Trials Number

[b] The Breathe Easy groups are under the umbrella of the British Lung Foundation and are patient support groups for those with chronic respiratory conditions, but especially COPD (https://www.blf.org.uk/support-for-you/breathe-easy)

Figure 3.4: Proposed logos for the COMET study, designed to include concepts around lungs and eosinophils. The patient representative selected the bottom logo.



3.3 Practice and participant recruitment

22 practices expressed interest in the study, which proceeded to the study being set up in 17 practices in Oxfordshire. Of the 5 which did not proceed with study set-up, 1 did not identify any eligible patients on their preliminary search, 2 decided not to proceed with

becoming a research practice,[a] and 2 were unable to participate due to another COPD study recruiting at those practices.

Table 3.2 shows the participating practices, with details about their population and COPD prevalence, and summary of recruitment statistics. Overall, 21.0% (623/2,960) of the COPD population were identified as eligible for the study and received the mail out, with a range 6.1 to 31.5%. Response rate was 18.3% (114/623) but also varied widely between practices (range 0.0 to 38.2%).

Figure 3.5 shows monthly and cumulative accrual. The study start date was delayed due to delays with the HRA (this was the first study in the department to go through the new HRA process in 2016). I had planned for the study to run for 18 months (12 months' recruitment with 6 months' follow-up) but recruitment slowed substantially during my maternity leave (March 2017 – February 2018) so I applied for two extensions and the study then ran for 28 months (January 2017 – April 2019).

Learning points for me in relation to the process of practice and patient recruitment included spirometry requirements being overly complicated and time-consuming for GPs doing the searches to deal with, not using Docmail which would have made the mail-out process more straightforward, and the difficulties of maintaining administrative rigour in study-set up and appointment scheduling without a permanent trial manager whilst I was on maternity leave (loss to follow-up, described later, was also much higher during this time).

[a] The study was popular with practices new to undertaking research because of the straightforward nature of the study and study nurses coming in to see patients, with minimal involvement needed from practice staff (although it was funded via the Clinical Research Network as a site-based study).

Table 3.2: Details of COMET participating practices

Practice code	Location	Population (n)	Deprivation score and decile[a b]	Aged over 65 years, %[a]	Smoking prevalence, %[a]	COPD QOF prevalence, n(%)[a]	Electronic search, n[c]	Study mail out, n(%)[d]	Responded to study, n(%)[e]	Recruited to study, n(%)[e]
England average		*8,035*	*21.8*	*17.3*	*17.2*	*1,113,417 (1.9)*	*Not applicable*			
Oxfordshire CCG average		*10,326*	*11.6*	*16.7*	*14.2*	*10,243 (1.4)*	*Not applicable*			
A	Small town	7,175	9.5 (10th)	20.7	14.8	104 (1.4)	88	27 (26.0)	6 (22.2)	6 (22.2)
B	City	4,390	16.9 (7th)	9.8	14.1	29 (0.7)	6	4 (13.8)	1 (25.0)	1 (25.0)
C	Small town/rural	4,875	16.8 (7th)	21.4	17.7	124 (2.5)	54	21 (16.9)	5 (23.8)	5 (23.8)
D	Small town/rural	15,337	10.4 (9th)	23.9	13.2	302 (2.0)	Missing	32 (10.6)	11 (34.4)	10 (31.3)
E	Small town/rural	13,955	6.6 (10th)	24.1	11.3	195 (1.4)	61	45 (23.1)	9 (20.0)	8 (17.8)
F	Small town/rural	10,618	7.8 (10th)	10.7	18.3	168 (1.6)	58	32 (19.0)	7 (21.9)	5 (15.6)
G	City	16,866	9.8 (10th)	12.6	9.4	165 (1.0)	16	10 (6.1)	0 (0.0)	0 (0.0)
H	City	10,357	33.2 (3rd)	11.1	28.7	286 (2.8)	82	82 (28.7)	7 (8.5)	5 (15.6)
I	City	13,303	21.7 (6th)	14.4	19.1	231 (1.7)	Missing	54 (23.4)	7 (13.0)	4 (7.4)
L	Small town	15,311	9.9 (10th)	15.8	13.2	187 (1.2)	Missing	56 (29.9)	12 (21.4)	11 (19.6)
M	City	7,137	16.1 (7th)	9.2	7.9	41 (0.6)	Missing	9 (22.0)	1 (11.1)	1 (11.1)
N	Large town	17,207	16.4 (7th)	17.9	20.1	292 (1.7)	Missing	92 (31.5)	9 (9.8)	8 (8.7)
P	City	15,242	15.0 (8th)	8.2	8.1	108 (0.7)	43	34 (31.5)	13 (38.2)	13 (38.2)
Q	Small town/rural	14,378	8.8 (10th)	19.7	13.9	170 (1.2)	61	39 (22.9)	6 (15.4)	5 (12.8)
T	City	16,030	14.9 (8th)	15.1	12.8	194 (1.2)	28	28 (14.4)	3 (10.7)	3 (10.7)
U	City	19,407	16.3 (7th)	3.7	17.6	94 (0.5)	33	16 (17.0)	1 (6.3)	0 (0.0)
V	Small town/rural	16,813	8.7 (10th)	19.9	13.5	270 (1.6)	91	42 (15.6)	16 (38.1)	11 (26.2)
Totals/study average		**218,401**	**14.0 (8th)**	**15.2**	**14.9**	**2,960 (1.4)**		**623 (21.0)**	**114 (18.3)**	**96 (15.4)**

[a] Information for these indicators taken from Public Health England National General Practice Profiles 2017/18 data (publicly available at https://fingertips.phe.org.uk/profile/general-practice).

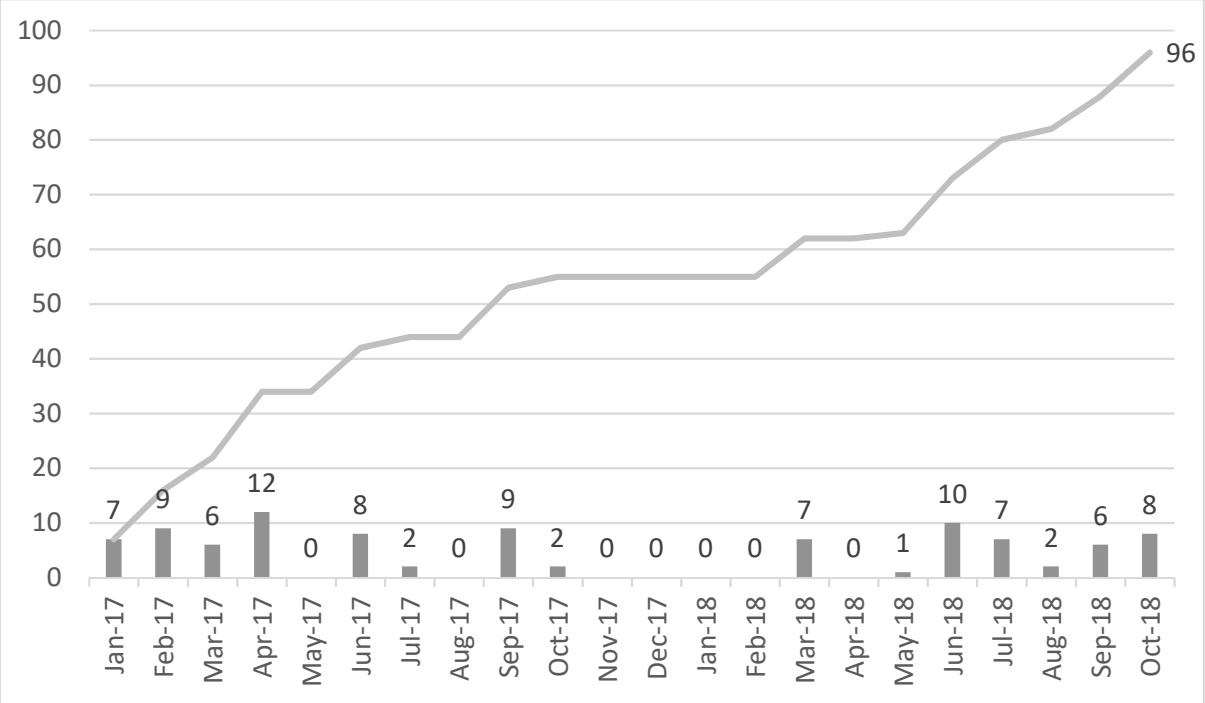
[b] Index Multiple Deprivation 2015, which provide relative levels of deprivation at the small area level in England. The range in Oxfordshire CCG is from 4.7 (least deprived) to 33.2 (most deprived). Deciles refer to comparison nationally. 1st decile is most deprived and 10th is least deprived.

[c] Data missing from this column because not all practices returned their screening log.

[d] This was usually reduced compared to electronic search because of manual removal of ineligible patients by GP. % is those of COPD population who were invited.

[e] % is those who had the mail out who responded/were recruited. Discrepancy between these columns (n=18) is due to some participants being ineligible for the study on further screening (n=6), or participants being unable to attend planned clinics/not attending baseline appointment (n=12).

Figure 3.5: Participant accrual by month (bars) and cumulatively (line)



3.4 Data management

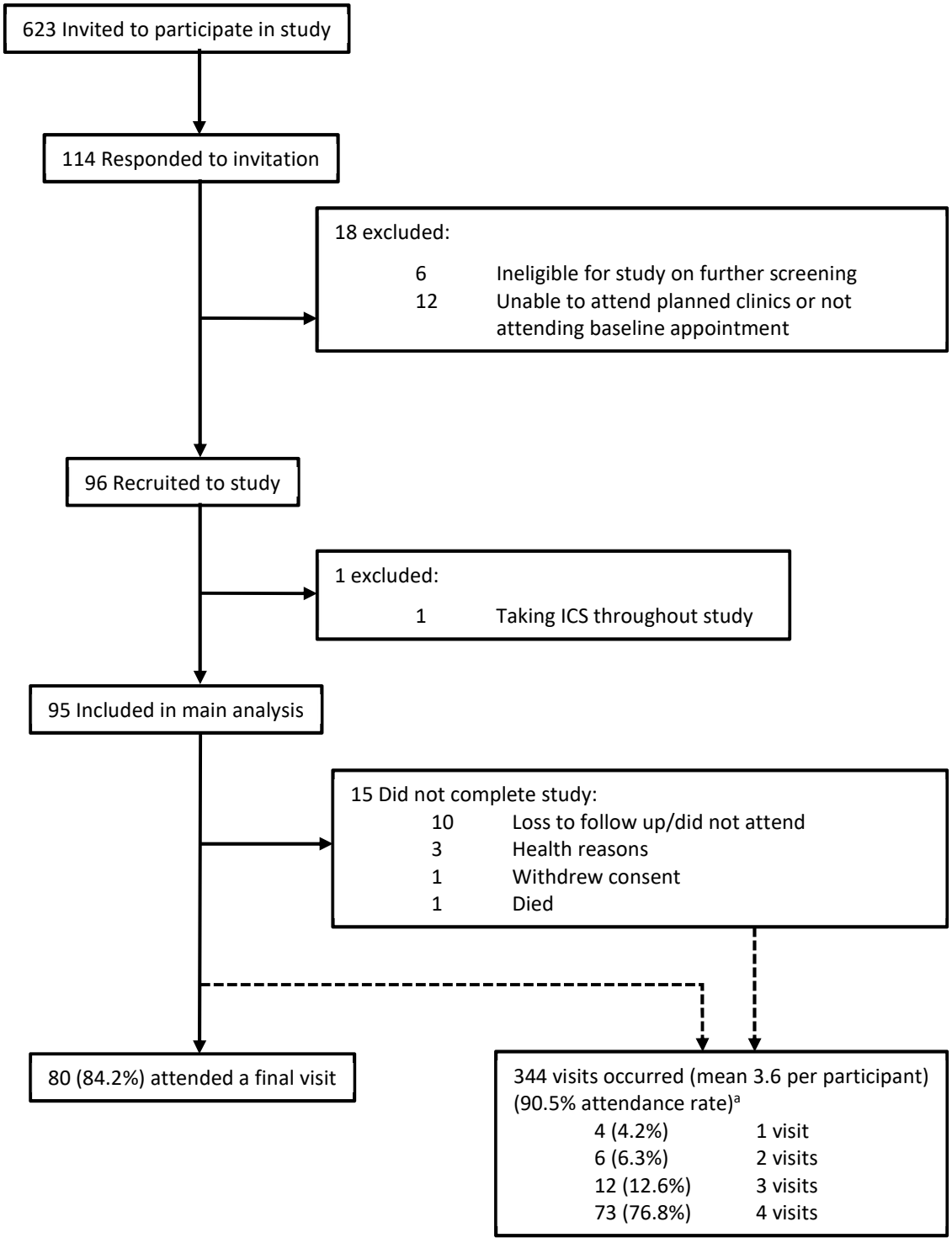
Data management was vastly more straightforward for the COMET study compared to the CPRD study, due to the smaller numbers and that the data had been entered by a small number of people with whom queries could be checked directly. I provided a set of plausible values for results to the data management team and they checked any discrepancies. Specific data management decisions are detailed as footnotes to Table 3.3.

3.5 Overall cohort demographics

Figure 1.6 shows the flow chart of participants to arrive at the final 95 patients included in the study cohort. Although 96 were recruited, one was found in retrospect to have been on an ICS-containing inhaler at the start of the study which was an exclusion criterion. There was a 90.5% attendance rate of planned follow-up with a mean 3.6 visits per participant. Time in the study ranged from 0-39 weeks (median 24, IQR 24-26), with a total

follow-up time of 42.3 years. For those who had more than one visit (n=91), time between visits ranged from 6.5-15.9 weeks (median 8.3, IQR 8-9). Table 3.3 summarises baseline characteristics of the study cohort; results from the CPRD study are shown alongside for comparison, discussed further in Section 3.6.2 below.

Figure 3.1: Study recruitment flow chart



[a] n=7 participants attended a final visit but had not attended all four study visits due to being unable to attend clinic times/did not attend, which could not be rescheduled

Table 3.3: Baseline characteristics of overall study cohort

Variable (n=95)	**n (%) unless stated**	***CPRD results for comparison (n (%) unless stated) (n=30,378)***
Demographic characteristics		
Age (mean, SD, range)	70.6 (9.27) (41-90)	*67.6 (10.8) (40-99)*
Age group in years		
40-49	1 (1.1)	*1,748 (5.8)*
50-59	9 (9.5)	*5,273 (17.4)*
60-69	30 (31.6)	*9,889 (32.6)*
70-79	40 (42.1)	*9,071 (29.7)*
80-89	14 (14.7)	*4,136 (13.6)*
>=90	1 (1.1)	*261 (0.9)*
Female sex	29 (30.5)	*13,288 (43.7)*
Respiratory disease characteristics		
Smoking status[a]		
Non-smoker	0 (0.0)	
Passive	2 (2.1)	
Ex-smoker	58 (61.1)	*16,313 (54.0)*
Current	35 (36.8)	*13,910 (46.0)*
Smoking pack years[b] **(mean, sd, range)**	40.1 (28.6) (1-138)	
Asthma history (>2 years previously)	3 (3.2)	*4,678 (15.4)*
History of atopy[c]	25 (26.3)	*7,945 (26.2)*
Exacerbations in last year		
0	67 (70.5)	*15,126 (49.8)*
1	22 (93.7)	*9,430 (31.0)*
>=2	6 (6.3)	*5,822 (19.2)*
Of which hospitalised	0 (0.0)	
Exacerbations in last two years		
0	59 (62.1)	
1	21 (22.1)	
>=2	15 (15.8)	
Maintenance medications at baseline		
No maintenance treatment	42 (44.2)	
Single long-acting bronchodilator	43 (45.3)	
LAMA	34 (35.8)	
LABA	9 (9.5)	
Dual long-acting bronchodilator[d]	10 (10.5)	
General health characteristics		
Charlson co-morbidity index[e]		
0	67 (70.5)	*18,835 (62.0)*
1	18 (19.0)	*4,524 (14.9)*
≥2	10 (10.5)	*7,019 (23.1)*

Variable (n=95)	**n (%) unless stated**	***CPRD results for comparison (n (%) unless stated) (n=30,378)***
Co-morbidities		
Heart failure	9 (9.5)	
Hypertension	45 (47.4)	
Cancerf	14 (14.7)	
Active	2 (2.1)	
Past	12 (12.6)	
Hay fever	12 (12.6)	
Eczema	11 (11.6)	
Autoimmune conditiong	17 (17.9)	
Any other chronic condition	50 (52.6)	
Previous long-term oral steroid use	0 (0.0)	
Other relevant long-term medicationsh	4 (4.2)	
Body mass index (kg/m^2) (mean, sd, range)	28.1 (5.06) (17.5-42.8)	
Baseline assessment and laboratory results		
Spirometry[i]		
FEV_1 (L) (mean, SD, range)	1.81 (0.63) (0.56-3.41)	
FVC (L) (mean, SD, range)	2.97 (0.99) (0.98-5.61)	
FEV_1/FVC ratio (%) (mean, SD, range)	62.3 (14.6) (33-99)	*2,737 (13.5)*
FEV_1 (% predicted) (mean, SD, range)	68.3 (17.7) (25-110)	*11,219 (55.2)*
Mild (≥80%)	28 (29.8)	*5,468 (26.9)*
Moderate (50-80%)	51 (54.3)	*907 (4.5)*
Severe (30-50%)	14 (14.9)	
Very severe (<30%)	1 (1.1)	
Positive bronchodilator reversibility (n=70)	22 (31.4%)	
MRC breathlessness scale		
1	19 (20.0)	*1,901 (16.2)*
2	55 (57.9)	*5,122 (43.7)*
3	15 (15.8)	*3,143 (26.8)*
4	6 (6.3)	*1,367 (11.7)*
5	0 (0.0)	*182 (1.6)*
Oxygen saturation (%) (mean, sd, range)	95.0 (2.55) (85-99)	
Respiratory symptom questionnaires[j]		
CCQ (mean, sd, range)	1.47 (1.03) (0.10-4.89)	
CAT (mean, sd, range)	13.19 (7.29) (1-32)	
Laboratory blood measurements (geometric mean, range)[k]		
Haemoglobin (g/L)	141.2 (114-170)	
Total white cell count (x10*9/L)	7.19 (3.46-12.59)	*7.44 (3.00-14.90)*
Neutrophil count (x10*9/L)	4.40 (1.44-8.14)	*4.39 (1.00-12.80)*
Lymphocyte count (x10*9/L)	1.77 (0.79-4.35)	
Eosinophil count (x10*9/L)	0.152 (0.01-0.71)	*0.20 (0.01-1.48)*
Low eosinophils (<0.15) (n,%)	41 (44.1)	*5,615 (30.8)*
High eosinophils (≥0.15) (n,%)	52 (55.9)	*12,620 (69.2)*

Variable (n=95)	n (%) unless stated	*CPRD results for comparison (n (%) unless stated) (n=30,378)*
Low eosinophils (<0.34) (n,%)	80 (86.0)	*14,692 (80.6)*
High eosinophils (≥0.34) (n,%)	13 (14.0)	*3,543 (19.4)*
Eosinophil count (% white cell count)	2.12 (0.11-9.67)	*2.70 (0.07-23.91)*
C-reactive protein (mg/L)	2.51 (0.2-55.1)	
Low CRP (≤5mg/L)	71 (75.5)	*2,920 (60.4)*
High CRP (>5mg/L)	23 (24.5)	*1,913 (39.6)*

For baseline characteristics, baseline result was used except where not available in which case result from subsequent visit used (laboratory bloods n=8, respiratory questionnaires n=1). For binary characteristics, only the affirmative is presented.

[a] Type of smoking (missing for n=2) included cigarettes (n=58), roll ups (n=9), cigars (n=1) alone, or the above in combination, also including pipes and spliffs (n=23).

[b] Smoking pack years is calculated as twenty cigarettes smoked each day for one year (missing data for n=5) and ranged from 1 to 138 (median 37.1, IQR 22.5 to 50).

[c] Atopy diagnosed if participants had a diagnosis of eczema, asthma or hay fever recorded.

[d] LAMA-LABA consisted of those with single inhaler LAMA-LABA (n=6) and those on both single agent inhalers (n=4).

[e] Charlson comorbidity index refers to number of comorbidities recorded in addition to COPD.[93]

[f] Excluding basal cell carcinomas. Active cancers were bladder cancer (operated, under follow-up, date not given) and chronic lymphocytic leukaemia (recently diagnosed).

[g] Autoimmune conditions included psoriasis (n=8), hypothyroidism (n=4), coeliac disease (n=2), rheumatoid arthritis (n=2) and ulcerative colitis (n=1).

[h] Other relevant long-term medications included methotrexate (n=2), leflunomide (n=1), hydroxychloroquine (n=2) and beclomethasone nasal spray (n=2)

[i] Valid post-bronchodilator spirometry was available for n=80 (85.1%) (either after administration of SABD or had already taken LABD) (spirometry missing for n=1). Non-valid spirometry (where it was not clear whether the participant had had bronchodilators) was included in analysis as this reflects everyday practice. Reversibility was tested in n=70 participants (they underwent both pre- and post-bronchodilator spirometry), and these figures are given above. However, this was only truly valid for n=36 participants (positive in n=13 (36.1%)) as the others had their pre-bronchodilator spirometry having already taken a SABD or LABD before the study visit. There was no significant association between positive reversibility and atopy (p=0.33) or asthma (p=0.11) although numbers were small for the latter.

[j] CCQ score is the overall clinical COPD control score, calculated by adding all the scores together and dividing the sum by the number of questions. The overall score varies between 0 (excellent control) to 6 (extremely poor control).[114] CAT score calculated as the total of composite score (up to two missing items set to the average of the non-missing item scores. The overall score varies between 0 (excellent COPD-related health status) to 40 (extremely poor COPD-related health status).[113]

[k] Geometric mean used as these are known from existing studies to be non-normally distributed. One patient had a diagnosis of chronic lymphocytic leukaemia and so full blood count results were excluded from analysis. Where CRP given as <0.2, this was counted as 0.2. Full blood count results missing for n=2 and CRP result missing for n=1. Eosinophil values of zero were counted as 0.01 for all analyses requiring transformation.

3.5.1 Missing data

The main missing data issue related to spirometry recording and study eligibility. An inclusion criterion for the study was presence of spirometry diagnostic for COPD recorded in the electronic notes. Although this was recorded as being present for 94 participants, only 43/94 (45.7%) had an FEV_1/FVC ratio recorded, which ranged from 35 to 93%. Only 34 participants had a ratio <70%, meaning that only 34/95 (35.8%) met formal study inclusion criteria. At baseline, using study spirometry, 69/95 (72.6%) had a ratio <70%, which increased to 81/95 (85.3%) for diagnostic spirometry at any point during the study. This meant that 12/95 (12.6%) participants had no spirometry diagnostic for COPD either recorded in the notes or measured during the study. Given that these are people who are managed in primary care as having a diagnosis of COPD, pragmatically I decided to include them in main analysis, but conduct a sensitivity analysis of key analyses excluding these participants.

3.5.2 Changes to baseline demographics during the study

There was one new diagnosis of hypertension, and one new other chronic condition; one started a beclomethasone nasal spray between the baseline and second visit. One participant started a LAMA, one stopped a LAMA and one started an ICS (between the third and fourth visit). I had planned to conduct a sensitivity analysis excluding eosinophil results of those who started an ICS during the study, but given the single participant this would affect I concluded that this was unlikely to significant change results.

3.5.3 Description of outcomes

19/95 (20.0%) participants experienced 20 exacerbations during follow-up. Ten of these exacerbations were within two weeks of a study visit; eosinophil results from these visits were excluded in sensitivity analysis in case they were affected by either the exacerbation itself or prescription of oral steroids.[2,3] One participant died during the study (over one month since her last study visit) of probable COPD-related causes in hospital (death certificate not available).

3.6 Discussion

3.6.1 Summary of findings

This chapter has described the methods of the COMET study, establishing an ICS-naïve cohort of patients with COPD in primary care, for answering specific thesis objectives in subsequent chapters. Baseline characteristics reflect a population of relatively mild patients with COPD: over two thirds had no exacerbations in the year prior to recruitment, most had mild/moderate airflow limitation severity, 44% were not using any maintenance treatment, and MRC breathlessness, CAT and CCQ scores were relatively low (Table 3.3).

3.6.2 Strengths and limitations

Planned sample size was reached, and over 90% of participants attended planned follow-up. Recruitment was from practices serving a diverse range of communities within Oxfordshire. Table 3.2 compares practices included in the COMET study with both Oxfordshire and England practices as a whole. In general, Oxfordshire is less deprived and with a lower smoking and COPD prevalence, although practices included in the COMET

study were slightly more towards the national average in terms of deprivation and smoking prevalence.

Comparison of baseline demographics of participants between the COMET study and CPRD study (Table 3.3) enables some judgements to be made about generalisability; for example COMET participants were more likely to be older, male, with fewer co-morbidities, and with no history of asthma, as well as milder markers of disease severity as discussed above.

However, the cohorts were not identical in terms of inclusion criteria, most importantly in that patients included in my CPRD study were recruited at the point of starting a new inhaled maintenance medication (including an ICS) i.e. probably at the point of deterioration of disease state; in contrast those in the COMET study were similarly ICS-naïve but with no plans for initiation or up-titration of maintenance medication (and with 44.2% receiving no maintenance treatment at recruitment). As we would expect, therefore, compared to CPRD those in the COMET study had fewer exacerbations (70.5% vs. 49.8% with no exacerbations in baseline year), better lung function (84.1% vs. 68.7% with mild or moderate airflow limitation)[a] and lower MRC breathlessness scale (77.9% vs. 59.9% with MRC 1 or 2).

As with all studies recruiting real participants, those choosing to participate in research studies will not represent the population eligible; our response rate to the postal invitation of 18.3% is broadly similar to those in other postal invitation studies.[129] Response rate

[a] Although as discussed in Section 2.2.9 there was significant missing data for airflow limitation severity in CPRD.

varied widely between practices (0.0 to 38.2%) which may relate to different levels of patient engagement in research.

There was also a wide range (6.1 to 31.5%) in number of patients eligible for the study from the overall COPD population for each practice which may reflect differences in spirometry coding (where this was assessed for inclusion) or ICS prescribing patterns (i.e. varying tendency to prescribe ICS)[a]; given that COPD monitoring and maintenance treatment decisions are often managed by a single nurse within each practice, it is probable that individual practice has a larger impact on study eligibility than it would in a disease managed by multiple clinicians.

A surprisingly high proportion (22%) of patients demonstrated positive bronchodilator reversibility, given that fixed airflow obstruction is one of the defining pathophysiological features of COPD.[10] Although some patients with COPD will have a degree of variable airflow obstruction,[10] this raises the question that these patients may actually have asthma rather than true COPD and may have been misdiagnosed (only 3.2% participants had a recorded past history of asthma). This is an important finding in terms of the primary care population who are being managed in everyday practice as if they have 'standard' COPD and may in fact have a more heterogenous disease state comprising COPD and asthma; this may also have implications in terms of eosinophil values (we would expect those with asthma to have higher eosinophils[75]), which is why I plan to exclude these patients in a sensitivity analysis of key analyses.

[a] Given that few practices completed the screening log, it is hard to establish the exact reasons for this.

Due to missing data for spirometry on the participant records, or non-diagnostic spirometry recorded, only a third of patients met formal spirometry criteria for study entry. Missing and variable diagnostic spirometry findings are common in primary care COPD: a recent primary care database study[130] investigating consistency of airflow obstruction in COPD over time found that FEV_1/FVC ratio was only recorded in 86.9% patients coded as having COPD,[a] and of those where it was recorded, 11.5% had no evidence of airflow obstruction on any measurement, and it varied above or below the 70% threshold on repeated measurements in 36.1%, which fits with the COMET study findings. Given that patients with non-diagnostic spirometry are clearly managed in primary care as if they have COPD, the pragmatic solution for a study to be generalisable to practice was to keep these participants in the study but to plan sensitivity analysis excluding them.

3.6.3 Comparison with other literature

The baseline characteristics of the COMET cohort are not dissimilar to those found in other published prospective cohort studies across a range of settings and countries.[47,131-137] However, COMET participants are in general at a milder or earlier disease state, as we would expect because of the inclusion criteria that participants were ICS-naïve (in contrast to other studies where the majority were using ICS[132,133,135]), and, unlike in the CPRD study, they were not at the point of needing to initiate/step up maintenance treatment. For example, mean FEV_1 percentage predicted in the COMET cohort was 68%, and in other studies ranged from 55 to 68%. This may also be explained by the fact that in other observational studies where eosinophils were not measured routinely as part of the

[a] This is considerably higher than the 45.7% who had FEV_1/FVC ratio recorded in the COMET study CRF. This may relate to study nurses struggling to find where this was recorded in the notes, as well as to a lack of original recording.

protocol, they tended to be measured more in those on ICS therapy and with frequent exacerbations, so elsewhere results for eosinophils are not necessarily reflective of the whole study population.[135]

3.6.4 Conclusions

This is a novel prospective cohort population of ICS-naïve patients with COPD in primary care. Baseline characteristics reflect a relatively mild population which could limit generalisability of later findings. Although duration of follow-up is relatively short and does not allow assessment of outcomes, this cohort should provide good ability to assess repeatability of eosinophils and assessment of the point-of-care device (where generalisability is less important in any case).

In conclusion, COMET participants are likely to be broadly representative of the primary care COPD population as a whole, within the confines of this being a relatively stable, ICS-naïve and therefore mild population.

Chapter 4: Eosinophils in a primary care COPD population: variation and repeatability

This chapter presents the results and discussion of the descriptive component of both the CPRD study (Aim Ia) and the COMET study (Aim I), integrated to enable comparison. Main methods for developing the cohorts were presented in Chapters 2 and 3 respectively, with detailed statistical methods presented at the start of each section.

To summarise, the aims for this part of the study were as follows (section number in parentheses refers to where results for this objective are presented):

CPRD Part Ia: To describe existing practice of blood eosinophil testing in ICS-naïve primary care patients with COPD in the period before starting a new inhaled maintenance treatment

Including specific objectives:

- To assess the number of routinely-collected blood eosinophil tests and to compare baseline characteristics of those who have an eosinophil count in their clinical record with those who have not, to assess validity of CPRD study findings (Section 4.1)
- To assess blood eosinophil distribution in the primary care COPD population (Section 4.2.2)
- To assess the association between higher blood eosinophil counts and clinical characteristics (Section 4.3.1)
- To assess within-person variation and stability over time of blood eosinophil counts, to decide whether the most recent value can be used in decision-making (Section 4.4.3)

COMET Part I: To describe biomarker levels including repeatability and variability in a prospective study

Including specific objectives:

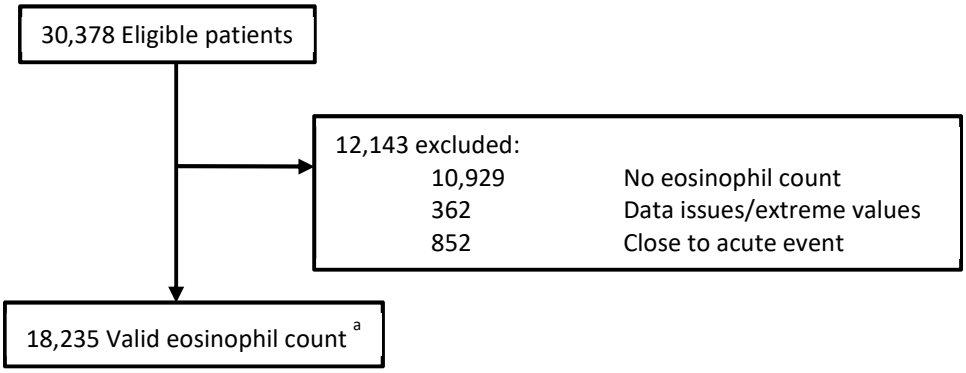
- To assess blood eosinophil distribution in the primary care COPD population (Section 4.2.3)
- To assess the association between higher blood eosinophils and clinical characteristics (Section 4.3.3)
- To assess within-person variation and stability over time of blood eosinophil counts, to decide whether the most recent value can be used in decision-making (Section 4.4.3)

4.1 Routine testing of eosinophils (CPRD only)

4.1.1 Frequency of eosinophil count testing

As we would expect for an observational study using routinely-collected data, not all patients (only 60.0%) had a valid eosinophil count available in their routine care records (Figure 4.1).

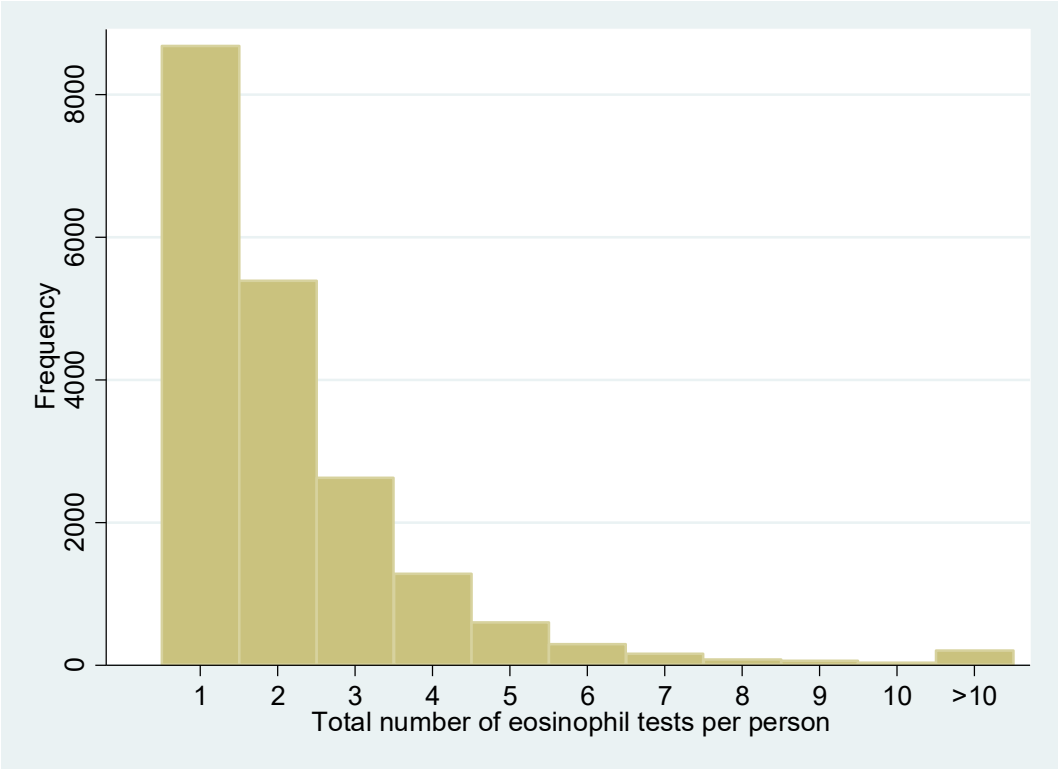
Figure 4.1: Flow chart of included patients



Earlier flow chart showing how those eligible were selected is shown in Figure 2.2.
[a] Valid eosinophil counts were those within the 2 years prior to the index date, with extreme values (zero or ≥1.5 x10*9/L) and those within 2 weeks of an acute event (exacerbation or pneumonia episode or C-reactive protein >100mg/L) excluded. See Section 2.2.5 for full details.

Eosinophil testing (including non-valid values) occurred in 19,449/30,378 (64.0%) patients, with a median frequency of 2 tests per person[a] in the two years prior to index date (IQR 1 to 3; range 1 to 42), although most patients had only had 1 test (Figure 4.2). 2 or more values were available for 51.9% patients (9,473/18,235).

Figure 4.2: Frequency of eosinophil count testing (CPRD)



This includes non-valid values for eosinophils to reflect overall testing frequency. Only those who had at least one test were included.

The most recent value (which was what was used for primary analysis) was median 164 days before the index date (IQR 55 to 339) (all values; median 185 days (IQR 66 to 365) for valid values only). Repeatability and variability of eosinophils for those with more than one value is discussed in Section 4.4 below.

[a] In those who had at least one test.

4.1.2 Baseline characteristics associated with eosinophil testing

Table 4.1 shows distribution of patients by baseline characteristics according to whether they had a valid eosinophil count or not, to assess validity of CPRD study findings. Patients with a valid eosinophil count were more likely to be older, female, ex-smokers, with less frequent exacerbations, and with more GP consultations and co-morbidities, and receiving the influenza vaccination. Eosinophil testing also increased with increasing year of index prescription ($p<0.001$), suggesting an increased rate of testing with time.

There was no significant difference in the primary outcome of time-to-first exacerbation comparing those with valid eosinophil count to those without in Cox regression (adjusted hazard ratio (n=28,614) 1.02 (95% CI 0.99 to 1.05, p=0.17).

Table 4.1: Distribution of patients by whether they had valid eosinophil count, by baseline characteristics

Baseline characteristic	Overall n=30,378 n (%)	No valid eosinophil count n=12,143 n (%)	Valid eosinophil count n=18,235 n (%)	Unadjusted odds ratio for valid eosinophil count vs. no valid eosinophil count (95% CI, p-value)	Adjusted odds ratio for valid eosinophil count vs. no valid eosinophil count [a] (95% CI, p-Value)
Demographic characteristics					
Age, mean (SD), years	67.6 (10.8)	65.3 (10.9)	69.1 (10.5)	1.03 (1.03-1.04), p<0.001	N/a
Age group in years					
40-49	1,748 (5.8)	1,027 (8.5)	721 (4.0)	0.36 (0.32-0.40), p<0.001	0.56(0.50-0.64), p<0.001
50-59	5,273 (17.4)	2,595 (21.4)	2,678 (14.7)	0.53 (0.49-0.57), p<0.001	0.75(0.70-0.82), p<0.001
60-69	9,889 (32.6)	4,192 (34.5)	5,697 (31.2)	0.70 (0.66-0.74), p<0.001	0.85(0.79-0.90), p<0.001
70-79	9,071 (29.7)	3,075 (25.3)	5,996 (32.9)	1.00 (ref)	1.00 (ref)
80-89	4,136 (13.6)	1,183 (9.7)	2,953 (16.2)	1.28 (1.18-1.39), p<0.001	1.15(1.05-1.25), p=0.002
>=90	261 (0.9)	71 (0.6)	190 (1.0)	1.37 (1.04-1.81), p=0.03	1.15(0.86-1.54), p=0.35
Female sex	13,288 (43.7)	5,192 (42.8)	8,096 (44.4)	1.07 (1.02-1.12), p=0.005	1.15(1.09-1.21), p<0.001
Socio-economic status [b]					
1 (least deprived)	4,394 (14.5)	1,702 (14.0)	2,692 (14.8)	1.00 (ref)	1.00 (ref)
2	6,167 (20.3)	2,422 (20.0)	3,745 (20.6)	0.98 (0.90-1.06), p=0.67	1.00(0.92-1.09), p=0.95
3	6,010 (19.8)	2,430 (20.0)	3,580 (19.7)	0.93 (0.86-1.01), p=0.11	1.01(0.93-1.10), p=0.75
4	7,433 (24.5)	2,986 (24.6)	4,447 (24.4)	0.94 (0.87-1.02), p=0.20	1.07(0.99-1.16), p=0.10
5 (most deprived)	6,358 (20.9)	2,600 (21.4)	3,758 (20.6)	0.91 (0.84-0.99), p=0.03	1.09(1.00-1.19), p=0.06
Respiratory disease characteristics					
Smoking status [b]					
Ex-smoker	16,313 (54.0)	5,778 (47.9)	10,535 (58.0)	1.00 (ref)	1.00 (ref)
Current smoker	13,910 (46.0)	6,277 (52.1)	7,633 (42.0)	0.67 (0.64-0.70), p<0.001	0.90(0.86-0.95), p<0.001
Asthma history					
No asthma history	24,453 (80.5)	9,454 (77.9)	14,999 (82.3)	1.00 (ref)	1.00 (ref)
Past asthma	4,678 (15.4)	2,112 (17.4)	2,566 (14.1)	0.77 (0.72-0.82), p<0.001	0.88(0.82-0.95), p<0.001
Current asthma	1,247 (4.1)	577 (4.8)	670 (3.7)	0.73 (0.65-0.82), p<0.001	0.89(0.79-1.01), p=0.08
History of atopy	7,945 (26.2)	2,970 (24.5)	4,975 (27.3)	1.16 (1.10-1.22), p<0.001	1.06(1.00-1.13), p=0.04

Baseline characteristic	Overall n=30,378 n (%)	No valid eosinophil count n=12,143 n (%)	Valid eosinophil count n=18,235 n (%)	Unadjusted odds ratio for valid eosinophil count vs. no valid eosinophil count (95% CI, p-value)	Adjusted odds ratio for valid eosinophil count vs. no valid eosinophil count [a] (95% CI, p-Value)
Airflow limitation severity [b]					N/a
Mild (≥80%)	2,737 (13.5)	923 (12.3)	1,81 (14.1)	1.00 (ref)	
Moderate (50-80%)	11,219 (55.2)	3,956 (52.8)	7,263 (56.6)	0.93 (0.86-1.02), p=0.13	
Severe (30-50%)	5,468 (26.9)	2,201 (29.4)	3,267 (25.5)	0.76 (0.69-0.83), p<0.001	
Very severe (<30%)	907 (4.5)	415 (5.5)	492 (3.8)	0.60 (0.52-0.70), p<0.001	
MRC breathlessness scale [b]					N/a
1 (least severe)	1,901 (16.2)	753 (18.6)	1,148 (15.0)	1.00 (ref)	
2	5,122 (43.7)	1,856 (45.8)	3,266 (42.6)	1.15 (1.04-1.29), p=0.009	
3	3,143 (26.8)	997 (24.6)	2,146 (28.0)	1.41 (1.25-1.59), p<0.001	
4	1,367 (11.7)	402 (9.9)	965 (12.6)	1.57 (1.36-1.83), p<0.001	
5 (most severe)	182 (1.6)	41 (1.0)	141 (1.8)	2.26 (1.57-3.23), p<0.001	
Exacerbations					
0	15,126 (49.8)	5,697 (46.9)	9,429 (51.7)	1.00 (ref)	
1	9,430 (31.0)	3,998 (32.9)	5,432 (29.8)	0.82 (0.78-0.87), p<0.001	0.72(0.67-0.76), p<0.001
2	3,886 (12.8)	1,653 (13.6)	2,233 (12.3)	0.82 (0.76-0.88), p<0.001	0.61(0.56-0.67), p<0.001
3 or more	1,936 (6.4)	795 (6.6)	1,141 (6.3)	0.87 (0.79-0.95), p=0.004	0.52(0.46-0.59), p<0.001
Pneumonia episodes					
0	24,019 (79.1)	9,553 (78.7)	14,466 (79.3)	1.00 (ref)	1.00 (ref)
1	4,925 (16.2)	2,034 (16.8)	2,891 (15.9)	0.94 (0.88-1.00), p=0.05	1.02(0.94-1.10), p=0.62
2 or more	1,434 (4.7)	556 (4.6)	878 (4.8)	1.04 (0.93-1.16), p=0.45	1.10(0.96-1.27), p=0.16
Oral steroid prescriptions					
0	23,826 (78.4)	9,414 (77.5)	14,412 (79.0)	1.00 (ref)	1.00 (ref)
1	4,912 (16.2)	2,044 (16.8)	2,868 (15.7)	0.92 (0.86-0.98), p=0.006	0.97(0.91-1.04), p=0.44
2	1,640 (5.4)	685 (5.6)	955 (5.2)	0.91 (0.82-1.01), p=0.07	0.91(0.81-1.02), p=0.11

Baseline characteristic	Overall n=30,378 n (%)	No valid eosinophil count n=12,143 n (%)	Valid eosinophil count n=18,235 n (%)	Unadjusted odds ratio for valid eosinophil count vs. no valid eosinophil count (95% CI, p-value)	Adjusted odds ratio for valid eosinophil count vs. no valid eosinophil count [a] (95% CI, p-Value)
Salbutamol inhalers					
0	10,202 (33.6)	4,160 (34.3)	6,042 (33.1)	1.00 (ref)	1.00 (ref)
1	6,503 (21.4)	2,544 (21.0)	3,959 (21.7)	1.07 (1.01-1.14), p=0.03	1.04(0.97-1.12), p=0.22
2	3,172 (10.4)	1,246 (10.3)	1,926 (10.6)	1.06 (0.98-1.15), p=0.13	1.00(0.92-1.09), p>0.99
3-5	4,282 (14.1)	1,606 (13.2)	2,676 (14.7)	1.15 (1.07-1.23), p<0.001	1.03(0.95-1.11), p=0.52
6 or more	6,219 (20.5)	2,587 (21.3)	3,632 (19.9)	0.97 (0.91-1.03), p=0.30	0.87(0.81-0.93), p<0.001
Theophylline use	344 (1.1)	135 (1.1)	209 (1.2)	1.03 (0.83-1.28), p=0.78	1.06(0.83-1.34), p=0.65
Oxygen use	130 (0.4)	47 (0.4)	83 (0.5)	1.18 (0.82-1.68), p=0.37	0.95(0.65-1.40), p=0.80
Nebuliser use	553 (1.8)	212 (1.8)	341 (1.9)	1.07 (0.90-1.28), p=0.43	1.03(0.85-1.24), p=0.78
General health characteristics					
Non-elective hospitalisations					
0	25,667 (84.5)	10,539 (86.8)	15,128 (83.0)	1.00 (ref)	1.00 (ref)
1	3,590 (11.8)	1,269 (10.5)	2,321 (12.7)	1.27 (1.18-1.37), p<0.001	1.04(0.96-1.13), p=0.30
2 or more	1,121 (3.7)	335 (2.8)	786 (4.3)	1.63 (1.43-1.86), p<0.001	1.16(1.01-1.34), p=0.04
GP consultations					
0-3	11,138 (36.7)	6,083 (50.1)	5,055 (27.7)	1.00 (ref)	1.00 (ref)
4-7	10,216 (33.6)	3,805 (31.3)	6,411 (35.2)	2.03 (1.92-2.14), p<0.001	2.01(1.90-2.13), p<0.001
8 or more	9.024 (29.7)	2,255 (18.6)	6,769 (37.1)	3.61 (3.40-3.84), p<0.001	3.47(3.24-3.70), p<0.001
Charlson comorbidity index					
0	18,835 (62.0)	9,024 (74.3)	9,811 (53.8)	1.00 (ref)	1.00 (ref)
1	4,524 (14.9)	1,376 (11.3)	3,148 (17.3)	2.10 (1.96-2.26), p<0.001	1.69(1.57-1.82), p<0.001
2 or more	7,019 (23.1)	1,743 (14.4)	5,276 (29.0)	2.78 (2.61-2.96), p<0.001	1.90(1.78-2.04), p<0.001
Influenza vaccination	19,057 (62.7)	6,555 (54.0)	12,502 (68.6)	1.86 (1.77-1.95), p<0.001	1.29(1.22-1.37), p<0.001
Pneumococcal vaccination	10,119 (33.3)	3,746 (30.9)	6,373 (35.0)	1.20 (1.15-1.26), p<0.001	1.03(0.97-1.09), p=0.29

Percentages are column percentages. See Table 2.6 for details and time periods for variables. (ref), reference group

[a] Odds ratio calculated using logistic regression. Adjusted odds ratios include baseline variables significant p<0.10 in univariate analysis or those thought to be clinically relevant. n=30,207 due to complete case analysis. Airflow limitation severity and MRC breathlessness scale not included in adjusted model due to large amounts of missing data (inclusion did not change results). Year of index prescription not displayed due to multiple categories but included in adjusted model. Categorical variable used for age.

[b] n=30,362 for socio-economic status, n=30,223 for smoking status, n=20,331 for airflow limitation severity and n=11,715 for MRC breathlessness scale, due to missing data.

4.2 Eosinophil count distribution in the primary care population

4.2.1 Additional methods detail and sensitivity/subgroup analysis

Eosinophil distribution was assessed both as a continuous measure and using different binary/categorical cut-offs (primary threshold 0.15 x10*9/L). For CPRD the most recent valid eosinophil count in the two years before initiation of new inhaled maintenance medication (index date) was used for distribution analysis, whereas for COMET the mean laboratory venous blood eosinophil count available for study participants was used. Using the CPRD I examined the distribution more closely to decide how to manage the data statistically, particularly in relation whether I would need to transform it for analysis (further details below).

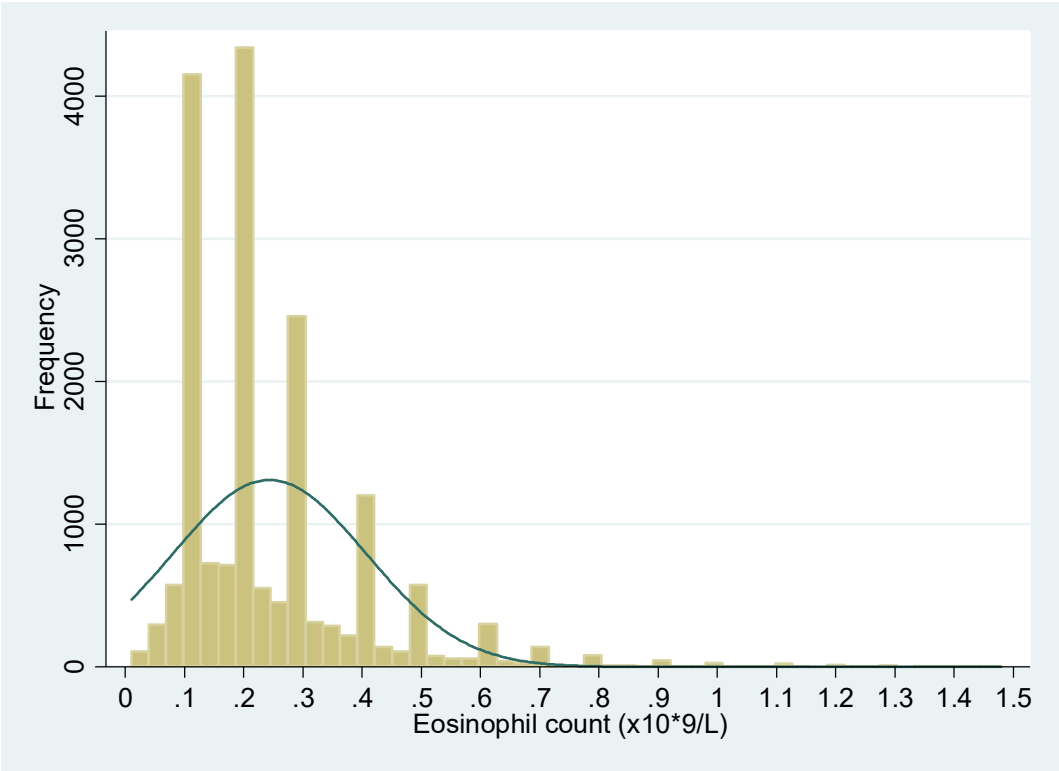
Planned sensitivity analysis excluded those with active asthma (CPRD) or bronchodilator reversibility (COMET), and alternative cut-offs for stratifying participants into groups by eosinophil count (0.10, 0.20, 0.30, 0.34 (post-hoc, as this had been used in other recently published studies[74,95]), 0.40 and 0.50 x10*9/L; percentage eosinophils (<2%, ≥2-<4% and ≥4%)); low (<0.15), medium (0.15-<0.34) and high (≥0.34) groups.

4.2.2 Routinely collected using the CPRD

<u>Continuous</u>

Figure 4.3 shows the distribution of eosinophil count, with histogram spikes likely due to some analysers rounding to the nearest 0.1 decimal place.

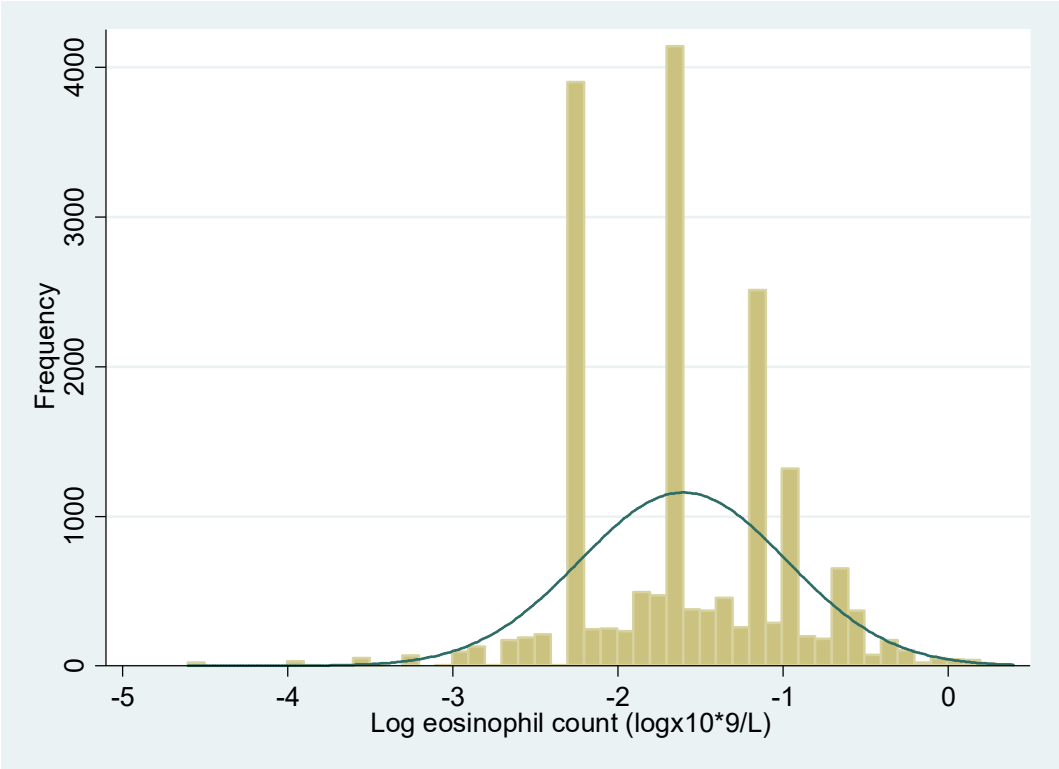
Figure 4.3: Distribution of most recent eosinophil count (CPRD)



Line shows overlaid normal density curve. Histogram spikes are likely due to some analysers rounding to the nearest 0.1 decimal place.

As can be seen in Figure 4.3, the data is right-skewed. I used the Stata *ladder* command to establish whether any transformations would normalise the distribution and only natural log was returned as viable, which improved the tests for normality and the histogram (Figure 4.4). I therefore transformed the data and proceeded to use logarithmically transformed eosinophils for all continuous analyses. The geometric mean was 0.20 x10*9/L (95% CI 0.20 to 0.20 x10*9/L) and the median was 0.20 (IQR 0.10-0.30) x10*9/L, with a range as expected from data management steps to exclude extreme values (see Section 2.2.5) of 0.01 to 1.48 x10*9/L.

Figure 4.4: Distribution of logarithmically transformed most recent eosinophil count (CPRD)



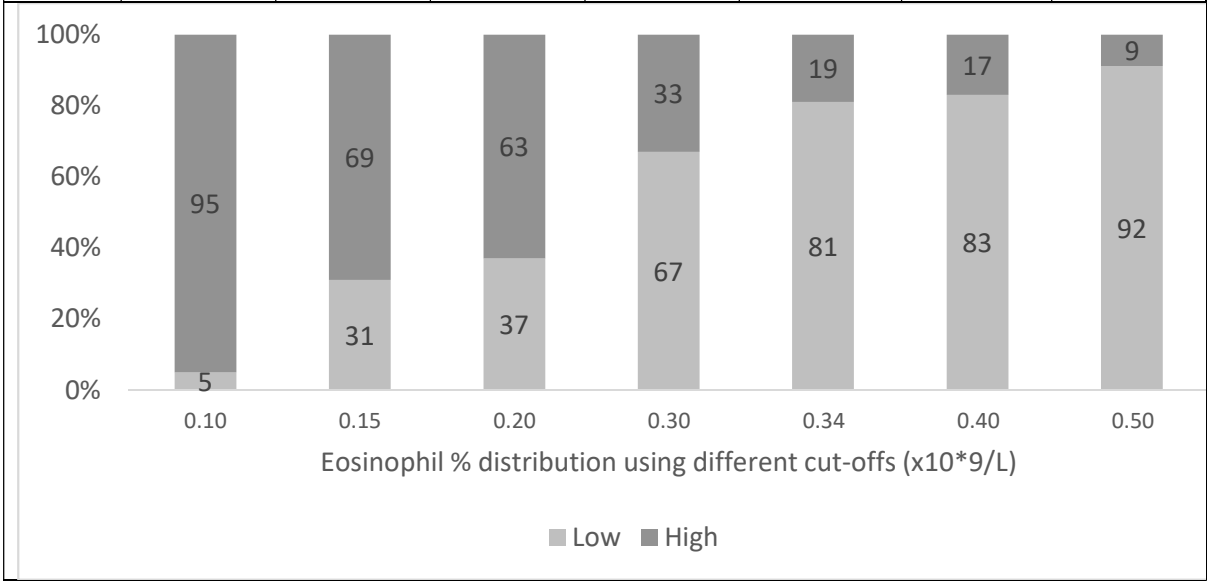
Line shows overlaid normal density curve. Histogram spikes are likely due to some analysers rounding to the nearest decimal place in x10*9/L units.

Binary

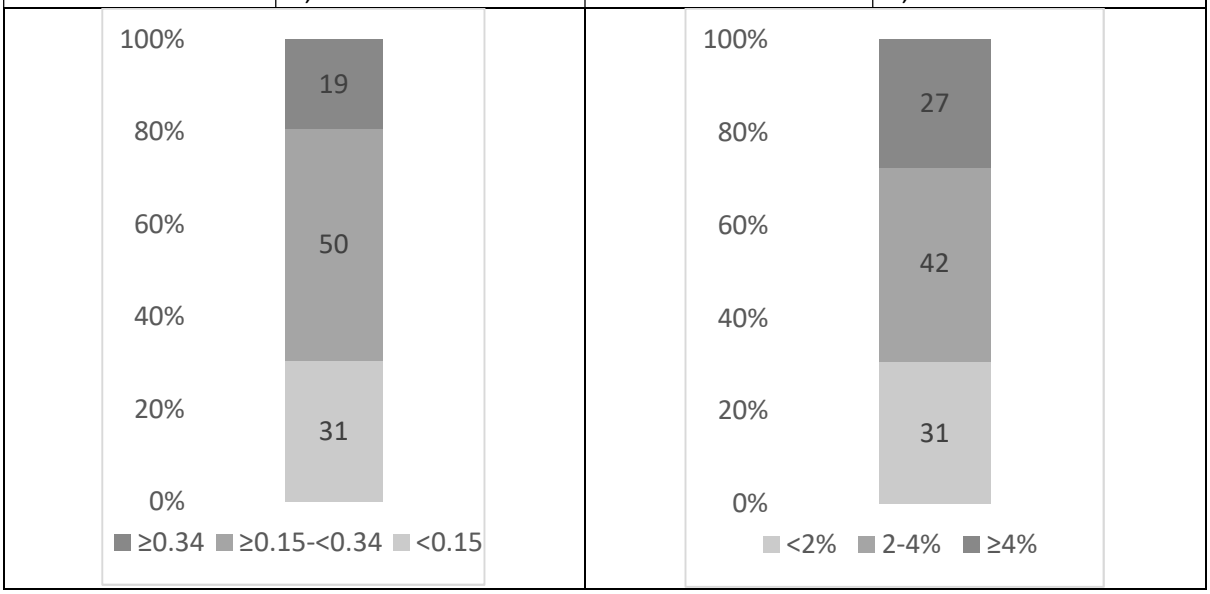
Figure 4.5 shows distribution of patients between groups depending on where eosinophil threshold was placed. For the primary threshold of 0.15 x10*9/L, 69.2% patients were classified as being in the high eosinophil group; when this threshold was increased to 0.34 x10*9/L, only 19.3% patients were in the high eosinophil group. Repeating this excluding those with active asthma (n=670) made little difference to percentage groupings (data not shown). Division into low, medium and high categories (Figure 4.5B) found that 50% patients are in the 'medium' category (0.15 to <0.34 x10*9/L).

Figure 4.5: Distribution of patients between eosinophil groups using different thresholds (CPRD) A) Single threshold B) Low, medium and high categorisation C) Using % eosinophils

	A) Eosinophil threshold (x10*9/L)						
	0.10	**0.15**	**0.20**	**0.30**	**0.34**	**0.40**	**0.50**
Low	984	5,615	6,807	12,178	14,692	15,201	16,676
High	17,251	12,620	11,428	6,057	3,543	3,034	1,559



B) Eosinophil threshold (x10*9/L)		C) Eosinophil threshold (%) [a]	
<0.15	5,615	<2%	5,604
0.15-0.34	9,077	2-4%	7,654
≥0.34	3,543	≥4%	4,952



[a] Eosinophil percentages are as percentage of total leucocytes; leucocytes missing for n=25.
Percentage totalling 101% for 0.50 x10*9/L threshold is due to rounding.

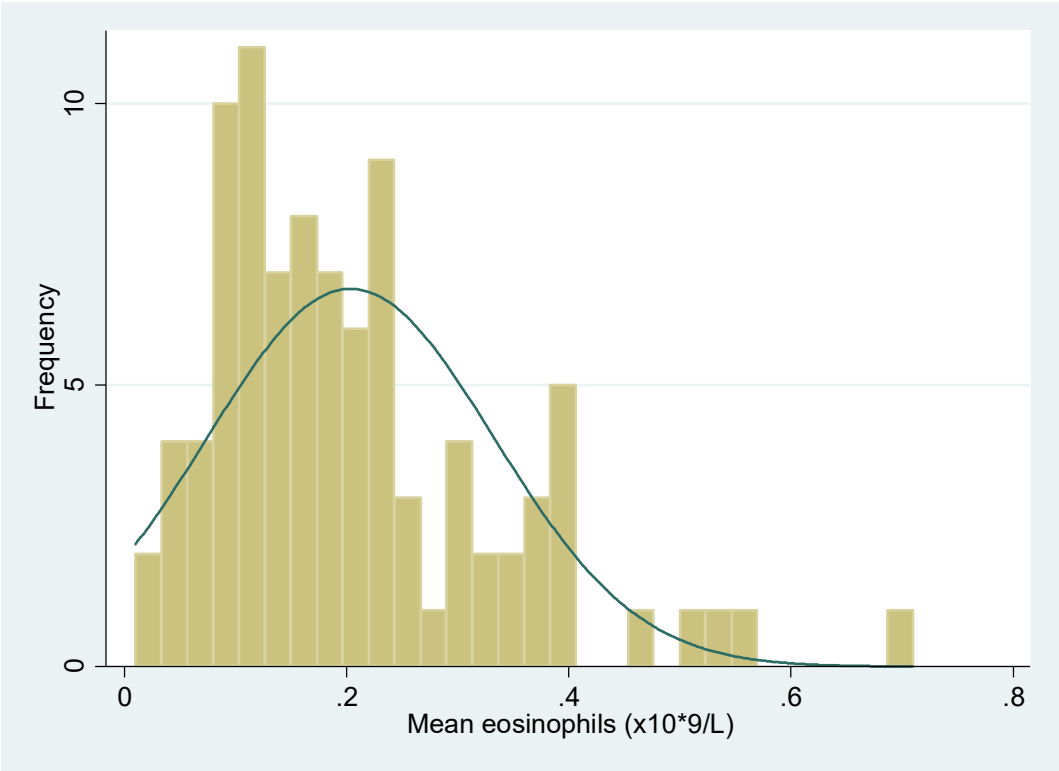
4.2.3 Prospectively collected in the COMET study

322 eosinophil results were available for 93 patients. Missing results (n=22, as 344 study visits took place) were due to participant refusal (needle phobia) (2 visits/1 participant), difficulty obtaining the specimen (12 visits/8 participants – including one participant who could not be bled on any of four visits), unable to locate the blood results on EMIS (4 visits/4 participants), and a participant with chronic lymphocytic leukaemia whose blood results were omitted from analysis (4 visits/1 participant). Four participants (4.3%) only had one eosinophil count available; all remaining participants had multiple eosinophil counts (including all four counts available for 60/93 (64.5%)).

Continuous

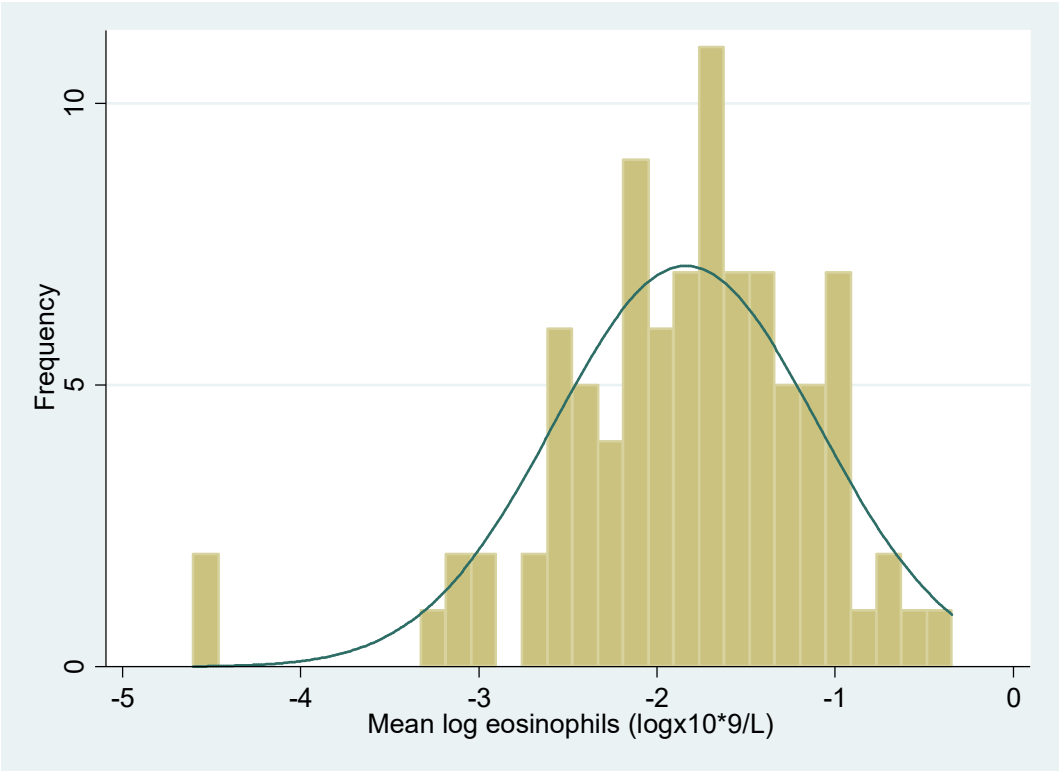
Figure 4.6 shows the distribution of the mean eosinophil count, which, as right-skewed, was also log-transformed for continuous analyses (Figure 4.7). The geometric mean was 0.16 x10*9/L (95% CI 0.14 to 0.19 x10*9/L) and the median was 0.18 (IQR 0.11-0.26) x10*9/L, with a range of 0.01 to 0.71 x10*9/L.

Figure 4.6: Distribution of mean eosinophil count (COMET)



Line shows overlaid normal density curve.

Figure 4.7: Distribution of logarithmically transformed mean eosinophil count (COMET)



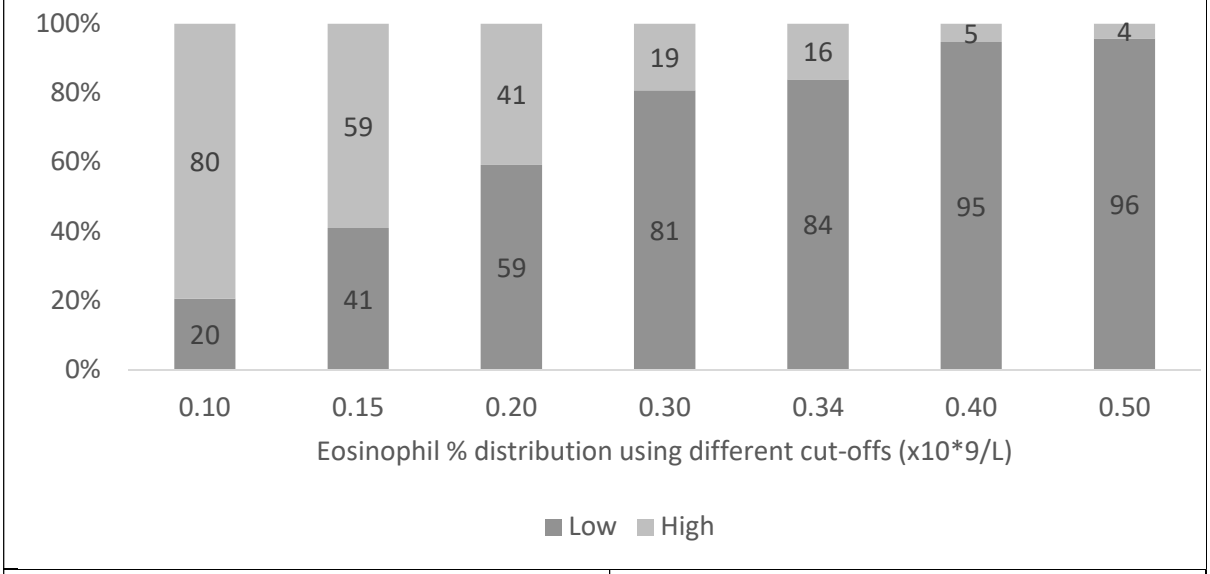
Line shows overlaid normal density curve.

Binary

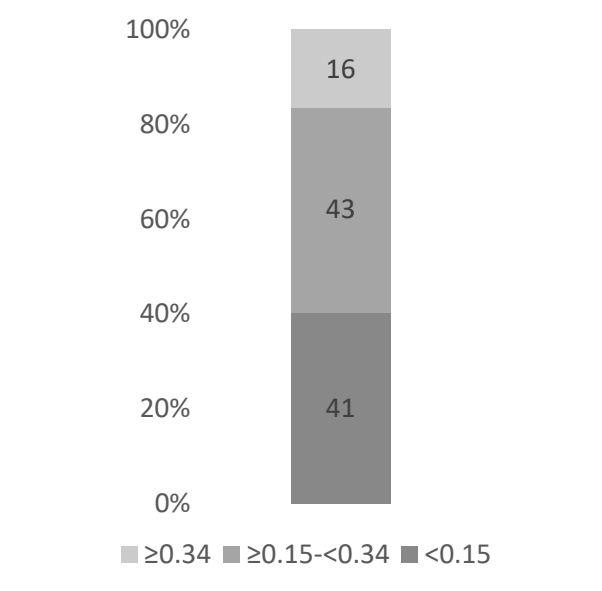
Figure 4.8 shows distribution of patients between groups depending on where eosinophil threshold was placed. For the primary threshold of 0.15 x10*9/L, 59.1% patients were classified as being in the high eosinophil group; when this threshold was increased to 0.34 x10*9/L, only 16.1% patients were in the high eosinophil group. Repeating this excluding those with positive bronchodilator reversibility at baseline (n=22) made little difference to percentage groupings (data not shown). Division into low, medium and high categories (Figure 4.8B) found that 43% patients are in the 'medium' category (0.15 to <0.34 x10*9/L).

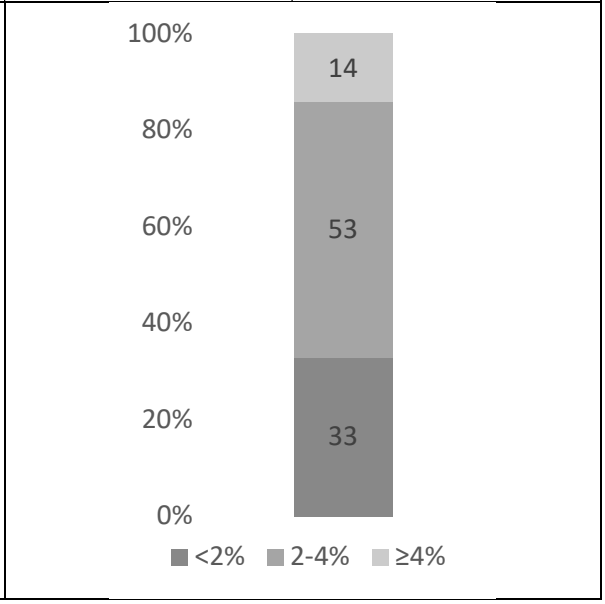
Figure 4.8: Distribution of participants between eosinophil groups using different thresholds (COMET) A) Single threshold B) Low, medium and high categorisation C) Using % eosinophils

	A) Eosinophil threshold (x10*9/L)						
	0.10	**0.15**	**0.20**	**0.30**	**0.34**	**0.40**	**0.50**
Low	19	38	55	75	78	88	89
High	74	55	38	18	15	5	4



B) Eosinophil threshold (x10*9/L)		C) Eosinophil threshold (%) [a]	
<0.15	38	<2%	31
0.15-0.34	40	2-4%	49
≥0.34	15	≥4%	13





[a] Eosinophil percentages are as percentage of total leucocytes.

4.3 Association of eosinophils with baseline characteristics

4.3.1 Additional methods detail and sensitivity/subgroup analysis

Using the primary threshold of 0.15 x10*9/L to define low and high eosinophil groups, I compared those who were in each group by baseline characteristics using logistic regression (or linear regression when assessing eosinophils as a continuous variable, appropriately transformed as applicable). Characteristics were included in regression models as covariates if significant ($p<0.10$) in univariate analysis, or thought to be of potential clinical importance.

For CPRD, sensitivity analyses excluded those with active asthma and those with a history of atopy. For COMET, sensitivity analyses excluded those with a history of atopy, those with positive bronchodilator reversibility, those without spirometry diagnostic for COPD, and excluding eosinophil values close to exacerbation events.[a]

4.3.2 Routinely collected using the CPRD

Table 4.2 shows the distribution of patients between low and high eosinophil groups. Patients were more likely to be in the higher eosinophil group if they were younger, male, ex-smokers, with a history of atopy, more exacerbations, increased prescriptions for oral steroids and salbutamol inhalers, high GP consultation rates, and more co-morbidities. There was no association with active or historical asthma. Sensitivity analyses excluding those with a history or atopy (n=4,975) and excluding those with active asthma (n=670) made little difference to results (data not shown). I also addressed the same question looking at eosinophils as a

[a] Planned sensitivity analyses were to be excluding those with history of asthma and excluding those eosinophil counts taken after initiating ICS during the study but numbers were very small (n=3 and n=1 respectively) so this was not done.

continuous variable (logarithmically transformed) using linear regression and found the same variables to be significantly associated with eosinophil count (data not shown).

Table 4.2: Distribution of patients by eosinophil group, by baseline characteristics (CPRD)

Baseline characteristic	Overall n=18,235 n (%)	Low eosinophils (<0.15 x10*9/L) n=5,615 n (%)	High eosinophils (≥0.15 x10*9/L) n=12,620 n (%)	Unadjusted odds ratio for high eosinophil vs. low eosinophil group (95% CI, p-value)	Adjusted odds ratio for high eosinophil vs. low eosinophil group [a] (95% CI, p-Value)
Demographic characteristics					
Age, mean (SD), years	69.1 (10.5)	69.5 (10.5)	68.9 (10.5)	0.99 (0.99-1.00), p<0.001	N/a
Age group in years					
40-49	721 (4.0)	190 (3.4)	531 (4.2)	1.24 (1.04-1.48), p=0.02	1.43 (1.19-1.71), p<0.001
50-59	2,678 (14.7)	826 (14.7)	1,852 (14.7)	1.00 (0.90-1.10), p=0.92	1.09 (0.99-1.21), p=0.09
60-69	5,697 (31.2)	1,706 (30.3)	3,991 (31.6)	1.04 (0.96-1.12), p=0.35	1.07 (0.99-1.16), p=0.11
70-79	5,996 (32.9)	1,843 (32.8)	4,153 (32.9)	1.00 (ref)	1.00 (ref)
80-89	2,953 (16.2)	990 (17.6)	1,963 (15.6)	0.88 (0.80-0.97), p=0.008	0.85 (0.77-0.93), p=0.001
>=90	190 (1.0)	60 (1.1)	130 (1.0)	0.96 (0.70-1.31), p=0.81	0.92 (0.67-1.26), p=0.60
Female sex	8,096 (44.4)	2,995 (53.3)	5,101 (40.4)	0.59 (0.56-0.63), p<0.001	0.58 (0.55-0.62), p<0.001
Socio-economic status [b]					N/a
1 (least deprived)	2,692 (14.8)	838 (14.9)	1,854 (14.7)	1.00 (ref)	
2	3,745 (20.6)	1,151 (20.5)	2,594 (20.6)	1.02 (0.92-1.13), p=0.74	
3	3,580 (19.7)	1,118 (19.9)	2,462 (19.5)	1.00 (0.89-1.11), p=0.93	
4	4,447 (24.4)	1,365 (24.3)	3,082 (24.4)	1.02 (0.92-1.13), p=0.70	
5 (most deprived)	3,758 (20.6)	1,137 (20.3)	2,621 (20.8)	1.04 (0.94-1.16), p=0.45	
Respiratory disease characteristics					
Smoking status [b]					
Ex-smoker	10,535 (58.0)	3,164 (56.6)	7,371 (58.6)	1.00 (ref)	1.00 (ref)
Current smoker	7,633 (42.0)	2,423 (43.4)	5,210 (41.4)	0.92 (0.87-0.98), p=0.01	0.92 (0.86-0.99), p=0.02
Asthma history					
No asthma history	14,999 (82.3)	4,653 (82.9)	10,346 (82.0)	1.00 (ref)	1.00 (ref)
Past asthma	2,566 (14.1)	766 (13.6)	1,800 (14.3)	1.06 (0.96-1.16), p=0.24	1.04 (0.95-1.15), p=0.37
Current asthma	670 (3.7)	196 (3.5)	474 (3.8)	1.09 (0.92-1.29), p=0.33	1.02 (0.86-1.22), p=0.81
History of atopy	4,975 (27.3)	1,426 (25.4)	3,549 (28.1)	1.15 (1.07-1.23), p<0.001	1.15 (1.07-1.23), p<0.001

Baseline characteristic	Overall n=18,235 n (%)	Low eosinophils (<0.15 x10*9/L) n=5,615 n (%)	High eosinophils (≥0.15 x10*9/L) n=12,620 n (%)	Unadjusted odds ratio for high eosinophil vs. low eosinophil group (95% CI, p-value)	Adjusted odds ratio for high eosinophil vs. low eosinophil group [a] (95% CI, p-Value)
Airflow limitation severity [b]					N/a
Mild (≥80%)	1,81 (14.1)	546 (13.8)	1,268 (14.3)	1.00 (ref)	
Moderate (50-80%)	7,263 (56.6)	2,221 (56.2)	5,042 (56.7)	0.98 (0.87-1.09), p=0.69	
Severe (30-50%)	3,267 (25.5)	1,005 (25.5)	2,262 (25.5)	0.97 (0.86-1.10), p=0.62	
Very severe (<30%)	492 (3.8)	177 (4.5)	315 (3.5)	0.77 (0.62-0.95), p=0.01	
MRC breathlessness scale [b]					N/a
1 (least severe)	1,148 (15.0)	357 (14.7)	791 (15.1)	1.00 (ref)	
2	3,266 (42.6)	1,024 (42.1)	2,242 (42.8)	0.99 (0.85-1.14), p=0.87	
3	2,146 (28.0)	700(28.8)	1,446 (27.6)	0.93 (0.80-1.09), p=0.37	
4	965 (12.6)	308 (12.7)	657 (12.6)	0.96 (0.80-1.16), p=0.69	
5 (most severe)	141 (1.8)	43 (1.8)	98 (1.9)	1.03 (0.70-1.50), p=0.88	
Exacerbations					
0	9,429 (51.7)	2,985 (53.2)	6,444 (51.1)	1.00 (ref)	1.00 (ref)
1	5,432 (29.8)	1,655 (29.5)	3,777 (29.9)	1.06 (0.98-1.14), p=0.13	1.06 (0.98-1.14), p=0.15
2	2,233 (12.3)	644 (11.5)	1,589 (12.6)	1.14 (1.03-1.26), p=0.01	1.13 (1.02-1.26), p=0.03
3 or more	1,141 (6.3)	331 (6.0)	810 (6.4)	1.13 (0.99-1.30), p=0.07	1.10 (0.95-1.27), p=0.20
Pneumonia episodes					N/a
0	14,466 (79.3)	4,495 (80.1)	9,971 (79.0)	1.00 (ref)	
1	2,891 (15.9)	860 (15.3)	2,031 (16.1)	1.06 (0.98-1.16), p=0.16	
2 or more	878 (4.8)	260 (4.6)	618 (4.9)	1.07 (0.92-1.24), p=0.36	
Oral steroid prescriptions					
0	14,412 (79.0)	4,507 (80.3)	9,905 (78.5)	1.00 (ref)	1.00 (ref)
1	2,868 (15.7)	853 (15.2)	2,015 (16.0)	1.07 (0.98-1.17), p=0.11	1.06 (0.96-1.16), p=0.25
2	955 (5.2)	255 (4.5)	700 (5.6)	1.25 (1.08-1.45), p=0.003	1.21 (1.04-1.42), p=0.02

Baseline characteristic	Overall n=18,235 n (%)	Low eosinophils (<0.15 x10*9/L) n=5,615 n (%)	High eosinophils (≥0.15 x10*9/L) n=12,620 n (%)	Unadjusted odds ratio for high eosinophil vs. low eosinophil group (95% CI, p-value)	Adjusted odds ratio for high eosinophil vs. low eosinophil group [a] (95% CI, p-Value)
Salbutamol inhalers					
0	6,042 (33.1)	1,952 (34.8)	4,090 (32.4)	1.00 (ref)	1.00 (ref)
1	3,959 (21.7)	1,244 (22.2)	2,715 (21.5)	1.04 (0.96-1.14), p=0.35	1.02 (0.93-1.11), p=0.69
2	1,926 (10.6)	571 (10.2)	1,355 (10.7)	1.13 (1.01-1.27), p=0.03	1.12 (1.00-1.26), p=0.05
3-5	2,676 (14.7)	779 (13.9)	1,897 (15.0)	1.16 (1.05-1.28), p=0.003	1.15 (1.04-1.28), p=0.007
6 or more	3,632 (19.9)	1,069 (19.0)	2,563 (20.3)	1.14 (1.05-1.25), p=0.003	1.16 (1.05-1.27), p=0.002
Theophylline use	209 (1.2)	58 (1.0)	151 (1.2)	1.16 (0.86-1.57), p=0.34	N/a
Oxygen use	83 (0.5)	24 (0.4)	59 (0.5)	1.09 (0.68-1.76), p=0.71	N/a
Nebuliser use	341 (1.9)	102 (1.8)	239 (1.9)	1.04 (0.83-1.32), p=0.72	N/a
General health characteristics					
Non-elective hospitalisations					N/a
0	15,128 (83.0)	4,614 (82.2)	10,514 (83.3)	1.00 (ref)	
1	2,321 (12.7)	746 (13.3)	1,575 (12.5)	0.93 (0.84-1.02), p=0.11	
2 or more	786 (4.3)	255 (4.5)	531 (4.2)	0.91 (0.78-1.07), p=0.25	
GP consultations					
0-3	5,055 (27.7)	1,569 (27.9)	3,486 (27.6)	1.00 (ref)	1.00 (ref)
4-7	6,411 (35.2)	1,877 (33.4)	4,534 (35.9)	1.09 (1.00-1.18), p=0.04	1.06 (0.98-1.15), p=0.16
8 or more	6,769 (37.1)	2,169 (38.6)	4,600 (36.5)	0.95 (0.88-1.03), p=0.25	0.91 (0.84-0.99), p=0.03
Charlson comorbidity index					
0	9,811 (53.8)	3,114 (55.5)	6,697 (53.1)	1.00 (ref)	1.00 (ref)
1	3,148 (17.3)	968 (17.2)	2,180 (17.3)	1.05 (0.96-1.14), p=0.30	1.02 (0.94-1.12), p=0.63
2 or more	5,276 (29.0)	1,533 (27.3)	3,743 (29.7)	1.14 (1.06-1.22), p=0.001	1.15(1.06-1.25), p<0.001
Influenza vaccination	12,502 (68.6)	3,861 (68.8)	8,641 (68.5)	0.99 (0.92-1.06), p=0.70	N/a
Pneumococcal vaccination	6,373 (35.0)	1,951 (34.8)	4,422 (35.0)	1.01 (0.95-1.08), p=0.70	N/a

Percentages are column percentages. See Table 2.6 for details and time periods for variables. (ref), reference group

[a] Odds ratio calculated using logistic regression. Adjusted odds ratios include baseline variables p<0.10 in univariate analysis (adding these did not improve the model (p=0.80)). n=18,168 due to complete case analysis. Airflow limitation severity and MRC breathlessness scale not included in adjusted model due to large amounts of missing data (inclusion did not change results). Year of index prescription not displayed due to multiple categories but included in adjusted model. Categorical variable used for age.

[b] n=18,222 for socio-economic status, n=18,168 for smoking status, n=12,836 for airflow limitation severity and n=7,666 for MRC breathlessness scale, due to missing data.

4.3.3 Prospectively collected in the COMET study

Table 4.3 shows the distribution of patients between low and high eosinophil groups. There was no clear association of any baseline variable with eosinophil group. Sensitivity analyses as described in Section 4.3.1 above made little difference to results (data not shown). Post-hoc assessment of positive bronchodilator reversibility as a covariate also found no association with eosinophil group (unadjusted OR 1.00 (95%CI 0.38 to 2.64, p=1.00); adjusted OR 1.13 (95%CI 0.28 to 4.50), p=0.86).

I also addressed the same question looking at eosinophils as a continuous variable (logarithmically transformed) using linear regression and again found no significant association of any variables with eosinophil count (data not shown). The largest difference was in sex (geometric mean eosinophil count 0.13x10*9/L in females and 0.18x10*9/L in males (p=0.08)), in keeping with CPRD study findings where males had significantly higher eosinophils.

Table 4.3: Distribution of patients by eosinophil group, by baseline characteristics (COMET)

Baseline characteristic	Overall n=93 n (%)	Low eosinophils (<0.15 x10*9/L) n=38 n (%)	High eosinophils (≥0.15 x10*9/L) n=55 n (%)	Unadjusted odds ratio for high eosinophil vs. low eosinophil group (95% CI, p-value)	Adjusted odds ratio for high eosinophil vs. low eosinophil group[a] (95% CI, p-Value)
Demographic characteristics					
Age, mean (SD), years	70.5 (9.3)	70.3 (10.0)	70.6 (8.9)	1.00 (0.96-1.05), p=0.89	N/a
Age group in years					
40-49	1 (1.1)	1 (2.6)	0 (0)	N/a	N/a
50-59	9 (9.7)	4 (10.5)	5 (9.1)	1.62 (0.38-6.96), p=0.52	1.24 (0.28-5.55), p=0.78
60-69	30 (32.3)	8 (21.1)	22 (40.0)	3.56 (1.27-9.94), p=0.02	3.64 (1.28-10.35), p=0.02
70-79	39 (41.9)	22 (57.9)	17 (30.9)	1.00 (ref)	1.00 (ref)
80-89	13 (14.0)	2 (5.3)	11 (20.0)	7.12 (1.39-36.5), p=0.02	6.77 (1.30-35.28), p=0.02
>=90	1 (1.1)	1 (2.6)	0 (0.0)	N/a	N/a
Female sex	29 (31.2)	16 (42.1)	13 (23.6)	0.43 (0.17-1.04), p=0.06	0.46 (0.17-1.26), p=0.13
Respiratory disease characteristics					
Smoking status[b]					N/a
Ex- or passive smoker	58 (62.4)	23 (60.5)	35 (63.6)	1.00 (ref)	
Current smoker	35 (37.6)	15 (39.5)	20 (36.4)	0.88 (0.37-2.05), p=0.76	
Smoking pack years (n=88)	39.9 (28.8)	37.1 (28.7)	41.9 (29.0)	1.01 (0.99-1.02), p=0.45	N/a
History of asthma	3 (3.2)	2 (5.3)	1 (1.8)	0.33 (0.03-3.81), p=0.38	N/a
History of atopy	23 (24.7)	11 (29.0)	12 (21.8)	0.68 (0.27-1.77), p=0.44	N/a
Exacerbations					N/a
0	65 (69.9)	24 (63.2)	41 (74.6)	1.00 (ref)	
1	22 (23.7)	11 (29.0)	11 (20.0)	0.59 (0.22-1.55), p=0.28	
2 or more	6 (6.5)	3 (7.9)	3 (5.5)	0.59 (0.11-3.13), p=0.53	
Airflow limitation severity (n=92)					N/a
Mild (≥80%)	28 (30.4)	10 (26.3)	18 (33.3)	1.00 (ref)	
Moderate (50-80%)	50 (54.4)	22 (57.9)	28 (51.9)	0.71 (0.27-1.83), p=0.48	
Severe (30-50%)	13 (14.1)	5 (13.2)	8 (14.8)	0.89 (0.23-3.46), p=0.87	
Very severe (<30%)	1 (1.1)	1 (2.6)	0 (0.0)	N/a	

Baseline characteristic	Overall n=93 n (%)	Low eosinophils (<0.15 x10*9/L) n=38 n (%)	High eosinophils (≥0.15 x10*9/L) n=55 n (%)	Unadjusted odds ratio for high eosinophil vs. low eosinophil group (95% CI, p-value)	Adjusted odds ratio for high eosinophil vs. low eosinophil group[a] (95% CI, p-Value)
MRC breathlessness scale					N/a
1 (least severe)	19 (20.4)	7 (18.4)	12 (21.8)	1.00 (ref)	
2	53 (57.0)	26 (68.4)	27 (49.1)	0.61 (0.21-1.78), p=0.36	
3	15 (16.1)	3 (7.9)	12 (21.8)	2.33 (0.49-11.23), p=0.29	
4	6 (6.5)	2 (5.3)	4 (7.3)	1.17 (0.17-8.09), p=0.88	
5 (most severe)	0 (0.0)	0 (0.0)	0 (0.0)	N/a	
Oxygen saturation (mean, SD, %)	95.0 (2.5)	95.3 (2.2)	94.9 (2.8)	0.93 (0.78-1.10), p=0.39	N/a
FeNO (mean, SD, ppb) (n=92)	25.2 (20.4)	27.4 (26.9)	23.6 (14.2)	0.99 (0.97-1.01), p=0.39	N/a
Low (<25)	55 (59.8)	21 (55.3)	34 (63.0)	1.00 (ref)	
Medium (25-50)	29 (31.5)	13 (34.2)	16 (29.6)	0.76 (0.31-1.89), p=0.56	
High (>50)	8 (8.7)	4 (10.5)	4 (7.4)	0.62 (0.14-2.74), p=0.53	
Respiratory symptom questionnaires					N/a
CCQ (mean, SD)	1.46 (1.04)	1.43 (1.05)	1.48 (1.04)	1.04 (0.70-1.56), p=0.84	
CAT (mean, SD)	13.2 (7.4)	12.8 (7.3)	13.4 (7.5)	1.01 (0.95-1.07), p=0.72	
General health characteristics					
Charlson comorbidity index					N/a
0	66 (71.0	25 (65.8)	41 (74.6)	1.00 (ref)	
1	18 (19.4)	9 (23.7)	9 (16.4)	0.61 (0.21-1.74), p=0.36	
2 or more	9 (9.7)	4 (10.5)	5 (9.1)	0.76 (0.19-3.11), p=0.71	
Body mass index (mean, SD, kg/m^2)	28.1 (5.1)	27.5 (5.9)	28.6 (4.4)	1.05 (0.96-1.14), p=0.28	N/a

Percentages are column percentages. See Table 3.3 for details and time periods for variables. (ref), reference group

[a] Odds ratio calculated using logistic regression. Adjusted odds ratios include baseline variables p<0.10 in univariate analysis (adding these did not improve the model (p=0.99)). n=91 due to complete case analysis. Categorical variable used for age.

[b] Passive smokers classified as ex-smokers due to small numbers (n=2).

4.4 Repeatability and variability

4.4.1 Additional methods detail and sensitivity/subgroup analysis

This section focuses on patients who had more than one valid eosinophil count during the two years prior to index date (CPRD, 29,799 values for 9,473 patients) or during study follow-up (COMET, 318 values for 89 participants) i.e. those with multiple values. The various techniques used to assess repeatability are divided into those assessing eosinophils on a continuous and binary scale.

Continuous

I calculated the mean, standard deviation, co-efficient of variation (CV) and intra-class correlation co-efficient (ICC) using a random effects model, as appropriate for assessing within-person variation with multiple values per individual.[138-141] The intra-class correlation co-efficient (ICC) tells us about *"the concordance, the extent to which repetition of the test yields the same values under the same conditions in the same individuals"*.[141] Evidence of proportionality was assessed graphically and whether the correlation between mean and standard deviation as measured using Kendall's tau method[140] was equal to zero, and eosinophils appropriately transformed to deal with this. It was assumed for the purposes of the main repeatability analysis that variation could be attributed to the biomarker rather than a change in the participant's condition over the relatively short time period of eosinophil monitoring.

In order to understand the relationship better on a continuous scale, I also used linear regression to assess how the within-person standard deviation and CV varied by baseline characteristics, as done elsewhere,[142] in addition to subgroup analyses of ICC according to

subgroups of pre-specified baseline characteristics (age < or ≥70, sex, smoking status, low (0 or 1) or high (≥2) baseline exacerbation frequency in previous year, and history of asthma (and positive bronchodilator reversibility (COMET only)) and atopy), by splitting the data and fitting models to each set.

For the most recent two values (CPRD) and the first two values, with first and last values as comparison (COMET), Bland-Altman methods were used to measure the mean difference between the measurements on a continuous scale (logarithmic to remove the effect of differences increasing with magnitude).[143,144]

Sensitivity analyses for CPRD included those eosinophil values within two weeks of acute events, and for COMET excluded those without spirometry diagnostic for COPD, and eosinophil counts within two weeks of an exacerbation.

Binary

Cohen's kappa test (using two values as described in last paragraph above) was used to assess the repeatability for binary categorisation of eosinophils into 'high' and 'low' cut-offs (using thresholds of 0.15 and 0.34 x10*9/L), and diagnostic accuracy statistics were calculated to assess how well the most recent or baseline value ('index test') predicted the mean of eosinophils over time ('reference test'), using both ≥0.15 and ≥0.34 x10*9/L thresholds, to assess validity.[143] For COMET, the baseline result was excluded from the calculation of the mean, but this was not possible for CPRD with limited numbers of patients who had had more than two tests.

4.4.2 Routinely collected using the CPRD

Continuous scale

I found that the within-person variation was proportional to the within-person mean (Figure 4.9) and this was confirmed using Kendall's tau method (tau-b 0.36, p<0.001) which measures if there is any relationship between two quantities (in this case mean and SD). Converting the eosinophil counts to logarithmic scale removed this proportionality (tau-b 0.002, p=0.80), so this was used for all subsequent analyses.

Figure 4.9: Individual patient's standard deviations plotted against their means (CPRD)

n=29,799 values for 9,473 patients

Using the random effects model, the geometric mean was 0.20 x10*9/L (mean identical to that for the most recent valid eosinophil count used in the distribution analysis above). The CV was 41.5% and the ICC was 0.68 (95% CI 0.67 to 0.69), representing good agreement.[143] When values close to acute events were included in sensitivity analysis, there was slightly

higher variation (33,230 values for 10,365 patients: geometric mean 0.20 x10*9/L, CV 43.7%, ICC 0.66 (95% CI 0.65 to 0.67. Table 4.4 shows the variability in eosinophil count in subgroups of pre-specified baseline characteristics as detailed in Section 4.4.1 above. The largest difference was in sex, with females showing greater within-person variability (ICC 0.66 in females vs. 0.69 in males), but even this difference did not reach statistical significance.

Table 4.4: Variability in eosinophil count by baseline characteristics (CPRD)

	Values (n=)	Patients (n=)	Geometric mean (x10*9/L)	Geometric SD	CV (%)	ICC (95% CI)
Overall	29,799	9,473	0.20	1.415	41.5	0.68 (0.67-0.69)
Age						
<70	12,892	4,209	0.20	1.405	40.5	0.68 (0.67-0.69)
>=70	16,907	5,264	0.20	1.423	42.3	0.69 (0.67-0.70)
Sex						
Male	16,526	5,258	0.22	1.409	40.9	0.69 (0.67-0.70)
Female	13,273	4,215	0.18	1.424	42.4	0.66 (0.65-0.68)
Smoking status						
Ex	18,686	5,799	0.20	1.413	41.3	0.68 (0.67-0.69)
Current	11,049	3,650	0.20	1.419	41.9	0.69 (0.67-0.70)
Exacerbations						
0 or 1	24,377	7,756	0.20	1.415	41.5	0.68 (0.67-0.69)
>=2	4,818	1,537	0.21	1.418	41.8	0.67 (0.65-0.70)
Asthma history						
None	24,363	7,808	0.20	1.416	41.6	0.68 (0.67-0.69)
Historical	4,384	1,332	0.20	1.416	41.6	0.68 (0.66-0.70)
Current	1,052	333	0.21	1.403	40.3	0.69 (0.64-0.73)
Atopy history						
None	21,354	6,826	0.20	1.411	41.1	0.69 (0.68-0.70)
Atopy	8,445	2,647	0.21	1.426	42.6	0.67 (0.66-0.69)

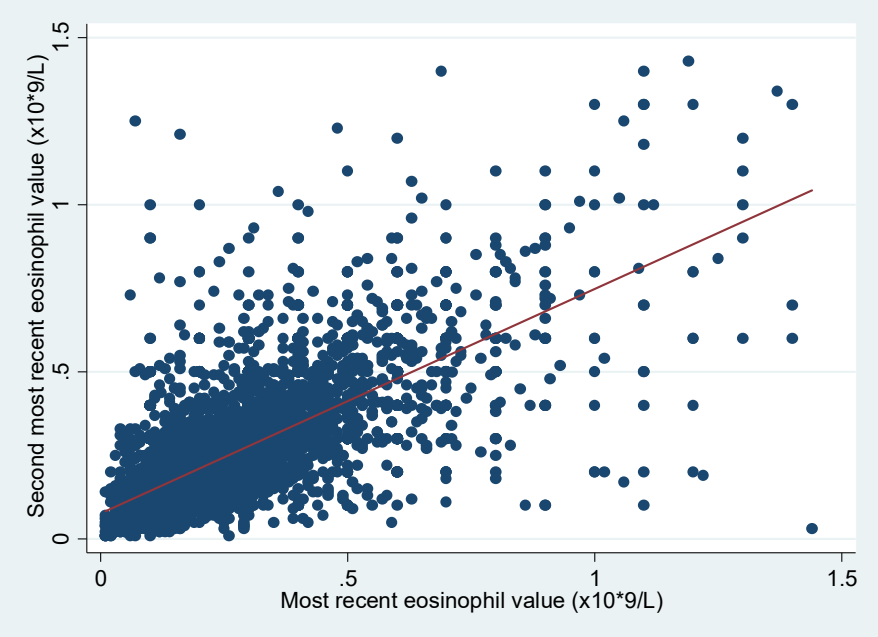
Figures calculated using random effects model. Only valid eosinophil counts are included (those close to acute events excluded). SD, standard deviation. CV, co-efficient of variation. ICC, intra-class correlation co-efficient.

I also assessed variability by baseline characteristics using CV and geometric SD as dependent variables, and found no association of any of the same pre-specified baseline characteristics with variability (data not shown).

Lastly, Bland-Altman approaches assessed the agreement between the most recent two values (n=9,473). As expected, correlation was high (r=0.70, p<0.001) (Figure 4.10). Figure 4.11 shows the Bland-Altman plot. The mean difference was <0.01 x10*9/L (SD 0.12, 95% CI -0.01 to 0.00). Limits of agreement (within two standard deviations) were -0.25 to +0.24 x10*9/L). Repeating the analysis with eosinophils close to exacerbation events included (n=10,365) increased the width of the limits of agreement by a small amount (mean difference <0.001 x10*9/L (SD 0.13, 95% CI -0.01 to 0.00), limits of agreement -0.26 to +0.25 $x10^9$/L).

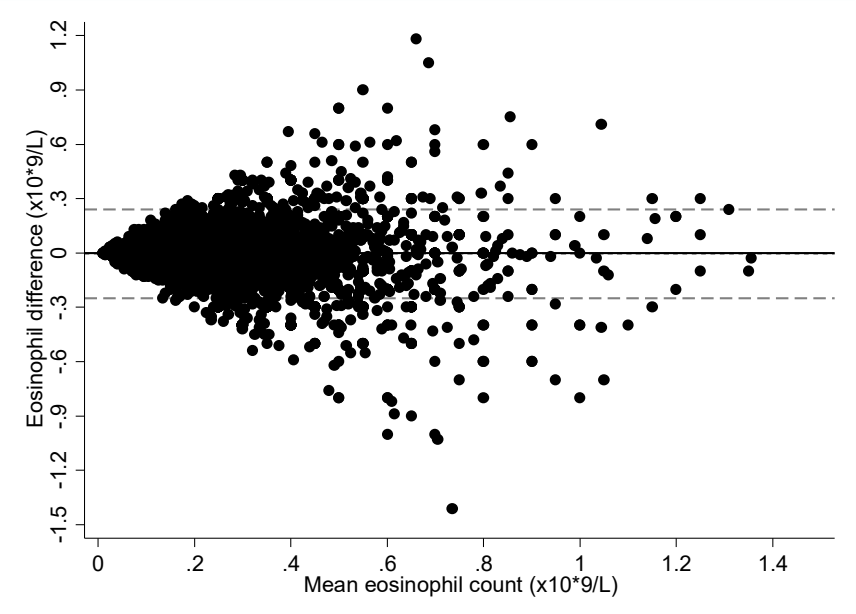
There was a small but significant negative correlation of mean difference with the absolute mean (-0.06, p<0.001), and clearly visible increase in the spread as the magnitude of the eosinophil count mean increased. Figure 4.12 therefore shows the Bland-Altman plot displayed on the logarithmic scale due to the relationship between the difference and the mean, which removed the significant correlation (r=-0.02, p=0.07). Logarithmic ratio analysis gives a mean difference ratio of 0.99 (95% CI 0.98 to 1.00) (where 1.00 would be perfect agreement), with limits of agreement from 62% below to 159% above the other value.

Figure 4.10: Scatter plot of most recent eosinophil count against second most recent eosinophil count (CPRD) (n=9,473)



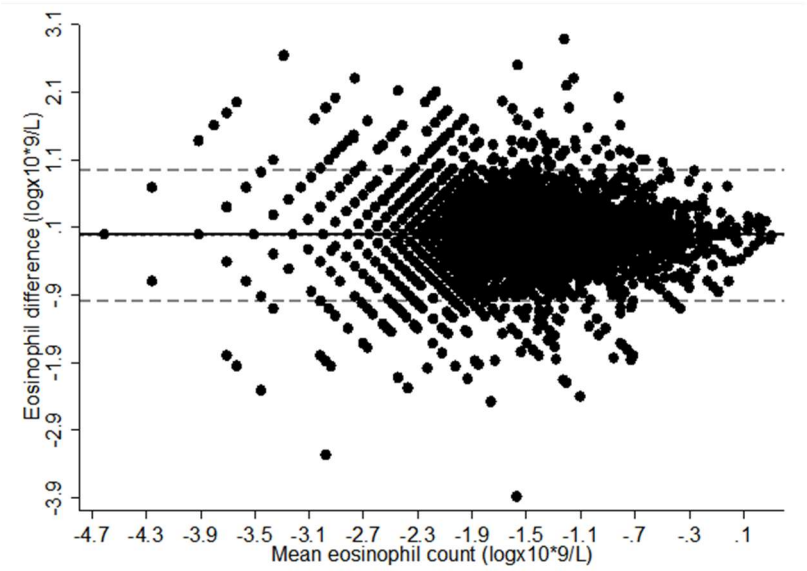
r=0.70, p<0.001

Figure 4.11: Bland-Altman plot comparing difference against mean of most recent vs. second most recent eosinophil count (CPRD)



Dotted line shows the mean difference (<0.01 x10*9/L, 95% CI -0.01 to 0.00) (indistinguishable from solid line which shows zero). Dashed lines show 2 standard deviations above and below the mean (+0.24 and -0.25 respectively). Range -1.41 to +1.18.

Figure 4.12: Bland-Altman plot comparing difference against mean of most recent vs. second most recent eosinophil count (log transformed) (CPRD)



Dotted line shows the mean difference (-0.01 log x10*9/L) (indistinguishable from solid line which shows zero). Dashed lines show 2 standard deviations above and below the mean (+0.95 and -0.98 respectively). Range -3.87 to +2.88. All these measurements are on the log scale; exponentiated figures give ratios. Mean difference ratio is 0.99 (95% CI 0.98 to 1.00). For limits of agreement, this converts to 0.38 to 2.59, which means that for 95% of cases the two measurements may differ by 62% below to 159% above.

Binary scale

For binary classification into 'high' and 'low' eosinophil groups, Cohen's kappa was used to assess repeatability between eosinophil values for the most recent two values (n=9,473). Cohen's kappa (κ) was 0.53 for a 0.15 x10*9/L cut-off and 0.54 for a 0.34 x10*9/L cut-off (representing moderate agreement[143]), with little change when values close to acute events were included (κ=0.52 and 0.54 respectively, n=10,365).

Table 4.5 shows diagnostic accuracy analysis to assess the predictive value of the most recent value for classifying someone as 'high' or 'low' eosinophil group, based on their mean value ('reference test').

At the primary 0.15 x10*9/L threshold, a ‘high’ most recent result is 97.1% (95%CI 96.7 to 97.5%) predictive of this being the patient’s ‘true’ eosinophil group, but a ‘low’ most recent result is less predictive (71.2%, 95% CI 69.5 to 72.8%). Using the higher threshold of 0.34 x10*9/L, the converse is true: a ‘high’ most result is less (88.3%, 95%CI 86.7 to 89.7%) predictive of this being the ‘true’ value than a ‘low’ most recent result (93.6% predictive, 95%CI 93.0 to 94.1%). Results did not differ greatly when values close to acute events were included (Table 4.5).

Table 4.5: Diagnostic accuracy analysis assessing most recent eosinophil value vs. mean value (CPRD)

	Index test group (most recent eosinophil value)	Low eosinophil group (mean) (n=)	High eosinophil group (mean) (n=)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+ (95% CI)	LR- (95% CI)
Excluding values close to acute events (primary analysis)									
0.15x10*9/L threshold	Low eosinophil (n=) High eosinophil (n=)	2,040/2,230 190/2,230	826/7,243 6,417/7,243	88.6 (87.8-89.3)	91.5 (90.2-92.6)	97.1 (96.7-97.5)	71.2 (69.5-72.8)	10.4 (9.07-11.9)	0.12 (0.12-0.13)
0.34x10*9/L threshold	Low eosinophil (n=) High eosinophil (n=)	7,117/7,336 219/7,336	487/2,137 1,650/2,137	77.2 (75.4-79.0)	97.0 (96.6-97.4)	88.3 (86.7-89.7)	93.6 (93.0-94.1)	25.9 (22.7-29.5)	0.23 (0.22-0.25)
Including values close to acute events									
0.15x10*9/L threshold	Low eosinophil (n=) High eosinophil (n=)	2,232/2,454 222/2,454	921/7,911 6,990/7,911	88.4 (87.6-89.1)	91.0 (89.7-92.1)	96.9 (96.5-97.3)	70.8 (69.2-72.4)	9.77 (8.61-11.1)	0.13 (0.12-0.14)
0.34x10*9/L threshold	Low eosinophil (n=) High eosinophil (n=)	7,738/8,000 262/8,000	532/2,365 1,833/2,365	77.5 (75.8-79.2)	96.7 (96.3-97.1)	87.5 (86.0-88.9)	93.6 (93.0-94.1)	23.7 (21.0-26.7)	0.23 (0.22-0.25)

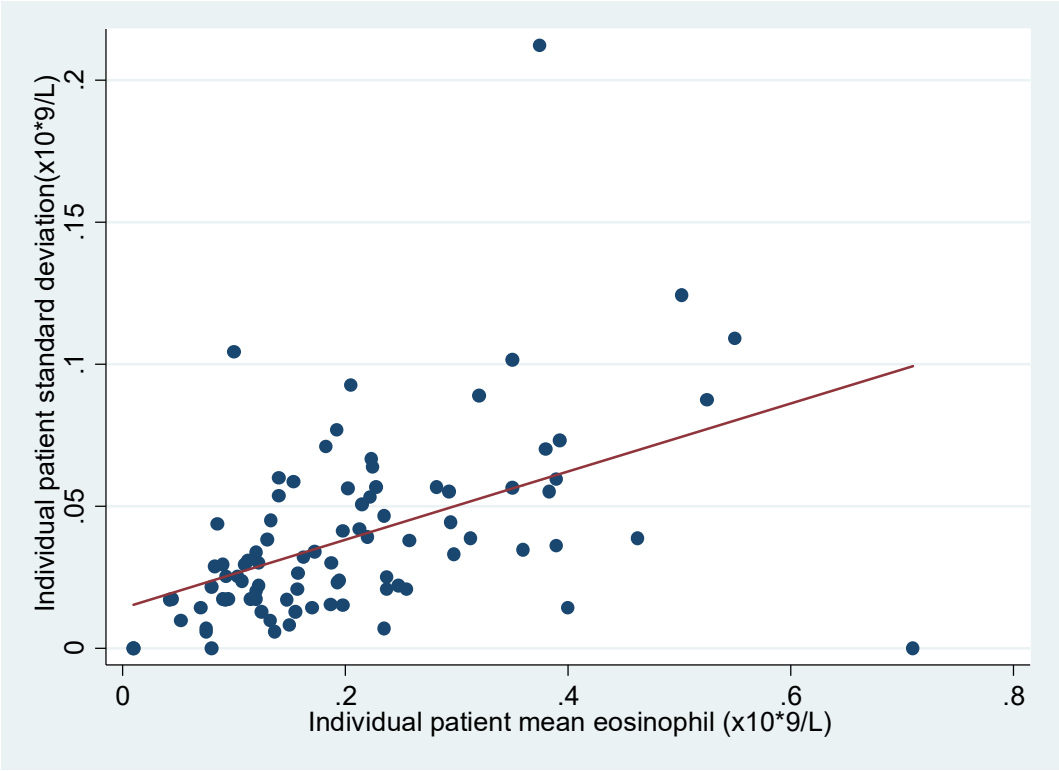
Only includes valid eosinophil values (see Section 2.2.5). Patients with only one eosinophil value have been excluded. Most recent result included in calculation of the patient mean. PPV, positive predictive value. NPV, negative predictive value. LR+, positive likelihood ratio. LR-, negative likelihood ratio.

4.4.3 Prospectively collected in the COMET study

Continuous scale

As for CPRD, I found that the within-person variation was proportional to the within-person mean (Figure 4.13) and this was confirmed using Kendall's tau method (tau-b 0.40, p<0.001). Converting the eosinophil counts to logarithmic scale removed this proportionality (tau-b -0.13, p=0.06), so this was used for all subsequent analyses.

Figure 4.13: Individual patient's standard deviations plotted against their means (COMET)



n=318 values for 89 patients

Using the random effects model, the geometric mean was 0.16 x10*9/L (mean identical to that for the within-person geometric mean eosinophil count used in the distribution analysis above). The CV was 38.5% and the ICC was 0.83 (95% CI 0.77 to 0.87), representing excellent

agreement.[143] Sensitivity analyses as described in Section 4.4.1 above produced very similar results (data not shown). Table 4.4 shows the variability in eosinophil count in subgroups of pre-specified baseline characteristics. There are significant differences between the subgroups in terms of non-overlapping confidence intervals for ICC, with eosinophils appearing more stable (higher ICC) in those who are older, male, ex-smokers with no atopy but who do have positive bronchodilator reversibility.

Table 4.6: Variability in eosinophil count by baseline characteristics (COMET)

	Values (n=)	Patients (n=)	Geometric mean (x10*9/L)	Geometric SD	CV (%)	ICC (95% CI)
Overall	318	89	0.16	1.385	38.5	0.83 (0.77-0.87)
Age						
<70	131	37	0.17	1.537	53.7	0.74 (0.61-0.84)
>=70	187	52	0.15	1.254	25.4	0.91 (0.86-0.94)
Sex						
Male	217	62	0.18	1.285	28.5	0.90 (0.85-0.93)
Female	101	27	0.13	1.559	55.9	0.64 (0.46-0.79)
Smoking status						
Ex-smoker[a]	200	55	0.17	1.259	25.9	0.90 (0.85-0.93)
Current	118	34	0.15	1.560	56.0	0.75 (0.61-0.85)
Exacerbations						
0 or 1	298	83	0.16	1.395	39.5	0.82 (0.76-0.87)
>=2	20	6	0.20	1.203	20.3	0.91 (0.72-0.98)
Asthma history						
None	308	86	0.16	1.392	39.2	0.83 (0.77-0.87)
Historical	10	3	0.16	1.101	10.1	0.90 (0.56-0.99)
Reversibility						
Negative	241	67	0.16	1.432	43.2	0.70 (0.60-0.79)
Positive	77	22	0.16	1.204	20.4	0.97 (0.94-0.99)
Atopy history						
None	239	67	0.17	1.314	31.4	0.89 (0.84-0.92)
Atopy	79	22	0.15	1.566	56.6	0.57 (0.37-0.76)

Figures calculated using random effects model. CV, co-efficient of variation. ICC, intra-class correlation co-efficient. Geometric means are slightly different from those given in earlier sections because this analysis excludes those with only one value (n=4).

[a] Passive smokers classified as ex-smokers due to small numbers (n=2).

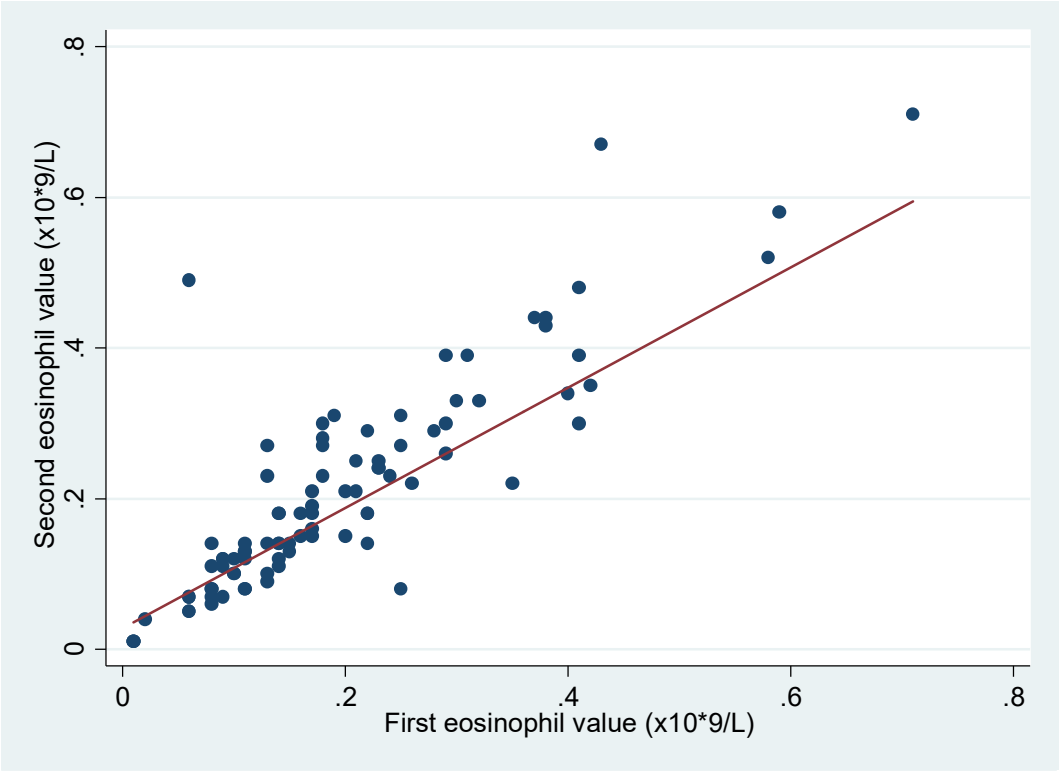
In the regression model[a] using CV and geometric SD as dependent variables to assess variability by baseline characteristics, sex and positive bronchodilator reversibility showed a significant association with SD (p=0.03 and p=0.04 respectively), but no significant association with CV.

Lastly, Bland-Altman approaches assessed the agreement between the first two values. As expected, correlation was high (r=0.87, p<0.001) (Figure 4.14). Figure 4.15 shows the Bland-Altman plot. The mean difference was 0.02 x10*9/L (SD 0.07, 95% CI 0.00 to 0.03). Limits of agreement (within two standard deviations) were -0.16 to +0.13 x10*9/L). There was no significant correlation of mean difference with the absolute mean (-0.17, p=0.12). Repeating the analysis using the first and last values for each participant made minimal difference to results (mean difference 0.01 x10*9/L (SD 0.08, 95% CI 0.01-0.03), limits of agreement -0.17 to +0.15 x10*9/L). Sensitivity analyses as described in Section 4.4.1 above did not result in any significant change to results (data not shown). Figure 4.16 shows the Bland-Altman plot displayed on the logarithmic scale.[b] This gives a mean difference ratio of 0.94 (95% CI 0.87 to 1.01) (where 1.00 is perfect agreement) and limits of agreement of 53% below to 89% above the previous value.

[a] Regression model adjusted for sex, age category, baseline exacerbations, asthma, smoking status, and positive reversibility and built using stepwise build.

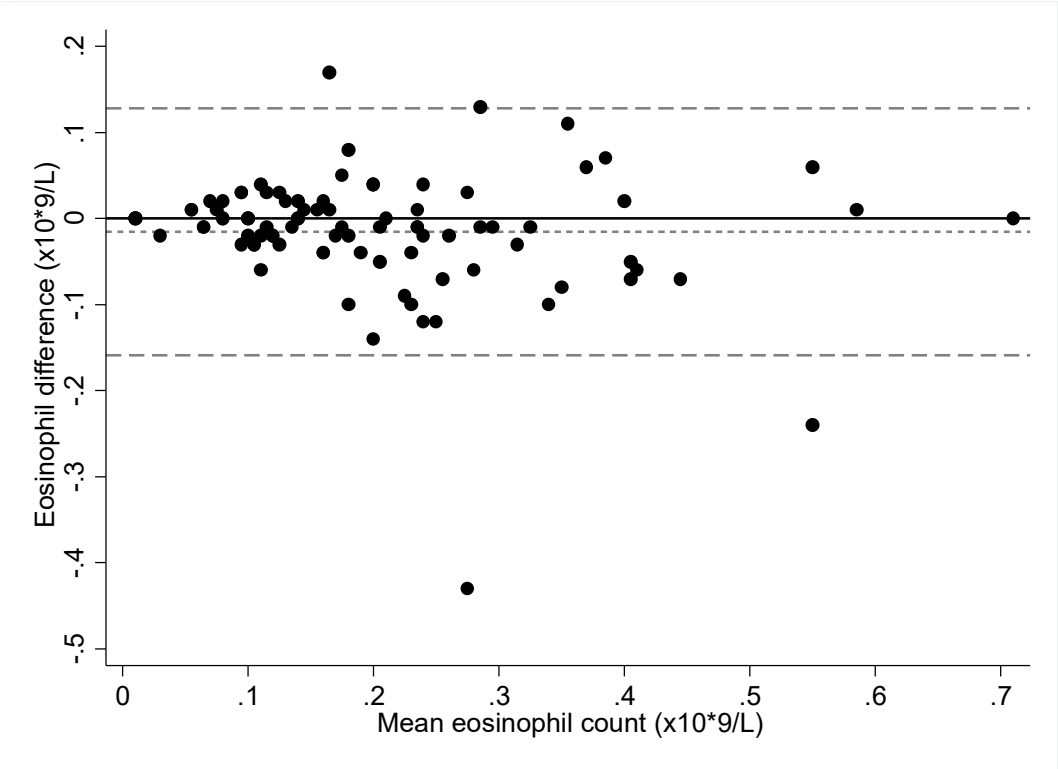
[b] Although there was no significant correlation between the difference and the mean, doing logarithmic analysis would enable easier comparison with CPRD results.

Figure 4.14: Scatter plot of first eosinophil count against second eosinophil count (COMET) (n=89)



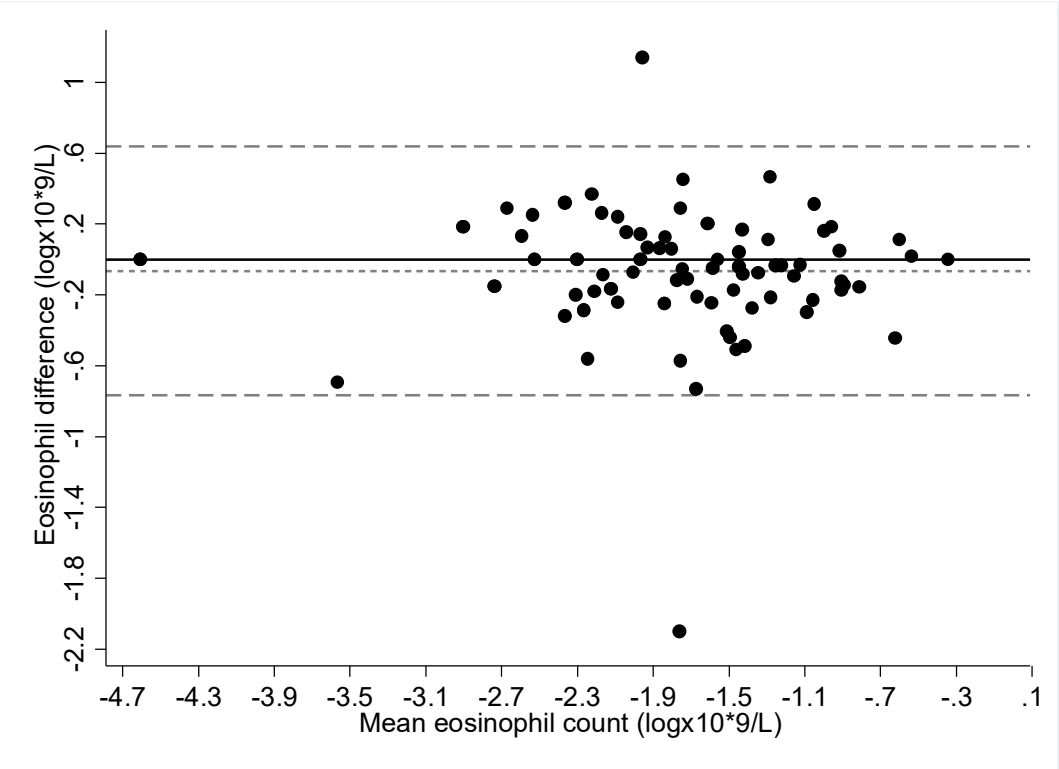
r=0.87, p<0.001

Figure 4.15: Bland-Altman plot comparing difference against mean of first vs. second eosinophil count (COMET)



Dotted line shows the mean difference (-0.02 x10*9/L, 95% CI 0.00 to 0.03). Solid line indicates zero. Dashed lines show 2 standard deviations above and below the mean (+0.13 and -0.16 respectively). Range -0.43 to +0.17.

Figure 4.16: Bland-Altman plot comparing difference against mean of first vs. second eosinophil count (log transformed) (COMET)



Dotted line shows the mean difference (-0.06 log x10*9/L). Solid line indicates zero. Dashed lines show 2 standard deviations above and below the mean (+0.64 and -0.77 respectively). Range -2.10 to +1.14. All these measurements are on the log scale; exponentiated figures give ratios. Mean difference ratio is 0.94 (95% CI 0.87 to 1.01). For limits of agreement, this converts to 0.47 to 1.89, which means that for 95% of cases the two measurements may differ by 53% below to 89% above.

Binary scale

For binary classification into 'high' and 'low' eosinophil groups, Cohen's kappa was used to assess repeatability between eosinophil values for the first two values (n=89). Cohen's kappa (κ) was 0.79 for a 0.15 x10*9/L cut-off and 0.78 for a 0.34 x10*9/L cut-off (representing substantial agreement[143]). When first and last values were used instead, agreement was reduced to 0.61 and 0.71 respectively (but still representing substantial agreement[143]).

Table 4.7 shows diagnostic accuracy analysis to assess the predictive value of the baseline value for classifying someone as ‘high’ or ‘low’ eosinophil group, based on their mean value (‘reference test’).

At the primary 0.15 x10*9/L threshold, a ‘high’ baseline result is 90.9% (95%CI 80.0 to 97.0%) predictive of this being the patient’s ‘true’ eosinophil group, and a ‘low’ baseline result is 88.2% (95% CI 72.5 to 96.7%) predictive. Using the higher threshold of 0.34 x10*9/L, the converse is true: a ‘high’ baseline is less (81.3%, 95%CI 54.4 to 96.0%) predictive of this being the ‘true’ value than a ‘low’ baseline result (97.3% predictive, 95%CI 90.5 to 99.7%).

Table 4.7: Diagnostic accuracy analysis assessing baseline eosinophil value vs. mean value (COMET)

	Index test group (baseline eosinophil value)	Low eosinophil group (mean) (n=)	High eosinophil group (mean) (n=)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+ (95% CI)	LR- (95% CI)
0.15 x10*9/L threshold	Low eosinophil (n=) High eosinophil (n=)	30/35 5/35	4/54 50/54	92.6 (82.1-97.9)	85.7 (69.7-95.2)	90.9 (80.0-97.0)	88.2 (72.5-96.7)	6.5 (2.9-14.6)	0.09 (0.03-0.22)
0.34 x10*9/L threshold	Low eosinophil (n=) High eosinophil (n=)	71/74 3/74	2/15 13/15	86.7 (59.5-98.3)	95.9 (88.6-99.2)	81.3 (54.4-96.0)	97.3 (90.5-99.7)	21.4 (6.9-65.9)	0.14 (0.04-0.51)

Patients with only one eosinophil value have been excluded. Baseline value is excluded from calculation of the participant mean. PPV, positive predictive value. NPV, negative predictive value. LR+, positive likelihood ratio. LR-, negative likelihood ratio.

4.5 Discussion

This chapter has compared the distribution, baseline characteristics and variation of blood eosinophils in both the CPRD and COMET cohorts. Each study is discussed in turn, followed by a final section bringing findings from both studies together.

4.5.1 CPRD study

Summary of findings

Eosinophils had been tested in the previous two years for 64% of patients, at a median of 5.4 months before the initiation of inhaled maintenance treatment. The eosinophil geometric mean was 0.20 x10*9/L. Using a threshold of 0.15 x10*9/L for binary categorisation, 69% patients were classified as being in the 'high' eosinophil group, which, as expected, decreased to 19% if this binary threshold was increased to 0.34 x10*9/L. This was seen because half (50%) of patients fall into a 'medium' category between 0.15 and 0.34 x10*9/L. Patients who were more likely to be in the higher eosinophil group were found to be younger, male, ex-smokers, atopic, with frequent exacerbations (including the need for more prescriptions for oral steroids or GP consultations), increased requirement of salbutamol (suggesting increased symptom burden), and more co-morbidities. However, there was no association with active or historical asthma. Although interesting, these statistically significant associations may be related to large sample size rather than to clinically important differences.

Variation between repeated measurements increased as the eosinophil count increased. ICC was 0.68 (95% CI 0.67 to 0.69), representing good agreement.[143] On continuous analysis, the mean difference was small (<0.01 x10*9/L) and confidence limits included

there being no difference between values on both the untransformed and logarithmic scales, but with clear increase in limits of agreement as the eosinophil value increased (i.e. much more variability with increasing eosinophil count). Higher variation occurred when values close to acute events were included, but not in a way which is likely to translate into clinical significance (ICC reduced to 0.66). Degree of variability did not differ by baseline characteristics either using subgroup analysis to calculate ICC, or regression analysis using other statistical markers of variation. Comparing only two values, there was moderate/substantial agreement using binary categorisations (κ=0.53 and 0.54 for 0.15 and 0.34 x10*9/L cut-offs respectively);[143] in diagnostic accuracy analysis the measurement in question ('index test') was only highly predictive of this being the 'true' group if this was the group with higher prevalence (i.e. depending on which cut-off was being used).

Strengths and limitations

This study is the largest and most detailed so far assessing distribution of eosinophil count and variability from patients with COPD in the CPRD. My findings add to the existing evidence in several ways. I performed sensitivity analyses excluding a history of asthma, atopy and the proximity of measurement of eosinophil count to exacerbations, which in turn produced similar results to the main analyses. This suggests reliability of the main findings and thus generates answers to the study objectives, which focused on those patients starting a new inhaled maintenance medication that may or may not have included an ICS. Careful consideration was given to defining and isolating valid eosinophil counts at the data management stage, incorporating clinical judgement and discussion with laboratory staff – for example in relation to any effect on eosinophil count of acute respiratory illness, or acute infection, or season of blood test (Section 2.3.3). However,

incorporating further sensitivity analyses relating to decisions made about eosinophils at this data management stage, for example including eosinophil counts of zero or excluding less conventional units, would have increased confidence in my findings. My analysis of eosinophil testing has advantages over several other approaches, in that I used different, more appropriate and rigorous statistical methods in which both binary and continuous assessment of eosinophil count were analysed, such as ICC and Bland-Altman which are not reliant on the use of a single threshold to determine repeatability. I also included assessment using the primary eosinophil threshold of 0.15 x10*9/L, and secondary threshold of 0.34 x10*9/L for the majority of analyses, and for eosinophil distribution at five additional eosinophil threshold values.

The cohort size was reduced by only being able to assess those who had valid eosinophil counts: only 64% had had full blood count (and therefore eosinophils) tested in the two years prior to the index date. Although patients may have had a full blood count before this period, it suggests that compliance with the guideline recommendation to do a full blood count at the point of COPD diagnosis[10] is not universally followed. It seems more likely that patients living with COPD will have had a full blood count for reasons other than their COPD. Although findings were similar when results within two weeks of an acute respiratory illness or when individuals with an elevated CRP were excluded (Section 2.3.3), there are many other reasons a patient might have had a blood test. Full blood counts may have been requested, for example, during an acute illness (perhaps infection or anaemia) or as part of assessing other chronic diseases such as chronic renal failure, which were not recorded in this study, but could have had an effect on eosinophil count, or COPD outcomes. Patients with a valid eosinophil count were more likely to be older, with more

GP consultations and co-morbidities, which may be surrogate markers of high contact with primary care services and likelihood of having more frequent blood tests in general, rather than anything related to the COPD. There was an increased testing in general over time, which may relate to a more general propensity to involve blood tests as part of primary care diagnosis and management. Importantly, there was no difference in primary outcome between whether patients had been tested or not, suggesting that using this data to answer subsequent study objectives is likely to be valid.

Most full blood count tests were taken in the six months before initiation of new inhaled maintenance medication (median 5.4 months), and therefore fairly recent, but some blood tests will have been taken up to two years before initiation. This may have added more variability and changes in relation to baseline characteristics, which could change during that time, as well as greater distance from outcomes assessed. In future studies and in additional analyses of my data, length of time since full blood count measurement could be included in further sensitivity analyses.

As discussed in Section 1.2.3, the eosinophil count is likely to vary in individuals with co-morbidities other than COPD. Many of these were not recorded in this study, although key co-morbidities such as asthma and atopy were recorded. However, atopy is a broad definition rarely coded in its own right, and so this group of patients may have been incorrectly identified. In this study, higher eosinophils were associated with atopy and increased prescriptions for oral steroids and salbutamol inhalers, but not associated with active or historical asthma diagnoses. This may therefore reflect those with a more asthma-like phenotype, but with no asthma-related code in their primary care record. Variability was not associated with these underlying co-morbidities in my study. Additional sensitivity

analyses here would have been useful for further delineating these relationships and increasing our confidence in these findings.

Diagnostic accuracy assessment of repeatability was performed as this was recommended as one of the statistical techniques which could be used for binary-categorised measurements,[143] and has been used in other CPRD studies.[100] However, the most recent value ('index test') had to be used in the calculation of the mean due to the small numbers of those who had three or more eosinophil tests, and this risks introducing incorporation bias, which is a potential limitation.[145]

Comparison with other literature

Despite differences in inclusion criteria in other study cohorts (discussed in Section 2.6.2), my study findings are generally consistent with those in the published literature, particularly for eosinophil distribution and repeatability. However, key differences will now be discussed in turn.

In terms of eosinophil distribution, the different thresholds used by other studies, or use of relative rather than absolute eosinophils, make comparisons difficult. Other CPRD studies which examined a continuous rather than binary distribution, found a mean eosinophil count of 0.20[100] and 0.23[95] x10*9/L (vs. 0.20 x10*9/L in my study), but it is not clear for the geometric mean was not used in one of the other studies, which would have resulted in a higher untransformed mean with a right-skewed distribution. Other database studies[107] have also found spikes in histogram distributions due to rounding of eosinophil values to the nearest 0.1 x10*9/L.

Multiple post-hoc analysis of ICS trials has been conducted. A systematic review, by Cheng et al, found that the percentage of those classified as greater than 2% eosinophils (relative to total leucocyte count) varied from 32 to 75% between studies, with a mean of 60%;[109] using the same threshold, the percentage was higher (69.2%) in this study. My data from a primary care population is likely to be more representative of the wider COPD population than this data by Cheng et al. As discussed in Section 1.2.1, COPD trial populations are very different to the general COPD population,[16,17] and eosinophil counts taken from primary care records are likely to be extremely accurate. It may be because those in COPD trials are more likely to be recruited in secondary care with more severe disease and more frequent exacerbations, and eosinophil counts are known to differ between such populations and those cared for predominantly in primary care.[101,146] In this study, I found that patients with more frequent exacerbations were more likely to be in the higher eosinophil group, and those with more severe airflow limitation were more likely to be in the lower eosinophil category. The finding that higher eosinophils are associated with increased exacerbations is now recognised as a feature of the utility of eosinophils in COPD.[35]

Other studies have also varied in terms of association of baseline characteristics with eosinophil count. Several studies have found no association with baseline characteristics,[56,131,133,137] but have a much smaller sample size relative to my CPRD study, so it may be that the large study size here enables weak relationships to be better elucidated. The most repeatable finding between studies appears to be the higher eosinophil counts in males,[47,91,107], with conflicting findings with regards smoking status, age, and exacerbation history,[47,91] although some studies, including ECLIPSE, also found high eosinophils were associated with higher FEV_1 (which was present in unadjusted

analysis in my CPRD cohort).[47,147] I found no association with asthma history, which has been found to be associated with higher eosinophils in some other studies;[75,91,107] this may be because my ICS-naïve inclusion criterion has excluded those with a more asthma-like phenotype who might be more likely to have been on ICS for some time. However, this is not universal, and a study comparing those with asthma and COPD found similar blood eosinophil levels (0.20 x10*9/L) between groups, but a much higher sputum eosinophil (2.6% (95% CI 1.6-4.2) in asthma vs. 1.2% (95% CI 0.8-1.9) in COPD).[44] It is widely recognised that smoking per se affects sputum counts in patients with COPD (less likely to smoke in asthma) and this could thus explain sputum differences in asthma and COPD.[148] As sputum differential counts are not routinely measured in primary care, I could not make any evaluation of this in my studies.

The aspects of the CPRD study on eosinophil repeatability add significantly to the literature, as the majority of studies focus on a single eosinophil count rather than repeated measures. For example, the DiSantostefano *et al* study,[91] which provides other useful data on associations of eosinophil count with baseline characteristics, is limited by being a single snapshot of patients included in the NHANES survey. This was based on spirometry findings and not a clinician diagnosis of COPD, as well as being a selected population of under 80 years old and with various co-morbidities excluded. Findings may therefore be less generalisable to routine clinical practice.

There have been few database studies addressing the question of eosinophil repeatability, and those that have used classification into groups based on stability over time,[95,100] which was similar to my diagnostic accuracy analysis. In their CPRD study, Landis *et al* looked at diagnostic accuracy of staying above threshold values and summarised their findings

beautifully as "*The probability of correct classification is lowest for individuals whose true mean is close to the threshold of interest*".[100] This would mean that using a low threshold of 0.15 x10*9/L to guide ICS treatment would result in the majority of patients being given an ICS due to a raised value at some point.

Landis *et al* found repeated values available for a similar number of patients compared to my study (54% vs. 52%), despite a different cohort definition of patients in the 6 months after COPD diagnosis.[100] There was similar ICC on continuous analysis in this study (0.64) and in another database study (Kerkhof *et* al) using the OPCRD (0.56),[149a] compared to 0.68 in my CPRD study. The Landis study similarly found that ICC decreased when those with more exacerbations in the baseline period were included;[100] the Kerkhof study deliberately did not adjust for baseline exacerbations due to concerns that this could result in overadjustment bias.[149,150] Findings for how baseline characteristics can predict variation have been rather contrasting.[95,100] The Landis study interestingly did an autocorrelation analysis to determine after what duration of time a repeat eosinophil count would be completely independent of the previous one, which resulted in a suggestion that one should wait at least fourteen days before repeating.[100]

4.5.2 COMET study

Summary of findings

The geometric mean for eosinophil counts was 0.16 x10*9/L. Eosinophil counts were slightly lower in COMET than in the CPRD sample (59% 'high' using 0.15 cut-off; 16% using 0.34 cut-off; and 43% in 'medium' category (vs. 69%/19%/50% in CPRD)). There was no

[a] This value is taken from correspondence related to another study, and is reported from unpublished work by the author.

statistically significant association between eosinophil counts and any baseline characteristic, apart from a trend towards a higher count in males (difference 0.05 x10*9/L, p=0.08), suggesting that the lack of associations in COMET compared to CPRD may be related to the smaller sample size.

As in the CPRD study, variation between repeated measurements increased as the eosinophil count increased. The ICC was 0.83 (95% CI 0.77 to 0.87), representing excellent agreement.[143] On continuous analysis, mean difference was small (0.02 x10*9/L) and again there was no difference between values on both the untransformed and logarithmic scales, but with clear increase in variability as eosinophil count increased. In contrast to the CPRD study, eosinophil counts in this study were significantly more stable over time in those who were older, male, ex-smokers with no atopy but who did have positive bronchodilator reversibility. Comparing only two values, there was moderate/substantial agreement using binary categorisations (κ=0.79 and 0.78 for 0.15 and 0.34 x10*9/L cut-offs respectively);[143] in diagnostic accuracy analysis the measurement in question ('index test') was only highly predictive of this being the 'true' group if this was the group with higher prevalence (i.e. depending on which cut-off was being used).

Strengths and limitations

The COMET study is a novel, hypothesis-driven individually-recruited observational study that prospectively recorded repeated eosinophil measurements in a steroid-naïve COPD population in primary care. The findings presented here are novel and potentially useful, especially the finding about eosinophil repeatability which has not previously been studied in this way, or with such statistical rigour. Most participants had four study-specific eosinophil counts performed, without the biases associated with retrospective database

studies (i.e. it not being completely clear why the full blood count was done). Eosinophils were, on average, lower in the prospective COMET cohort than in the CPRD retrospective cohort (0.16 vs. 0.20) more stable (lower SD and IQR of mean), and with greater repeatability of repeated measurements. This could relate to the slightly differing populations, as discussed in Section 3.6.2, where those in CPRD are more likely to be at the point of a deteriorating disease state rather than fairly stable; that more extreme values are found in the CPRD cohort were not captured by the smaller sample size of COMET; or that the COMET study, by its design, was in a more controlled study setting and testing was over a shorter overall duration. This shorter study duration is a limitation though, in that it would also have been helpful to know how eosinophil count varies over a longer duration in this population. Duration of follow up was contained by feasibility parameters of the doctoral program nature of the COMET study.

Sensitivity analyses were conducted for mean vs. single eosinophil value, bronchodilator reversibility and excluding those who did not fulfil diagnostic criteria for COPD, and these had minimal impact on results. However, sensitivity analyses in a small prospective, hypothesis-driven cohort study are likely to be less important compared to larger, retrospective database studies. Many patients did not have “gold standard” diagnostic spirometry conducted either at baseline or previously recorded in their notes, and there was a high proportion (22%) of patients with bronchodilator reversibility, suggesting that some patients had asthma rather than COPD (as previously discussed in Section 3.6.2). However, this is the reality of general practice, in that many of these patients are being managed as having COPD, and in some respects, this is more useful for translation of findings to everyday practice, compared with studies that relied on strict spirometry entry

criteria in terms that may not be attainable in routine primary care. As also discussed in Section 3.6.2 in relation to cohort demographics, the study population (by virtue of being steroid-naïve and fit enough to want to participate in a study) was made up of those who had less severe and greater stability of disease, with relatively few exacerbations. This may make the findings of eosinophil distribution and variability less generalisable to the whole COPD population, particularly those who would be at the point of initiating or increasing inhaled maintenance medication.

Comparison with other literature

Eosinophil distribution in the COMET study resulted in a high number of patients being classed as having 'high' eosinophil counts (69%), which would result in a very high number of people being given ICS, if this were used as the cut-off for treatment. This proportion is much higher than in the trial populations, and likely to be reflective of lower values generally in primary care, which is a novel finding. These findings are likely to be valid, as both studies indicate this, and the potential reasons for the difference compared to trials are discussed above in Sections 2.6.1, 2.6.2 and 4.5.1. That said, in the COMET study the generalisability of findings to all COPD patients is a potential issue for external validity, as patients were generally stable and with mild disease, rather than requiring further medical input resulting in a change of their medication.

Looking at absolute eosinophil counts, findings are similar to other prospective cohort studies, including a large German COPD cohort of 2,741 patients, where a fifth or fewer of patients had 'high' eosinophils when a high threshold of 0.30 or 0.34 x10*9/L was used, but when this reduced to 0.15 x10*9/L it encompassed the majority of patients.[134,135]

The COMET study found a higher eosinophil count in males which is similar to other studies, but given the use of the mean eosinophil value to look for associations with baseline characteristic and the fact that only 93 patients could be included in this analysis, sample size is likely to be a limitation for precision of my parameter estimation.

In contrast, the use of repeated values to assess variability of eosinophil values is a key strength of this study, as this has rarely been investigated elsewhere, and 318 samples were available for this analysis. The ICC for COMET was 0.83 (95% CI 0.77 to 0.87) (excellent agreement)[143] and this is higher than in the Leicester MRC COPD cohort (ICC 0.79 over 3 months),[35] which is not unexpected as this was a secondary care population in which most patients were receiving inhaled corticosteroids where we would expect a greater variability. Interestingly, repeatability of sputum (rather than blood) eosinophil counts has only been moderate (0.63[151] and 0.49[152]), albeit over shorter durations of 2 and 12 weeks respectively, and this suggests that blood eosinophil count may be a more stable biomarker to use, as well as being easier to obtain than sputum counts.

The finding that variability of eosinophil count increases with magnitude of eosinophil count (i.e. it is less repeatable for higher values) has been replicated in other prospective cohort studies.[131] In keeping with this, concordance between two values decreases as the eosinophil cut-off increases;[153] and with a low threshold of 0.15 x10*9/L, 65 to 74% patients had at least one count above this value when repeated.[132,135] This means that the majority of patients would be classified as 'high' eosinophils and potentially be prescribed ICS if this cut-off were being used to guide ICS prescribing.

4.5.3 Conclusions

The various objectives on eosinophil testing, distribution, association with baseline characteristics and repeatability have been fulfilled. It is a great strength that similar questions targeted at very different cohorts, one in a primary care database and another in a prospective observational study, with different inclusion criteria, resulted in similar findings, particularly for repeatability where the COMET study provides a large number of data points, and where both study findings are congruent with other published study findings. This is the only prospective study that has examined repeatability and stability of eosinophils in a novel, detailed and statistically accurate way, in a primary care population. The study designs may also bring potential biases in terms of reasons for FBC being tested (CPRD), and in terms of generalisability in terms of the relatively mild included population (COMET), but multiple strategies were used to minimise these biases.

Implications for clinical practice and future research will be discussed in detail in the final chapter. However, key points to take forwards include that the majority of primary care patients lie in the 'medium' category of eosinophils 0.15 to 0.34 x10*9/L, such that if a single binary threshold is used, where it is placed will make a big difference to how patients are classified; and that as repeatability varies according to the eosinophil count, a single value is likely to be more useful for decision-making at lower eosinophil counts.

Chapter 5: Eosinophil counts in primary care COPD populations: association with outcomes

This chapter presents the results and discussion of the descriptive component of the CPRD study (aim Ib), assessing the association of blood eosinophils with disease prognosis. The cohort was established primarily for the purpose of answering aim II, and therefore these results are presented as exploratory analysis.

Main methods for developing the cohort were presented in Chapter 2, but detailed statistical methods, including subgroup and sensitivity analyses, are presented here.

To summarise, aims for this part of the study were as follows:

Ib: To investigate whether baseline blood eosinophil count predicts disease outcomes over time, in the population starting a new inhaled maintenance treatment

Including specific objectives:

- To assess disease outcomes in the time period following starting the new inhaled maintenance treatment
- To assess the contribution of baseline blood eosinophil counts to disease outcomes

Outcomes for the entire cohort (not just those who had valid eosinophil counts) were described in Section 2.5. Results in this chapter focus on the whole population commencing a new inhaled maintenance medication, regardless of what the drug group was (Chapter 6 will go on to detail analyses by drug group (ICS vs. non-ICS) to establish ICS responsiveness by eosinophil group).

5.1 Methods

5.1.1 Detailed statistical methods

A Cox proportional hazards model was used to assess disease outcomes (time-to-first exacerbation, pneumonia, hospitalisation and death) in the period following starting the new inhaled maintenance treatment (index group), by eosinophil group. I excluded patients with events in the first 30 days following index date to reduce protopathic bias (when treatment appears to cause the outcome due to lag time from first symptoms and start of treatment before diagnosis), as in other studies.[89] For the main models, the proportional hazards assumption was assessed both graphically and using formal statistical tests; for those variables where it was not met ($p<0.05$), the model was re-run using the time-dependent variable command for these variables to check that it did not make any difference to the outcomes of interest.

5.1.2 Subgroup and sensitivity analyses

I conducted subgroup analyses by exacerbation history and smoking status, and stratifying eosinophils into low (<0.15), medium (0.15-<0.34) and high (≥0.34) groups. The addition of sub-group analysis from current smokers followed recent publication of post-hoc analysis of trials suggesting that current smokers particularly benefit from ICS[59].

Sensitivity analyses of the exacerbation outcome were as follows:

- different cut-offs for blood eosinophils (0.10, 0.20, 0.30, 0.34 (as this had been used in other recently published studies[74,95]), 0.40 and 0.50 x10*9/L); percentage eosinophils (<2%, ≥2-<4% and ≥4%)); low (<0.15), medium (0.15-<0.34) and high

(≥0.34) groups; and continuously (which tells us if there is a linear effect for presence or absence of association which is most useful to look at for overall association; transformed data were used as appropriate)

- using mean of blood eosinophils over prior two years, rather than most recent value before index date
- including blood eosinophil values close to an acute event
- excluding those with the highest eosinophils (≥0.5 x10*9/L)
- including season of eosinophil test (see Section 2.3.3)
- excluding patients with current asthma and any history of asthma
- excluding patients with a history of atopy
- including those who experienced an event in the first month after index date
- including airflow limitation severity and MRC breathlessness scale in the model (see Section 2.2.9)
- adding drug type to the model[a]

5.2 Time-to-first exacerbation outcome

963 patients had an exacerbation in the first month after initiating treatment and were excluded from this analysis. The remaining 17,272 patients provided 77,189 years of follow-up (median 4.1 years per person (IQR 2.2 to 6.4; range 0.5 to 11.2)), of whom 12,529 (72.5%) experienced an exacerbation during follow-up. Table 5.1 shows the main Cox regression model and Figure 5.1 shows the Kaplan-Meier curve; there was a longer time-to-first exacerbation in the high eosinophil group but this did not quite reach significance (adjusted HR 0.96 (95% CI 0.93 to 1.00, p=0.07).

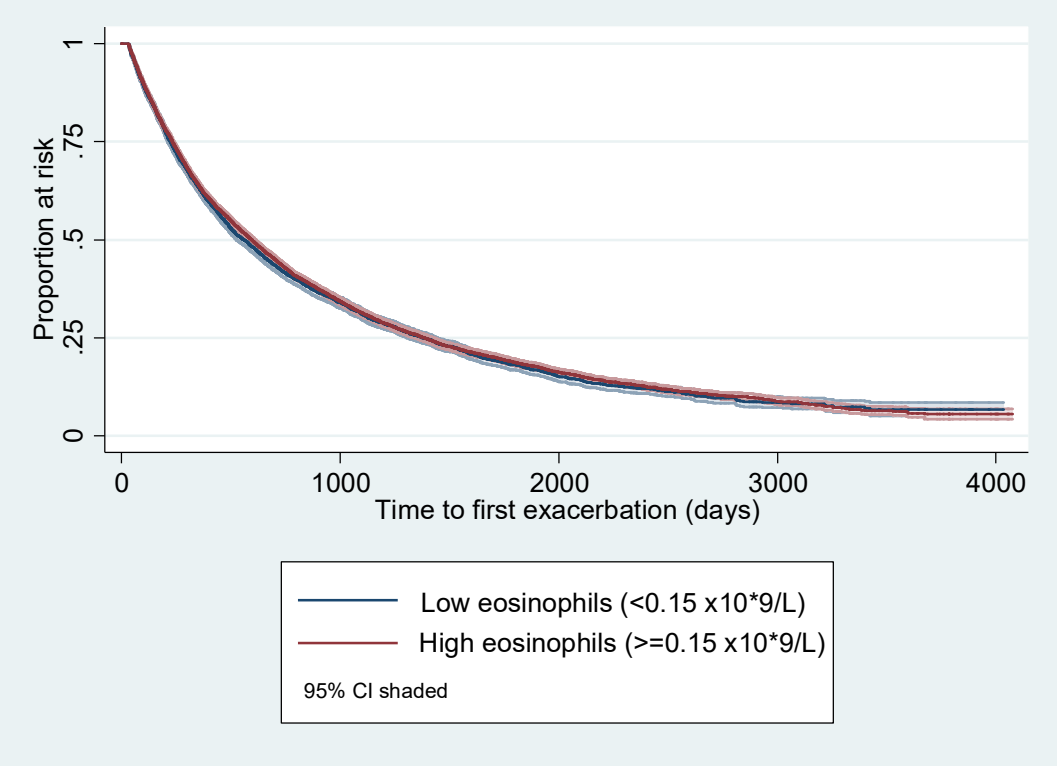
[a] Thia was following queries at conferences whether an association in the continuous model was related to the effect of drug type.

Table 5.1: Cox regression model for time-to-first exacerbation of cohort with valid eosinophil counts

Valid blood eosinophil count	Median time-to-first exacerbation (years) (95% CI)	Unadjusted hazard ratio for time-to-first exacerbation (95% CI, p-value) n=17,272	Adjusted hazard ratio for time-to-first exacerbation (95% CI, p-value) n=17,194
Low (<0.15 x10*9/L)	1.53 (1.44-1.61)	1.00 (ref) n=5,354	1.00 (ref) n=5,322
High (≥0.15 x10*9/L)	1.63 (1.57-1.68)	0.98 (0.94-1.01), p=0.22 n=11,918	0.96 (0.93-1.00), p=0.07 n=11,872

Hazard ratios calculated using Cox regression, adjusted for: age group; sex; socio-economic status; smoking status; asthma history; atopy history; baseline exacerbations, pneumonia episodes, oral steroid prescriptions, and salbutamol inhaler prescriptions; theophylline, nebuliser and oxygen use; baseline non-elective hospitalisations and GP consultations; Charlson co-morbidity index; influenza and pneumococcal vaccination; and year of index prescription. Variables were included in multivariate analysis if $p<0.10$ in univariate analysis or likely clinical importance (asthma status). Adjusted n=17,194 due to complete case analysis (missing data for socio-economic status and smoking status). For some variables in the model the proportional hazards assumption was not met (baseline exacerbations, pneumonia episodes, oral steroid prescriptions, and salbutamol inhaler prescriptions; nebuliser use; baseline non-elective hospitalisations and GP consultations; pneumococcal vaccination). However, incorporating them into the model with the time-dependent variable command made no difference to the key results.
(ref), reference group

Figure 5.1: Kaplan-Meier curve for time-to-first exacerbation in high vs. low eosinophil groups



5.2.1 Analysis with different eosinophil thresholds

Distribution of patients between eosinophil count groups using different thresholds was shown in Figure 4.5. Table 5.2 shows unadjusted and adjusted hazard ratios for time-to-first exacerbation for different eosinophil thresholds, as well as continuous analysis. There was no, or weak, association of blood eosinophil count with exacerbation outcome when eosinophil count was analysed as a binary variable with different thresholds in unadjusted or adjusted analyses. There was no association when blood eosinophils were grouped into three categories by count (<0.15, 0.15-<0.34, ≥0.34 x10*9/L) or by percentage (<2, 2-4, ≥4%) in unadjusted or adjusted analyses. There was a weak association between higher eosinophils and a longer time-to-first exacerbation (i.e. better prognosis) in continuous

adjusted analysis using log-transformed eosinophils (adjusted HR 0.97, 95% CI 0.94 to 1.00, p=0.03).

Table 5.2: Outcomes for time-to-first exacerbation for different eosinophil thresholds (CPRD) (sensitivity analysis)

	Unadjusted hazard ratio[c] for high vs. low eosinophil group (95% CI, p-value)	Adjusted hazard ratio[c] for high vs. low eosinophil group (95% CI, p-value)
Eosinophil thresholds[a] (sensitivity analysis)		
0.10 x10*9/L	1.00 (0.92-1.08), p=0.97	0.98 (0.90-1.06), p=0.54
0.15 x10*9/L (main analysis)	0.98 (0.94-1.01), p=0.22	0.96 (0.93-1.00), p=0.07
0.20 x10*9/L	0.99 (0.95-1.03), p=0.56	0.98 (0.94-1.01), p=0.22
0.30 x10*9/L	0.99 (0.96-1.03), p=0.74	0.97 (0.94-1.01), p=0.15
0.34 x10*9/l	0.98 (0.94-1.03), p=0.50	0.95 (0.91-1.00), p=0.03
0.40 x10*9/L	1.00 (0.95-1.04), p=0.88	0.97 (0.92-1.01), p=0.15
0.50 x10*9/L	1.00 (0.94-1.07), p=0.99	0.97 (0.91-1.03), p=0.28
Eosinophil categorical analysis (subgroup analysis)		
<0.15 x10*9/L (n=5,354)	1.02 (0.98-1.06), p=0.29	1.02 (0.98-1.07), p=0.23
0.15-0.34 x10*9/L (n=8,575)	1.00 (ref)	1.00 (ref)
≥0.34 x10*9/L (n=3,343)	0.99 (0.95-1.04), p=0.77	0.96 (0.92-1.01), p=0.09
Eosinophil percentages[b] (subgroup analysis)		
<2% (n=5,312)	1.02 (0.98-1.06), p=0.37	1.02 (0.98-1.06), p=0.40
2-4% (n=7,290)	1.00 (ref)	1.00 (ref)
≥4% (n=4,645)	1.00 (0.96-1.05), p=0.96	0.98 (0.94-1.02), p=0.34
Eosinophils as continuous variable (logarithmically transformed) (sensitivity analysis)		
Continuous	0.99 (0.96-1.02), p=0.41	0.97 (0.94-1.00), p=0.03

(ref), reference group

[a] n for the different binary thresholds of eosinophil count are detailed in Figure 4.5.

[b] Eosinophil percentages are as percentage of total leucocytes; leucocytes missing for n=25.

[c] Cox regression model as detailed in Table 5.1 (n=17,272 unadjusted and n=17,194 adjusted). Proportional hazards assumption was valid for all eosinophil-related variables.

5.2.2 Subgroup and sensitivity analyses of time-to-first exacerbation outcome

Subgroup and sensitivity analyses are shown in Table 5.3. These are broadly divided into disease-related, eosinophil-related and methodological subgroup and sensitivity analyses, and results are given for two eosinophil thresholds (0.15 and 0.34 x10*9/L) and continuous eosinophils. The weak association of higher eosinophils with better outcomes was only present in current smokers. There was a much stronger association of higher eosinophils

with better prognosis in those with asthma and in those with atopy. There was no association with baseline exacerbation frequency. Including those who had an exacerbation in the first month after initiation of maintenance treatment, despite increasing the sample size, removed the association. The sensitivity analysis adding drug type to the model did not alter the effect size. There was no change in results in complete case analysis including airflow limitation severity and MRC breathlessness scale, or various eosinophil-related sensitivity analyses (Table 5.3).

Table 5.3: Subgroup and sensitivity analyses for time-to-first exacerbation by baseline blood eosinophils

Groups as applicable	**Adjusted hazard ratio (95% confidence interval, p-value) [a]**		
	0.15 x10*9/L eosinophil threshold	**0.34 x10*9/L eosinophil threshold**	**Continuous eosinophils[b]**
Main analysis			
(n=17,272)	0.96 (0.93-1.00), p=0.07	0.95 (0.91-1.00), p=0.03	0.97 (0.94-1.00), p=0.03
Disease-related subgroup and sensitivity analyses			
Smoking status (subgroup analysis)			
Ex-smokers (n=9,988)	0.97 (0.92-1.02), p=0.18	0.97 (0.92-1.03), p=0.35	0.98 (0.94-1.01), p=0.22
Current smokers (n=7,218)	0.97 (0.91-1.02), p=0.24	0.92 (0.86-0.99), p=0.03	0.96 (0.92-1.00), p=0.06
Asthma status (main analysis includes all asthma)			
Excluding active asthma (n=16,644)	0.97 (0.93-1.01), p=0.11	0.96 (0.91-1.00), p=0.06	0.97 (0.95-1.00), p=0.07
Excluding all asthma (n=14,240)	0.96 (0.92-1.00), p=0.04	0.98 (0.93-1.03), p=0.40	0.98 (0.95-1.01), p=0.16
Only those with asthma (n=3,032)	0.99 (0.90-1.08), p=0.80	0.84 (0.76-0.93), p=0.001	0.93 (0.87-0.99), p=0.02
Atopy (main analysis includes those with atopy)			
Excluding any atopy (n=12,581)	0.98 (0.94-1.03), p=0.43	0.98 (0.93-1.03), p=0.44	0.99 (0.95-1.02), p=0.41
Only those with atopy (n=4,691)	0.91 (0.85-0.98), p=0.02	0.88 (0.81-0.96), p=0.003	0.92 (0.87-0.97), p=0.003
Baseline exacerbation frequency (subgroup analysis)			
Low exacerbation rate (0 or 1) (n=14,204)	0.97 (0.93-1.01), p=0.16	0.97 (0.92-1.02), p=0.18	0.98 (0.95-1.01), p=0.14
Higher (≥2) exacerbation rate (n=3,068)	0.96 (0.88-1.05), p=0.37	0.94 (0.85-1.03), p=0.18	0.96 (0.91-1.03), p=0.26

Groups as applicable	Adjusted hazard ratio (95% confidence interval, p-value) [a]		
	0.15 x10*9/L eosinophil threshold	**0.34 x10*9/L eosinophil threshold**	**Continuous eosinophils[b]**
Methodological subgroup and sensitivity analyses			
Including severity and MRC breathlessness scale (not included in main analysis due to large amounts of missing data)			
Including severity and MRC (n=6,578)[c]	0.98 (0.91-1.05), p=0.51	1.00 (0.93-1.09), p=0.92	0.99 (0.94-1.04), p=0.79
Protopathic bias (main analysis excludes those with exacerbation in first month after treatment initiation)			
Including outcome in first month (n=18,235)	0.98 (0.94-1.02), p=0.26	0.96 (0.92-1.00), p=0.06	0.98 (0.95-1.01), p=0.14
Adding drug type (whether maintenance treatment initiated ICS vs. non-ICS) to the model			
Including drug type (n=17,272)[c]	0.96 (0.93-1.00), p=0.06	0.95 (0.91-0.99), p=0.03	0.97 (0.94-1.00), p=0.03
Eosinophil-related subgroup and sensitivity analyses			
Eosinophil means (main analysis uses most recent eosinophil result)			
Using mean of all previous results (n=17,272)	0.99 (0.95-1.03), p=0.55	0.95 (0.91-0.99), p=0.02	0.97 (0.94-1.00), p=0.04
Including season of eosinophil test as variable in model			
Including eosinophil test season (n=17,272)[c]	0.96 (0.93-1.00), p=0.06	0.95 (0.91-1.00), p=0.03	0.97 (0.94-1.00), p=0.03
Excluding those with eosinophils ≥0.50 x10*9/L			
Excluding eosinophils ≥0.50 x10*9/L (n=15,818)	0.97 (0.93-1.00), p=0.08	0.95 (0.89-1.00), p=0.05	0.96 (0.93-1.00), p=0.04
Including eosinophil values close to acute events (exacerbation/pneumonia/episode/C-reactive protein >100mg/L) which main analysis excludes			
Including eosinophils close to acute event (n=18,073)	0.97 (0.94-1.01), p=0.13	0.96 (0.92-1.00), p=0.05	0.97 (0.95-1.00), p=0.04

[a] Hazard ratios are for time-to-first exacerbation comparing high eosinophil with low eosinophil group (hazard ratio >1 indicates higher risk in high eosinophil group), or continuous analysis. Model is adjusted for covariates as in detailed in legend for Table 5.1. Analyses are sensitivity analyses except where stated as subgroup analyses.

[b] Continuous eosinophils were logarithmically transformed for analyses.

[c] Inclusion of severity and MRC breathlessness scale in the model did improve it (p<0.001) and also for inclusion of drug type (p=0.002) but test season did not (p=0.14).

5.3 Other outcomes

Time-to-event analyses for the other outcomes are presented in Table 5.4, using the 0.15 and 0.34 x10*9/L thresholds, and for continuous eosinophils.

Table 5.4: Other outcomes for time-to-first event by baseline blood eosinophils

Number experiencing outcome/total	Adjusted hazard ratio (95% confidence interval, p-value)[a]		
	0.15 x10*9/L eosinophil threshold	**0.34 x10*9/L eosinophil threshold**	**Continuous eosinophils[b]**
Pneumonia episodes			
n=8,188/17,616	0.96 (0.92-1.01), p=0.14	0.96 (0.91-1.02), p=0.15	0.97 (0.93-1.00), p=0.05
Hospitalisation due to any cause			
n=12,446/17,307	0.95 (0.91-0.98), p=0.006	0.95 (0.91-0.99), p=0.02	0.96 (0.93-0.99), p=0.003
Hospitalisation due to pneumonia			
n=2,836/18,194	0.81 (0.75-0.87), p<0.001	0.93 (0.85-1.02), p=0.14	0.88 (0.83-0.93), p<0.001
Hospitalisation due to COPD			
n=4,821/18,081	0.89 (0.84-0.95), p<0.001	0.96 (0.89-1.03), p=0.23	0.94 (0.90-0.99), p=0.02
Death due to any cause			
n=3,836/18,235	0.88 (0.82-0.94), p<0.001	0.95 (0.87-1.03), p=0.19	0.91 (0.86-0.96), p<0.001
Death due to pneumonia			
n=134[c]/18,235	0.59 (0.42-0.85), p=0.004	1.33 (0.89-2.00), p=0.16	0.79 (0.60-1.04), p=0.10
Death due to COPD			
n=962/18,235	0.76 (0.66-0.87), p<0.001	0.90 (0.76-1.06), p=0.21	0.84 (0.76-0.93), p=0.001

[a] Hazard ratios are for time-to-first event comparing high eosinophil with low eosinophil group (hazard ratio >1 indicates higher risk in high eosinophil group), or continuous analysis. Model is adjusted for covariates as detailed in legend to Table 5.1. As in the exacerbations analysis, those experiencing the event of interest in the first month after initiating treatment were excluded.

[b] Continuous eosinophils were logarithmically transformed for analyses.

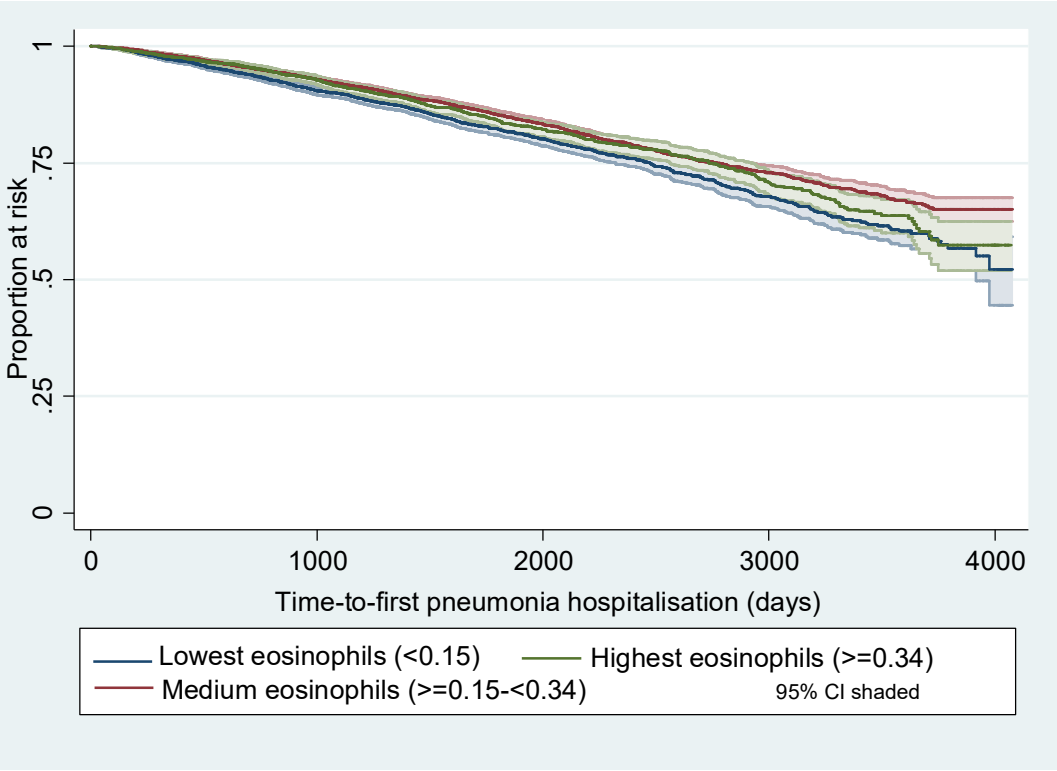
[c] Low number of deaths due to pneumonia likely to be because of changes in coding of primary cause of death by the Office for National Statistics away from acute causes to chronic underlying causes (CPRD ONS Death Registration Data Data Specification V1.5 (15 August 2016).

There was a strong association of higher eosinophils with a better prognosis for hospitalisations due to pneumonia, hospitalisations due to COPD, and death due to any cause, pneumonia or COPD, particularly at the 0.15 x10*9/L threshold and using continuous eosinophils, but not present at the 0.34 x10*9/L threshold.

Further analyses were carried out to assess this strong association of higher eosinophils with better prognosis. Subgroup analysis by baseline blood eosinophil group ((low (<0.15), medium (0.15-<0.34), or high (≥0.34 x10*9/L)) for pneumonia hospitalisation showed a high risk in the lowest eosinophil group, with similar risks between the medium and high groups (HR 0.81 (0.74 to 0.88, p<0.001) in the medium vs. low eosinophil group and HR 0.81 (0.73 to 0.91, p<0.001) in the high vs. low group). Figure 5.2 shows a Kaplan-Meier survival curve of time-to-first pneumonia hospitalisation by baseline eosinophil group for these three groups.

Adding drug type to the model (in case of this being reflective of responsiveness or not to ICS treatment in the high vs. low eosinophil groups) did not alter results (HR 0.81 (95%CI 0.75 to 0.87, p<0.001) for pneumonia hospitalisation at the 0.15 x10*9/L threshold.

Figure 5.2: Time-to-first pneumonia hospitalisation by baseline eosinophil group



5.4 Discussion

5.4.1 Summary of findings

This chapter has covered the association of baseline eosinophil count with disease outcomes over time, using the CPRD cohort. For the time-to-first exacerbation outcome, using the 0.15 x10*9/L threshold for classifying eosinophils as 'high' or 'low', there was a trend towards better prognosis in the high eosinophil group (adjusted HR 0.96 (95% CI 0.93 to 1.00, p=0.07), and this persisted across all binary thresholds except for 0.34 x10*9/L, where it just reached significance (p=0.03). In continuous analysis, there was a weak association of higher eosinophils with longer time-to-first exacerbation (adjusted HR 0.97, 95% CI 0.94 to 1.00, p=0.03). This association was i) only present in current smokers; ii) much stronger in those with asthma or atopy, and iii) did not seem to relate to ICS use during follow-up.

There was strong association of higher eosinophils with a longer time to event (i.e. better prognosis) for hospitalisations due to COPD or pneumonia, and death due to any cause, pneumonia or COPD, particularly at the 0.15 x10*9/L threshold and using continuous eosinophil analysis. These associations were not seen at the 0.34 x10*9/L threshold, which is likely to be because the highest risk of adverse outcome is in the lowest (<0.15 x10*9/L) eosinophil group.

5.4.2 Strengths and limitations

Due to the large cohort, and resultant narrow confidence intervals, with results repeatable at various eosinophil thresholds and in multiple sensitivity analyses, we can be fairly confident in the findings that there is a prognostic benefit to higher eosinophils in this

cohort; and that very low eosinophils (<0.15 x10*9/L) are likely to be associated with a worse prognosis across all outcome measures assessed. However, additional sensitivity analyses by data management decisions in relation to isolating eosinophil count, for example how different units were dealt with and limits for probable anomalous values, would add confidence to the findings. Overadjustment bias[150] is unlikely to be an issue due to similar results across both unadjusted and adjusted analyses.

Most patients experienced an exacerbation in follow-up (72.5%); although I used an exacerbation definition based on a validated algorithm,[88] it is possible that symptoms related to exacerbations may be misinterpreted and milder exacerbations not be captured. However, missing information for these is likely to be equally distributed between the eosinophil groups.

In a study using routinely collected data, it is possible that eosinophils were tested for other reasons (and indeed there was a difference between those tested and not tested, see Section 4.1.2), and this might result in confounding in relation to assessment of prognosis. However, we would expect this to be similar between baseline eosinophil groups. The time-to-first exacerbation analysis excluded eosinophil counts close to an exacerbation event, because of the risk that this might influence the value, but a sensitivity analysis including these values made little difference to results. This was also found in post-hoc sensitivity analysis in the Kerkhof *et al* OPCRD study where there was no relevant difference in results after excluding those patients with blood eosinophil counts measured at an exacerbation.[75] Sensitivity analysis using the mean of eosinophil counts before the index date rather than the most recent value also did not significantly change results.

The main outcome of interest related to exacerbations, but I also explored another eight outcomes. Exploring multiple hypotheses, even when pre-specified, carries the risk of finding positive associations simply by virtue of multiple testing. This could happen due to chance five percent of the time, when using a p-value of 0.05.[154] In relation to prognosis, all outcomes were in the same direction (hazard ratio less than 1), despite varying p-values and confidence limits, suggesting that multiple testing is unlikely to be an important issue here.

5.4.3 Comparison with other literature

There have been contrasting findings in the literature in terms of association of eosinophils with disease outcomes in COPD, although cohort definitions and method of measuring outcomes have varied between studies, which might explain the differences. There is difficulty defining optimal eosinophil cut-off points, and other studies have used a wide range of eosinophil count thresholds, which also makes comparisons between studies difficult. It is a strength of my study that findings remained consistent across sensitivity analysis using different eosinophil count thresholds, and this is the first study to assess such a wide range of thresholds, in a primary care population. The population included in my study is less selective than in prospective observational studies, certainly in terms of disease severity and co-morbidities, albeit that it is the ICS-naïve group commencing an inhaled maintenance medication.

Early general population studies in the Netherlands[50] and Copenhagen[74] suggested that blood eosinophilia (defined using 0.275 and 0.34 x10*9/L thresholds respectively) is associated with increased all-cause mortality[50] and exacerbations during follow-up;[74] however the Copenhagen study used pre-bronchodilator spirometry, and studies on the

general population in other countries may not be directly applicable to patients with COPD in the UK. The Kerkhof *et al* OPCRD study mentioned above looked at risk factors for having two or more exacerbations during follow-up and found an OR 1.29 (95% CI 1.10-1.51) for eosinophilia ≥0.5 x10*9/L,[75] whereas at this threshold I found no prognostic effect (HR 0.97 (95% CI 0.91 to 1.03), p=0.28). This study was also restricted to ex-smokers, which was replicated in a further OPCRD study by the same group, where blood eosinophils ≥0.45 x10*9/L were associated with higher exacerbation rate in the following year.[105] Although I did not find a higher risk in ex-smokers, the protective effect of higher blood eosinophils was only present in current smokers, which might partly explain the different findings. There are issues of bias in epidemiological studies of a 'healthy smoker' effect, where those who have health problems are more likely to quit.[155]

Another study using the CPRD (Oshagbemi *et al*, which had similar overall aims to the hypothesis-testing component of my CPRD study, addressed in Chapter 6) has shown no association of baseline eosinophils with outcomes,[106] and likewise there has been no association found in some prospective cohort studies,[133,134,137,156] although these might be limited by small sample size (where we would not expect a small benefit to be apparent) as well as different inclusion criteria. There was also no association with outcomes found in post-hoc analysis of the FLAME[a] trial,[56] which excluded patients with very high eosinophil counts (>0.6 x10*9/L); excluding eosinophil counts ≥0.5 x10*9/L did not make any difference to my results in sensitivity analysis. Studies of large blood biomarker panels

[a] FLAME (Effect of Indacaterol Glycopyronium vs Fluticasone Salmeterol on COPD Exacerbations) study, which compared LABA/LAMA with LABA/ICS.

investigating exacerbations over time found only poor reproducibility between cohorts in terms of utility of blood biomarkers.[157]

However, other studies have demonstrated an association of higher eosinophils with better exacerbation outcomes.[147] Particularly, various studies have shown no difference in exacerbation outcomes, but improvements in other outcomes, such as all-cause mortality[131,132,136,158] or rate of FEV_1 decline[134] or emphysema progression.[47] My finding that there was a strong association of lower eosinophils with pneumonia hospitalisations and deaths has been replicated in a post-hoc meta-analysis of ten ICS trials (HR for pneumonia adverse events low vs. high eosinophils 1.31 (95% CI 1.06 to 1.62)).[159]

Because of the contrasting findings with several other studies, I explored whether this could relate to my specific study cohort of those initiating a new maintenance treatment, on the grounds that the higher eosinophil group could be identifying those who would then do well on an ICS treatment. However, on examining the association with drug type (ICS vs. non-ICS), although this did improve the statistical model, it did not make any difference to the hazard ratios for high vs. low, or continuous, eosinophil count. Other database studies have found that those with eosinophils ≥0.15 x10*9/L had more health care resource usage and higher exacerbation rates, irrespective of inhaler use.[160] It is also possible that other different study inclusion criteria could account for differences: some studies excluded all patients with asthma and/or atopy,[56,131,132] and I found a particularly strong association of higher eosinophils with better prognosis in subgroup analysis looking only at those with asthma or atopy. This suggests that some of the positive prognostic association with eosinophil group found overall may be the inclusion of patients with asthma or atopy, even with adjustment for baseline characteristics such as severity and

prior exacerbation frequency, which might be expected to be less severe in a population with asthma-like features which would potentially be more steroid-responsive. This also fits with a prospective cohort study suggesting that COPD patients with more asthma-like features (but without an asthma diagnosis) had better outcomes and mortality than those without that asthma phenotype.[134]

Others have postulated that the contrasting findings between studies in terms of predictive value of eosinophils for disease outcomes may relate to more complicated eosinophil biology than previously thought, and only a weak correlation between eosinophils in sputum versus peripheral blood.[161] Particularly, higher blood eosinophil counts may have a beneficial effect on survival because eosinophils constitute a major component of the innate immune response against infections.[162] This is further supported when retrospective analyses have shown that eosinopaenia (defined as eosinophils <0.05 x10*9/L) is associated with an increased risk of sepsis and worse outcome in patients presenting with COPD exacerbations.[101] This might also explain why in general it is those studies with a high number of exacerbators which show an increased risk of poor outcomes with high eosinophils, whereas those which have a lower number of exacerbators do not.[163]

5.4.4 Conclusions

In summary, the relationship between eosinophils and prognosis is likely to be complicated. This study shows a weak association of higher eosinophils with reduced exacerbation risk, and a stronger association with pneumonia, hospitalisation and mortality outcomes, but this is not replicated throughout the literature; however my study is likely to be more generalisable and my findings are replicable across multiple eosinophil

thresholds. Certainly, we should not assume from these findings that therapies geared towards reducing the eosinophil count would necessarily be beneficial, as we move in the next chapter towards looking at the role of blood eosinophils in predicting inhaled corticosteroid responsiveness.

Chapter 6: Use of blood eosinophils to predict inhaled steroid responsiveness

This chapter presents the detailed methods, results and discussion of the hypothesis-testing component of the CPRD study (aim II), which had objectives as follows:

II: To test whether baseline blood eosinophil count predicts inhaled steroid responsiveness

Including specific objectives:

- To compare disease outcomes over time between patients starting treatment with ICS and those starting treatment with a non-ICS inhaled maintenance treatment
- To stratify the above by baseline blood eosinophil count to assess whether this modifies effectiveness of treatment (whether disease outcomes differ between treatment exposure in different blood eosinophil groups)
- To investigate whether there is dose-response for this effect, by different cut-offs of eosinophil count and different doses of ICS treatment

Overall methods for establishing the larger cohort for this study were described in Chapter 2. This chapter describes the smaller cohort of those who continued on maintenance medication for at least six months, with data management steps for this, distribution of patients between drug groups by baseline characteristics, and outcome analysis with subgroup and sensitivity analysis and secondary outcomes.

6.1 Methods

6.1.1 Detailed statistical methods

A Cox proportional hazards model was used to assess disease outcomes (primary outcome: time-to-first exacerbation; secondary outcomes: pneumonia, hospitalisation and death) in the period following starting the new inhaled maintenance treatment, by drug group (ICS

vs. non-ICS). Inclusion of an interaction term looked for effect modification by blood eosinophils (due to the difference in response to treatment between eosinophil groups being more relevant than the effect size itself). I elected not to use propensity score methods for Aim II analysis because this would be unlikely to completely eliminate potential confounding,[164] and our interest in the interaction rather than the absolute hazard ratios for ICS vs. non-ICS (which is better assessed in trials rather than observational cohort studies).

I excluded patients with events in the first 30 days following index date to reduce protopathic bias (when treatment appears to cause the outcome due to lag time from first symptoms and start of treatment before diagnosis), as in other studies.[89] For the main models, the proportional hazards assumption was assessed both graphically (*stphplot*) and using a formal statistical test (*estat phtest*); for those variables where it was not met ($p<0.05$), the model was re-run using the time-dependent variable command for these variables to check that it did not make any difference to the outcomes of interest.

6.1.2 Subgroup and sensitivity analyses

Subgroup and sensitivity analyses were exactly as detailed for assessment of outcomes by eosinophil group (Section 5.1.2), as well as subgroups by ICS dose (detailed in Section 2.2.7). Post-hoc sensitivity analysis mainly responded to unforeseen issues with the data or to attempt to explain associations:

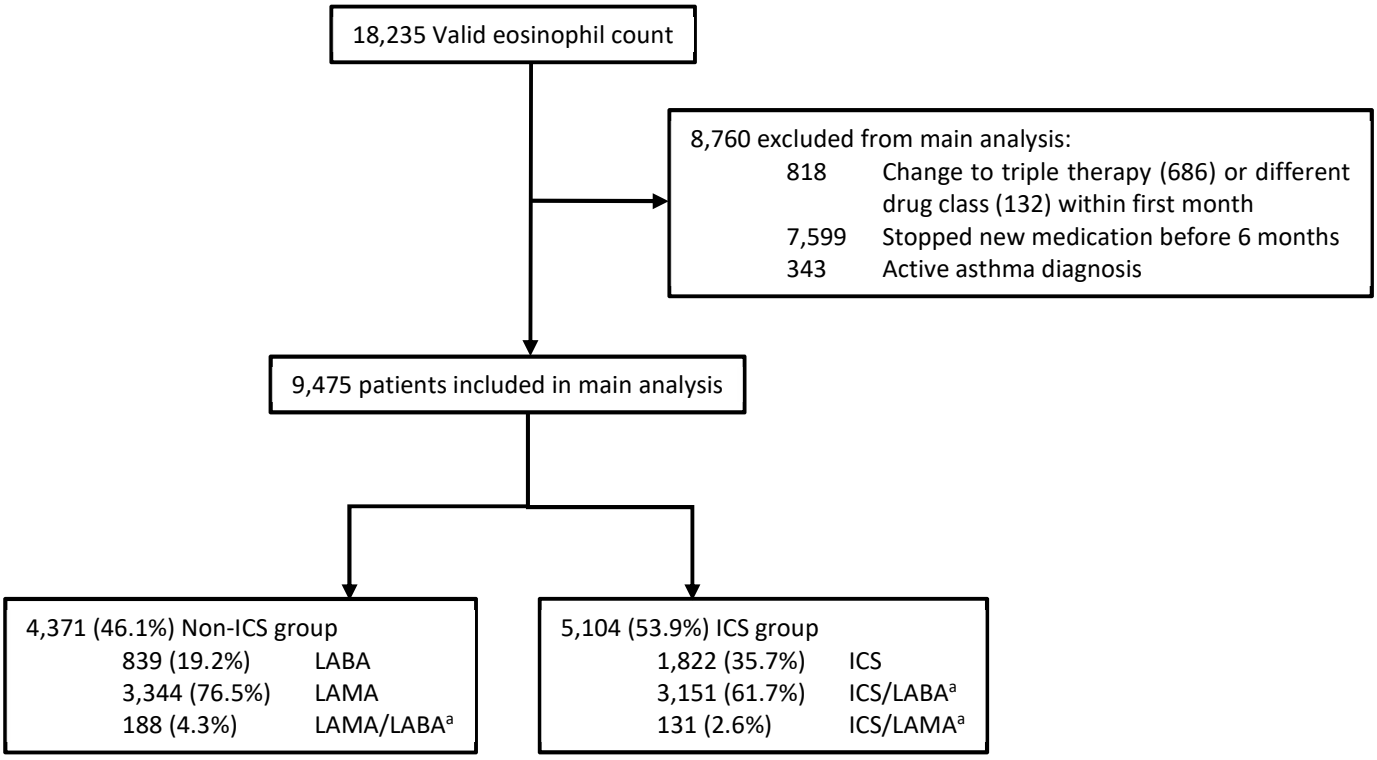
- including those who remained on their index medication for less than 6 months
- censoring by duration of index medication
- censoring by time to initiation of a new drug from the alternative drug class (i.e. change of category ICS to non-ICS or vice versa)

- censoring by duration of medication and time to initiation of new drug (whichever occurred earlier)
- using mean of the most recent two or three eosinophil counts rather than the single most recent

6.2 Data management

Figure 6.1 shows the inclusion of patients for this part of the study. As planned, those who had an active asthma diagnosis were removed (n=343), and those who had not continued their new medication for at least six months (n=7,599), although both were included as part of sensitivity analyses.

Figure 6.1: Flow chart of included patients (CPRD aim II)

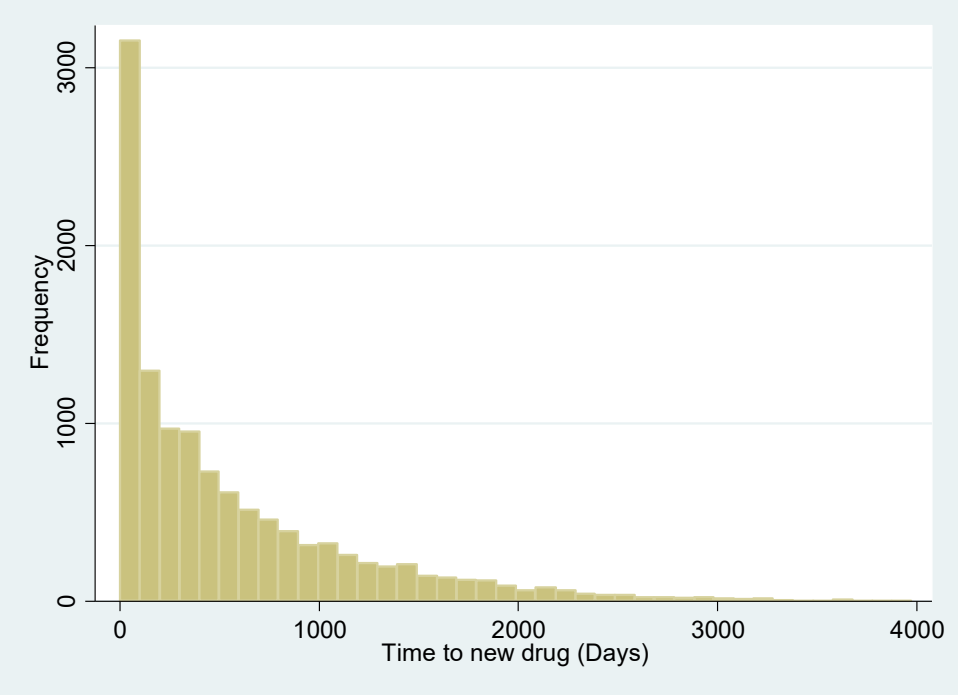


Flow charts for earlier stages of the study are shown in Figure 2.2 and Figure 4.1.
[a] Combination classes were either a single combined inhaler or separate inhalers with prescription issued on the same date.

This latter exclusion, leading to removal of 41.7% of otherwise eligible patients, made me concerned that there might be other issues relating to treatment choice and adherence which might potentially impact conclusions. Particularly, that there may be patients in the non-ICS group who changed to an ICS during the follow-up of the study, or vice versa (less likely as most patients would try non-ICS therapies first, but I wanted to investigate and manage both groups similarly to reduce bias). I investigated addition of drugs from another class and found that indeed 11,734/18,235 (64.3%) had started a new drug class during their follow-up period.

Time-to-new drug was not normally distributed (Figure 6.2), with 1400 patients changing to a new drug within the first 30 days after index date. I hypothesised that this might be medications prescribed separately, prescribing errors or advice from a pharmacist or advice from a respiratory nurse that a different device type might suit better. Where this led to a re-categorisation of specific drug group (e.g. LABA to LAMA), I re-categorised to the new drug group. However, as I could not be certain whether this was a change or an addition, I excluded patients who changed from ICS to non-ICS to ICS group and vice versa (n=132) and those for whom the addition of the new drug would then mean that they were on triple therapy (n=686), as these would have originally been excluded from the whole cohort. This was a post-hoc decision leaving 9,475 patients in the main analysis. I also imported the duration of the medication of interest and date of the new medication if applicable, in order to conduct sensitivity analyses censoring by these dates.

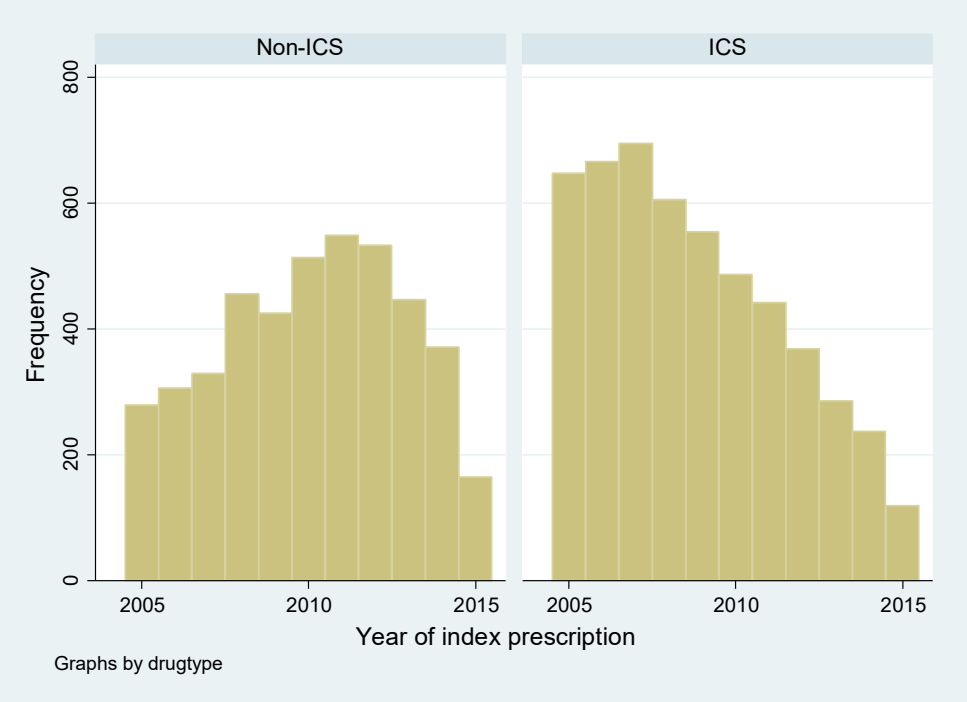
Figure 6.2: Histogram of time-to-new drug (n=18,235)



6.3 Maintenance treatment groups

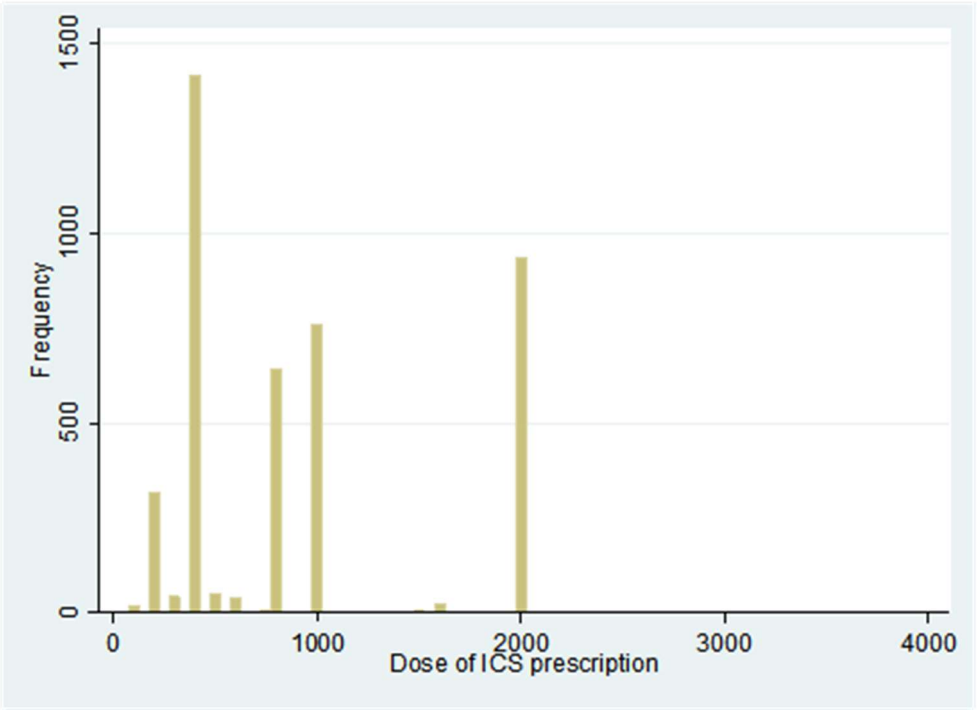
There were 4,371 (46.1%), patients in the non-ICS group (prescribed LABA 19%, LAMA 77%, LAMA/LABA 4%) and 5,104 (53.9%) in the ICS group (prescribed ICS 36%, ICS/LABA 62%, ICS/LAMA 3%) (Figure 6.1). Prescriptions for ICS decreased by 81.6% over the decade of the study, whereas non-ICS prescriptions remained constant (Figure 6.3).

Figure 6.3: Histogram of year of index prescription, by drug group



Of those in the ICS group, most were receiving low dose ICS (BDP-equivalent ≤500µg (n=1,852, 43.3%), >500-1000µg (n=1,455, 34.0%) and >1000µg (n=975, 22.8%) (missing for n=822)) (Figure 6.4).

Figure 6.4: Histogram of dose of ICS therapy (n=4,282)



Dose of ICS prescription is given as estimated equivalent daily doses of beclomethasone dipropionate (BDP).

Table 6.1 shows baseline characteristics and the distribution of patients between ICS and non-ICS treatment groups (odds ratios calculated using logistic regression as for eosinophil group distribution in Section 4.3.2). Patients were more likely to be prescribed an ICS therapy if they were younger, female, had previous asthma, more severe breathlessness (higher MRC), a higher baseline exacerbation frequency, oral steroid or theophylline use, or a higher rate of hospital admissions.

A high eosinophil count (≥0.15 x10*9/L) occurred in 69.0%. There was no difference in treatment distribution between the ICS and non-ICS groups by eosinophil group (p=0.71).

Table 6.1: Distribution of patients between ICS and non-ICS groups by baseline characteristics

Baseline characteristic	Overall n=9,475 n (%)	Non-ICS group n=4,371 n (%)	ICS group n=5,104 n (%)	Unadjusted odds ratio for ICS vs. non-ICS group (95% CI, p-value)	Adjusted odds ratio for ICS vs. non-ICS group [a] (95% CI, p-Value)
Demographic characteristics					
Age, mean (SD), years	69.7 (10.0)	70.0 (9.7)	69.4 (10.2)	0.99 (0.99-1.00), p=0.005	N/a
Age group in years					
40-49	265 (2.8)	87 (3.5)	178 (3.5)	1.92 (1.47-2.50), p<0.001	1.92 (1.45-2.55), p<0.001
50-59	1,227 (13.0)	554 (13.2)	673 (13.2)	1.14 (1.00-1.30), p=0.06	1.10 (0.95-1.27), p=0.20
60-69	3,019 (31.9)	1,387 (32.0)	1,632 (32.0)	1.10 (1.00-1.22), p=0.06	1.14 (1.03-1.27), p=0.01
70-79	3,332 (35.2)	1,611 (33.7)	1,721 (33.7)	1.00 (ref)	1.00 (ref)
80-89	1,543 (16.3)	687 (16.8)	856 (16.8)	1.16 (1.03-1.32), p=0.01	1.17 (1.03-1.33), p=0.02
>=90	89 (0.9)	45 (0.9)	44 (0.9)	0.92 (0.60-1.39), p=0.06	0.90 (0.58-1.41), p=0.66
Female sex	4,111 (43.4)	1,809 (41.4)	2,302 (45.1)	1.16 (1.07-1.26), p<0.001	1.11 (1.02-1.21), p=0.02
Socio-economic status [b]					
1 (least deprived)	1,323 (14.0)	563 (12.9)	760 (14.9)	1.00 (ref)	1.00 (ref)
2	1,927 (20.4)	886 (20.3)	1,041 (20.4)	0.87 (0.76-1.00), p=0.05	0.88 (0.76-1.02), p=0.08
3	1,836 (19.4)	886 (20.3)	950 (18.6)	0.79 (0.69-0.92), p=0.006	0.77 (0.66-0.89), p<0.001
4	2,387 (25.2)	1,130 (25.9)	1,257 (24.6)	0.82 (0.72-0.94), p=0.005	0.81 (0.70-0.93), p=0.003
5 (most deprived)	1,995 (21.1)	902 (20.7)	1,093 (21.4)	0.90 (0.78-1.03), p=0.08	0.85 (0.74-0.99), p=0.04
Respiratory disease characteristics					
Smoking status [b]	3,946 (41.8)	1,836 (42.1)	2,110 (41.6)		N/a
Ex-smoker				1.00 (ref)	
Current smoker				0.98 (0.90-1.06), p=0.61	
Asthma >2 years previously	1,098 (11.6)	269 (6.2)	829 (16.2)	2.96 (2.56-3.42), p<0.001	2.64 (2.27-3.07), p<0.001
History of atopy	2,493 (26.3)	1,107 (25.3)	1,386 (27.2)	1.10 (1.00-1.20), p=0.04	1.04 (0.95-1.15), p=0.40
Airflow limitation severity [b]					N/a [a]
Mild (≥80%)	838 (11.9)	401 (11.3)	437 (12.5)	1.00 (ref)	
Moderate (50-80%)	3,878 (55.0)	2,110 (59.4)	1,768 (50.6)	0.77 (0.66-0.89), p=0.001	
Severe (30-50%)	2,010 (28.5)	914 (25.7)	1,096 (31.4)	1.10 (0.94-1.30), p=0.25	
Very severe (<30%)	322 (4.6)	127 (3.6)	195 (5.6)	1.41 (1.08-1.83), p=0.01	

Baseline characteristic	Overall n=9,475 n (%)	Non-ICS group n=4,371 n (%)	ICS group n=5,104 n (%)	Unadjusted odds ratio for ICS vs. non-ICS group (95% CI, p-value)	Adjusted odds ratio for ICS vs. non-ICS group [a] (95% CI, p-Value)
MRC breathlessness scale [b]					N/a [a]
1 (least severe)	588 (13.8)	303 (12.2)	285 (15.9)	1.00 (ref)	
2	1,794 (42.0)	1,080 (43.5)	714 (39.9)	0.70 (0.58-0.85), p<0.001	
3	1,260 (29.5)	763 (30.7)	497 (27.8)	0.69 (0.57-0.84), p<0.001	
4	550 (12.9)	299 (12.0)	251 (14.0)	0.89 (0.71-1.13), p=0.34	
5 (most severe)	80 (1.9)	39 (1.6)	41 (2.3)	1.12 (0.70-1.78), p=0.64	
Exacerbations					
0	4,887 (51.6)	2,433 (55.7)	2,454 (48.1)	1.00 (ref)	1.00 (ref)
1	2,829 (29.9)	1,250 (28.6)	1,579 (30.9)	1.25 (1.14-1.37), p<0.001	1.22 (1.10-1.37), p<0.001
2	1,165 (12.3)	466 (10.7)	699 (13.7)	1.49 (1.31-1.69), p<0.001	1.46 (1.24-1.72), p<0.001
3 or more	594 (6.3)	222 (5.1)	372 (7.3)	1.66 (1.39-1.98), p<0.001	1.51 (1.20-1.90), p<0.001
Pneumonia episodes					
0	7,484 (79.0)	3,514 (80.4)	3,970 (77.8)	1.00 (ref)	1.00 (ref)
1	1,500 (15.8)	660 (15.1)	840 (16.5)	1.13 (1.00-1.26), p=0.04	0.89 (0.77-1.01), p=0.08
2 or more	491 (5.2)	197 (4.5)	294 (5.8)	1.32 (1.10-1.59), p=0.003	0.85 (0.67-1.07), p=0.17
Oral steroid prescriptions					
0	7,501 (79.2)	3,625 (82.9)	3,876 (75.9)	1.00 (ref)	1.00 (ref)
1	1,490 (15.7)	578 (13.2)	912 (17.9)	1.48 (1.32-1.65), p<0.001	1.39 (1.22-1.57), p<0.001
2	484 (5.1)	168 (3.8)	316 (6.2)	1.76 (1.45-2.13), p<0.001	1.55 (1.25-1.91), p<0.001
Salbutamol inhalers					
0	2,870 (30.3)	1,359 (31.1)	1,511 (29.6)	1.00 (ref)	1.00 (ref)
1	1,926 (20.3)	961 (22.0)	965 (18.9)	0.90 (0.80-1.01), p=0.08	0.88 (0.78-0.99), p=0.04
2	929 (9.8)	428 (9.8)	501 (9.8)	1.05 (0.91-1.22), p=0.50	0.91 (0.78-1.07), p=0.26
3-5	1,449 (15.3)	660 (15.1)	789 (15.5)	1.18 (0.95-1.22), p=0.26	0.89 (0.78-1.02), p=0.09
6 or more	2,301 (24.3)	963 (22.0)	1,338 (26.2)	1.25 (1.12-1.40), p<0.001	0.95 (0.84-1.07), p=0.36
Theophylline use	97 (1.0)	17 (0.4)	80 (1.6)	4.08 (2.41-6.89), p<0.001	2.61 (1.51-4.53), p=0.001
Oxygen use	46 (0.5)	19 (0.4)	27 (0.5)	1.22 (0.68-2.19), p=0.51	N/a
Nebuliser use	157 (1.7)	48 (1.1)	109 (2.1)	1.97 (1.40-2.77), p<0.001	1.25 (0.87-1.81), p=0.23

Baseline characteristic	Overall n=9,475 n (%)	Non-ICS group n=4,371 n (%)	ICS group n=5,104 n (%)	Unadjusted odds ratio for ICS vs. non-ICS group (95% CI, p-value)	Adjusted odds ratio for ICS vs. non-ICS group [a] (95% CI, p-Value)
General health characteristics					
Non-elective hospitalisations					
0	7,767 (82.0)	3,663 (83.8)	4,104 (80.4)	1.00 (ref)	1.00 (ref)
1	1,277 (13.5)	529 (12.1)	748 (14.7)	1.26 (1.12-1.42), p<0.001	1.20 (1.05-1.36), p=0.006
2 or more	431 (4.6)	179 (4.1)	252 (4.9)	1.26 (1.03-1.53), p=0.02	1.20 (0.97-1.48), p=0.09
GP consultations					
0-3	2,699 (28.5)	1,280 (29.3)	1,419 (27.8)	1.00 (ref)	1.00 (ref)
4-7	3,381 (35.7)	1,586(36.3)	1,795 (35.2)	1.02 (0.92-1.13), p=0.69	0.97 (0.87-1.08), p=0.54
8 or more	3,395 (35.8)	1,505 (34.4)	1,890 (37.0)	1.13 (1.02-1.25), p=0.02	1.01 (0.90-1.12), p=0.91
Charlson comorbidity index					
0	5,007 (52.8)	2,233 (51.1)	2,774 (54.4)	1.00 (ref)	1.00 (ref)
1	1,655 (17.5)	754 (17.3)	901 (17.7)	0.96 (0.86-1.08), p=0.50	0.96 (0.85-1.08), p=0.49
2 or more	2,813 (29.7)	1,384 (31.7)	1,429 (28.0)	0.83 (0.76-0.91), p<0.001	0.90 (0.81-1.00), p=0.05
Influenza vaccination	6,710 (70.8)	3,106 (71.1)	3,604 (70.6)	0.98 (0.90-1.07), p=0.63	N/a
Pneumococcal vaccination	3,403 (35.9)	1,507 (34.5)	1,896 (37.2)	1.12 (1.03-1.22), p=0.007	0.96 (0.87-1.05), p=0.37
Blood eosinophil count (x10*9/L)					N/a
≥0.15	6,535 (69.0)	3,023 (69.2)	3,512 (68.8)	0.98 (0.90-1.07), p=0.71	
Geometric mean	200	200	201	1.02 (0.96-1.09), p=0.57	

Percentages are column percentages. See Table 2.6 for details and time periods for variables.

[a] Odds ratio calculated using logistic regression. Adjusted odds ratios include baseline variables significant p<0.10 in univariate analysis. Inclusion of non-significant variables did not improve the model (p=0.75). n=9,468 due to complete case analysis. Airflow limitation severity and MRC breathlessness scale not included in adjusted model due to large amounts of missing data. Year of index prescription not displayed due to multiple categories but included in adjusted model.

[b] n=9,468 for socio-economic status, n=9,442 for smoking status, n=7,048 for airflow limitation severity and n=4,272 for MRC breathlessness scale, due to missing data.

(ref), reference group

6.4 Primary analysis

468 patients had an exacerbation in the first month after initiating treatment (58.1% in ICS group) and were excluded from the primary analysis. The remaining 9,007 patients provided 38,421 years of follow-up (median 3.8 years per person (IQR 2.1 to 6.0; range 0.5 to 11.1), of whom 6,478 (71.9%) experienced an exacerbation during follow-up. Table 6.2 shows the main Cox regression model; addition of an interaction term for eosinophil group with drug group significantly improved the model (p=0.01).

Table 6.2: Cox regression model for time-to-first exacerbation of hypothesis-testing cohort

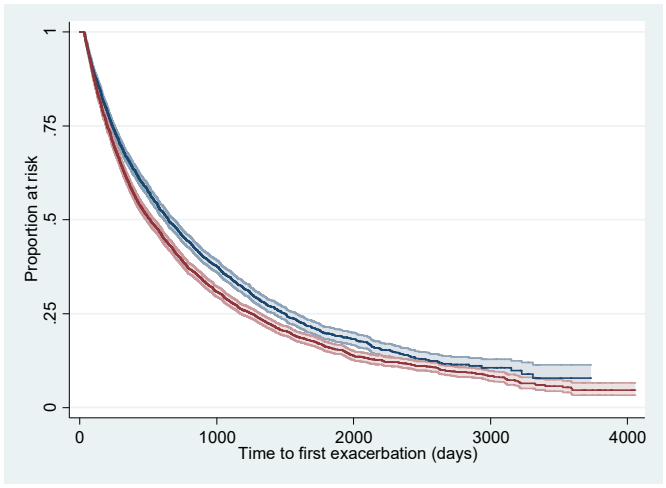
Baseline characteristic/variable	**Unadjusted hazard ratio for time-to-first exacerbation (95% CI, p-value) (n=9,007)**	**Adjusted hazard ratio for time-to-first exacerbation (95% CI, p-value) (n=8,967)**
Blood eosinophil count		
Low (<0.15 x10*9/L) (n=2,819)	1.00	1.00
High (≥0.15 x10*9/L) (n=6,188)	0.99 (0.94-1.04), p=0.64	0.98 (0.93-1.03), p=0.38
Drug group		
Non-ICS (n=4,175)	1.00	1.00
ICS (n=4,832)	1.17 (1.12-1.23), p<0.001	1.08 (1.03-1.14), p=0.002
Interaction (drug group # eosinophil group)	N/a	
ICS drug group, in low eosinophil group		1.19 (1.09-1.31), p<0.001
ICS drug group, in high eosinophil group		1.04 (0.98-1.10), p=0.23
Interaction hazard ratio		0.87 (0.78-0.97), p=0.01

Hazard ratios calculated using Cox regression and adjusted for covariates as follows: age group; sex; socio-economic status; smoking status; asthma history; atopy history; baseline exacerbations, pneumonia episodes, oral steroid prescriptions, and salbutamol inhaler prescriptions; theophylline, nebuliser and oxygen use; baseline non-elective hospitalisations and GP consultations; Charlson co-morbidity index; influenza and pneumococcal vaccination; and year of index prescription. All variables were included in multivariate analysis rather than just those p<0.10 in univariate analysis due to likely clinical significance and concern that lack of significance may be sample size-related for these variables. Adjusted n=8,967 due to complete case analysis (missing data for socio-economic status and smoking status). For some variables in the model the proportional hazards assumption was not met (baseline exacerbations, pneumonia episodes, oral steroid prescriptions, and salbutamol inhaler prescriptions; baseline non-elective hospitalisations and GP consultations). However, incorporating them into the model with the time-dependent variable command made no difference to the key results.

The median time-to-first exacerbation was 1.77 (95% CI 1.68 to 1.88) years in the non-ICS group and 1.40 (95% CI 1.32 to 1.48) years in the ICS group (unadjusted HR ICS vs. non-ICS 1.17, 95% CI 1.12 to 1.23; p<0.001; adjusted HR 1.08, 95% CI 1.03 to 1.14); p=0.002). Following

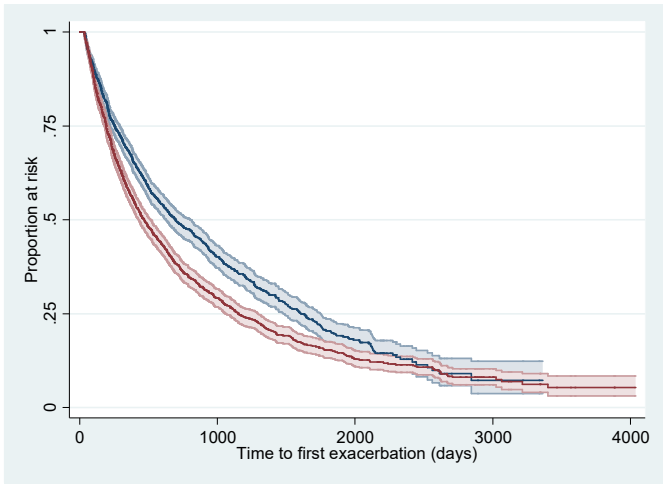
stratification for baseline eosinophils using the interaction term, the adjusted HR was 1.19 (95% CI 1.09 to 1.31; p<0.001) in the low eosinophil group and 1.04 (95% CI 0.98 to 1.10; p=0.23) in the high eosinophils group (15% absolute difference; interaction of eosinophil group with treatment group 0.87, 95% CI 0.78 to 0.97, p=0.01) (bottom row of Table 6.2 and summarised in Figure 6.5).

Figure 6.5: Kaplan-Meier curves for time-to-first exacerbation in ICS (red) vs. non-ICS (blue) groups, A) overall and B) C) stratified by baseline blood eosinophil group (95% CI shaded)



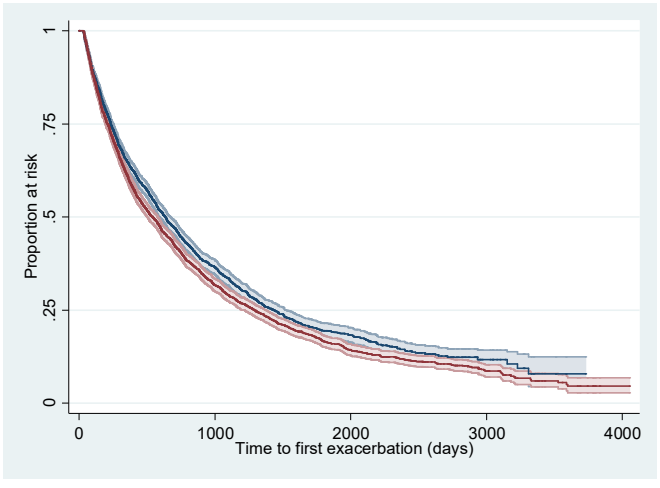
A) Whole group

Adjusted hazard ratio
1.08 (95% CI 1.03-1.14)
p=0.002
n=8,967



B) Low eosinophil group (<0.15 x10*9/L)

Adjusted hazard ratio
1.19 (95% CI 1.09-1.31)
p<0.001
n=2,797



C) High eosinophil group (≥0.15 x10*9/L)

Adjusted hazard ratio
1.04 (95% CI 0.98-1.1)
p=0.23
n=6,170

6.5 Analysis with different eosinophil thresholds

Table 6.3 shows distribution of patients between treatment groups by different eosinophil thresholds.[a] Increasing the threshold used to define the 'high eosinophil' group from ≥0.15 to ≥0.34 x10*9/L decreased the number of patients in the 'high' group from 69.0% to 19.4%. There was no clear association of eosinophil group with treatment group.

Table 6.3: Distribution of patients between ICS and non-ICS groups by different blood eosinophil thresholds

Eosinophil threshold (x10*9/L)	Overall n=9,475 n (%)	Non-ICS group n=4,371 n (%)	ICS group n=5,104 n (%)	Unadjusted odds ratio ICS vs. non-ICS group (95% CI, p-value)	Adjusted odds ratio ICS vs. non-ICS group (95% CI, p-value)
≥0.10	8,954 (94.5)	4,140 (94.7)	4,814 (94.3)	0.93(0.78-1.11), p=0.40	N/a
≥0.15	6,535 (69.0)	3,023 (69.2)	3,512 (68.8)	0.98 (0.90-1.07), p=0.71	N/a
≥0.20	5,924 (62.5)	2,741 (62.7)	3,183 (62.4)	0.99 (0.91-1.07), p=0.73	N/a
≥0.30	3,144 (33.2)	1,438 (32.9)	1,706 (33.4)	1.02 (0.94-1.12), p=0.59	N/a
≥0.34	1,842 (19.4)	807 (18.5)	1,035 (20.3)	1.12 (1.01-1.24), p=0.03	1.15 (1.04-1.29), p=0.01
≥0.40	1,574 (16.6)	687 (15.7)	887 (17.4)	1.13 (1.01-1.26), p=0.03	1.16 (1.04-1.31), p=0.01
≥0.50	815 (8.6)	359 (8.2)	456 (8.9)	1.10 (0.95-1.27), p=0.21	N/a
Continuous (log scale)				1.02 (0.96-1.09), p=0.57	N/a

Odds ratio calculated using logistic regression including baseline covariates significant p<0.10 in univariate analysis (as shown in Table 6.1). Percentages are column percentages of those above the eosinophil threshold.

Table 6.4 shows sensitivity and subgroup analysis by different eosinophil thresholds and subgroups. As the eosinophil threshold increased, the HR for ICS vs. non-ICS treatment decreased and the interaction HR became less statistically significant. Stratification of eosinophils into low (<0.15), medium (0.15-<0.34) and high (≥0.34) groups found increased

[a] This is similar to what was shown in Figure 4.5 but this is the more narrow population for the hypothesis-testing component of the CPRD study.

risk in those with low eosinophils only. Analysis by percentage eosinophil groups (<2%, 2-4% and ≥4%) also showed decreasing HR with increasing eosinophil category.

Table 6.4: Outcomes and interactions for time-to-first exacerbation for different eosinophil thresholds and subgroups

	Hazard ratio [b] for ICS vs non-ICS (95% CI, p-value)	Interaction hazard ratio [b] of eosinophils with treatment group (95% CI, p-value)
Eosinophil thresholds (sensitivity analysis)		
0.10 x10*9/L	1.25 (1.00-1.55), p=0.05	0.86 (0.69-1.08), p=0.19
0.15 x10*9/L (main analysis)	1.19 (1.09-1.31), p<0.001	0.87 (0.78-0.97), p=0.01
0.20 x10*9/L	1.17 (1.08-1.27), p<0.001	0.88 (0.80-0.98), p=0.02
0.30 x10*9/L	1.12 (1.05-1.19), p<0.001	0.90 (0.81-1.01), p=0.06
0.34 x10*9/L (post-hoc)	1.09 (1.03-1.16), p=0.002	0.95 (0.84-1.08), p=0.43
0.40 x10*9/L	1.09 (1.03-1.15), p=0.002	0.96 (0.84-1.10), p=0.53
0.50 x10*9/L	1.08 (1.03-1.15), p=0.003	0.98 (0.82-1.18), p=0.83
Eosinophil categorical analysis (subgroup analysis)		
<0.15 x10*9/L (n=2,819)	1.19 (1.09-1.31), p<0.001	1.15 (1.02-1.29), p=0.01
0.15-0.34 x10*9/L (n=4,451)	1.04 (0.97-1.12), p=0.29	1.00 (ref)
≥0.34 x10*9/L (n=1,737)	1.04 (0.93-1.17), p=0.50	1.00 (0.88-1.15), p=0.98
Eosinophil percentages[a] (subgroup analysis)		
<2% (n=2,811)	1.17 (1.07-1.28), p=0.001	1.08 (0.96-1.21), p=0.21
2-4% (n=3,795)	1.08 (1.00-1.17), p=0.04	1.00 (ref)
≥4% (n=2,388)	1.00 (0.90-1.10), p=0.93	0.92 (0.81-1.04), p=0.18
Eosinophils as continuous variable (logarithmically transformed) (sensitivity analysis)		
Continuous	1.18 (1.09-1.27), p<0.001	0.89 (0.82-0.96), p=0.004

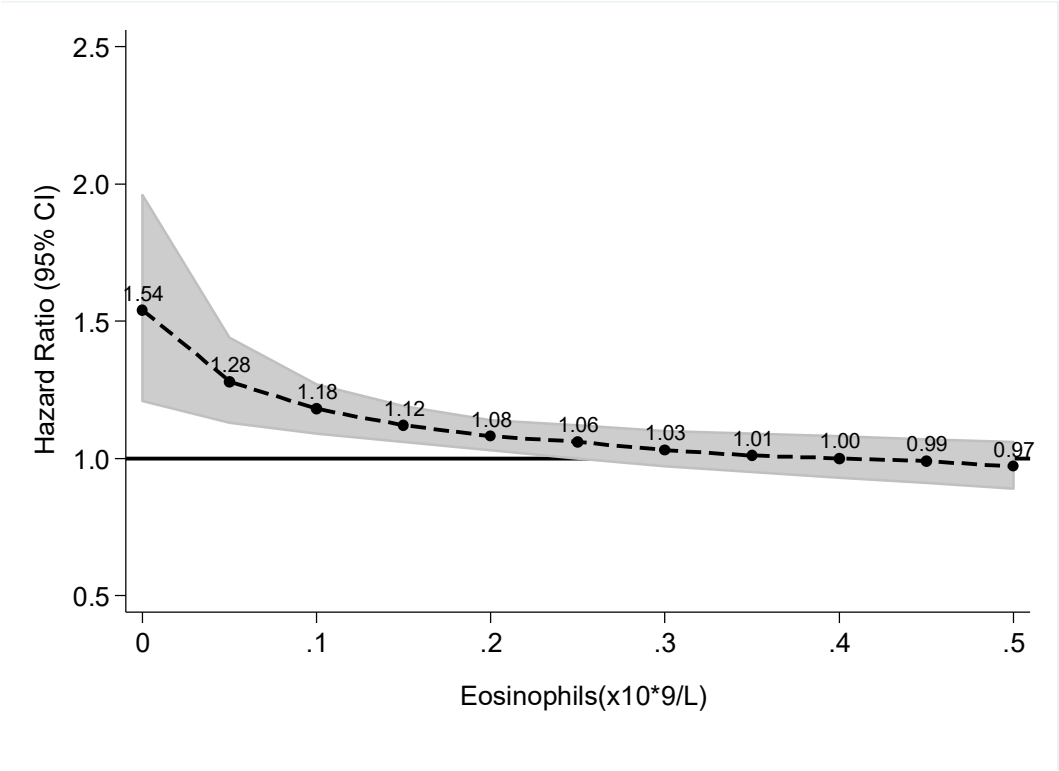
(ref), reference group

[a] Eosinophil percentages are as percentage of total leucocytes; leucocytes missing for n=13.

[b] Adjusted Cox regression model including interaction term as detailed in Table 6.2 legend (n=8,967). Hazard ratios are given for low eosinophil group for sensitivity analyses except for continuous eosinophils where this is set at 0.10 x10*9/L; hazard ratio in the high eosinophil group can be calculated by multiplying the hazard ratio in the low group by the interaction term. Proportional hazards assumption was valid for all eosinophil-related variables.

Analysis using log-transformed eosinophils as a continuous variable found an interaction HR of 0.89 (95% CI 0.82 to 0.96; p=0.004), with decreasing hazard ratio for ICS treatment as eosinophil count increased, again with particularly high HR at the lower eosinophil counts (Figure 2).

Figure 6.6: Graph and table showing hazard ratios for time-to-first exacerbation for ICS vs. non-ICS treatment, at different eosinophil counts



Eosinophil threshold (x10*9/L)	Adjusted hazard ratio (95% CI, p-value)
0.01	1.54 (1.21-1.96), p<0.001
0.05	1.28 (1.13-1.44), p<0.001
0.10	1.18 (1.09-1.27), p<0.001
0.15	1.12 (1.06-1.19), p<0.001
0.20	1.08 (1.03-1.14), p=0.002
0.25	1.06 (1.00-1.12), p=0.05
0.30	1.03 (0.97-1.10), p=0.29
0.35	1.01 (0.95-1.09), p=0.67
0.40	1.00 (0.93-1.08), p=0.98
0.45	0.99 (0.91-1.07), p=0.73
0.50	0.97 (0.89-1.06), p=0.55

Hazard ratios are from Cox regression including the interaction term and adjusted for covariates as detailed in Table 6.2, but with eosinophils in the model as a continuous variable (logarithmically transformed). The interaction of eosinophils with ICS treatment group was significant in this model (p=0.004). Deviation of the association from log-linearity was assessed by a likelihood ratio test comparing models with categorical eosinophils (p=0.23). Shaded area shows 95% confidence intervals.

6.6 Subgroup and sensitivity analyses of main analysis

I have broadly divided these into disease-related, eosinophil-related and methodological subgroup and sensitivity analyses, as shown in Table 6.5, and subsequent sections refer to results within this table except where stated. Results are given for two eosinophil thresholds (0.15 and 0.34 x10*9/L) and continuous eosinophils (which tells us if there is a linear effect modification). Interactions were generally not significant at the 0.34 threshold, as in the whole group analysis by eosinophil threshold above (Table 6.4).

Table 6.5: Subgroup and sensitivity analyses for time-to-first exacerbation ICS vs. non-ICS and interaction with blood eosinophil count

Groups as applicable	0.15 x10*9/L eosinophil threshold		0.34 x10*9/L eosinophil threshold		Continuous eosinophils[a]
	Hazard ratio in low group[b]	Interaction[c]	Hazard ratio in low group[b]	Interaction[c]	Interaction[c]
Main					
(n=9,007)	1.19 (1.09-1.31), p<0.001	0.87 (0.78-0.97) p=0.01	1.09 (1.03-1.16), p=0.002	0.95 (0.84-1.08), p=0.43	0.89 (0.82-0.96), p=0.004
Disease-related subgroup and sensitivity analyses					
Smoking status (post-hoc subgroup analysis)					
Ex-smokers (n=5,261)	1.15 (1.02-1.30), p=0.02	0.91 (0.79-1.05), p=0.22	1.09 (1.01-1.18), p=0.02	0.95 (0.80-1.12), p=0.52	0.92 (0.83-1.03), p=0.14
Current smokers (n=3,779)	1.24 (1.09-1.43), p=0.002	0.83 (0.70-0.97), p=0.02	1.10 (1.01-1.20), p=0.03	0.96 (0.79-1.18), p=0.73	0.85 (0.76-0.96), p=0.009
Asthma status (main analysis excludes asthma coded in previous two years but includes those with history of asthma)					
Excluding any asthma (n=7,981)	1.21 (1.10-1.33), p<0.001	0.85 (0.76-0.96), p=0.006	1.09 (1.02-1.15), p=0.007	0.98 (0.85-1.12), p=0.74	0.88 (0.81-0.96), p=0.004
Including active asthma (n=9,326)	1.20 (1.10-1.31), p<0.001	0.87 (0.78-0.96), p=0.008	1.10 (1.04-1.16), p=0.001	0.94 (0.83-1.06), p=0.31	0.88 (0.82-0.95), p=0.002
Atopy (main analysis includes those with atopy)					
Excluding any atopy (n=6,648)	1.19 (1.07-1.33), p=0.001	0.88 (0.78-1.00), p=0.04	1.09 (1.02-1.17), p=0.009	1.00 (0.86-1.16), p=0.98	0.92 (0.83-1.01), p=0.07
Dose of ICS (subgroup analysis)					
≤500µg BDP equivalent (n=5,921)	1.14 (1.01-1.29), p=0.03	0.89 (0.77-1.03), p=0.11	1.09 (1.01-1.18), p=0.02	0.83 (0.70-0.99), p=0.03	0.86 (0.77-0.95), p=0.004
500-1000 µg BDP equivalent (n=5,552)	1.22 (1.08-1.40), p=0.002	0.79 (0.68-0.93), p=0.003	1.04 (0.96-1.13), p=0.36	1.02 (0.85-1.23), p=0.80	0.90 (0.80-1.01), p=0.08
>1000 µg BDP equivalent (n=5,095)	1.29 (1.11-1.50), p=0.001	0.91 (0.77-1.09), p=0.31	1.20 (1.09-1.32), p<0.001	1.04 (0.85-1.28), p=0.69	0.92 (0.81-1.05), p=0.22
Methodological subgroup and sensitivity analyses					
Including severity and MRC breathlessness scale (not included in main analysis due to large amounts of missing data)					
Including severity and MRC (n=3,706)	1.17 (1.01-1.36), p=0.04	0.85 (0.72-1.02), p=0.08	1.05 (0.96-1.16), p=0.29	1.00 (0.81-1.23), p=0.98	0.91 (0.79-1.04), p=0.15

Groups as applicable	0.15 x10*9/L eosinophil threshold		0.34 x10*9/L eosinophil threshold		Continuous eosinophils[a]
	Hazard ratio in low group[b]	Interaction[c]	Hazard ratio in low group[b]	Interaction[c]	Interaction[c]
Protopathic bias (main analysis excludes those with exacerbation in first month after treatment initiation)					
Including outcome in first month (n=9,475)	1.19 (1.09-1.30), p<0.001	0.87 (0.78-0.96), p=0.007	1.10 (1.04-1.16), p=0.001	0.92 (0.81-1.04), p=0.17	0.88 (0.81-0.95), p=0.001
Intention-to-treat (main analysis only includes those who stayed on their new medication for at least 6 months) (post-hoc)					
Including <6m treatment duration (n=15,941)	1.13 (1.05-1.21), p=0.001	0.91 (0.84-0.99), p=0.026	1.07 (1.02-1.18), p=0.003	0.93 (0.84-1.02), p=0.14	0.93 (0.87-0.99), p=0.02
Censoring by initiation of new drug in alternative treatment group (ICS or non-ICS) (post-hoc)					
Censoring by time to new drug (n=9,007)	1.31 (1.17-1.46), p<0.001	0.82 (0.72-0.93), p=0.002	1.17 (1.09-1.25), p<0.001	0.87 (0.75-1.01), p=0.07	0.85 (0.77-0.94), p=0.001
Censoring by duration of time on new medication (post-hoc)					
Excluding <6m treatment duration (n=9,007)	1.24 (1.12-1.37), p<0.001	0.87 (0.77-0.98), p=0.02	1.13 (1.06-1.21), p<0.001	0.97 (0.84-1.11), p=0.63	0.89 (0.82-0.97), p=0.01
Including <6m treatment duration (n=15,941)	1.23 (1.11-1.36), p<0.001	0.88 (0.79-0.99), p=0.04	1.14 (1.07-1.22), p<0.001	0.94 (0.82-1.07), p=0.35	0.89 (0.82-0.97), p=0.008
Censoring by initiation of new drug in alternative treatment group (ICS or non-ICS) or duration of time on new medication (earlier date where both apply) (post-hoc)					
Excluding <6m treatment duration (n=9,007)	1.33 (1.18-1.49), p<0.001	0.82 (0.72-0.94), p=0.005	1.19 (1.10-1.28), p<0.001	0.89 (0.76-1.05), p=0.17	0.86 (0.77-0.95), p=0.004
Including <6m treatment duration (n=15,941)	1.30 (1.16-1.46), p<0.001	0.85 (0.74-0.97), p=0.02	1.20 (1.11-1.28), p<0.001	0.87 (0.74-1.02), p=0.08	0.86 (0.78-0.95), p=0.003
Eosinophil-related subgroup and sensitivity analyses					
Eosinophil means (main analysis uses most recent eosinophil result)					
Using mean of all previous results (n=9,007)	1.18 (1.07-1.30), p=0.001	0.89 (0.79-0.99), p=0.03	1.10 (1.04-1.16), p=0.002	0.94 (0.83-1.07), p=0.36	0.90 (0.83-0.98), p=0.01
Using mean of last two results (n=9,007)	1.20 (1.08-1.32), p<0.001	0.88 (0.78-0.98), p=0.02	1.10 (1.04-1.17), p=0.001	0.93 (0.83-1.05), p=0.25	0.90 (0.83-0.98), p=0.01
Using mean of last three results (n=9,007)	1.19 (1.08-1.31), p<0.001	0.88 (0.78-0.98), p=0.02	1.10 (1.03-1.16), p=0.002	0.95 (0.84-1.08), p=0.42	0.90 (0.82-0.97), p=0.009
Including season of eosinophil test as variable in model (post-hoc)					
Including eosinophil test season (n=9,007)	1.19 (1.09-1.30), p<0.001	0.87 (0.78-0.97), p=0.01	1.10 (1.03-1.16), p=0.002	0.95 (0.84-1.08), p=0.45	0.89 (0.82-0.96), p=0.004

Groups as applicable	0.15 x10*9/L eosinophil threshold		0.34 x10*9/L eosinophil threshold		Continuous eosinophils[a]
	Hazard ratio in low group[b]	Interaction[c]	Hazard ratio in low group[b]	Interaction[c]	Interaction[c]
Excluding those with eosinophils ≥0.50 x10*9/L (post-hoc)					
Excluding eosinophils ≥0.50 x10*9/L	1.18 (1.08-1.30), p<0.001	0.87 (0.78-0.97), p=0.01	1.09 (1.03-1.15), p=0.004	0.93 (0.79-1.09), p=0.41	0.86 (0.78-0.94), p=0.002
Including eosinophil values close to acute events (exacerbation/pneumonia/episode/C-reactive protein >100mg/L) which main analysis excludes					
Including eosinophils close to acute event (n=9,007)	1.18 (1.08-1.29), p<0.001	0.89 (0.80-0.99), p=0.03	1.10 (1.03-1.16), p=0.002	0.95 (0.84-1.08), p=0.46	0.90 (0.83-0.97), p=0.007

BDP, beclomethasone dipropionate estimated equivalent. 95% confidence intervals and p-values are given.

[a] Continuous eosinophils were logarithmically transformed for analyses.

[b] Hazard ratios are for time-to-first exacerbation comparing ICS with non-ICS treatment groups (hazard ratio >1 favours non-ICS treatment), in the low eosinophil group. Model is including the interaction term and adjusted for covariates as in Table 6.2. Analyses are sensitivity analyses except where stated as subgroup analyses.

[c] Interaction is the hazard ratio for the interaction of baseline blood eosinophils with treatment group, describing magnitude of difference (hazard ratio <1 describes reduced overall hazard ratio in ICS group, with higher eosinophils). Hazard ratio in the high eosinophil group can be calculated by multiplying the hazard ratio in the low group by the interaction term.

6.6.1 Disease-related subgroup and sensitivity analyses

In subgroup analysis by smoking status, only current smokers showed a significant interaction of blood eosinophils with treatment group. Including those with current asthma, and excluding those with any asthma, made very little difference to results. When those with history of atopy were excluded, the interaction hazard ratio remained similar, but the significance reduced (which may be due to the reduction in sample size by approximately one third in excluding these people). There was no clear dose-response effect of dose on response to ICS treatment.

Subgroup analysis stratified by baseline exacerbation frequency showed risk of exacerbations on ICS was lower in those with high eosinophils and history of frequent exacerbations compared to those with low eosinophils and less frequent exacerbations (0.94, 95% CI 0.82 to 1.07, p=0.34 vs. 1.21, 95% CI 1.10 to 1.34, 27% absolute difference, p=0.001 respectively, Table 6.6). Risk of exacerbation on ICS treatment was also lower overall independent of baseline eosinophil group in those with higher baseline exacerbation rate.

Table 6.6: Subgroup analysis of ICS vs. non-ICS treatment, stratified by blood eosinophil group and by baseline exacerbation frequency

	Whole group (no interaction term)	**Low eosinophil group (<0.15 x10*9/L)**	**High eosinophil group (≥0.15 x10*9/L)**	**Interaction HR and p-value**
Low exacerbation rate (0 or 1)	1.11 (1.05-1.18) p<0.001 n=7,367	1.21 (1.10-1.34), p=0.001 n=2,299	1.07 (1.00-1.15), p=0.06 n=5,068	0.88 (0.78-0.99) p=0.04
Higher exacerbation rate (≥2)	1.01 (0.90-1.13) p=0.91 n=1,600	1.18 (0.97-1.44), p=0.11 n=498	0.94 (0.82-1.07), p=0.34 n=1,102	0.79 (0.62-1.00) p=0.06

Hazard ratios (HR) are for time-to-first exacerbation after treatment initiation, for ICS vs. non-ICS treatment. Hazard ratios are from Cox regression including the interaction term and adjusted for covariates as listed in Table 6.2.

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6.6.2 Eosinophil-related subgroup and sensitivity analyses

Sensitivity analyses using the eosinophil count average of several counts instead of the most recent value, excluding the highest values (≥0.50 x10*9/L), including eosinophil values close to acute events, and including season of eosinophil test in the model, made no difference to overall results (Table 6.5).

6.6.3 Methodological subgroup and sensitivity analyses

Including severity and MRC breathlessness scale in the model reduced the significance of the interaction, but not the absolute hazard ratio, likely related to the large reduction in sample size of approximately half, due to complete case analysis. Inclusion of patients who experienced an event in the first month after treatment initiation (excluded from main analysis to reduce protopathic bias) made minimal difference to results.

Median duration of treatment with the medication of interest was 0.51 years (IQR 0.08-1.92) in the ICS group and 1.12 years (IQR 0.29-2.89) in the non-ICS group. Once those with under 6 months' treatment duration had been excluded for the main analysis, this increased to 1.91 years (IQR 0.96-3.84) in the ICS group and 2.10 years (IQR 1.09-3.89) in the non-ICS group. Where an alternative treatment group drug had been prescribed during follow-up (3,301/5.389 (61.3%) in ICS group and 2,676/4,429 (60.4%) in non-ICS group, p=0.40), time-to-new drug was longer in the ICS group than in the non-ICS group (median 390 (IQR 141-874) vs. 330 (IQR 122-691) days) (p<0.001). Sensitivity analyses using various combinations of censoring dates and exclusions by time on medication or time-to-new drug (Table 6.5), ranging from full 'intention-to-treat' through to full 'on-treatment' analysis, made very little difference to overall results, despite widely different sample sizes and follow-up times.

6.7 Secondary outcomes

Time-to-event analyses for different eosinophil thresholds for the pre-specified secondary outcomes are presented in Table 6.7. ICS use was associated with a higher rate of pneumonia at eosinophil levels below 0.15 x10*9/L, but the interaction of eosinophils with drug group only reached significance for pneumonia hospitalisations (HR in low eosinophil group 1.26, 95% CI 1.05-1.50; 26% absolute difference p-value for interaction p=0.04) (Table 6.8). Numbers of those experiencing the outcome were small for pneumonia deaths (n=61/9,475)[a] but there was a large magnitude of difference between eosinophil groups (66% absolute difference, p=0.14).

[a] Low number of deaths due to pneumonia likely to be because of changes in coding of primary cause of death by the Office for National Statistics away from acute causes to chronic underlying causes (CPRD ONS Death Registration Data Data Specification V1.5 (15 August 2016).

Table 6.7: Secondary outcomes for time-to-first event ICS vs. non-ICS and interaction with blood eosinophil count

Number experiencing outcome/total	Whole group, excluding interaction term	0.15 x10*9/L eosinophil threshold		0.34 x10*9/L eosinophil threshold		Continuous eosinophils[a]
	Hazard ratio [b]	Hazard ratio [b]	Interaction [c]	Hazard ratio [b]	Interaction[c]	Interaction[c]
Pneumonia episodes						
n=4,210/9,192	1.06 (1.00-1.13) p=0.06	1.10 (0.99-1.24), p=0.09	0.95 (0.83-1.08), p=0.44	1.06 (0.99-1.14), p=0.10	1.01 (0.87-1.19), p=0.86	0.99 (0.89-1.09), p=0.77
Hospitalisation due to any cause						
n=6,392/9,007	1.00 (0.95-1.06), p=0.95	1.04 (0.95-1.14), p=0.42	0.95 (0.85-1.06), p=0.35	1.01 (0.95-1.07), p=0.78	0.97 (0.86-1.10), p=0.67	0.96 (0.89-1.04), p=0.32
Hospitalisation due to pneumonia						
n=1,533/9,449	1.08 (0.97-1.20), p=0.16	1.26 (1.05-1.50), p=0.01	0.80 (0.64-0.99), p=0.04	1.13 (1.00-1.27), p=0.05	0.79 (0.61-1.03), p=0.08	0.88 (0.75-1.04), p=0.13
Hospitalisation due to COPD						
n=2,621/9,384	1.05 (0.97-1.14), p=0.21	1.17 (1.02-1.35), p=0.03	0.85 (0.72-1.01), p=0.07	1.05 (0.96-1.15), p=0.29	1.02 (0.83-1.25), p=0.85	0.92 (0.81-1.04), p=0.18
Death due to any cause						
n=2,071/9,475	0.97 (0.88-1.06), p=0.46	1.01 (0.87-1.19), p=0.86	0.93 (0.77-1.12), p=0.45	0.97 (0.87-1.07), p=0.52	0.99 (0.79-1.25), p=0.96	1.00 (0.87-1.15), p=0.96
Death due to pneumonia						
n=61/9,475	0.73 (0.42-1.25), p=0.25	1.19 (0.50-2.84), p=0.70	0.44 (0.15-1.31), p=0.14	0.64 (0.35-1.17), p=0.15	1.74 (0.46-6.55), p=0.41	0.87 (0.38-1.99), p=0.75
Death due to COPD						
n=568/9,475	1.05 (0.88-1.25), p=0.61	1.07 (0.80-1.43), p=0.66	0.97 (0.68-1.39), p=0.87	1.04 (0.86-1.26), p=0.68	1.03 (0.66-1.62), p=0.90	1.06 (0.81-1.40), p=0.66

[a] Continuous eosinophils were logarithmically transformed for analyses.

[b] Hazard ratios are for time-to-first event comparing ICS with non-ICS treatment groups (hazard ratio >1 favours non-ICS treatment), in the low eosinophil group (except where stated for second column). Model is including the interaction term and adjusted for covariates as listed in Table 6.2. As for exacerbations in main analysis, those experiencing the event of interest in the first month after initiating treatment were excluded.

[c] Interaction is the hazard ratio for the interaction of baseline blood eosinophils with treatment group, describing magnitude of difference (hazard ratio <1 describes reduced overall hazard ratio in ICS group, with higher eosinophils). Hazard ratio in the high eosinophil group can be calculated by multiplying the hazard ratio in the low group by the interaction term.

Table 6.8: Pneumonia outcomes for ICS vs non-ICS treatment, stratified by baseline blood eosinophil group

	Whole group (no interaction term)	Low eosinophil group (<0.15 x10*9/L)	High eosinophil group (≥0.15 x10*9/L)	Interaction HR and p-value
Pneumonia episodes	1.06 (1.00-1.13) p=0.06 n=9,153	1.10 (0.99 to 1.24), p=0.09 n=2,832	1.05 (0.97 to 1.13), p=0.24 n=6,321	0.95 (0.83 to 1.08), p=0.44
Hospitalisation due to pneumonia	1.08 (0.97-1.20) p=0.16 n=9,409	1.26 (1.05 to 1.50), p=0.01 n=2,910	1.00 (0.88 to 1.14), p>0.99 n=6,499	0.80 (0.64 to 0.99), p=0.04
Death due to pneumonia	0.73 (0.42-1.25), p=0.25 n=9,435	1.19 (0.50 to 2.84), p=0.70 n=2,918	0.53 (0.27 to 1.05), p=0.07 n=6,517	0.44 (0.65 to 4.42, p=0.14

Hazard ratios are for time-to-first event after treatment initiation, for ICS vs. non-ICS treatment. Hazard ratios are from Cox regression including interaction term and adjusted for covariates as detailed in Table 6.2.

6.8 Discussion

6.8.1 Summary of findings

This chapter has addressed whether baseline blood eosinophils counts predict inhaled steroid responsiveness. Approximately half of those patients commencing a new inhaled maintenance treatment were prescribed ICS (54%) and half were prescribed a non-ICS treatment (46%). Patients were more likely to be prescribed an ICS treatment if they were younger, female, had previous asthma, more severe breathlessness, higher baseline exacerbation frequency, oral steroid or theophylline use, or a higher rate of hospital admissions at baseline.

Comparing ICS with non-ICS treatment, those treated with ICS had a shorter time-to-first exacerbation (adjusted HR 1.08, 95% CI 1.03 to 1.14) i.e. worse outcome. A significant interaction with baseline blood eosinophil count was found (p=0.01) at the primary threshold of 0.15 x10*9/L, translating as a 15% lower absolute risk of exacerbation in

patients with higher eosinophils who were prescribed an ICS treatment than in patients with lower eosinophils who were prescribed ICS. The interaction term was no longer significant as the threshold for defining 'high eosinophils' was increased and the risk of exacerbation with ICS appeared greatest in those with lower eosinophils (<0.15 x10*9/L) when patients were stratified into 'low', 'medium' and 'high' eosinophil groups. In continuous eosinophil analysis, only at eosinophil values in the region of 0.30 to 0.40 did the hazard ratio reach equivalence (i.e. confidence interval crossed 1.00) between the ICS and non-ICS groups.

The significant interaction of blood eosinophil count with treatment group was particularly pronounced in current smokers, but asthma sensitivity analyses did not alter results. Risk of exacerbation on ICS was highest in those with both low eosinophils and a low exacerbation frequency (and vice versa). There was no clear dose-response effect of dose on response to ICS treatment.

In secondary outcome analyses, there was a higher risk of pneumonia hospitalisation in patients receiving ICS treatment compared to those not receiving ICS, and this risk was greatest in patients with eosinophil counts <0.15 x10*9/L, again with a significant interaction of eosinophils with treatment group (p=0.04) but this did not reach significance for other outcome measures, probably due to low occurrence of outcomes such as pneumonia deaths.

6.8.2 Strengths and limitations

This study design has several strengths. Those related to the cohort in general, such as evaluation of steroid-naïve patients, access to a large number of real-world patients in

routine clinical practice rather than a highly selected trial population,[16] and data which is high quality and representative of the UK population,[76] have been discussed in previous chapters (Section 2.6.1), as well as potential limitations in relation to missing data (Section 2.2.9) and outcome measures (Section 5.4.2). Specific strengths in relation to this chapter's hypothesis-testing objective include the new-user cohort design which avoids immortal time bias that may be present in pharmaco-epidemiological studies,[84] and enables comparison between two therapies without need for a run-in period or need to discontinue treatment, creating run-in bias.[165-167] This is the first study which has used these specific methods to answer this clinical question (differences discussed further in Section 6.8.3 below).

Blood results and prescriptions are generally inputted automatically so these key variables of interest should have virtually complete coverage, and be accurate as to what was prescribed and when. Nonetheless, drugs prescribed are not necessarily taken by patients and adherence to maintenance medication in COPD is often poor.[168] Furthermore, prescribing of inhaled therapy for COPD is not always uniform.[33,169] My finding that almost 1 in 5 patients were initiated on ICS monotherapy for their COPD does not conform to national and international COPD guidelines,[10,13] but actually this is likely to reflect real-life practice and has been replicated in other database studies.[169,170] I found that those prescribed ICS had more 'asthma-like' features (e.g. younger, female, previous asthma, oral steroid or theophylline use), which could suggest that these were patients being thought of and managed as asthma rather than COPD patients, and would explain the decision to use ICS monotherapy; but sensitivity analyses excluding or including all asthma did not change results, suggesting that this was not the case, and if anything we would expect

patients with asthma started on ICS therapy to do better. Decreased propensity to prescribe ICS vs. non-ICS treatments over time is also likely to reflect changing guidelines and increased concerns over the association of ICS treatment with pneumonia over this time period.[23-25]

In this hypothesis-testing analysis (Aim II) only those patients who had continued on their new treatment for at least 6 months were included. This reduced the sample size by almost half, suggesting that many patients do not continue on their new medication beyond one or two months. This may be because of a conscious trialling the benefit of a medication, a change to an alternative, or simply the patient failing to continue requesting prescriptions. Certainly, adherence to prescribed medications has been found to be sub-optimal in many people living with COPD.[168] My findings corroborate those in the Suissa *et al* study[108], in that 52.2% of patients were censored due to discontinuation of initial medication, and a further 12.6% switched treatment (and they only did an on-treatment analysis). In my study, sensitivity analysis using the full intention-to-treat population, as well as complete on-treatment analysis, made minimal difference to these results and this increases confidence in my findings in relation to this prescribing issue. Other methodological sensitivity analyses including inclusion of those with an outcome in the first month (removed to eliminate protopathic bias), and inclusion of co-variates with large amounts of missing data, made minimal difference to overall findings. However, further sensitivity analysis focusing on data management issues for determining eosinophil counts, and decisions in relation to medication classes and duration of treatments, would have added confidence to findings.

In observational studies of treatment comparisons, there is likely to be residual confounding by indication, which is not completely eliminated by adjustment for baseline variables, and this may partly explain the worse outcome seen with ICS treatment in this study compared to in trials, which have in general found either no or a small benefit of ICS on exacerbation outcomes,[18-21] including 'real-life' trials in primary care, such as the Salford Lung Study.[171] Against this is that I found no association of ICS treatment with either hospitalisation or death due to any cause, suggesting that the association with poorer respiratory outcomes may be a true effect. Either way, it is the difference in treatment effect size between eosinophil groups, rather than the absolute values, which are important for assessing the role of eosinophils in predicting ICS responsiveness. The fact that the observed eosinophil-treatment effect in this study was consistent across repeated different methodological sensitivity analyses, and a dose-response relationship was seen using continuous analysis of eosinophils, in addition to allocation above and below differential eosinophil thresholds, strongly suggests that this relationship is likely to be real.

6.8.3 Comparison with other literature

Two other (recently published) studies have attempted to answer the same objective using the CPRD. Oshagbemi *et al* found a similar hazard ratio of exacerbations in patients prescribed ICS vs. non-ICS treatment, but that stratification of ICS use by either absolute or relative eosinophil counts did not result in significant differences in risk.[106] However, their methods were quite different to mine in that they classified ICS exposure as current vs. never in a time-dependent manner based on recency to exposure (i.e. not new-user method), as well as that they excluded all patients with asthma and those who had had any exacerbations in the baseline period. Given that my study findings suggest that baseline

exacerbation frequency also interacts with baseline eosinophil count as a marker of ICS responsiveness, it is perhaps unsurprising that they did not find any association. The other CPRD study, by Suissa *et al*[108] was a new-user cohort study but directly comparing LABA-ICS with LAMA (not all ICS vs. non-ICS therapies), which found a slightly lower HR for exacerbations than in my study (0.95 (95% CI 0.90 to 1.01) vs. 1.08 (95% CI 1.03 to 1.14)), but a higher HR for pneumonia risk (HR 1.37 (95% CI 1.17 to 1.60 vs. 1.06 (95% CI 1.00 to 1.13)). Suissa *et al* did not exclude patients who commenced both treatments close together in time (only if actually on the same date); patients were not ICS-naïve; they did not report that they had conducted sensitivity analyses to assess whether handling continuation of initial medication made any difference to results; and they used high-dimensional propensity score rather than multivariate modelling. Despite these differences, they found that LABA-ICS inhalers were only more effective than LAMAs in patients with blood eosinophil concentrations >4% or counts >0.30 x10*9/L; this is a similar association to in my study but with the benefit of ICS seen at lower eosinophil counts (mine only reached equivalence at 0.30 x10*9/L). My study found a similar dose response of decreasing HR with increasing eosinophil category when I looked by relative rather than absolute eosinophil counts.

A systematic review and meta-analysis including five of the post-hoc analyses of ICS trials (Cheng *et al,* which included studies up to 2017) found no significant difference between ICS vs. non-ICS treatment at <2% eosinophils, but a relative risk of 0.816 (95% CI 0.672 to 0.990, p=0.04) in the ≥2% eosinophil group,[109] and similar findings have been found in continuous eosinophil analysis of previous trials, except that the benefit of ICS was seen at lower eosinophil counts of 0.10[59] and 0.18[60] x10*9/L. Certainly, non-ICS treatment appears

more favourable in the lowest eosinophil groups (<0.15 x10*9/L).[56] Another more recent systematic review of ICS escalation (Oshagbemi *et al*) found a reduction in exacerbation risk with absolute blood eosinophil thresholds ranging from ≥0.10 to ≥0.34 x10*9/L.[172]

The important discrepancy between results obtained using a variety of eosinophil count thresholds makes comparisons between studies somewhat problematic, and developing guidance for practice more difficult. I have conducted sensitivity analyses using several different eosinophil count thresholds, as well as analysis using a continuous variable, which strengthens my findings in relation to overall association and mine is one of the first studies to do this. However, although informative, my findings cannot unequivocally guide the optimal threshold for clinical use due to the biases associated with the use of observational data to answer this question, as previously discussed. The distribution of eosinophil count in RCTs compared to my cohort (discussed in Section 4.5.1) may have determined the choice of cut-off points for the RCTs, but there is ongoing controversy concerning optimal thresholds. Given my finding that two-thirds of patients in my primary care sample had an eosinophil count above 0.15 x10*9/L (Section 4.2.2), which is greater than in the RCTs, in retrospect, I might not have chosen to use this low threshold; however, I did add an analysis of a 0.34 x10*9/L threshold in response to emerging data whilst conducting the study.

Observational cohort studies have had mixed findings, but are limited by sample size and methodology concerns.[137,156] Analysis of the IMPACT trial which investigated new single-inhaler triple therapy (SIIT) effectiveness vs. dual LAMA-LABA found that the magnitude of benefit of ICS-containing vs. non-ICS arms in reducing exacerbation rates increased in proportion to blood eosinophil count, as well as for other outcomes including symptoms

scores and FEV_1.[173] A CPRD study looking at rates of FEV_1 decline found no relationship with blood eosinophil count.[174]

These differences in findings between observational studies and RCTs may be explained by patients who are more unwell being commenced on ICS treatment vs. non-ICS, and indeed this was confirmed in the differences between the two groups at baseline (Table 6.1). As discussed in Section 6.8.2 above, this is likely to relate to other unknown confounders which cannot be adjusted for. Indeed, other database studies also showed a less marked benefit of ICS treatment,[108] which could be a combination of residual confounding and the fact that a broader, less severe and less selective population is included in the primary care population. That said, the RCT findings were replicated in the Salford Lung Study[171] which recruited patients from primary care, suggesting that residual confounding is the bigger methodological issue. The inclusion of patients with historical asthma in my study may result in ICS initiation in those with a more asthma-like phenotype being prescribed ICS. However, if this were the case, we would probably expect those commenced on ICS to do better rather than worse, and in fact sensitivity analyses including current asthma or excluding historical asthma did not change the results, which a strength of this study.

I found that blood eosinophils predicted ICS responsiveness most in those with a high baseline exacerbation frequency (≥2 in baseline year) or who are current smokers. The association with exacerbation frequency has been found in the other CPRD studies,[106,108] although the Oshagbemi study did not include the full spectrum of exacerbation frequency.[106] My finding in current smokers is in agreement with some studies, where only current smokers showed differential responses to ICS by eosinophil count.[59] However, aside from eosinophil interactions, smoking status also independently predicts response to

ICS-LABA in reducing exacerbations, with former smokers more ICS-responsive in trials,[59,173,175] and a post-hoc cluster analysis to identify predictors of ICS responsiveness also identified those with a smoking history >46 pack-years as non-responders, although patients were categorised on the basis of cumulative smoking exposure rather than as current vs. ex-smokers, as in my study.[176] There was no difference in ICS effectiveness between smoking subgroups in my study, although groups were relatively small.

In terms of pneumonia outcomes, my finding that there is higher risk of pneumonia in patients with COPD receiving ICS therapy with eosinophils below 0.15 x10*9/L than in those with higher eosinophils (which was greatest in severe pneumonia events) has been replicated by other studies.[108,159] However, the systematic review of post-hoc analyses of trials found contrasting findings,[109] although this only included two studies.[56,94]

6.8.4 Conclusions

The hypothesis-testing component of my CPRD study has been rigorously conducted with detailed attention given to overcoming potential biases. My findings corroborate those in other studies, despite slightly difference methods and cohort definitions, such that we can definitely conclude that blood eosinophils do predict ICS responsiveness. Certainly, highest risk of ICS treatment (or when non-ICS treatment should certainly be favoured) is in those with the lowest eosinophils (<0.15 x10*9/L), both for exacerbation and (probably) pneumonia outcomes; and this risk is highest in infrequent exacerbators. I have found that ICS only become equivalent to non-ICS in terms of exacerbation risk at values of 0.30 to 0.40 x10*9/L, but exactly where in the eosinophil range ICS they become beneficial varies widely between studies. Sensitivity analysis demonstrates that decisions to initiate ICS can probably be made irrespective of whether the last recorded eosinophil value or an average

of two, three or all previous results is used, with no need to exclude those taken close to exacerbations. Relationship between smoking status, eosinophil count and ICS treatment is likely to be complex, with the literature overall suggesting that ex-smokers do better on ICS, but in my study and others that eosinophils appear to only be predictive in current smokers.

Chapter 7: Use of near-patient eosinophils: accuracy and feasibility

This chapter presents results and discussion of the near-patient testing component of my overall thesis questions (COMET study aims II and III), to include method comparison of the different testing techniques (POC capillary and venous samples, and laboratory samples) and the participant survey. General methods for establishing the COMET cohort and baseline characteristics were presented in Chapter 2; distribution, variation and repeatability of laboratory venous eosinophils were presented in Chapter 4. Methods specific to objectives in this chapter are presented at the start of each section below.

Aims for this part of the study were as follows:

COMET Part II: To investigate use of near-patient eosinophils compared to laboratory eosinophils

Including specific objectives:

- *To assess method comparison of near-patient eosinophils compared to laboratory eosinophils*
- *To compare capillary blood testing with venous blood testing*

COMET Part III: To assess the feasibility and acceptability of undertaking such measurements in a primary care setting

- Including acceptability of both laboratory and near-patient blood tests, testing at the COPD annual review, and being part of the research study

7.1 Method comparison of near-patient eosinophils

The primary comparison was between POC capillary (finger-prick) eosinophils using the Hemocue® WBC-DIFF machine and laboratory venous eosinophils, but due to the risk that there might be a difference between venous and capillary eosinophil counts due to biological differences rather than measurement differences (discussed in Section 3.2.5), secondary comparisons were made between POC venous and laboratory venous eosinophils, and POC capillary and POC venous eosinophils (where the POC venous sample was obtained from the venous EDTA sample which would subsequently be sent to the laboratory).

7.1.1 Additional methods detail and sensitivity/subgroup analysis

As in Chapter 4, statistical analysis methods have been carried out assessing eosinophils both as a continuous measure and using a binary threshold (0.15 and 0.34 x10*9/L as previously). For analysis as a continuous measure, I used a paired t-test to calculate and compare the mean differences between paired measurements. This assumes that the differences are normally distributed, so I plotted the differences as histograms to check this, and then proceeded using untransformed data. I also calculated Pearson's correlation co-efficient, and performed a Bland-Altman analysis.[177-179]

For binary categorisation of eosinophils into 'high' and 'low' cut-offs, Cohen's kappa test was used to assess the inter-measurement agreement, and diagnostic accuracy statistics were calculated, using the venous blood eosinophil count as the reference test, and near-patient blood eosinophil count as the index test.[143]

Pairs of observations on the same individual were assumed to be independent and so more complex measures to account for non-independence of observations were not adopted.[178] Laboratory results were rounded to the nearest one decimal place to enable better comparison with the POC machine which only gives readings to one decimal place.

No specific sensitivity or subgroup analyses were performed for near-patient testing analysis aspects of the study.

7.1.2 Available results

322 laboratory eosinophil results were available for 93 participants (baseline characteristics of this population were detailed in Section 3.5, and reasons for missing laboratory results were detailed in Section 3.5.1); 318 POC capillary eosinophil results were available for 93 participants (missing for n=22 due to machine error or problem (n=18) or difficulty obtaining the sample (n=4); 319 POC venous eosinophil results were available for 93 participants (missing for n=21 due to machine error/issue (n=9), a participant issue e.g. refused or difficult to bleed (n=11) or reason not given (n=1)). This meant that paired results were available for n=303 (POC capillary/laboratory venous), n=315 (POC venous/laboratory venous) and n=306 (POC capillary/POC venous), on 92 participants.

7.1.3 Continuous analysis

Table 7.1 shows the mean difference using the paired t-test for each method comparison. There was a small but significant difference of 0.01 x10*9/L between POC capillary and POC venous, and laboratory venous eosinophils (p=0.01 and p=0.03 respectively), but no difference between POC capillary and POC venous samples (p=0.43).

Table 7.1: Method comparison using paired t-test

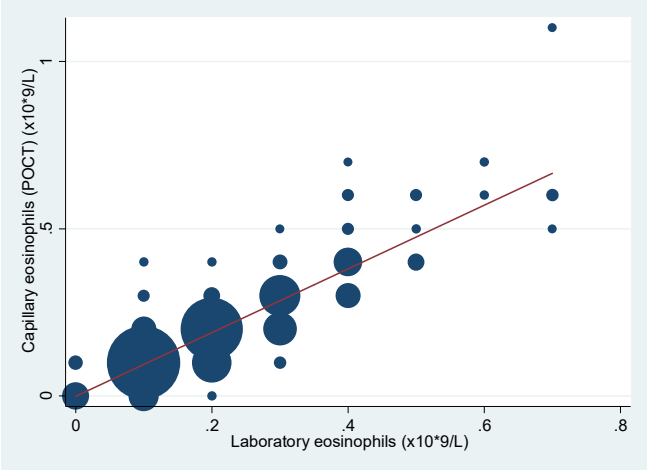
Paired samples (n=)	Laboratory venous (mean (95% CI), SD)	POC capillary (mean (95% CI), SD)	POC venous (mean (95% CI), SD)	Mean difference (mean (95% CI), SD)	p-value
303	0.20 (0.19-0.22), 0.13	0.19 (0.18-0.21), 0.14	N/a	0.01 (0.00-0.02), 0.07	0.01
315	0.20 (0.19-0.22), 0.13	N/a	0.20 (0.18-0.21), 0.13	0.01 (0.00-0.01), 0.06	0.03
306	N/a	0.19 (0.18-0.21), 0.14	0.20 (0.18-0.21), 0.13	0.00 (-0.01-0.01), 0.08	0.43

Eosinophil data were not transformed for this analysis so means presented are not geometric means (and why they are different from lower mean (0.16) presented in earlier analyses in Chapter 4).

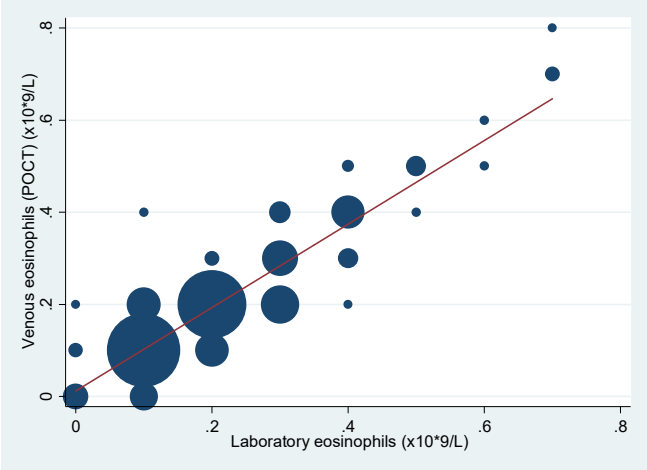
There was a strong correlation between paired samples using the different methods (r=0.86 for POC capillary vs. laboratory venous; r=0.90 for POC venous vs. laboratory venous; r=0.84 for POC capillary vs. POC venous (Figure 7.1). Figure 7.2 shows the Bland-Altman plots for the method comparison. For the main analysis comparing POC capillary with laboratory venous measurements, the limits of agreement were -0.14 to 0.16 x10*9/L, which was similar for the other comparisons. There were weak statistically significant correlations of measurement difference with the mean for comparisons of POC capillary vs. laboratory venous (r=-0.19, p=0.001) and POC capillary vs. POC venous (r=-0.17, p=0.003) but not for POC venous vs. laboratory venous (r=-0.03, p=0.64).

Figure 7.1: Scatter plots of measurement method comparisons A) POC capillary vs. laboratory venous B) POC venous vs. laboratory venous C) POC capillary vs. POC venous

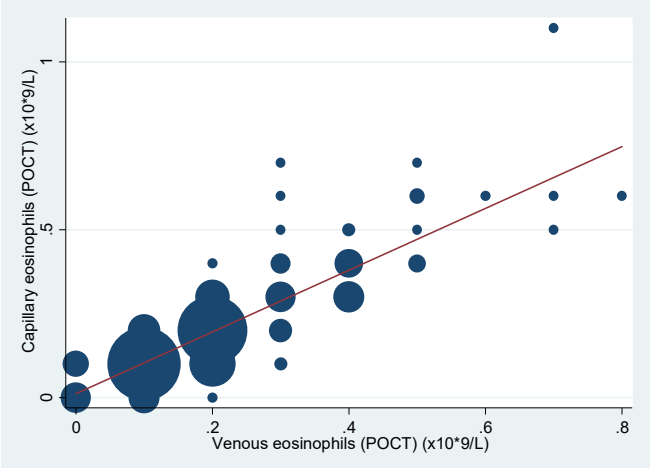
A)



B)

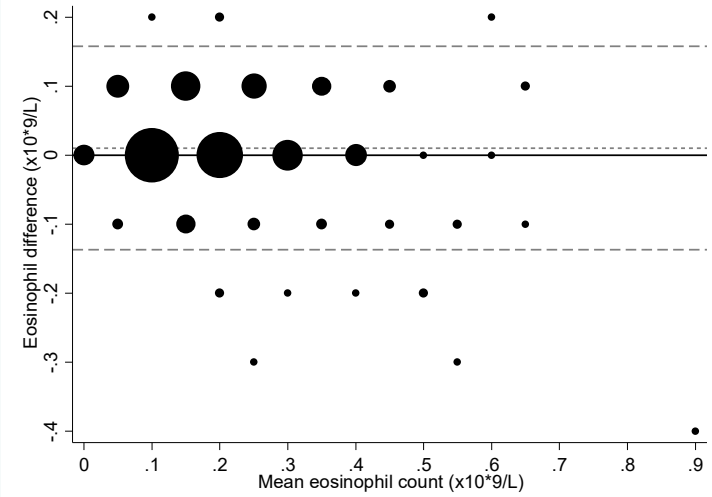
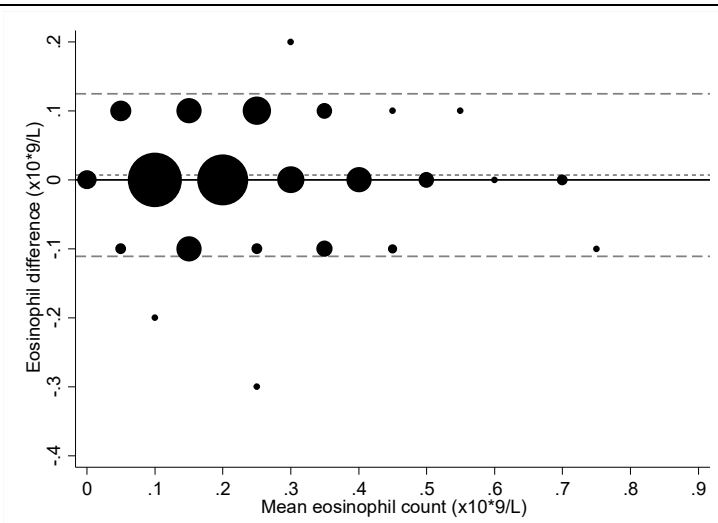
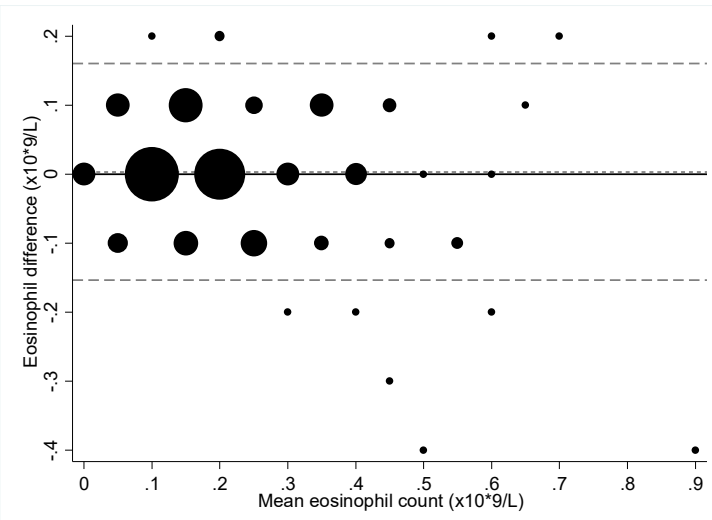


C)



Pearson's correlation co-efficient A) r=0.86 (p<0.001), n=303 B) r=0.90 (p<0.001), n=315 C) r=0.84 (p<0.001), n=306. Each point is displayed weighted by the frequency of observations, with the area proportional to the number of observations at that point.

Figure 7.2: Bland-Altman plots for measurement method comparisons A) POC capillary vs. laboratory venous B) POC venous vs. laboratory venous C) POC capillary vs. POC venous

A)		n=303 Mean difference (95%CI, SD): 0.01 (0.00-0.02, 0.07) Limits of agreement (+/-2SD): -0.14-0.16 Overall difference range: -0.4-0.2 Correlation of difference with mean (p-value): r=-0.19 (p=0.001)
B)		n=315 Mean difference (95%CI, SD): 0.01 (0.00-0.01, 0.06) Limits of agreement (+/-2SD): -0.11-0.13 Overall difference range: -0.3-0.2 Correlation of difference with mean (p-value): r=-0.03 (p=0.64)
C)		n=306 Mean difference (95%CI, SD): 0.00 (-0.01-0.01, 0.08) Limits of agreement (+/-2SD): -0.15-0.16 Overall difference range: -0.4-0.2 Correlation of difference with mean (p-value): r=-0.16 (p=0.004)

Each point is displayed weighted by the frequency of observations, with the area proportional to the number of observations at that point. Dotted line shows the mean difference. Solid line indicates zero. Dashed lines show limits of agreement (two standard deviations above and below the mean).

A post-hoc sensitivity analysis was conducted excluding two extremely outlying results (both resulting in differences of 0.4 x10*9/L between samples), to assess the influence on overall results.[177] This had no effect on the overall mean difference, but did slightly narrow the limits of agreement and made the correlation of difference with mean no longer significant.

7.1.4 Binary analysis

Cohen's kappa (κ) was 0.74 for the primary analysis of POC capillary vs. laboratory venous eosinophils, using the 0.15 x10*9/L threshold (p<0.001), and ranging from 0.67 to 0.78 for the other measures, indicating substantial agreement throughout (Table 7.2).[143]

Table 7.2: Agreement between measurement method paired samples (Cohen's kappa)

Eosinophil threshold	POC capillary vs. laboratory venous	POC venous vs. laboratory venous	POC capillary vs. POC venous
0.15 x10*9/L	0.74 (p<0.001)	0.76 (p<0.001)	0.69 (p<0.001)
0.34 x10*9/L	0.77 (p<0.001)	0.78 (p<0.001)	0.67 (p<0.001)

Table 7.3 shows diagnostic accuracy analysis using POC capillary eosinophils as the 'index test' and laboratory eosinophils as the 'reference test' i.e. assuming that the laboratory result is the gold standard for the 'correct' value. At the 0.15 x10*9/L threshold, the sensitivity of POC capillary eosinophils was 84.9% (95% CI 78.8 to 89.8%) and the specificity was 90.3% (95% CI 83.7 to 94.9%), which decreased and increased respectively as the threshold for defining 'high eosinophils' increased to 0.34 x10*9/L.

Table 7.3: Diagnostic accuracy analysis assessing POC capillary eosinophils vs. laboratory venous eosinophils using binary thresholds

	Index test group (POC capillary eosinophils)	**Low eosinophil group (laboratory) (n=)**	**High eosinophil group (laboratory) (n=)**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**	**PPV (%) (95% CI)**	**NPV (%) (95% CI)**	**LR+ (95% CI)**	**LR- (95% CI)**
0.15 x10*9/L threshold	Low eosinophil (n=) High eosinophil (n=)	112/124 12/124	27/179 152/179	84.9 (78.8-89.8)	90.3 (83.7-94.9)	92.7 (87.6-96.2)	80.6 (73.0-86.8)	8.8 (5.1-15.1)	0.17 (0.12-0.24)
0.34 x10*9/L threshold	Low eosinophil (n=) High eosinophil (n=)	258/264 6/264	9/39 30/39	76.9 (60.7-88.9)	97.7 (95.1-99.2)	83.3 (67.2-93.6)	96.6 (93.7-98.4)	33.9 (15.1-76.0)	0.24 (0.13-0.42)

PPV, positive predictive value. NPV, negative predictive value. LR+, positive likelihood ratio. LR-, negative likelihood ratio.

7.2 Acceptability of near-patient testing

The survey developed and used for this part of the study was discussed in Section 3.2.7 and 3.2.8 and a copy of the survey can be found in Appendix O.

7.2.1 Survey results

80/95 (84.2%) participants attended a final study visit, and 76/80 (95.0%) completed a survey. Survey results (both quantitative and qualitative aspects) are presented in Table 7.4. Participants had in general not found the blood tests too uncomfortable (mean score 8.8 (SD 2.1) for venous blood test and 9.1 for finger prick test (SD 1.8), and participants would be very happy to have these as part of their COPD annual review, with comments such as *"I don't mind blood tests at all, they don't hurt and if a solution can be found for managing COPD it is well worth it"* [female in sixties]. In general, satisfaction for blood tests was higher than for breathing tests (Table 7.4).

Participants found the COPD annual review helpful (mean score 9.1 (SD 1.7)), with more mixed (but generally positive) attitudes towards extra testing as part of this. In free text comments some participants commented on the benefits in terms of reassurance, but others also identified potential anxieties: *"I am both reassured and made anxious by being tested"* [female in seventies].

Participants had had in general a very positive experience of taking part in the study (mean score 9.4 (SD 1.1)) and the free text comments reflected this. Participants had particularly

enjoyed building a relationship with the study nurses,[a] and having information about their condition and new tests for the future (Table 7.4 free text comments).[b]

[a] The detailed survey results were specifically fed back to the Clinical Trials Unit study nurse team.
[b] Comments regarding FeNO are included here for completion but will not be discussed further.

Table 7.4: Participant satisfaction survey results

Survey question	n=	Mean [a] (SD)
About the blood tests		
I found the blood test from my arm uncomfortable (10=Not at all uncomfortable)	76	8.8 (2.1)
I found the blood test from my finger uncomfortable (10=Not at all uncomfortable)	76	9.1 (1.8)
I don't mind putting up with the discomfort of a blood test if it helps with managing my COPD (10=I don't mind at all)	76	9.6 (0.9)
I would be happy to have a finger prick blood test as part of my COPD annual review (10=Very happy)	76	9.7 (0.7)
I would be happy to have a blood test from my arm as part of my COPD annual review (10=Very happy)	76	9.5 (1.0)
Any thoughts or comments about the blood tests and the process of getting the blood tests (free text)	28	N/a
• No problems/concerns/don't mind	18	N/a
• Even if a bit of discomfort worth it for helping manage COPD *"I don't mind blood tests at all, they don't hurt and if a solution can be found for managing COPD it is well worth it"*	5	
• Go along with opinion of health care professionals *"If health care professionals think I need it I will have it"*	1	
• Would prefer finger prick to blood test *"I feel nervous when having arm blood tests. The first finger prick was quite painful but improved from the second."*	2	
• Finger test more painful	1	
• Miscellaneous *"Tell everyone to drink lots of water beforehand"*	1	
About the breathing tests		
I find spirometry is easy to perform (10=Very easy)	76	7.1 (2.4)
I find FeNO is easy to perform (10=Very easy)	76	7.8 (2.1)
The visual display made it easier for me to understand how to use the FeNO machine (10=I completely agree)	76	8.9 (1.7)
I would be happy to have FeNO as part of my COPD annual review (10=Very happy)	76	9.5 (0.9)
Any thoughts or comments about the breathing tests and the process of doing this (free text)	21	N/a
• No problems/concerns/don't mind *"Very impressed by FeNO!"*	11	N/a
• Regardless of ease would be happy to have it if beneficial to them	2	
• Happy to help contribute to research even if uncomfortable	2	
• First time difficult with FeNO/need to repeat test	2	
• Specific feedback about machines *"Screens need to be a bit bigger" "I find the tube on spirometry too wide. The mouth piece on the FeNO machine is easier to use."*	2	
• Found it tiring	1	
• Inducing anxiety *"Raises anxieties in case results are not good"*	1	

About the COPD annual review [b]		
I find the annual review helpful (10=I completely agree)	70	9.1 (1.7)
In general, I feel happier if I have had a lot of tests (10=I completely agree)	71	7.8 (2.6)
I would like to have instant feedback on my results (rather than having to wait for a result of a test) (10=I completely agree)	71	7.6 (2.7)
I would be more motivated to look after my COPD because of additional testing (10=I completely agree)	71	7.1 (2.8)
Having these tests regularly would strengthen my relationship with my GP or nurse (10=I completely agree)	70	7.5 (2.6)
Any thoughts or comments about the COPD annual review and extra testing in general (free text)	15	N/a
• Good *"I think it's a very good thing. I'm lucky to have it available." "It is a relief to know that I am being looked after! Thank you."*	6	N/a
• Prefer not to visit doctors *"If I have to come in I'll come in"*	2	
• Would prefer/welcome increased frequency e.g. twice a year	2	
• Tests (and extra tests) give reassurance	3	
• Mixed *"I am both reassured and made anxious by being tested"*	1	
• Research-orientated *"If it helps other people worse than me that's the main thing"*	1	
About being in this study		
I have enjoyed being part of this study	76	9.4 (1.1)
What did you find worked well? (free text)	51	N/a
• All of it/no problems	33	N/a
• Friendly nurses/relationship built up with the team	5	
• Good explanations about the tests/understanding new research methods	5	
• Good to be helping with a study	1	
• Organisational aspects e.g. *"on time"*	1	
• Personal interest *"It's been interesting to see what the difference was from 1 test to the next and what results I got."*	1	
• Spirometer	1	
• FeNO machine	3	
• Miscellaneous *"Getting it over and done with"*	1	
What did you find made it difficult? (free text)	45	N/a
• Nothing	29	N/a
• Difficulty of some of the breath tests e.g. *"doing 3 spirometry blows", "FeNO" "salbutamol inhaler difficult to use"*	8	
• Felt less well after breath tests *"coughing after breath tests" "weak feelings after puffing and blowing"*	3	
• Blood tests	2	
• Communications with booking staff	1	
• *"How happy the staff was"*	1	
• *"Worry about a possible worsening"*	1	

What would have made it easier for you? (free text)	35	N/a
• Nothing *"It was a very easy process. Don't think it could have been better." "A perfect study!"* • Organisational aspects e.g. reminder letter, weekend appointments, response to e-mails • Miscellaneous e.g. *"bacon sandwich", "if I stopped smoking" "Feno all the way" "cup of tea" "an inhaler you could activate independently" "if I didn't have to breathe through the tubes" "more frequent visits for COPD"* • *"Harder or easier are irrelevant, the results are what matter"* • Being told results	23 3 7 1 1	N/a
Any additional comments about the study (free text)	29	N/a
• Nice/cheerful staff *"The lady who conducted the tests was delightful."* • Pleased to have taken part • Well conducted study • Hope the results will be useful • Increased knowledge of condition/found it interesting • No further comments/good • Miscellaneous e.g. *"keep going" "would appreciate some feedback eventually"*	4 8 2 5 4 4 2	N/a

[a] Numerical results were scored using a Visual Analogue Scale from 0 to 10, measured using a ruler and then given to the nearest whole figure. Direct quotes are shown in italics.

[b] There were a surprisingly large number of missing answers for the section 'About the COPD annual review'. For one participant the blank page was accompanied by the comment 'No review done in practice I've been reviewed at the chest clinic' but for others there was no clear reason.

7.3 Discussion

7.3.1 Summary of findings

This chapter has assessed use of the Hemocue® WBC-DIFF machine compared with laboratory eosinophils, as well as comparing use of capillary and venous blood testing, and acceptability to patients. Correlation was high between POC capillary vs. laboratory venous (r=0.86), POC venous vs. laboratory venous (r=0.90) and POC capillary vs. POC venous (r=0.84). There was a small but significant difference of 0.01 x10*9/L between POC eosinophils (both capillary and venous) and laboratory eosinophils, and no difference between POC capillary and venous samples; this difference is too small to be of clinical significance and in any case is below the lower limit of detection of the Hemocue® machine which gives results to the nearest 0.1 x10*9/L. Limits of agreement on Bland-Altman analysis were approximately +/-0.15 x10*9/L. For binary analysis, agreement between measurement pairs were in the range κ=0.67 to 0.78, which indicates substantial agreement,[143] and in diagnostic accuracy analysis, sensitivity and specificity were 85 and 90% respectively at the 0.15 x10*9/L threshold, changing to 77 and 98% respectively at the 0.34 x10*9/L threshold.

Participant survey completion rate was high (95%). Participants had mostly not found the finger prick blood test uncomfortable (and less uncomfortable than the venous blood test), and satisfaction for blood tests was higher than for breathing tests. Attitudes towards extra testing as part of the COPD annual review were in general positive, although some participants recognised that there could be additional anxiety caused by testing. Participants had had a generally positive experience of taking part in the COMET study.

7.3.2 Strengths and limitations

This is the first study to investigate POC eosinophils in a hypothesis-driven, individually consented, prospective primary care ICS-naïve COPD population, examining feasibility, usability (including patient opinion) and repeatability in such detail. There were a large number of paired samples available for participants in this cohort (n=303 to 315), which gives the largest number of data points to date that examines method comparison of blood eosinophils (as discussed in Section 7.3.3 below). I also assessed a range of different method comparison methods, which reassures me that my findings are likely to be robust.

Missing data for POC capillary tests were largely due to machine errors rather than difficulty obtaining the sample from participants. This is in contrast to missing data for venous samples which were largely due to difficulty obtaining the venous sample. This highlights that this method of measuring eosinophils may be useful in clinical practice for patients who are difficult to bleed. The number of machine errors formally recorded (and resulting in no sample tested) does not, however, represent the number of machine errors which occurred. The study nurses reported that it sometimes took several attempts to get the Hemocue® machine to process the sample. However, this was not formally recorded in the CRF to be able to capture this quantitatively but would have been useful for determining acceptability to practice staff. This is important because in the clinical research study setting there is sufficient time to run repeated tests, but this would not be the case in routine clinical practice and might limit usability. Furthermore, having the machine only being used by a small number of people who quickly became proficient in managing its foibles, does not enable us to draw conclusions about how this would work with a range of (potentially untrained) practice staff using the machine. A point-of-care test can only be

fully evaluated in the setting in which it will ultimately be used,[180] and this needs to involve evaluation from clinicians as well as patients.[181] Other studies have not reported any issue with machine errors, and it is possible that this occurred in this study due to the machine being moved around frequently between different study sites, although another local study using the device in the Oxford hospitals Emergency Department has recently abandoned its use due to frequent machine errors (personal communication).

Blood eosinophils do show physiological diurnal variation,[182] and it is possible that this might have affected results. However, blood tests were taken at a time commonly used in primary care for taking laboratory samples, to enable them to reach the laboratory the same day (i.e. morning or early afternoon). Use of near-patient testing might mean that clinics could run later in the day as this would no longer be a limitation, and so it is possible that agreement might vary if this were the case.

For diagnostic accuracy assessment, there is a question over which test should be deemed the 'gold standard'. I decided to use the laboratory venous sample as the reference standard, as this is the current practice. However, it is possible that capillary eosinophils might be more representative of tissue eosinophils (and therefore correlate better with lung tissue eosinophils than peripheral blood eosinophils, which is debated),[156] as well as being 'fresher' as there is no time delay for transport to the laboratory. Diagnostic accuracy assessment for binary method comparison is also of limited utility where many of the points of variation are around the threshold points, as discussed in Section 4.5.1); I could potentially have used Receiver Operating Characteristic curves to assess probability of predicting correspondence across various eosinophil thresholds as used in one study.[183]

There was good response rate to the participant survey, and this may relate to giving it out at the last appointment and linking its completion to receipt of the gift voucher (which may more generally have encouraged participation in the research, aside from the survey).[184] Participants appear to have found it straightforward to complete, and have given appropriate answers, which was probably helped by piloting the survey with the PPI representative. Although there was no available validated survey to use, I was able to base it on previously published studies addressing similar questions.[70,125,126] However, the depth of the qualitative answers is limited due to the size of the free text boxes, and need for writing (which may be difficult in an elderly population with poor eyesight), and a qualitative interview study would be needed to be able to draw firmer conclusions on the acceptability of POC eosinophil testing to patients. Furthermore, there is the limitation that levels of satisfaction in relation to the testing procedures may result simply from participants being part of a study (and likely an engaged, compliant subgroup of patients) rather than attributable to the testing procedures themselves (the Hawthorne effect).[70] There is also a tendency for survey participants to give positive responses,[123] and so views may not be representative of the whole primary care COPD population.

7.3.3 Comparison with other literature

This is the only study which has assessed the Hemocue® WBC-DIFF device in COPD patients in primary care, with multiple paired samples, and also comparing capillary and venous results for eosinophils. Other studies have generally focused on other white blood cells, and not necessarily published data on eosinophils, and give headline figures for method comparison in terms of results for correlation.[183,185-187] There have been repeated criticisms of this approach, as correlation assesses the strength of the linear relationship between

measurements, not the agreement, and high correlation does not necessarily indicate good agreement; Bland-Altman methods to assess mean difference and limits of agreement are superior.[144,177]

Correlation between POC capillary and laboratory venous eosinophils has been found to be r=0.97 in healthy volunteers (n=20),[185] 'poor' correlation in a paediatric population (n=158),[188] and r=0.87 in patients presenting routinely to a remote clinic in Australia (n=53),[187] compared to r=0.86 in the COMET study. There was a mean difference of 0.04 (95% CI -0.07 to -0.02 x10*9/L) in POC capillary vs. laboratory venous eosinophils and 0.00 (95% CI -0.03 to 0.02 x10*9/L) for POC vs. laboratory venous samples in the latter Australian study. The correlations between POC capillary and laboratory venous eosinophil test results (with cautions regarding this method as discussed above) are similar in the COMET study to those found in the Australian clinic study, but lower than the high correlation found in healthy volunteers. This variation in results may be due to low eosinophil counts in healthy volunteers as well as a more controlled environment, and indicates the importance of testing a device in the clinical setting in which it will ultimately be used.

Two studies have specifically looked at the Hemocue® WBC-DIFF device in patients with respiratory disease. In 76 patients with severe asthma, there was correlation of r=0.85 between POC capillary and laboratory venous sample, and, as in the COMET study, eosinophils were generally lower on the POC machine compared to venous laboratory values (mean eosinophils 0.48 vs. 0.61 x10*9/L eosinophils).[183] I also found that eosinophils were higher in laboratory venous samples, but by a much smaller difference (0.01 x10*9/L), which may relate to the much higher eosinophil values in a severe asthma population. This

would fit with another study in healthy (n=19), asthmatic (n=12) and COPD (n=10) patients which found an eosinophil geometric mean of 0.2 x10*9/L for both POC and laboratory results, as in our study.[186] They found a correlation of r=0.85 and no significant difference between POC and laboratory results (p=0.78), which may relate to the much smaller sample size not allowing a small difference to be detectable. As in the COMET study, they found a small amount of proportional bias at higher levels of eosinophil counts, but did not consider this to be clinically significant.

I found closer agreement between POC capillary and POC venous samples than in either of these compared with laboratory venous samples. Differences have been found in blood count parameters between venous and capillary blood (n=24 healthy volunteers), with significantly higher white cell counts in finger prick compared to venous blood (p<0.001), particularly granulocytes (which includes eosinophils).[121] This latter study also found higher inter-measurement variation in the fingertip, with decreasing numbers of leucocytes found with repeated sampling, which they proposed might be due to immediate local accumulation of granulocytes due to skin puncture. It is recommended that the first drop of blood be wiped away, and using as large a drop of blood as possible without squeezing the finger,[189] which is what is recommended in the Hemocue® WBC-DIFF device instructions, and this might explain why there has been no difference between capillary vs. venous blood in studies specifically using the Hemocue® WBC-DIFF device (p=0.105 for total leucocytes[120] and p=0.46 for eosinophils in COMET). The studies in respiratory patients have assessed reproducibility of repeated samples on the same individual[183,186] (which I did not do), and found this to be acceptable and within the desirable Westgard specifications[190] for total error, imprecision and bias; another study found that

reproducibility reduced at higher eosinophil counts and did not meet these criteria,[185] but this was in patients with schizophrenia rather than those with respiratory disease.

In terms of acceptability, only one study has specifically addressed this for the Hemocue® WBC-DIFF device, and this was using it for clozapine monitoring in schizophrenia in the Netherlands. They used a VAS for patients to rate their subjective experiences of various aspects of blood sampling, and found a consistent pattern favouring capillary blood sampling over venous sampling, and practitioners also preferred it (with no mention of machine errors).[191]

Near-patient testing has been more extensively studied in medical conditions other than COPD, particularly for anticoagulant therapy monitoring (International Normalised Ratio, INR) and diabetes (glycosylated haemoglobin, HbA1c), as these are conditions where near-patient testing would enable an immediate management decision to be made, and avoids the need for waiting for a result, often involving a second visit. Actionable information at the point of care would also be the potenial utility of eosinophil testing in COPD. A large study (n=1664 dual measurements) comparing near-patient vs. laboratory tests for INR, found that mean difference depended on the average INR result, and increased as average INR increased, similar to in my study for eosinophils.[192] Another study (n=46) used a cross-over design over 6 months to compare the two testing modalities and found no significant difference between them, and that the mean difference increased as average INR increased.[193] A meta-analysis assessed effectiveness of the near-patient test in terms of INR control and clinical outcomes, and found reduced deaths and thromboembolic events in the near-patient group.[194] This was for self-testing of INR, so one would in fact expect greater variability than with clinician-testing. Although my study was not of sufficient

duration or with a comparator group, to be able to assess clinical outcomes in this way, it remains one of the largest and first in a population with COPD. Application thus of POC for eosinophils in COPD needs to be further assessed in respect of outcomes but remains eminently tangible to future implementation in clinical practice.

In diabetes, a systematic review and meta-analysis included 61 studies[195] which examined a range of devices for near-patient HbA1c testing, and assessed mean difference, variability, precision, and diagnostic accuracy around an HbA1c threshold. There was considerable variation between results from different devices, but also between studies of tests using the same device. As discussed earlier in this section, my study found no meaningful difference between capillary and venous eosinophils, but this was not the case for diabetes monitoring, where a near-patient testing study similarly comparing results for samples found a much higher differentiation between poorly and well-controlled blood glucose levels when results from testing capillary blood were used.[196] It may be that capillary samples better reflect true tissue level results in terms of glucose homeostasis compared to a venous sample, whereas this may not be the case for eosinophils.

Surveys have also been conducted to assess patient and clinician acceptability for POC testing for other conditions. A similar survey to mine also used VAS to determine if patients were more satisfied with near-patient testing than laboratory testing (for diabetes, hyperlipidaemia and anticoagulant therapy monitoring).[70] They found that patients would rather have blood taken by finger prick than by needle, and our scores were similar for the questions on motivation to look after the chronic disease because of the POC testing, strengthening the relationship with the health care professional, and finding instant feedback helpful. In a study of acceptability of near-patient testing for HbA1c by primary

care nurses, using both survey and qualitative interview components,[125] it emerged strongly that patients in both study groups were typically very satisfied with usual test arrangements, as we also found in relation to the current COPD annual review. In the HbA1c study, nurses reported a strong advantage of near-patient testing in terms of having the result available for discussion with the patient. However, the usefulness of an instant result did vary between surgeries according to the nurse's level of responsibility for making management changes and the availability of a doctor during nurse-led clinics, and the same would likely be true if the Hemocue® WBC-DIFF device were used in COPD management. A recent qualitative study[197] focusing on HbA1c near-patient testing found that patients found a single appointment more convenient, and reduced previous anxiety they had felt while waiting for the result. However, clinicians expressed concern about potential cost of the devices, as this would be in addition to the laboratory testing which is a single fee for service and does not specifically itemise HbA1c testing. This would be a factor in the implementation of eosinophil near-patient testing, as discussed further in the next chapter.

However, findings from these acceptability studies are not directly comparable because they assess POC tests as a replacement for existing laboratory testing, whereas in our context this would be an add-on test (as no laboratory test is generally currently performed routinely as part of the COPD annual review). In a qualitative interview study of patients and clinicians addressing acceptability of an add-on test (for respiratory tract infection), patients did identify fewer reconsultations to get results as a potential benefit.[126]

7.3.4 Conclusions

I found close agreement between POC capillary and laboratory eosinophils, using the Hemocue® WBC-DIFF machine, and the mean difference of 0.001 x10*9/L is unlikely to be

clinically significant, and is below the lower limit of detection of the machine in any case. This corroborates other published findings, although there is limited existing research in this area. Any small differences between capillary and venous measurements are unlikely to be clinically relevant. Study participants found the testing acceptable and would be amenable to its implementation into routine practice as part of the annual COPD review, although firm conclusions are limited by survey methods and potentially a highly selected population. Use of near-patient testing may have particularly advantages for those who are difficult to bleed, but its use may be limited by a relatively large number of machine errors and a need for repeated samples, although this has not been reported in other published studies.

Chapter 8: Conclusions

In this final chapter I will draw together objectives, results and discussion from other chapters, and place it together in the context of other literature and guidelines which have been published during my doctoral project; review strengths and limitations of the methods I have used to answer my specific objectives; and discuss implications of my work for clinical practice, future policy, and further research. I will not repeat detailed discussion of methodological strengths and weaknesses or comparison with other study findings as these have been discussed in detail in each chapter's Discussion section (Chapters 2 to 7).

My specific contributions to my different thesis projects, and broader reflections on what I have learned through undertaking this programme of work, are laid out in the subsequent epilogue.

8.1 Key findings in relation to thesis objectives

My overall hypothesis was that primary care COPD patients with higher baseline blood eosinophils are likely to do better on ICS treatment compared to those with lower eosinophils. I aimed to better characterise this phenotype, establish relationship of blood eosinophils to disease outcomes and whether blood eosinophil levels could predict ICS responsiveness, and assess the use of a near-patient test for blood eosinophils which could potentially be used to streamline the COPD annual review process.

Specific objectives were summarised in Box 1.1 and are repeated here with a summary of study findings, with initial implications for clinical practice going forwards shown in bold, which will be discussed and formed into recommendations later in this chapter.

To describe existing practice of blood eosinophil testing in ICS-naïve primary care patients with COPD in the period before starting a new inhaled maintenance treatment

- In current primary care practice, almost 65% of the COPD population have an eosinophil count measured within 2 years of commencing a new inhaled maintenance treatment

This finding is important as it implies that the practice of measuring eosinophils is possible and frequently done in the course of routine primary care, and that the results available in the clinical records of the majority of COPD patients could be used to inform clinical practice and direct treatment.

To assess blood eosinophil distribution in the primary care COPD population

- *There is a right-skewed distribution of eosinophil counts with a geometric mean of 0.20 and 0.16 x10*9/L in the CPRD and COMET cohorts respectively*
- *Using thresholds to categorise eosinophil counts into groups, approximately half of patients fall into a 'medium' category of eosinophil counts in the range 0.15 to 0.34 x10*9/L (50% in CPRD and 43% in COMET)*
- *Using a threshold of 0.15 x10*9/L, 69% (CPRD) and 59% (COMET) of patients with COPD have eosinophil counts above the threshold*

Eosinophil counts had a slightly different mean between my CPRD and COMET study data, but this difference is small and unlikely to have any implication in result interpretation. A significant majority of patients have eosinophil levels greater than 0.15x10*9/L, meaning use of this threshold alone to guide ICS initiation would result in the majority of patients commencing ICS treatment.

To assess the association between higher blood eosinophil counts and clinical characteristics

- Patients are more likely to have higher eosinophils if they are younger, male, ex-smokers, with a history of atopy, more exacerbations, higher prescriptions for oral steroids or salbutamol inhalers, high GP consultation rates or more co-morbidities
- In this cohort, there is no association between eosinophil counts and historical or active asthma

There is a clinical difference in patients with higher eosinophils which may help in distinguishing how these are to be interpreted in clinical practice.

To assess within-person variation and stability over time of blood eosinophil counts, to decide whether the most recent value can be used in decision-making

- Variation between repeated eosinophil measurements increases with higher eosinophil counts
- There is good and excellent agreement as measured by the ICC for repeated measures of eosinophil counts in CPRD and COMET respectively
- Using binary thresholds of 0.15 and 0.34 x10*9/L for categorising eosinophils, there is moderate/substantial agreement for CPRD and COMET
- Higher variation occurs when eosinophil values close to acute events are measured, but this effect is small and unlikely to be clinically significant in interpretation of repeatability

There is a good repeatability with repeated measures of eosinophils, and if these are available in clinical practice, interpretation over several tests is appropriate. However, one single result, away from an acute event, may also be useful if repeated measures are not available.

To investigate whether baseline blood eosinophil count predicts disease outcomes over time, in the population starting a new inhaled maintenance treatment

- There is an association, albeit weak, between lower baseline eosinophil count and subsequent exacerbations, whether this is determined using cut-offs or continuous analysis
- This association is present only in current smokers and is much stronger in those with asthma or atopy, when other groups were excluded in subgroup analysis
- There is strong association of eosinophils with reduced risk of being hospitalised with pneumonia, COPD, and death due to any cause, pneumonia or COPD, particularly using the 0.15 x10*9/L threshold
- The highest risk for poor outcomes is in the lowest (<0.15 x10*9/L) eosinophil count category and this is independent of treatment group (ICS vs. non-ICS)

Using eosinophil count to predict disease course is unlikely to be clinically helpful on an individual basis compared to at an epidemiological level. In my CPRD cohort, outcomes were worse in the lowest eosinophil groups, independent of ICS treatment, which adds to a somewhat mixed existing evidence base in this area (as other studies have conflicting findings).

To test whether baseline blood eosinophil count predicts inhaled steroid responsiveness and whether there is a dose-response (by eosinophil count and ICS dose) for this effect

- There is a statistically significant interaction between ICS treatment and blood eosinophil count, translating as a 15% lower absolute risk of subsequent exacerbations in patients with higher baseline eosinophil counts who are prescribed an ICS treatment, compared with patients with lower eosinophils who are prescribed ICS
- In patients prescribed an ICS there is an eosinophil dose-response with risk of subsequent exacerbation greatest in those with lower eosinophil counts (i.e., <0.15 x10*9/L); ICS only appeared to become beneficial in terms of reducing exacerbations at much higher eosinophil counts (≥0.45 x10*9/L or more)

- The significant interaction of blood eosinophil count with treatment group is particularly pronounced in current smokers and exacerbation risk is highest in those with both low eosinophils and a low baseline exacerbation frequency
- There is a higher risk of pneumonia hospitalisation in patients receiving ICS treatment in patients with a baseline eosinophil count <0.15 x10*9/L

Eosinophil count can be used to predict risk-benefit of ICS treatment: at lower eosinophil levels (and especially <0.15 x10*9/L) there is a higher risk of exacerbations and pneumonia hospitalisation with ICS treatment. In this cohort, benefit of ICS treatment was only seen in those with baseline eosinophil counts ≥0.45 x10*9/L. ICS treatment should particularly be avoided in those with low eosinophil counts and low baseline exacerbation frequency, but could be considered in those with higher eosinophil counts in combination with other features such as exacerbations (as in GOLD guidelines[198], see below).

To investigate use of near-patient eosinophils compared to laboratory eosinophils, and feasibility and acceptability of undertaking such measurements in a primary care setting

- There is high correlation between near-patient and laboratory eosinophil counts and substantial agreement using binary eosinophil thresholds
- Participants who used the Hemocue® WBC-DIFF machine in the study setting found it acceptable, and in general preferred finger prick blood tests to laboratory blood tests and breathing tests
- Near-patient testing is feasible to undertake in primary care

Hemocue® WBC-DIFF machine could be used in practice to provide an eosinophil count result at the point of care, replacing the need for laboratory testing for this purpose, but requirements for training might limit its use.

8.2 Context of research in relation to published literature and guidelines

A large body of evidence published during my doctoral project and discussed in individual chapters, is now part of clinical guidelines (international, national and local), which I summarise below. I then briefly discuss two other areas it would be remiss of me not to discuss as part of this thesis, to help place this research in the wider context: ICS withdrawal and non-pharmacological management of COPD.

8.2.1 Current COPD guidelines

New NICE guidelines were published in 2018,[199] a long awaited update to the somewhat outdated 2010 guidelines,[10] and incorporating some of the emerging evidence on blood eosinophils in COPD. These advocate considering LABA/ICS as initial treatment for those who have 'asthmatic features/features suggesting steroid responsiveness', which encompasses any previous, secure diagnosis of asthma or atopy, a higher blood eosinophil count, substantial variation in FEV_1 over time, or substantial diurnal variation in peak expiratory flow. They make no suggestion of what eosinophil values might constitute 'a higher blood eosinophil count', which is not helpful for use in clinical practice by non-specialists, particularly given that this refers to higher values within the normal laboratory range. They suggest stepping up treatment to triple therapy on a 3-month trial basis in those who have frequent exacerbations (defined as ≥2 in previous year, or ≥1 hospitalisation), as the benefit of fewer exacerbations on ICS treatment would likely outweigh the increased risk of pneumonia.[199] In my cohort there was no increased benefit of ICS treatment in those with asthma or atopy, acknowledging that these patients had an increased propensity to be prescribed ICS which may have created unmeasured

confounding in this area. My concern is that these recommendations have very loose criteria for considering ICS treatment initiation, and, particularly if a low binary eosinophil count threshold were used alongside these guidelines, would lead to the majority of patients being considered for ICS as initial therapy and potentially coming to harm.

The Australian COPD-X guidelines do not make a clear statement about use of eosinophil count, other than to say that there are 'benefits [of ICS treatment] in some outcomes demonstrated in those with high eosinophil counts' (>0.15 x10*9/L).[200] The American Thoracic Society guidelines do not make a recommendation for or against ICS as an additive therapy in those with blood eosinophilia, except in those with a history of one of more exacerbations requiring treatment in the previous year. They defined blood eosinophilia as ≥2% blood eosinophils or ≥0.15 x10*9/L.[201] Again, given my findings of high prevalence of such 'eosinophilia' in primary care, this low threshold would result in the majority of patients with exacerbation history being prescribed ICS, but this was the group that I identified as being the most likely to benefit from ICS treatment in my exacerbation subgroup analysis (Table 6.6).

New GOLD guidelines published in 2019[198] added a new section appraising the evidence on use of blood eosinophils in COPD, which broadly fits with my appraisal of the literature and which my study findings also support, and so I will not repeat this in detail here. Based on this, they suggested algorithms both for initiation of pharmacological management, and follow-up treatment especially in exacerbation prevention. They recommended that as initial pharmacological treatment, ICS/LABA should be considered if the patient has both

blood eosinophils ≥0.30 x10*9/L and GOLD stage D[a]. For follow-on treatment (regardless of GOLD stage), ICS should be added if the patient remains symptomatic and has blood eosinophils ≥0.30 x10*9/L OR ≥0.10 x10*9/L and frequent exacerbations.[198] Here the higher eosinophil threshold of ≥0.30 x10*9/L, combined with an exacerbation history, for initiation of ICS treatment, fits best with my clinical recommendations based on my thesis findings, with a reduction in threshold only if frequent exacerbations occur despite alternative therapies.

In recognition that it is hard for non-specialist primary care clinicians to use guidelines in parallel, the Primary Care Respiratory Society (PCRS) have produced a pragmatic guide to COPD management for use in primary care, which incorporates both NICE and GOLD guidelines. Their suggestions for management based on eosinophils more closely follow GOLD, but acknowledge that there is still some debate on the use of blood eosinophils to guide ICS use in COPD.[202]

Local Oxfordshire Clinical Commissioning Group guidelines have recently been published on prescribing in COPD in primary care,[203] and in my view demonstrate how the NICE guideline[199] leaves the use of blood eosinophils in guiding treatment approaches worryingly open to individual interpretation. As in the NICE guideline, these guidelines divide patients into two groups based on those with asthmatic features/features suggesting steroid responsiveness (including 'a higher blood eosinophil count', as per NICE) in which case initial prescribing of ICS/LABA, or no such features, in which case LAMA/LABA. My concern with this guideline is that they have selected a very low

[a] GOLD Stage D is MRC breathlessness scale ≥2 or CAT score ≥10 AND frequent exacerbations (≥2 or ≥1 with hospitalisation, in the previous year).

eosinophil threshold of 0.10 x10*9/L which would result in the majority of primary care patients (95% and 80% in my CPRD and COMET studies respectively, see Section 4.2) being classified in the asthmatic category and being prescribed ICS/LABA as first-line maintenance treatment. My study findings indicate that this approach would expose many people to an increased risk of pneumonia and other poor outcomes with a very small chance of benefit in terms of reduction in exacerbations, if these guidelines were to be followed based on this threshold. I also did not demonstrate a consistent association between asthma and eosinophils in my primary care populations, so it might be overly simplistic to rely on one or the other.

Asthma-COPD overlap (ACO) also deserves mention but has come in and out of fashion over the last few years. Guidelines were published in 2015, which define ACO as persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD.[204] These have not been updated and there is now more of a consensus that airways disease is a spectrum from asthma to COPD with some overlapping features, and that we should identify these 'treatable traits' rather than attempt to put patients into one box or another,[205] as I have been doing in this project by identifying ICS responsiveness on the basis of blood eosinophils.

8.2.2 ICS withdrawal

From my CPRD study, and the wider literature, we know that many patients are prescribed ICS treatment outside of guideline recommendations; and once a regular medication is started patients may continue on it indefinitely, which is why the new NICE guidelines recommend a trial of treatment with review after 3 months to assess benefit.[199] It would follow that if blood eosinophils can be used to guide initiation of ICS treatment, they could

also be used to identify candidates for withdrawal of ICS treatment. A detailed discussion of the evidence in this area is beyond the scope of this thesis, but increasing evidence is emerging that blood eosinophils can be used in this context. Post-hoc analyses of the WISDOM[a] trial found that eosinophil thresholds of 0.30 and 0.40 x10*9/L identified patients with more exacerbations after withdrawal of ICS,[54] and this was greatest in those with ≥2 exacerbations per year.[206] A prospective trial of ICS withdrawal (SUNSET[b]) also found greater lung function loss and higher exacerbation risk in those with blood eosinophils ≥0.30 x10*9/L at baseline.[207] However, this has not been replicated in recent CPRD studies (both published[208] and my own as yet unpublished work in this area (see Preface and Appendix A)). GOLD guidelines recommend that blood eosinophils ≥0.30 x10*9/L be used to identify patients with the greatest likelihood of experiencing more exacerbations after ICS withdrawal,[198] and a PCRS pragmatic guide for primary care recommends trialling ICS withdrawal if the patient has no asthma history or blood eosinophils <0.60 x10*9/L, or low exacerbation frequency AND blood eosinophils <0.40 x10*9/L.[209]

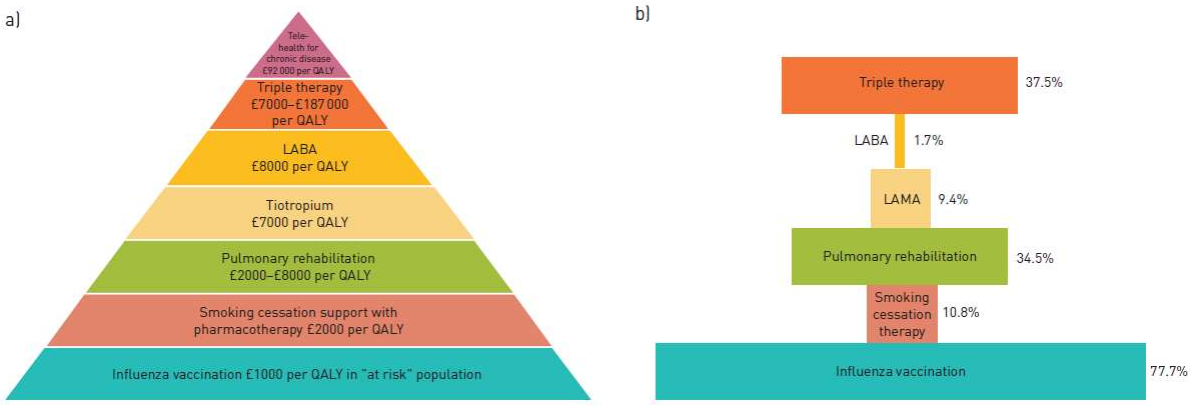
8.2.3 Non-pharmacological management in COPD

In a thesis which focuses on the use of a biomarker to guide use of a pharmacological intervention, it would be easy to assume that finding the best inhaled therapy for an individual patient is the be all and end all of COPD management. However, there has been increasing recognition that non-pharmacological approaches, such as smoking cessation therapy, pulmonary rehabilitation, promotion of self-management, increasing uptake of

[a] WISDOM trial: Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management.
[b] SUNSET trial: Long-term triple therapy de-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease

pneumococcal and influenza vaccinations and optimising treatment of co-morbidities (as set out in current guidelines),[198,199] deliver the highest value in terms of patient benefit in relation to cost. However, provision of these therapies in clinical practice is frequently sub-optimal, as summarised in Figure 8.1 reproduced from my recent editorial on this topic.[210] Although this does not change the conclusions of my thesis, I feel it is important to place my findings in the context of the bigger picture of COPD management challenges.

Figure 8.1: COPD value pyramids



a) The COPD value pyramid is a model designed to aid clinicians and providers to make value-based decisions for people and populations with COPD, through assessing the comparative value of interventions in terms of cost per individual per quality-adjusted life year (QALY). Reproduced with permission of the London Respiratory Network 2013.[211] b) The equivalent value pyramid providing a representation of the proportion of people who were receiving value-based interventions for COPD in primary care in Wales in 2014–2015. Reproduced with permission from the National Asthma and COPD Audit Programme (NACAP), Royal College of Physicians.[212]

8.3 Strengths and limitations of overall thesis methods

My findings substantially add to the evidence base in the area of blood eosinophils in COPD and are firmly rooted in a UK primary care population, making them uniquely applicable and useful for UK primary care practitioners. My CPRD study complements and extends what others have done but used different methods which were thorough and statistically rigorous, particularly in my attempts to account for flaws and potential data issues, including from my own clinical experiential knowledge of UK primary care. However, in

doing this I have introduced fairly complex data management and analysis, which was both challenging and time-consuming, and there is an attractive simplicity to other studies which have done a more straightforward analysis comparing LABA/ICS with LAMA (rather than any ICS vs. non-ICS treatment), such as the Suissa study, even if this has potential biases.[108] I excluded patients stepping up to triple therapy (as did other studies) so cannot firmly draw conclusions in relation to this group, only those initiating a new maintenance treatment. My findings in relation to the threshold at which ICS treatment benefit outweighs risk differed significantly from results from many trials, where this threshold was much lower, as discussed in detail in Section 6.8.3. These discrepancies in thresholds between findings from observational studies and randomised trials, and potential biases associated with observational study designs including confounding by indication, is why I have based my recommendation for ICS treatment as ≥0.30 x10*9/L, in combination with exacerbation history, as in GOLD guidelines,[198] placing my research findings in the context of existing literature. Future database study work could include validating my findings in other primary care databases, for example using CPRD Aurum[213] or the Secure Anonymised Information Linkage (SAIL)[214] which provides data from primary care in Wales and would provide a different population.

The COMET study is a novel cohort of primary care patients and provides the largest available dataset in this population on blood eosinophil repeatability and near-patient sampling. A major challenge of this study was to optimally characterise blood eosinophils at the point of stepping up or initiating a new inhaled maintenance treatment. In limiting eligibility in order to achieve this, the cohort does not truly represent the overall population, and is likely to have included patients whose COPD disease state would have

remained mild and stable on short-acting bronchodilators alone for many years; and indeed this mild disease state is reflected in the baseline characteristics (Section 3.5). A longer duration of follow-up for the COMET study would have enabled me to assess outcomes such as exacerbation frequency in relation to baseline eosinophil count but would have unlikely been feasible within the timeframe of a doctoral project.

A novel feature of my cohorts compared to others is the focus on the ICS-naïve population. Although the Kreindler study suggests that the effect of ICS on peripheral blood eosinophil counts is likely small enough on average not to affect patient stratification using cut-off values,[215] others have suggested that this might be more important in those on higher doses of ICS, where the mean difference between groups was as much as 0.05 x10*9/L.[216] This difference is likely to be clinically relevant and means it is useful for me to have characterised the ICS-naïve population specifically.

Another novel feature of my cohorts is that I have identified patients with co-morbidities of asthma or atopy which could affect the eosinophil count, or the ICS response, as discussed in Section 1.2.3, and conducted sensitivity and subgroup analyses to measure the contributions of these to my overall findings. In contrast to expectations, these co-morbidities did not make a difference to eosinophil distribution or ICS responsiveness, potentially suggesting that using asthma history as a criterion for ICS initiation as in the NICE guidelines[199] may be inappropriate. However, the requirement for my cohort to be ICS-naïve, at least in the last year, may have identified an unusual group of patients with 'asthma' in their clinical records, and it is possible that those with co-morbidities may respond differently. That said, the inclusion of patients with co-morbidities is a key

advantage of my primary care database study compared to restricted inclusion criteria trials in terms of future generalisability of findings.

Part of the reason for the premise of my initial hypothesis was the relationship found between peripheral and lung eosinophils,[1] and the earlier research on sputum eosinophils as a biomarker of both oral and inhaled corticosteroid responsiveness.[3,4,7] Although I have clearly demonstrated that there is a subgroup of primary care COPD patients with higher blood eosinophils, the wider literature has become more conflicting about how well blood eosinophils represent lung eosinophils, with some studies showing no correlation[132,217] and others a stronger relationship.[156,218] It is possible that the association of blood eosinophils with ICS response is not just about eosinophil numbers but also about eosinophil function.[219] The fact that trials of monoclonal antibody therapies have not been universally beneficial at reducing exacerbations in COPD patients with higher eosinophils[220,221] certainly suggests that the role of eosinophils in COPD is quite complicated, and this needs further basic science and clinical studies to better elucidate. Bacterial and viral infections are common in COPD, adding further complexity, with significant interplay with eosinophil immunobiology.[35] However, for primary care management, it is more important to know how we can use blood eosinophils in a clinical setting, which is what I have demonstrated, and so detailed eosinophil biology is less relevant here.

My findings for both the CPRD and COMET studies are likely generalisable to the whole primary care population in the UK (see Section 2.6.1 and 3.6.2) but may not be so generalisable globally, particularly where health systems differ. Nonetheless, similarities have been found in comparisons of the CPRD and the US population,[222] and the discussion

sections of each chapter comparing my findings with the wider literature draw on studies from across the globe.

8.4 Implications for practice, policy and further research

I have divided these into the different components examined throughout the thesis.

8.4.1 Routine testing of full blood count

My CPRD study findings demonstrate that NICE guidelines which recommend routine testing of full blood count as part of diagnosis[10] are probably not widely followed, and certainly regular testing of full blood count does not currently occur. Given that I have demonstrated that blood eosinophil counts in the routine primary care medical record could have an important role in guiding management of COPD, my recommendation is that full blood count be tested more frequently and minimum every two years so that this could be used to guide management. This recommendation could form part of future guidelines and opportunities for practice audit.

My sensitivity analyses for eosinophil distribution, repeatability and ICS responsiveness indicate minimal difference when eosinophil values close to exacerbation events are included, so pragmatically these values can probably be used in practice. However, if full blood count were to be taken regularly as part of COPD annual review, it would reduce any uncertainty in this regard, as viral and bacterial infections can both increase and decrease eosinophil counts in COPD.[223]

8.4.2 Eosinophil distribution

My findings on eosinophil thresholds indicate that most COPD patients in primary care fall into a 'medium' category of eosinophils 0.15 to 0.34 x10*9/L. Given that there is a

continuous dose-response relationship between blood eosinophils in terms of both outcomes and ICS responsiveness, the use of a binary threshold within this range seems somewhat arbitrary; and exactly where this threshold is placed within this range will make a large difference to how patients are categorised, and subsequent management decisions. However, basing decisions on a continuous scale is likely to be over-complicated for a non-specialist primary care setting. Based on my findings, I would recommend the use of three categories: low (<0.15 x10*9/L), medium (0.15 to 0.33 x10*9/L) and high (≥0.34 x10*9/L), which could then be subsequently validated in future prospective studies.

8.4.3 Eosinophil repeatability

I have demonstrated good repeatability of eosinophils in repeated measures analyses, although this is reduced when using binary thresholds due the large number of patients in the 'medium' range, as described above. Sensitivity analyses of key analyses using the mean eosinophils, or the two or three most recent values, have not changed results. My suggestion is that pragmatically busy clinicians could look just at the last recorded eosinophil value in decision-making. However, repeatability is not perfect, and variability increases as eosinophil values increase, so where computer system features exist to easily glance at all previous results, it would be prudent to do this, or repeat the test, particularly for higher eosinophil values and in younger, female smokers, although evidence is less clear on the latter point. Research elsewhere has suggested that where a repeat test is needed, it is done at least 14 days after the first.[100]

8.4.4 Association of eosinophils with disease outcomes

I found that the risk of disease outcomes was worse in the lowest eosinophil groups, but this does not fit with previous findings, which includes many studies with heterogeneous inclusion criteria and results, making it hard to draw firm conclusions. Differences may relate to different biology, as well as definitions, of exacerbations vs. pneumonia episodes, and confounding by ICS treatment makes research in this area difficult, such that further research is needed to better elucidate the relationships.[163] Certainly, the relationship between blood eosinophils and prognosis is likely to be complicated, and presently there is no useful role for blood eosinophils in discussing prognosis or future exacerbation risk on an individual patient basis.

8.4.5 Use of blood eosinophils to target ICS treatment

My study findings, and the wider literature, demonstrate a clear dose-response relationship between increasing blood eosinophils and response to ICS therapy. This means that there are subgroups of patients who are more likely to benefit from ICS, and to whom it can be appropriately targeted. Other CPRD and post-hoc studies have demonstrated a benefit of ICS treatment at lower levels of blood eosinophils than in my study, and led to conclusions, and guideline recommendations that ICS benefit outweighs pneumonia risk at approximately 0.30 x10*9/L.[108,198] I found that mortality from pneumonia appeared to be attenuated in patients with COPD, on ICS and with eosinophils above 0.15 x10*9/L, but whether ICS confers mortality benefit in this group of patients with COPD needs to be further explored. Certainly, recent studies have found that dual LAMA-LABA (not specifically examined in my CPRD study) is superior to LABA-ICS regardless of blood eosinophil level,[56] and as effective in preventing exacerbations and with fewer severe

pneumonias.[224] Benefit of ICS-containing regimens is undoubtedly higher in those with a high exacerbation frequency, and smoking status certainly influences the relationship between ICS effect and blood eosinophil count, but the details and direction of this need to be further researched.

My findings lead me to broadly support the recent GOLD guidelines that ICS should be considered in those with blood eosinophils ≥0.30 x10*9/L and frequent exacerbations.[198] However, integrating my own findings with the existing literature, I would recommend a more limited approach to ICS prescribing which advises against ICS treatment at low blood eosinophil levels (<0.15 x10*9/L), where there is a lower likelihood of treatment benefit, and potential harms; considers ICS treatment in the 'high' range ≥0.34 x10*9/L if frequent exacerbations; and only considers ICS treatment in the 'medium' range between these thresholds if there are both frequent exacerbations and a failure to respond to initial dual bronchodilator therapy. This more limited approach is likely to result in fewer patients being prescribed an ICS when the risk of harm may be greater than the chance of benefit.

8.4.6 Near-patient testing

I have demonstrated that the Hemocue® WBC-DIFF machine using capillary blood has an acceptable analytic performance when compared to laboratory eosinophil count using venous samples, and that the point-of-care test is acceptable to patients.

It is economic and system factors which are likely to ultimately determine its uptake and use in the primary care setting. The economic and opportunity costs of having an actionable result at the point of care will need to be set against waiting time and requiring an additional appointment to discuss and act on a result obtained from central laboratory

testing. Integration of the new test into routine clinical practice and addressing factors for implementation are important next steps.[225] There needs to be further work incorporating reproducibility testing, and use of the machine by those who would ultimately be using it in practice,[226] as well as addressing training aspects and scaling up delivery to multiple practices. Costs are a key concern for clinicians as a barrier to implementation of near-patient testing in other disease areas such as HbA1c testing,[197] so health economic analysis is essential, as well as in general doing further work to establish clinicians' perspectives on use of the devices in practice.

8.5 Final conclusions

Blood eosinophils represent a key therapeutic, if not prognostic, biomarker in the primary care management of COPD, and are feasible for use in a primary care setting. The future of primary care management of COPD is likely to involve integrating clinical features such as exacerbation frequency, and perhaps smoking status, with eosinophil count, to enable a more personalised approach to pharmacological management of COPD, which should be done in parallel with non-pharmacological treatment strategies. Near-patient testing of blood eosinophils is a potential avenue for the future to enable rapid decisions to be made within the community setting in a single clinic visit. Further future research could include an RCT of eosinophil-guided maintenance treatment in primary care with a long-term follow-up to assess disease outcomes, utilising the data collected in this thesis about eosinophil thresholds and repeatability. Such a study could incorporate qualitative and health economic assessments of both the change to patient pathway in terms of monitoring eosinophil count more closely, and potential implementation of near-patient testing in practice.

Epilogue: A personal journey (continued)

This thesis is wholly the product of my work, save where I have referred to the input or assistance of others. I devised, carried out and wrote up the studies comprised within it. More specifically, my work has included refining the research questions, developing the ideas for projects to answer the overall hypothesis, writing the funding proposal and obtaining the funding, writing the study protocols, ethics approvals, COMET study management and development of study materials and CRFs, most of practice and patient recruitment, some COMET study visits, some aspects of data management, statistical analysis, and writing up study findings. I have also had input from my supervisors in an advisory capacity for these components, most notably from statistics advisors (Emily McFadden, Margaret Smith and Jason Oke) in relation to analysis aspects. Key components performed by others include the data cleaning for the CPRD and part of the data management of this (done by Margaret Smith), conversion of COMET paper CRFs to the online CRF and management of this (CTU data management team), some of the trial administration and patient recruitment telephone calls (CTU trial managers while I was on maternity leave), and the majority of COMET study visits (CTU nursing team).

During my time as a doctoral student, I have developed as a clinical academic and now feel more capable of leading independent research in future. In terms of specific learning outcomes I have achieved, these have been particularly in the areas of statistical analysis (particularly epidemiological methods, large data management and use of Stata), and set-up/management of a multiple site study recruiting in primary care using the CTU, and the different personnel involved in this. Preparing the funding application was also the first time I had put together a large grant application as lead applicant, and was a useful

experience of the detail required for this to be successful. I have attended formal courses in meta-analysis (1 day, University of Oxford), introductory and advanced analysis of linked health data (2 x 1 week, Swansea University), epidemiological analysis courses in logistic and linear regression, and rates and survival analysis (1 week and 2 days, University of Bristol) as well as undertaking software training courses run by the IT department on use of Stata, Endnote and Word (7 half days).

With hindsight I was perhaps overly ambitious about what I could achieve within the scope of a doctoral project. However, I was able successfully to adapt during the course of the project both by making the changes to its scope explained in the preface (i.e. not undertaking a duplicative systematic review, and focusing specifically on blood eosinophils rather than other biomarkers) and by making use of the capacity of others to assist as explained above (and in particular with the CTU nursing team carrying out most study visits).

I found the experience of working with the CTU for COMET useful and enjoyable. Despite having to overcome some administrative difficulties, I really benefitted from working with colleagues who brought huge expertise from their different multi-disciplinary backgrounds. This was particularly true of the respiratory background of the lead study nurse, Heather Rutter. I have also benefitted from working in a department where people bring different skills, and perhaps especially the expertise of the statistics team. For example, I have provided general clinical input into others' studies whilst they have helped me with Stata coding.

During the course of my doctoral studies substantial work has been done by others in the field of my research, with the result that my findings are now less novel than they would

have been earlier. Although it was initially disappointing to receive notifications every week of similar studies being published, I have also seen the value of being able to reflect on my work in the context of other studies with different methods and different findings.

In terms of future work, I plan to convert the studies discussed in this thesis into papers for submission to peer-reviewed journals. I plan to validate my CPRD study in the Secure Anonymised Information Linkage (SAIL) database in Wales, and also to conduct additional analysis of COMET to include the FeNO and periostin data. I would like to consider whether a biomarker-directed randomised controlled trial would be achievable and useful. Certainly, I would like to continue research broadly in the area of respiratory disease in primary care, and near-patient testing.

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Appendix A: Publications and conference presentations

Publications (October 2014 onwards)

Ashdown HF, Fleming S, Spencer EA, Thompson MJ, and Stevens RJ. Diagnostic accuracy study of three alcohol breathalysers marketed for sale to the public. BMJ Open 2014;4:e005811. doi: 10.1136/bmjopen-2014-005811.

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Fisher RFR, **Ashdown HF**, Brettell R, McCartney D. Re: UK academic general practice and primary care. BMJ 2015;351:h4164 (rapid response letter).

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Moore A, **Ashdown HF**, Harnden A. Pertussis has low prevalence in adults with acute cough and is difficult to distinguish clinically from other causes. Evidence Based Medicine 2016. 21(3) doi: 10.1136/ebmed-2015-110353.

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Heath L and **Ashdown HF**. Ask the expert: electronic cigarettes. Innovait 2016 DOI: 10.1177/1755738016654935

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Croxson CH, **Ashdown HF**, Hobbs FR. GPs' perceptions of workload in England: a qualitative interview study. Br J Gen Pract 2017; 67 (655): e138-e147. doi: 10.3399/bjgp17X688849.

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Moore A, **Ashdown HF**, Shinkins B, Roberts NW, Grant CC, Lasserson DS and Harnden A. Clinical characteristics of pertussis-associated cough: a diagnostic systematic review and meta-analysis. Chest 2017; 152(2):353-367. doi: 10.1016/j.chest.2017.04.186.

Abel L, Dakin HA, Roberts N, **Ashdown HF**, Butler CC, Hayward G, Van den Bruel A, Turner PJ and Yang Y. Is stratification testing for treatment of chronic obstructive pulmonary disease exacerbations cost-effective in primary care? An early cost-utility analysis. International J Technol Assess Health Care 2019; 35(2):116-125. doi: 10.1017/S0266462318003707

Ashdown H, Steiner M. Delivering high value therapies in COPD: the secret is in the marketing. Eur Respir J 2019; 53(4): 1900215 doi: 10.1183/13993003.00215-2019.

Frazer JS, Barnes GE, Woodcock V, Flanagan E, Littlewood T, Stevens RJ, Fleming S and **Ashdown HF**. Variability in body temperature in healthy adults and in patients receiving chemotherapy: prospective observational cohort study. J Med Eng Technol 2019; 43(5):323-33 doi: 10.1080/03091902.2019.1667446.

Ashdown HF, Smith M, McFadden E, Pavord ID, Butler CC, Bafadhel M. Blood eosinophils to guide inhaled maintenance therapy in a primary care COPD population. (In preparation)

Ashdown HF, Dickinson S, Morris K, Gayle A, Chalmers JD. Withdrawal of inhaled corticosteroids in COPD patients using primary care electronic records: a descriptive cohort study. (In preparation)

Conference presentations (October 2014 onwards)

Only those directly related to doctoral project are listed below.

Society of Academic Primary Care (South West Region), University of Birmingham (2015)

Inflammatory biomarkers as a predictor of exacerbation frequency in COPD: a systematic review of biomarkers applicable to primary care (elevator pitch)

'Cutting edge research in the consulting room' – GP research update day, Oxford (2015)

Point-of-care tests in airways disease (oral presentation)

Society of Academic Primary Care, University of Oxford (2015)

Inflammatory biomarkers as a predictor of exacerbation frequency in COPD: a systematic review of biomarkers applicable to primary care (poster presentation)

Primary Care Respiratory Society (2015)

Inflammatory biomarkers as a predictor of exacerbation frequency in COPD: a systematic review of biomarkers applicable to primary care (poster presentation)

Primary Care Respiratory Society (2016)

Use of blood eosinophil count to predict inhaled steroid responsiveness in patients with COPD using UK primary care health records (poster presentation)

North American Primary Care Research Group, Colorado Springs, USA (2016)

Use of blood eosinophil count to predict inhaled steroid responsiveness in patients with COPD using UK primary care health records (poster presentation)

Primary Care Respiratory Society (2018)

Characterisation of blood eosinophils and their association with disease outcomes in steroid-naïve COPD patients in primary care: descriptive cohort study using the Clinical Practice Research Datalink (CPRD) (oral presentation)

Use of blood eosinophils to predict outcomes under inhaled maintenance treatment in steroid-naïve COPD patients in primary care: new user cohort study using the Clinical Practice Research Datalink (CPRD) (oral presentation)

British Thoracic Society (2018)

Characterisation of blood eosinophils and their association with disease outcomes in steroid-naïve COPD patients in primary care: descriptive cohort study using the Clinical Practice Research Datalink (poster presentation)

Use of blood eosinophils to predict outcomes under inhaled maintenance treatment in steroid-naïve COPD patients in primary care: new user cohort study using the Clinical Practice Research Datalink (poster presentation)

Society of Academic Primary Care (South West Region), University of Southampton (2019)

Characterisation of blood eosinophils and their association with disease outcomes in steroid-naïve COPD patients in primary care: descriptive cohort study using the Clinical Practice Research Datalink (oral presentation)

Use of blood eosinophils to predict outcomes under inhaled maintenance treatment in steroid-naïve COPD patients in primary care: new user cohort study using the Clinical Practice Research Datalink (oral presentation)

Primary Care Respiratory Society (2019)

Stability of eosinophil counts over time, and analytic performance of point-of-care eosinophil testing with a view to guiding personalised inhaled corticosteroid prescribing for COPD (oral presentation)

Appendix B: Example search strategy

Ovid MEDLINE In-Process and Other Non-Indexed Citations and Ovid MEDLINE [1946-]

1. exp Pulmonary Disease, Chronic Obstructive/
2. Bronchitis, Chronic/
3. Emphysema/
4. ((chronic adj3 bronchit*) or emphysem* or copd or coad or cobd or aecopd or aecoad or aecobd or aecb or (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respir*))).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. Eosinophilia/
7. Eosinophils/
8. Neutrophils/
9. Leukocytes/
10. Leukocytosis/
11. Leukocyte Count/
12. Inflammation/bl [Blood]
13. Inflammation Mediators/bl [Blood]
14. Biological Markers/bl [Blood]
15. Biomarkers, Pharmacological/bl [Blood]
16. C-Reactive Protein/
17. (eosinophil* or neutrophil* or leukocyte* or leucocyte* or (inflamm* adj3 marker*) or (inflamm* adj3 mediator*) or (inflamm* adj3 biomarker*) or crp or (c-reactive adj protein*) or (c adj reactive adj protein*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
18. (blood or serum).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
19. Breath Tests/
20. Nitric Oxide/
21. 19 and 20
22. ((fraction adj3 exhaled adj3 nitric adj3 oxide) or feno or (fraction adj3 exhaled adj3 no)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
23. exp animals/ not humans.sh.
24. 6 or 7 or 8 or 9 or 10 or 11 or 17
25. 18 and 24
26. 12 or 13 or 14 or 15 or 16 or 21 or 22 or 25
27. 5 and 26
28. 27 not 23

Appendix C: CPRD study protocol

Approved by Independent Scientific Advisory Committee (ISAC) June 2016. Appendix submitted to ISAC consisted entirely of code lists and is therefore not presented separately: see Appendix D for final code lists used.

ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

ISAC use only: Protocol Number Date submitted		**IMPORTANT** **If you have any queries, please contact ISAC Secretariat:** ISAC@cprd.com

Section A: The study

1. Study Title

Use of blood eosinophil count to predict inhaled steroid responsiveness in patients with COPD using primary care health records

2. Has any part of this research proposal or a related proposal been previously submitted to ISAC?

Yes ☐ No ☒

If Yes, please provide previous protocol numbers:

3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)

Yes ☒ No ☐

If Yes, please state the name of the reviewing Committee(s) and provide an outline of the review process and outcome:

The outline plan for this study, including objectives, research questions, methods, selection criteria, data measurements, and outcome measures and analysis, was included as part of an application for a National Institute for Health Research (NIHR) Doctoral Research Fellowship application in 2014. The application was reviewed by two assessors, and was highly scored, and then further discussed during the interview with a panel of approximately 30 people. Feedback of the proposal was extremely positive, suggesting only provision of further advanced statistical training and statistical supervision to complete the objectives, which has now been arranged, and funding was successfully granted to carry out the research as described in the application.

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety ☐	Drug Utilisation ☒	Disease Epidemiology ☒
Drug Effectiveness ☒	Pharmacoeconomics ☐	Methodological ☐
Health/Public Health Services Research ☐		Post-authorisation Safety ☐

Other* ☐

*Please specify the type of study in the lay summary

5. This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☐	Regulatory purposes	☐

Other

Section B: The Investigators

6. Chief Investigator (full name, job title, organisation name & e-mail address for correspondence- see guidance notes for eligibility)

Dr Helen Ashdown, Clinical Researcher, Nuffield Department of Primary Care Health Sciences, University of Oxford, helen.ashdown@phc.ox.ac.uk

CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	☒	
An updated CV is being submitted with this protocol	☐	

7. Affiliation (full address)

Nuffield Department of Primary Care Health Sciences
University of Oxford
Radcliffe Observatory Quarter
Woodstock Road
Oxford
OX2 6GG

8. Corresponding Applicant

Same as chief investigator	☒	
CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	☐	
An updated CV is being submitted with this protocol	☐	

9. List of all investigators/collaborators (*please list the full names, affiliations and e-mail addresses* of all collaborators, other than the Chief Investigator*)

Other investigator: Dr Mona Bafadhel, Senior Clinical Researcher, Nuffield Department of Medicine, University of Oxford, mona.bafadhel@ndm.ox.ac.uk

CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

Professor Chris Butler, Professor of Primary Care, Nuffield Department of Primary Care Health Sciences, University of Oxford, christopher.butler@phc.ox.ac.uk

CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

Other investigator: Dr Emily McFadden, Senior Statistical Epidemiologist, Nuffield Department of Primary Care Health Sciences, University of Oxford, emily.mcfadden@phc.ox.ac.uk

CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

Other investigator: Professor Mike Thomas, Professor of Primary Care Research, University of Southampton, D.M.Thomas@soton.ac.uk

CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

Other investigator: Professor Ian Pavord, Professor of Respiratory Medicine, Nuffield Department of Medicine, University of Oxford, ian.pavord@ndm.ox.ac.uk

CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

Other investigator: Dr Margaret Smith, Senior Statistician and Epidemiologist, Nuffield Department of Primary Care Health Sciences, University of Oxford, margaret.smith@phc.ox.ac.uk

CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

[Please add more investigators as necessary] **Please note that your ISAC application form and protocol **must** be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

10. Conflict of interest statement* (please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work)

HFA holds an NIHR Doctoral Research Fellowship which provides funding to undertake this work. She undertook a four month placement at Boehringer Ingelheim as part of her academic foundation programme in 2010 and had conference attendance provided by them in 2010. In April 2015 she ran the London marathon raising money for the British Lung Foundation.

MB holds an NIHR Post-Doctoral Fellowship and has received grants from the MRC and NIHR and non-financial support from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, and GlaxoSmithKline.

CCB has been paid for advisory meetings on point-of-care testing sponsored by Alere, who are providing CRP testing kits for a research project. He has also been paid for advisory board meetings for Roche Diagnostics.

In the last 3 years MT has received speaker's honoraria for speaking at sponsored meetings or satellite symposia at conferences from the following companies marketing respiratory and allergy products: Aerocrine, Astra Zeneca, Boehringer Ingelheim, GSK, MSD, Teva, Novartis, Pfizer and Sandoz. He has received honoraria for attending advisory panels with Aerocrine, Almirall, Astra Zeneca, Boehringer Ingelheim, Chiesi, GSK, MSD and Novartis. He has received sponsorship to attend international scientific meetings from GSK and Astra Zeneca. He has received funding for research projects from GSK. He is a member of the BTS SIGN Asthma guideline group and the NICE Asthma guideline group. Neither he nor any member of his close family has any shares in pharmaceutical companies.

IDP reports personal fees from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Aerocrine, Boston Scientific, and Novartis.

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI*

11. Experience/expertise available (please complete the following questions to indicate the experience/expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results

	Previous GPRD/CPRD Studies	**Publications using GPRD/CPRD data**
None	☐	☐
1-3	☐	☐
> 3	☒	☒

	Yes	**No**
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Emily McFadden and Margaret Smith	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Emily McFadden and Margaret Smith	☒	☐
Is experience of practising in UK primary care available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Helen Ashdown Chris Butler Mike Thomas	☒	☐

12. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

Kerkhof M, Freeman D, Jones R, Chisholm A, Price DB. Predicting frequent COPD exacerbations using primary care data. International journal of chronic obstructive pulmonary disease 2015; 10: 2439-50.

Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. Thorax 2016; 71:118-25.

DiSantostefano RL, Sampson T, Le HV, Hinds D, Davis KJ, Bakerly ND. Risk of pneumonia with inhaled corticosteroid versus long-acting bronchodilator regimens in chronic obstructive pulmonary disease: a new-user cohort study. PloS one 2014; 9(5): e97149.

Section C: Access to the data

13. Financial Sponsor of study

Pharmaceutical Industry	☐ *Please specify:*	Academia	☐ *Please specify:*
Government / NHS	☒ *Please specify:* NIHR	Charity	☐ *Please specify:*
Other	☐ *Please specify:*	None	☐

14. Type of Institution carrying out the analyses

Pharmaceutical Industry	☐ *Please specify:*	Academia	☒ *Please specify:* University of Oxford
Government Department	☐ *Please specify:*	Research Service Provider	☐ *Please specify:*
NHS	☐ *Please specify:*	Other	☐ *Please specify:*

15. Data source

The sponsor has direct access to CPRD GOLD and will extract the relevant data* ☒

A data set will be supplied by CPRD** ☐

CPRD has been commissioned to extract the relevant data and to perform the analyses ☐
Other ☐ *Please specify:*

*If data sources other than CPRD GOLD are required, these will be supplied by CPRD
** Please note that datasets provided by CPRD are limited in size. Applicants should contact CPRD (KC@CPRD.com) if a dataset of >300,000 patients is required.

16. Primary care data (please specify which primary care data set(s) are required)
Vision only (Default for CPRD studies) ☒
EMIS® only* ☐
Both Vision and EMIS®* ☐

Note: Vision and EMIS are different clinical systems, Vision data has traditionally been used for CPRD, EMIS is currently undergoing beta-testing.
**Investigators requiring the use of EMIS data must discuss the study with a member of CPRD staff before submitting an ISAC application*
Please list below the name of the person/s at the CPRD with whom you have discussed your request for EMIS data:

Section D: Data linkage

17. Does this protocol also seek access to data held under the CPRD Data Linkage Scheme?

Yes* ☒ No ☐

If No, please move to section E.

**Investigators requiring linked data must discuss the study with a member of CPRD staff. It is important to be aware that linked data are not available for all patients in CPRD GOLD, the coverage periods for each data source may differ and charges may be applied. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss your requirements before submitting your application.*
Please list below the name of the person/s at the CPRD with whom you have discussed your request:
A final draft of this protocol has been reviewed by Wilhelmine Meeraus
Please note that as part of the ISAC review of linkages, the protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

18. Please select the source(s) of linked data being requested:

☒ ONS Mortality Data
☒ Inpatient Hospital Episode Statistics
☐ Outpatient Hospital Episode Statistics
☐ NCDR Cancer Registry Data*
☐ MINAP
☐ Mother Baby Link

☒ Index of Multiple Deprivation
☐ Townsend Score
☐ Other** *Please specify:*

N.B. Inpatient HES requested is for basic HES.

Please note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website. They must also complete a **Cancer Dataset Agreement Form (available from CPRD) and provide a **System level Security Policy** for each organisation involved in the study.*

*** If "Other" is specified, please name an individual in CPRD that this linage has been discussed with.*

19. Total number of linked datasets requested including CPRD GOLD:

4

20. Is linkage to a local dataset with <1 million patients being requested?

Yes* ☐ No ☒

** If yes, please provide further details:*

21. If you have requested linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in response to question 5 above, have access to any of the linked datasets in a patient identifiable form, or associated with a patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

22. Does this study involve linking to patient *identifiable* data from other sources?

Yes ☐ No ☒

Section E: Validation/verification

23. Does this protocol describe a purely observational study using CPRD data (this may include the review of anonymised free text)?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*
*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

24. Does this study require anonymised free text?

Yes* ☐ No ☒

**Please note that work involving free text can only be performed on the July 2013 CPRD GOLD database build or earlier versions. CPRD can provide further advice on the use of anonymised free text.*

25. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** Please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐
Provision of anonymised records (e.g. hospital discharge summaries) Yes ☐ No ☐
Other (please describe)

[ψ] Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

26. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No ☒

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

27. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected:*

Section F: Signatures

28. Signature from the Chief Investigator

I confirm that the above information is to the best of my knowledge accurate, and I have read and understood the guidance to applicants.

Name: Helen Ashdown Date:29th April 2016 E. signature (type name): Helen Ashdown

Protocol Section

The following headings **must** be used to form the basis of the protocol. Pages should be numbered. All abbreviations must be defined on first use.

A. Lay Summary (Max. 200 words)

Chronic obstructive pulmonary disease (COPD) is a long-term respiratory condition which affects over one million people in the UK, usually as a result of smoking and causes cough and breathlessness which generally worsen with time. Steroid inhalers are commonly prescribed, but there is uncertainty over how beneficial they are to all patients living with COPD, and steroid inhalers are expensive and have been associated with a range of adverse effects including an increased risk of pneumonia. Some patients with COPD have higher levels of a type of cell called eosinophils in their blood and lungs suggesting greater inflammation in their lungs and thus greater chance of benefit from steroid inhalers. However, this hasn't been investigated yet in general practice using results of blood levels of eosinophils that have been routinely tested for other reasons. In this study, we will use general practice records to evaluate whether patients who have higher levels of blood eosinophils on routinely taken blood tests before starting treatment with inhaled steroids are more likely to have fewer exacerbations and less deterioration on treatment compared to patients with lower levels of blood eosinophils.

B. Technical Summary (Max. 200 words)

This study will use a new user cohort design to assess outcomes for a group of COPD patients who have not previously been prescribed an inhaled corticosteroid (ICS-naïve) and who then commence treatment with a new inhaled maintenance treatment (the index date). The descriptive component of the study will examine records of routine blood eosinophil testing in general practice and their values prior to starting a new inhaled maintenance treatment, their relationship to other baseline variables, and their stability over time. The hypothesis-testing component will test whether baseline blood eosinophil values predict disease outcomes, and outcomes under treatment (ICS responsiveness). The primary outcome will be acute exacerbations of COPD. Patients will be divided into two groups based on whether the new inhaled maintenance medication is an ICS or long-acting bronchodilator. Disease outcomes over time will be compared between those patients starting treatment with ICS and those starting treatment with a long-acting bronchodilator, with adjustment for baseline characteristics, and this will be stratified by baseline blood eosinophil values to determine whether this modifies effectiveness of treatment.

C. Objectives, Specific Aims and Rationale

The overall objective of this study is to describe blood eosinophil testing in the primary care population who started a new inhaled medication for COPD and whether eosinophil counts already in the clinical record might be useful in predicting benefit from ICS treatment.

Hypothesis

We hypothesise that there is a subgroup of COPD patients managed in primary care characterised by higher baseline blood eosinophil levels and who are likely to respond favourably to treatment with ICS; and that patients with lower eosinophil levels do not respond as favourably to ICS treatment.

Aim 1 (descriptive arm): To describe blood eosinophil testing in ICS-naïve primary care patients with COPD in the period before starting a new inhaled maintenance treatment

The number of blood eosinophil tests, and their values, in the 2 years prior to starting a new inhaled maintenance treatment will be examined. For those patients newly diagnosed with COPD in this period, the rate of testing at the time of new diagnosis (within 2 weeks either side of diagnosis date) will be assessed. The association between high eosinophils (defined as blood eosinophils >150 cells/μL) and other variables measured during this 2 year baseline period, e.g. NICE severity stage, exacerbations/year and bronchodilator reversibility (a full list of covariates is described below) will be investigated. Within- and between-person variation in blood eosinophil values will be assessed, and the most recent value will be compared with multiple values over the baseline period. Degree of correlation between eosinophil count and other biomarkers of inflammation, including CRP and neutrophil count, will be measured, and degree of overlap between groups of patients with high levels of these biomarkers will be assessed. Patients who have had eosinophils measured will be compared with those who have not in terms of their baseline variables.

Aim 2 (hypothesis-testing arm): To test whether baseline blood eosinophil values predict disease outcomes overall, and whether baseline blood eosinophil values predict outcomes under different treatments (ICS vs. non-ICS/ICS responsiveness)

Disease outcomes will be assessed in the time period following starting the new maintenance treatment. Disease outcomes will include exacerbations (time to first exacerbation, exacerbations/year and ≥2 exacerbations/year), episodes of pneumonia (time to first event and episodes/year), hospitalisation due to exacerbations and other causes (time to first event and episodes/year), death (time to event) and decline in FEV_1/year. Disease outcomes will be assessed in the whole population and by low and high eosinophil values, both unadjusted and adjusting for baseline variables.

Patients will be divided into two groups based on whether the new inhaled maintenance medication is an ICS or long-acting bronchodilator. These groups will be compared in terms of baseline variables (as in aim 1). Disease outcomes over time as described above will be compared between those patients starting treatment with ICS and those starting treatment with a long-acting bronchodilator, with adjustment for baseline characteristics, and this will be stratified by baseline blood eosinophil values to determine whether this modifies effectiveness of treatment. A dose-response relationship for this effect modification will be assessed, using both different cut-offs of eosinophil value, and different doses of ICS. The justification for this approach is that higher eosinophils are likely to be associated with worse prognosis,[1,2] and so eosinophil groups cannot be compared directly to determine ICS responsiveness.

Rationale

Characterising blood eosinophils within a primary care COPD population and understanding more about whether they can predict disease outcomes under ICS treatment will provide information on how eosinophils might be used both to help guide prognosis and potentially eosinophil-guided ICS treatment in future. This would help us to target inhaled steroid treatment more effectively and in a personalised way, to improve care of patients with COPD. Overall this will be a more efficient use of time and resources for patients and the NHS, and overall has the potential to reduce treatment and disease-related costs.

D. Background

Current COPD management and ICS use in primary care

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory condition affecting 1 million people in the UK, predominantly caused by smoking. It is characterised by airflow obstruction which is not fully reversible, and symptoms include breathlessness, cough and increased sputum. It accounts for more than £800 million in direct healthcare costs and causes an estimated 24 million lost working days per annum in the UK. Diagnosis is by a combination of clinical findings (history and examination), together with post-bronchodilator spirometry confirming airflow obstruction (forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.7). Severity is determined by degree of airflow obstruction using percentage of predicted FEV_1 (giving severity categories of mild, moderate, severe and very severe), and also by degree of breathlessness and frequency of exacerbations. Reversibility (change in airflow limitation in response to salbutamol) is not recommended as part of routine diagnosis, but can be helpful where there is suspicion of asthma.[3]

COPD is commonly managed in primary care using inhaled medication, with therapies added when patients experience frequent exacerbations or persistent breathlessness. Current NICE guidelines recommend a short-acting bronchodilator (beta-2 agonist, SABA, or muscarinic antagonist, SAMA), followed by long-acting bronchodilator (beta-2 agonist, LABA, or muscarinic antagonist, LAMA). Inhaled corticosteroids (ICS) are recommended in combination with LAMA or LABA for worsening symptoms or moderate or severe COPD (FEV_1 <50% predicted).[3] Although trials of long-term use of ICS for COPD have demonstrated some benefit in reducing exacerbations, their effects on rate of lung function decline are unclear, they can be associated with adverse effects including pneumonia and osteoporotic fractures,[4-8] and they are expensive to the NHS.[9] Nonetheless, studies of routinely collected data have shown that there is poor adherence to guidelines in primary care: ICS are widely used and patients tend to drift towards triple therapy (LABA, LAMA and ICS) in the years following COPD diagnosis.[9-11]

Eosinophilic inflammation in COPD

Early clinical and population-based cohort studies have shown that higher eosinophils are associated with poor outcomes in patients with COPD, including faster decline in lung function (sputum eosinophils)[12] and mortality (blood eosinophils).[1,2] Further research in secondary care used biological modelling to determine that there is a subset of COPD patients with increased airway eosinophil count at exacerbation, and blood eosinophil count was determined to be the best predictor of an exacerbation characterised by higher sputum eosinophils.[13] Two large studies of routinely collected primary care data (the Optimum Patient Care Research Database, OPCRD) and the general population (Copenhagen General Population Study), published in late 2015, found that raised blood eosinophils are associated with an increased risk of COPD exacerbations during follow-up, using cut-offs of 500 and 340 cells/µL (prevalence of raised eosinophils 10 and 16% respectively).[14,15] However, the latter was a general population study which used pre-bronchodilator spirometry, which may have led to inclusion of some patients with asthma, and studies on the general population in Denmark may not be directly applicable to patients with COPD in the UK.[15] Further, they have not investigated ICS-naïve patients or ICS responsiveness.

Earlier studies have shown that in patients with higher sputum eosinophil counts, treatment in stable state with both oral and inhaled steroids improved FEV_1, dyspnoea and quality of life,[16-

[19] and management by sputum eosinophil count resulted in a reduction in severe exacerbations.[20] Patients who respond to oral steroids in terms of improvements in FEV_1 had a raised blood and sputum eosinophil count at baseline.[21] In addition, a randomised placebo-controlled biomarker interventional study of eosinophil-directed treatment of exacerbations found a higher rate of treatment failure when COPD patients with lower blood eosinophils were treated with oral steroids.[22]

While eosinophilic airway and systemic inflammation characterises one subgroup of patients with COPD, there is also a subgroup of patients characterised by raised sputum neutrophils and serum C-reactive protein (CRP) at baseline, and this non-eosinophilic group was also found to be less steroid-responsive during exacerbations.[13,22]

Recently several retrospective post-hoc analyses of randomised controlled trials of ICS have been published which incorporate stratification by blood eosinophil count at baseline. Although various cut-offs for eosinophil count have been used and statistical significance varies between different analyses, broadly there is a greater response to ICS-containing preparations in patients with a higher baseline eosinophil count,[23-25] and there is a dose-response relationship of both rate of exacerbations and ICS-responsiveness according to degree of eosinophilic inflammation.[23]

How this project fits in

As ICS treatment suppresses eosinophil count,[16,17] and most patients in secondary care are already using ICS and have more severe disease, research to investigate whether baseline blood eosinophil count can predict steroid-responsiveness in long-term management of all patients with COPD needs to take place in a primary care setting. Recently published primary care database studies investigating eosinophilic phenotypes[14,15] have not specifically examined ICS-naïve patients or ICS responsiveness.

A database cohort study provides a means to test this retrospectively: due to recently published work and needing to define a specific population, this project will focus on the group of ICS-naïve patients who commence an ICS-containing medication or other inhaled maintenance medication (for comparison). Eosinophil count is routinely measured as part of full blood count (FBC), and both FBC and CRP are commonly requested blood tests in primary care for a variety of clinical reasons (and testing FBC is recommended in any case after a new diagnosis of COPD).[3] Information from this study may help identify biomarker information that is often already in the clinical record that could help GPs target expensive ICS treatment better to those patients most likely to benefit and avoid it in patients who are unlikely to benefit and may be harmed.

CPRD has been widely used previously for investigating aspects of COPD, although none, as far as we are aware, specifically investigating whether baseline blood eosinophils can predict ICS responsiveness, and this has been confirmed by the CPRD team (correspondence with Sophia Amjad, enquiry reference OCR5695).

In 2001 a study validated the use of diagnostic codes for accurately identifying patients with COPD in the GPRD, and found a high level of agreement between the database and the patient's GP[26] and further validation of COPD diagnosis codes recorded in the CPRD has recently taken place.[27,28] Risk factors for exacerbations have been explored defining exacerbations by primary care records, including prescriptions for oral steroids or antibiotics.[29] Nested case-control designs have been used to compare use of ICS in patients with COPD who

have an episode of pneumonia, including a GPRD study.[30] Another study used a new user cohort design to compare incidence of pneumonia in patients commencing ICS vs. patients commencing long-acting bronchodilators.[31]

E. Study Type

The first part of our study (aim 1) is descriptive, investigating association of blood eosinophil count with other baseline variables, and inter- and intra-patient variability of blood eosinophils. The second part (aim 2) is hypothesis-testing, investigating whether disease outcomes vary under ICS treatment depending on baseline blood eosinophil count.

F. Study Design

This will be a retrospective new-user cohort study of patients newly prescribed an inhaled maintenance medication, investigating outcomes under treatment stratified by a covariate of interest and with adjustment for baseline variables, with preliminary descriptive analysis of testing frequency and intra- and inter-patient variability. A new-user cohort design has been chosen for our hypothesis-testing component to minimise bias associated with including prevalent users.[32] Patients with high and low eosinophils starting on ICS cannot be compared directly because of the association of high eosinophils with poor prognosis over time,[1] therefore patients commencing ICS will be compared with patients commencing an alternative inhaled maintenance treatment, with stratification by baseline eosinophil count. These results will be adjusted to take into account baseline variables, such as disease severity, to minimise confounding by indication. Patients may also be commencing other new medications at the same time as ICS (see table in Section I below) e.g. LABA-ICS combination, which is a known limitation, but the chosen method should isolate the additive effect of ICS as far as possible (and is likely to be a similar effect between eosinophil groups).

G. Sample Size

We have estimated study power based upon counts provided by one of the CPRD Gold fob holders from the University of Oxford. All calculations were performed using Stata version 14.1 (StataCorp. Stata Statistical Software: Release 14.1. College Station, TX). We have estimated power for the hypothesis testing part of our study.

A random sample of 25 practices (577,928 records of 11,192,535 records, ~5.16% of the linked English practices in CPRD), gave 843 records fulfilling the criteria described in further detail in Section I below. Of these, 466 were getting a new ICS treatment and 377 were getting a new non-ICS treatment at the index date, of whom only 600 had an eosinophil record within 2 years of index date. Within each treatment group, we would expect approximately 25% of patients to have high eosinophil levels, and 75% to have low levels (estimate based on previous studies[15,23-25,33], but allowing for a lower eosinophil threshold and milder disease in our study). The table below gives estimated numbers expected, by eosinophil count within the CPRD.

Exposure group	Random sample of 5.16%	Estimated numbers with an eosinophil record	Scaled up to all CPRD practices 100%	Estimated numbers by eosinophil count	
				High eosinophil (25%)	Low eosinophil (75%)
ICS	466	332	6434	1609	4826
Non ICS	377	268	5194	1299	3896
TOTAL	843	600	**11628**	2908	8722
Expected HR (ICS vs non-ICS)				**0.72**	**0.90**

We expect hazard ratios (HR) for time to first exacerbation in the ICS vs non-ICS groups to be about 0.90 in the low eosinophil group and about 0.72 in the high eosinophil group (based on data from secondary analysis of ICS trials[23]). In the low eosinophil group, a HR of 0.90 can be estimated with a standard error of less than 0.01 with approximately 3800 events (power 90%, alpha 0.05). In the high eosinophil group, a HR of about 0.72 can be estimated with a standard error of 0.01 with approximately 1100 events (power 90%, alpha 0.05). Thus our expected patient numbers (8700 in the low eosinophil group and 2900 patients in the high eosinophil group) should give more than adequate power. Sensitivity analyses changing key parameters (estimated HR/n/standard deviation) were consistent with this.

This sample size calculation is based only on those practices with linked data (i.e. the fact that only half of practices have linkage is already taken into account).

H. Data Linkage Required (if applicable)

Linkage to basic HES data is requested as this provides the primary recorded cause of a hospitalisation: hospitalisation for acute exacerbations will form part of the definition of exacerbations, and this may not be accurately recorded in primary care records, thus improving the sensitivity in detecting the primary outcome. Exacerbations and pneumonia episodes severe enough to require hospitalisation will also be secondary outcomes. ONS mortality linkage is requested, as death due to COPD-related causes is another important secondary outcome and to enable comparison with other studies. Linkage to the Index of Multiple Deprivation is requested as high deprivation is associated with outcomes in COPD,[34] and it will be important to include deprivation as a covariate in my adjustment.

I. Study Population

The study population will be:

- diagnosis of COPD defined as:
  - COPD diagnosis code as previously validated in the CPRD[28] (see appendix)
  - ≥40 years of age
  - history of smoking (any previous recorded smoker or ex-smoker codes, entity code 4 and see appendix)
  - spirometry diagnostic of COPD at any previous point (entity code 395 <0.7 or 70%)
- patient is starting a new inhaled maintenance medication for COPD in the period 1st January 2005 (after the introduction of QOF targets in UK primary care) – 31st December 2014 – with those commencing triple therapy excluded (see table below and appendix)

- ICS-naïve (defined as patients who have no recorded prescriptions for ICS, or 3 or more oral steroid prescriptions (which may also suppress eosinophil levels), in the 12 months prior to the index date

The study start date (index date) will be the date of initiation of new inhaled maintenance medication. A new inhaled maintenance medication will be a prescription for a LABA, LAMA, ICS or combination, where a prescription for that drug category has not been issued in the previous 12 months. For the purposes of aim 2, patients will be categorised into ICS and non-ICS new maintenance medication groups:

New maintenance medication or combination	**Treatment group**
ICS	ICS
ICS + LABA	ICS
ICS + LAMA	ICS
ICS + LAMA + LABA	Excluded
LAMA	Non-ICS
LABA	Non-ICS
LAMA+LABA	Non-ICS

Excluded patients will be those with a diagnosis of asthma and asthma-COPD overlap syndrome (ACOS) (for the main analysis), bronchiectasis, cystic fibrosis, and pulmonary fibrosis.

Eligible patients will be registered with the practice and have continuous "up-to-standard" (UTS) data for a minimum of 24 months prior to and 6 months following index date (to ensure adequate recording of baseline covariates and outcomes). Eligibility will be defined using all UTS data prior to entry date. All patients must be from practices with data linkage for the entirety of the period they are in the study.

The study end date will be 30th September 2015 (or date of last available linked data). Follow-up will end at this date, or at the earliest of any of the following, at which censoring will occur: transfer out of CPRD; death; date of last upload of practice data to CPRD; change treatment (stop the medication of interest, change to an alternative, or add in another inhaled maintenance treatment).

Frequency variables will be assessed using all available follow-up data.

J. Selection of comparison group(s) or controls

Patients as above starting treatment with a long-acting bronchodilator (LAMA or LABA or combination) as their new medication, as defined above.

K. Exposures, Outcomes and Covariates

Aim 1: Description of baseline variables and eosinophil testing prior to commencing new inhaled maintenance medication

Exposures
- Blood eosinophils (entity code 168)

    - This should be recorded as a numerical value as number of cells per litre or microliter, or a percentage, where the total leucocyte count is also provided. Results will then be transformed to number of cells per microliter (cells/µL).
    - Excluded values will be: very high values likely to be incorrect or high due to an alternative cause; eosinophil count taken within 2 weeks either side of an exacerbation (defined below).
    - Eosinophil count will be stratified into high and low biomarker levels using a pre-specified cut-point of 150 cells/µL. A sensitivity analysis will look at different cut-offs of 100, 200, 300, 400 and 500 cells/µL for comparison with cut-offs used in existing literature,[14,15,23,25,35] and using eosinophils as a continuous variable.
    - The most recently recorded eosinophil value prior to the index date (including the same day), which must be in the 2 years prior to the index date, will be used in the main analysis
- Secondary exposures: Other inflammatory biomarker levels (CRP (entity code 280), blood neutrophil (entity code 184) and total leucocyte/white blood cell count (entity code 207)).

Covariates

- Time since first recorded COPD diagnosis (first date COPD coded with at least 2 years UTS data beforehand)
- Season (of blood eosinophil test) (classified as Spring (March-May), Summer (June-August), Autumn (September-November), Winter (December-February))
- Demographics
    - Age
    - Sex
    - Calendar year of index prescription
    - Socio-economic status (Index of Multiple Deprivation)
- Respiratory disease severity
    - Any history of atopy (presence of eczema/allergic rhinitis)
    - NICE severity classification (calculated by most recent spirometry (FEV1 % predicted) recorded before index date: entity code 394)
    - Bronchodilator reversibility (entity code 412)
    - Number of exacerbations in the year prior to index date (as defined in outcomes for Aim 2 below)
    - Number of pneumonia episodes in the year prior to index date (as defined in outcomes for Aim 2 below)
    - Prescriptions for respiratory medications
        - Number of prescriptions of oral steroids
        - Number of prescriptions of SABAs
        - Theophyllines
        - Oxygen use
        - Nebulised therapies
- General health
    - Number of hospitalisations
    - Number of GP visits
    - Charlson comorbidity index (we will define comorbidities using the recording of a relevant diagnostic code (Read code) and/or a treatment codes as appropriate. These methods will be based on our previous experience using data from the GPRD/CPRD (including protocol number 13_124R).
    - Vaccinations
        - Flu

- Pneumococcal

Aim 2: Hypothesis-testing arm

Exposures

- Blood eosinophil count as defined above (using the most recently recorded value prior to the index date, with a sensitivity analysis using mean values).
- New maintenance medication (ICS or long-acting bronchodilator): patients who start treatment with a new medication, and continue on it for at least 6 months after initiation (unless censored by death). Continuous use will be defined as duration of treatment (30 days) plus an additional 90 days grace period between scripts and scripts totalling at least 90 days' supply (usually 3 inhalers). Patients commencing treatment with triple therapy will be excluded from the main analysis. To examine a potential dose-response relationship in ICS-containing medications, the strength of ICS prescribed on the index date will be stratified into low, medium and high daily-dose of ICS (corresponding to estimated equivalent daily doses of beclomethasone dipropionate (BDP-CFC) of ≤500µg, >500-1000µg and >1000µg respectively), as in a previous CPRD ICS study.[31]

Outcomes

- Primary outcome – exacerbations of COPD (time-to-first exacerbation, as well as sensitivity analyses on number/year, and ≥2 exacerbations/year)
  - *Definition of exacerbations (any of the following, as recently validated in the CPRD[27], see appendix)*
    - Read code for exacerbation of COPD
    - Read code for lower respiratory tract infection (LRTI)
    - Prescription of exacerbation-specific antibiotic e.g. amoxicillin/macrolide/doxycycline and oral steroid for 5-14 days
    - Symptom of exacerbation (cough, breathlessness or sputum) with prescription of oral steroid or exacerbation-specific antibiotic
    - Hospital admission with a COPD or an acute respiratory code as the primary diagnosis of the hospitalisation (HES) (ICD-10 J00, J06, J09-18, J20-22, J40-44, J96) or COPD exacerbation code as any diagnosis within the episode of hospitalisation (J44.0, J44.1)
  - *Exacerbation exclusions*
    - An exacerbation (any of the above) occurring within two weeks of a previous exacerbation will be counted as the same exacerbation
    - Exacerbation events (as defined above) occurring on the same date as codes suggestive of a visit for annual COPD review or provision of rescue packs for COPD-specific antibiotics or oral steroids.[27]

We will also investigate secondary related outcomes:

- Pneumonia
  - Time to first event
  - Events/year

    - *Definition of pneumonia*
      - Read code for pneumonia (see appendix)
      - Hospital admission with a pneumonia code (HES) (J12-18)

- Death certificate with a pneumonia code as underlying or reported cause (ONS) (J10.0, J11.0, J12-18)

- Death (ONS) –due to COPD as underlying cause (J40-44), or due to any cause
  - Time to event
- Hospitalisation (HES) – due to any acute respiratory cause (ICD-10 J00, J06, J09-18, J20-22, J44.0, J44.1, J96), due to pneumonia (J10.0, J11.0, J12-18) or due to any cause
  - Time to first event
  - Events/year
- Rate of decline in % predicted FEV1 per year

Events occurring within the first month after initiating treatment will be excluded to avoid protopathic bias (treatment being initiated by the precipitating event).

Covariates
As described above for Aim 1.

L. Data/ Statistical analysis

Aim 1
The number of patients identified who meet inclusion criteria will be quantified. Patients will be compared in terms of baseline co-variates for those who have had eosinophils tested versus those who have not. This will be presented in a table with Chi-square, t-test or ANOVA as appropriate to assess statistical significance of differences between these groups. For those who have had eosinophils tested, the mean and median number of times of testing, time since COPD diagnosis and distribution of eosinophil values will be presented. For all baseline co-variates, eosinophil values will be summarised, with how this varies by severity and other variables. Further, patients will be divided into low and high eosinophil groups, and proportion of patients in each category by baseline co-variate will be presented e.g. reversibility. ANOVA will be used for categorical variables.

For multiple measurements, within- and between-person means and coefficients of variation will be assessed, and sensitivity and specificity of single value (index test) versus mean value eosinophil count (reference standard). Correlation between different biomarkers at baseline (including CRP, neutrophil count and total leucocyte count), the most recent value at index date, will also be assessed.

Aim 2
Disease outcomes as listed above will be described for the whole population, and the ICS and non-ICS groups individually. These will be compared using ratios depending on the analysis method used, which will then be stratified by baseline eosinophils. All analyses will be presented both unadjusted and adjusted for baseline co-variates.

For time-to-event analyses, we will use a Cox proportional hazards model to estimate hazard ratios (ICS vs non-ICS) stratified by eosinophil group, and including an interaction term. Event rates will be analysed with Poisson regression and binary variables with odds ratio using logistic regression. Numbers needed to treat will be calculated for different baseline eosinophil groups where possible.

Subgroup analyses will include investigating different doses of ICS to assess dose-response, as well as different thresholds of high and low eosinophil counts (see exposures section above for more detail). Sensitivity analyses will include using the mean of eosinophils in the last 2 years (excluding disallowed results, as above) versus the most recent value, using eosinophils as a continuous variable, and including patients with any history of asthma, and excluding patients with a history of atopy.

Data management and analyses will be carried out using Stata (StataCorp. Stat Statistical Software: College Station, TX).

M. Plan for addressing confounding

We have considered potential confounding carefully and plan to adjust for the list described above in the "exposures" section as covariates.

Aim 2: To adjust for confounding by indication (differential prescribing by clinicians according to baseline characteristics/severity), we will use adjust for potential confounders in our regression models.

N. Plan for addressing missing data

For the assessment of clinical diagnosis and outcomes in individuals, we will assume that absence of any relevant medical code in the clinical record means true absence of disease. We expect age, sex, and prescriptions to be well recorded in the cohort and so plan a complete case analysis.

O. Limitations of the study design, data sources and analytical methods

While we plan to adjust for factors relating to severity to minimise confounding due to indication, this is likely to remain a limitation of our analysis and will be discussed accordingly in resulting publications.

As with any database study, there are limitations relating to what has been coded – for example, from audit within Dr Ashdown's practice few exacerbations are coded with Read codes for exacerbations, which is why alternative methods are proposed here, following those used in other studies which have also used prescriptions[29] and more recent exacerbation validation studies in the CPRD.[36]

In comparing outcomes under treatment for patients with high and low eosinophil counts, it is possible that the eosinophil count used may not adequately reflect the true baseline value, as it is known to be affected by acute illness and exacerbations.[37] Excluding eosinophil counts recorded within 2 weeks of an exacerbation or oral steroid prescription should reduce this. We will also compare the most recent eosinophil count before index date with the mean of all eosinophil counts in the 2 years prior to the index date.

As with any study involving assessment of medication use, it is possible that what is coded as issued, may not actually be dispensed, or indeed used by the patient, so that is an assumption (and therefore limitation).

In censoring patients who have changed treatment, it is likely that those patients in the non-ICS group are likely to be censored earlier, due to the drift to ICS with deterioration in

symptoms.[10,11]. It is therefore possible that the ICS group will have longer to experience outcomes than those in the non-ICS group, introducing potential bias. However, the effect of this is likely to be limited in my analysis of high and low eosinophil groups, as both groups should have similar experience.

P. Patient or user group involvement (if applicable)

The overall aims for this project were discussed with a group of participants at a British Lung Foundation Breathe Easy group meeting, which is a support group for patients with lung conditions, many of whom have COPD. The patients felt that managing multiple inhalers was burdensome, and they welcomed research which might help to better target inhalers to the patients who would most benefit.

Q. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The results from this project will form part of a doctoral thesis which will have open access publication through the standard University of Oxford requirements. It is anticipated that this study will form at least one publication in a high impact peer-reviewed respiratory or primary care journal. This is estimated to take place in 2017.

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Appendices

Please see separate file.

Appendix D: CPRD code lists

CONTENTS

Inclusion and exclusion criteria

COPD diagnosis

Medical Code	Read Code	Read Term
794	H32..00	Emphysema
998	H3...11	Chronic obstructive airways disease
1001	H3...00	Chronic obstructive pulmonary disease
1446	H312200	Acute exacerbation of chronic obstructive airways disease
3243	H31..00	Chronic bronchitis
4084	663K.00	Airways obstructn irreversible
5710	H3z..00	Chronic obstructive airways disease NOS
5909	H312011	Chronic wheezy bronchitis
7884	H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec
9520	66YB.00	Chronic obstructive pulmonary disease monitoring
9876	H38..00	Severe chronic obstructive pulmonary disease
10802	H37..00	Moderate chronic obstructive pulmonary disease
10863	H36..00	Mild chronic obstructive pulmonary disease
10980	H322.00	Centrilobular emphysema
11019	8H2R.00	Admit COPD emergency
11150	H311.00	Mucopurulent chronic bronchitis
11287	66YM.00	Chronic obstructive pulmonary disease annual review
12166	H3y..00	Other specified chronic obstructive airways disease
13262	12D1.00	FH: Bronchitis/COAD
14798	H312100	Emphysematous bronchitis
15157	H31z.00	Chronic bronchitis NOS
15626	H310000	Chronic catarrhal bronchitis
18476	66YL.11	COPD follow-up
18501	66YI.00	COPD self-management plan given
18621	66YL.00	Chronic obstructive pulmonary disease follow-up
18792	9Oi..00	Chronic obstructive pulmonary disease monitoring admin
19003	66Ye.00	Emergency COPD admission since last appointment
19106	66Yd.00	COPD accident and emergency attendance since last visit
21061	H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn
23492	H320z00	Chronic bullous emphysema NOS
24248	H313.00	Mixed simple and mucopurulent chronic bronchitis
25603	H310.00	Simple chronic bronchitis
26018	66YS.00	Chronic obstructive pulmonary disease monitoring by nurse
26306	H320.00	Chronic bullous emphysema
27819	H312.00	Obstructive chronic bronchitis
28743	66Yf.00	Number of COPD exacerbations in past year
28755	9Oi0.00	Chronic obstructive pulmonary disease monitoring 1st letter
33450	H32z.00	Emphysema NOS
34202	9Oi1.00	Chronic obstructive pulmonary disease monitoring 2nd letter
34215	9Oi2.00	Chronic obstructive pulmonary disease monitoring 3rd letter
37247	H3z..11	Chronic obstructive pulmonary disease NOS
37371	66YD.00	Chronic obstructive pulmonary disease monitoring due
38074	9Oi4.00	Chronic obstructive pulmonary disease monitor phone invite
40159	H311000	Purulent chronic bronchitis
42258	9Oi3.00	Chronic obstructive pulmonary disease monitoring verb invite

Medical Code	Read Code	Read Term
42624	66YL.12	COAD follow-up
44525	H312z00	Obstructive chronic bronchitis NOS
45770	66Yg.00	Chronic obstructive pulmonary disease disturbs sleep
45771	66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep
45777	8CR1.00	Chronic obstructive pulmonary disease clini management plan
45998	66YT.00	Chronic obstructive pulmonary disease monitoring by doctor
46036	66Yi.00	Multiple COPD emergency hospital admissions
46578	H321.00	Panlobular emphysema
56860	H320000	Segmental bullous emphysema
60188	H320200	Giant bullous emphysema
61118	H310z00	Simple chronic bronchitis NOS
61513	H311z00	Mucopurulent chronic bronchitis NOS
65733	Hyu3100	[X]Other specified chronic obstructive pulmonary disease
66043	H31y.00	Other chronic bronchitis
67040	H3y..11	Other specified chronic obstructive pulmonary disease
68066	H31yz00	Other chronic bronchitis NOS
68662	H320100	Zonal bullous emphysema
93568	H39..00	Very severe chronic obstructive pulmonary disease
96931	14OX.00	At risk of chronic obstructive pulmonary diseas exacerbation
99948	9kf0.00	COPD patient unsuitable for pulmonary rehab - enh serv admin
101042	8BMW.00	Issue of chronic obstructive pulmonary disease rescue pack
102685	66YB000	Chronic obstructive pulmonary disease 3 monthly review
103007	66YB100	Chronic obstructive pulmonary disease 6 monthly review
103494	14B3.12	History of chronic obstructive pulmonary disease
103678	8BMa000	Chronic obstructiv pulmonary disease medication optimisation
103758	8Hkw.00	Referral to COPD community nursing team
103864	9kf0.11	COPD patient unsuitable for pulmonary rehabilitation
104117	661M300	COPD self-management plan agreed
104169	661N300	COPD self-management plan review
104265	9e03.00	GP OOH service notified of COPD care plan
104481	8CMV.00	Has chronic obstructive pulmonary disease care plan
104608	H3A..00	End stage chronic obstructive airways disease
104710	9NgP.11	On COPD (chr obstruc pulmonary disease) supportv cre pathway
104985	9NgP.00	On chronic obstructive pulmonary disease supprtv cre pathway
104998	8I61000	Chronic obstructve pulmonry disease rescue pack not indicatd
105457	8CMW500	Chronic obstructive pulmonary disease care pathway
106945	8IEZ.00	Chronic obstructive pulmonary disease rescue pack declined
107877	8IEy.00	Chronic obstructive pulmon dis wr self managem plan declined

Diagnosis exclusions

Medical Code	Read Code	Read Term
Bronchiectasis		
2195	H34..00	Bronchiectasis
15693	A115.00	Tuberculous bronchiectasis
20364	H340.00	Recurrent bronchiectasis
32679	H34z.00	Bronchiectasis NOS
41491	H341.00	Post-infective bronchiectasis
56427	P861.00	Congenital bronchiectasis
Alpha-1 anti-trypsin deficiency		
3019	C376200	Alpha-1-antitrypsin deficiency
Interstitial lung disease		
5519	H563.12	Cryptogenic fibrosing alveolitis
6051	H563100	Diffuse pulmonary fibrosis
6837	H563.00	Idiopathic fibrosing alveolitis
7791	H55..00	Postinflammatory pulmonary fibrosis
8317	H58y300	Interstitial lung disease NEC
16741	A114.00	Tuberculous fibrosis of lung
22536	H4y1000	Chronic pulmonary fibrosis following radiation
28229	H563z00	Idiopathic fibrosing alveolitis NOS
28853	N04y012	Fibrosing alveolitis associated with rheumatoid arthritis
43417	H4y2100	Chronic drug-induced interstitial lung disorders
44015	H4y2.00	Drug-induced interstitial lung disorders
46795	Q317100	Prematurity with interstitial pulmonary fibrosis
47782	H464200	Chronic pulmonary fibrosis due to chemical fumes
53205	H4y2000	Acute drug-induced interstitial lung disorders
65060	Hyu5000	[X]Other interstitial pulmonary diseases with fibrosis
91912	Hyu5100	[X]Other specified interstitial pulmonary diseases
94575	H433.00	Graphite fibrosis of lung
94894	H431.00	Bauxite fibrosis of lung
103472	H563200	Pulmonary fibrosis
103753	H563.13	Idiopathic pulmonary fibrosis
103785	H58y500	Respiratory bronchiolitis associated interstitial lung dis
104915	H58y700	Interstitial lung disease due to connective tissue disease
Cystic fibrosis		
6220	C370.00	Cystic fibrosis
18905	C370300	Cystic fibrosis with intestinal manifestations
18914	C370200	Cystic fibrosis with pulmonary manifestations
36622	C370111	Meconium ileus in cystic fibrosis
49770	C370z00	Cystic fibrosis NOS
65344	C370000	Cystic fibrosis with no meconium ileus
69017	C370100	Cystic fibrosis with meconium ileus
73065	C370y00	Cystic fibrosis with other manifestations
93380	C10N100	Cystic fibrosis related diabetes mellitus
100520	66k0.00	Cystic fibrosis annual review
100610	C370400	Arthropathy in cystic fibrosis
102922	C370800	Cystic fibrosis related cirrhosis
103224	C370500	Cystic fibrosis with distal intestinal obstruction syndrome
106432	C370900	Exacerbation of cystic fibrosis

Smoking

Medical Code	Read Code	Read Term	Category
Entity code 4 OR any of the following codes, with categorisation to determine whether current or ex-smoker (or unable to categorise (blank)):			
54	137..00	Tobacco consumption	Current
90	137S.00	Ex smoker	Ex
93	137P.00	Cigarette smoker	Current
776	137K.00	Stopped smoking	Ex
1822	1376	Very heavy smoker - 40+cigs/d	Current
1823	137P.11	Smoker	Current
1878	1374	Moderate smoker - 10-19 cigs/d	Current
3568	1375	Heavy smoker - 20-39 cigs/day	Current
7622	8CAL.00	Smoking cessation advice	Current
10211	13p..00	Smoking cessation milestones	
10558	137R.00	Current smoker	Current
10742	8HTK.00	Referral to stop-smoking clinic	Current
11356	9N2k.00	Seen by smoking cessation advisor	
11527	9N4M.00	DNA - Did not attend smoking cessation clinic	
12240	137G.00	Trying to give up smoking	Current
12878	137T.00	Date ceased smoking	Ex
12941	1372.11	Occasional smoker	Current
12942	137..11	Smoker - amount smoked	Current
12943	137J.00	Cigar smoker	Current
12944	1373	Light smoker - 1-9 cigs/day	Current
12946	137F.00	Ex-smoker - amount unknown	Ex
12947	137H.00	Pipe smoker	Current
12951	137Q.11	Smoking restarted	Current
12952	137Q.00	Smoking started	Current
12954	ZV4K000	[V]Tobacco use	Current
12955	1379	Ex-moderate smoker (10-19/day)	Ex
12956	137A.00	Ex-heavy smoker (20-39/day)	Ex
12957	1378	Ex-light smoker (1-9/day)	Ex
12958	1372	Trivial smoker - < 1 cig/day	Current
12959	137B.00	Ex-very heavy smoker (40+/day)	Ex
12960	137Z.00	Tobacco consumption NOS	Current
12961	1377	Ex-trivial smoker (<1/day)	Ex
12964	137C.00	Keeps trying to stop smoking	Current
12966	137V.00	Smoking reduced	Current
12967	137a.00	Pipe tobacco consumption	Current
16717	H310100	Smokers' cough	
18573	8H7i.00	Referral to smoking cessation advisor	
18926	67H1.00	Lifestyle advice regarding smoking	Current
19488	137O.00	Ex cigar smoker	Ex
26470	137N.00	Ex pipe smoker	Ex
30423	137c.00	Thinking about stopping smoking	Current
30762	137d.00	Not interested in stopping smoking	Current
31114	137b.00	Ready to stop smoking	Current
32687	E251.00	Tobacco dependence	
34126	13p0.00	Negotiated date for cessation of smoking	Current
38112	13p5.00	Smoking cessation programme start date	
41042	8CAg.00	Smoking cessation advice provided by community pharmacist	Current
41979	137e.00	Smoking restarted	Current

Medical Code	Read Code	Read Term	Category
46321	137f.00	Reason for restarting smoking	Current
62686	137h.00	Minutes from waking to first tobacco consumption	Current
74907	745H.00	Smoking cessation therapy	
90522	745Hz00	Smoking cessation therapy NOS	
91708	745Hy00	Other specified smoking cessation therapy	
94958	745H400	Smoking cessation drug therapy	
96992	9kc..00	Smoking cessation - enhanced services administration	
97210	137j.00	Ex-cigarette smoker	Ex
98137	67H6.00	Brief intervention for smoking cessation	Current
98154	8HkQ.00	Referral to NHS stop smoking service	Current
98245	8HBM.00	Stop smoking face to face follow-up	
98347	9ko..00	Current smoker annual review - enhanced services admin	Current
98447	9km..00	Ex-smoker annual review - enhanced services administration	Ex
98493	9kc0.00	Smoking cessatn monitor template complet - enhanc serv admin	
99838	137K000	Recently stopped smoking	Ex
100099	8IAj.00	Smoking cessation advice declined	Current
100495	137l.00	Ex roll-up cigarette smoker	Ex
100963	9km..11	Ex-smoker annual review	Ex
101338	137m.00	Failed attempt to stop smoking	Current
101764	13p5000	Practice based smoking cessation programme start date	
102361	9NS0200	Referral for smoking cessation service offered	Current
103507	8CdB.00	Stop smoking service opportunity signposted	Current
104185	8IEM.00	Smoking cessation drug therapy declined	Current
104230	8IEK.00	Smoking cessation programme declined	Current
104310	9ko..11	Current smoker annual review	Current
105710	8HBP.00	Smoking cessation 12 week follow-up	
105999	1V08.00	Smokes drugs in cigarette form	Current
106359	8T08.00	Referral to smoking cessation service	Current
106391	8IEo.00	Referral to smoking cessation service declined	Current
108966	9kc0.11	Smoking cessation ESA monitoring template completed	

Spirometry

Medical Code	Read Code	Read Term
Diagnostic of COPD – entity code 395 <0.7 or 70% or one of the following codes if associated with value:		
8512	339R.00	FEV1/FVC percent
11078	339T.00	FEV1/FVC > 70% of predicted
14455	3398	FEV1/FVC ratio normal
14456	339M.00	FEV1/FVC ratio
19832	339m.00	FEV1/FVC ratio after bronchodilator
23285	3399	FEV1/FVC ratio abnormal
25083	339U.00	FEV1/FVC < 70% of predicted
27141	339l.00	FEV1/FVC ratio before bronchodilator
FEV_1 (% predicted) – entity code 394 or 308 and one of the following codes if associated with value:		
6091	339S.00	Percent predicted FEV1
101079	339S000	Percentage predicted FEV1 after bronchodilation
FEV_1/FVC ratio – entity code 395 or 308 and one of the following codes if associated with value:		
8512	339R.00	FEV1/FVC percent
11078	339T.00	FEV1/FVC > 70% of predicted

Medical Code	Read Code	Read Term
14455	3398	FEV1/FVC ratio normal
14456	339M.00	FEV1/FVC ratio
19832	339m.00	FEV1/FVC ratio after bronchodilator
23285	3399	FEV1/FVC ratio abnormal
25083	339U.00	FEV1/FVC < 70% of predicted
27141	339l.00	FEV1/FVC ratio before bronchodilator
FEV1 (L) – entity code 394 or 308 and one of the following codes if associated with value:		
10320	339O.00	Forced expired volume in 1 second
19830	339b.00	FEV1 after bronchodilation

Inhaled maintenance medication

ICS/non-ICS and drug class refer to how drugs were categorised for more detailed analysis. ICS eq. refers to equivalence factors for calculation of estimated equivalent daily doses of beclomethasone diproprionate.

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
38	Beclometasone 100micrograms/dose inhaler	ICS	ICS	1
99	Becotide 100 inhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	1
454	Pulmicort 200microgram Inhaler (AstraZeneca UK Ltd)	ICS	ICS	1
465	Salmeterol 25micrograms/dose inhaler	Non-ICS	LABA	
549	Serevent 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd)	Non-ICS	LABA	
638	Seretide 250 Accuhaler (GlaxoSmithKline UK Ltd)	ICS	ICS/LABA	2
665	Seretide 100 Accuhaler (GlaxoSmithKline UK Ltd)	ICS	ICS/LABA	2
719	Salmeterol 50micrograms/dose dry powder inhaler	Non-ICS	LABA	
746	Tiotropium 18 microgram Capsule	Non-ICS	LAMA	
883	Becodisks 200microgram Disc (Allen & Hanburys Ltd)	ICS	ICS	1
895	Beclazone 100 Easi-Breathe inhaler (Teva UK Ltd)	ICS	ICS	1
896	Becotide easi-breathe 100microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)	ICS	ICS	1
908	Pulmicort 400 Turbohaler (AstraZeneca UK Ltd)	ICS	ICS	1
909	Budesonide 200micrograms/dose inhaler	ICS	ICS	1
910	Serevent diskhaler 50microgram Inhalation powder (Glaxo Wellcome UK Ltd)	Non-ICS	LABA	
911	Flixotide accuhaler 250 250microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)	ICS	ICS	2
947	Budesonide 50micrograms/actuation refill canister	ICS	ICS	1
956	Pulmicort 200 Turbohaler (AstraZeneca UK Ltd)	ICS	ICS	1
959	Budesonide 50micrograms/dose inhaler	ICS	ICS	1
960	Pulmicort 100 Turbohaler (AstraZeneca UK Ltd)	ICS	ICS	1
1100	Beclazone 100 inhaler (Teva UK Ltd)	ICS	ICS	1
1236	Becloforte 250micrograms/dose inhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	1
1242	Beclometasone 250micrograms/dose inhaler	ICS	ICS	1
1243	Beclazone 250 Easi-Breathe inhaler (Teva UK Ltd)	ICS	ICS	1
1258	Becotide 200 inhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	1
1259	Beclometasone 200micrograms/dose inhaler	ICS	ICS	1
1269	Becotide 50microgram/ml Nebuliser liquid (Allen & Hanburys Ltd)	ICS	ICS	1
1406	Becotide 50 inhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	1

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
1412	Flixotide 250microgram/actuation Inhalation powder (Allen & Hanburys Ltd)	ICS	ICS	2
1424	Flixotide 250microgram Disc (Allen & Hanburys Ltd)	ICS	ICS	2
1426	Flixotide 500microgram Disc (Allen & Hanburys Ltd)	ICS	ICS	2
1518	Flixotide 50microgram/actuation Inhalation powder (Allen & Hanburys Ltd)	ICS	ICS	2
1537	Becotide 200microgram Rotacaps (GlaxoSmithKline UK Ltd)	ICS	ICS	1
1551	Beclazone 250 inhaler (Teva UK Ltd)	ICS	ICS	1
1552	Becloforte easi-breathe 250microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)	ICS	ICS	1
1642	Budesonide 400micrograms/dose dry powder inhaler	ICS	ICS	1
1676	Flixotide 125microgram/actuation Inhalation powder (Allen & Hanburys Ltd)	ICS	ICS	2
1680	Pulmicort LS 50micrograms/dose inhaler (AstraZeneca UK Ltd)	ICS	ICS	1
1725	Beclazone 50 Easi-Breathe inhaler (Teva UK Ltd)	ICS	ICS	1
1727	Becotide easi-breathe 50microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)	ICS	ICS	1
1734	Beclometasone 100micrograms/dose breath actuated inhaler	ICS	ICS	1
1801	Ventide inhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	1
1861	AeroBec 100 Autohaler (Meda Pharmaceuticals Ltd)	ICS	ICS	1
1885	Beclazone 200 inhaler (Teva UK Ltd)	ICS	ICS	1
1951	Becodisks 400microgram Disc (Allen & Hanburys Ltd)	ICS	ICS	1
1956	Pulmicort 1mg Respules (AstraZeneca UK Ltd)	ICS	ICS	1
1959	Pulmicort 0.5mg Respules (AstraZeneca UK Ltd)	ICS	ICS	1
1974	Oxis 12 Turbohaler (AstraZeneca UK Ltd)	Non-ICS	LABA	
1975	Oxis 6 Turbohaler (AstraZeneca UK Ltd)	Non-ICS	LABA	
2092	Budesonide 200micrograms/dose dry powder inhaler	ICS	ICS	1
2125	Pulmicort 200microgram Refill canister (AstraZeneca UK Ltd)	ICS	ICS	1
2148	Beclometasone 400microgram disc	ICS	ICS	1
2159	AeroBec 50 Autohaler (Meda Pharmaceuticals Ltd)	ICS	ICS	1
2160	Beclometasone 50micrograms/dose breath actuated inhaler	ICS	ICS	1
2224	Serevent 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)	Non-ICS	LABA	
2229	Becodisks 100microgram Disc (Allen & Hanburys Ltd)	ICS	ICS	1
2282	Fluticasone propionate 500micrograms/dose dry powder inhaler	ICS	ICS	2
2335	Qvar 100 inhaler (Teva UK Ltd)	ICS	ICS	2
2440	Flixotide accuhaler 500 500microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)	ICS	ICS	2
2600	Beclometasone 250micrograms/dose breath actuated inhaler	ICS	ICS	1
2723	Fluticasone 25micrograms/dose inhaler	ICS	ICS	2
2892	Becloforte 400microgram disks (GlaxoSmithKline UK Ltd)	ICS	ICS	1
2893	Beclometasone 200micrograms disc	ICS	ICS	1
2951	Fluticasone 250microgram/actuation Pressurised inhalation	ICS	ICS	2
2992	Beclazone 50 inhaler (Teva UK Ltd)	ICS	ICS	1
3018	Beclometasone 50micrograms/dose inhaler	ICS	ICS	1
3065	Bextasol Inhalation powder (Allen & Hanburys Ltd)	ICS	ICS	1
3075	Becotide 400microgram Rotacaps (GlaxoSmithKline UK Ltd)	ICS	ICS	1
3119	Becloforte integra 250microgram/actuation Inhaler with compact spacer (Glaxo Laboratories Ltd)	ICS	ICS	1
3150	Beclometasone 100micrograms/actuation extrafine particle cfc free inhaler	ICS	ICS	1
3220	Qvar 50 Autohaler (Teva UK Ltd)	ICS	ICS	1

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
3289	Flixotide 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
3297	Salmeterol 50micrograms disc	Non-ICS	LABA	
3363	Becloforte 400microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	1
3546	Qvar 50 inhaler (Teva UK Ltd)	ICS	ICS	2
3556	Beclometasone 50micrograms with salbutamol 100micrograms/inhalation inhaler	ICS	ICS	1
3570	Budesonide 200micrograms/actuation refill canister	ICS	ICS	1
3666	Seretide 500 Accuhaler (GlaxoSmithKline UK Ltd)	ICS	ICS/LABA	2
3743	Filair 50 inhaler (Meda Pharmaceuticals Ltd)	ICS	ICS	1
3927	Filair 100 inhaler (Meda Pharmaceuticals Ltd)	ICS	ICS	1
3947	Becotide 100microgram Rotacaps (GlaxoSmithKline UK Ltd)	ICS	ICS	1
3989	Flixotide 100microgram Disc (Allen & Hanburys Ltd)	ICS	ICS	2
3993	Filair Forte 250micrograms/dose inhaler (Meda Pharmaceuticals Ltd)	ICS	ICS	1
4131	Fluticasone 100microgram Disc	ICS	ICS	2
4132	Fluticasone 125microgram/actuation Pressurised inhalation	ICS	ICS	2
4365	Beclometasone 100micrograms disc	ICS	ICS	1
4413	Qvar 100 Autohaler (Teva UK Ltd)	ICS	ICS	2
4499	Aerobec 250microgram/actuation Pressurised inhalation (Meda Pharmaceuticals Ltd)	ICS	ICS	1
4545	Pulmicort LS 50microgram Refill canister (AstraZeneca UK Ltd)	ICS	ICS	1
4601	Asmabec 100 Clickhaler (Focus Pharmaceuticals Ltd)	ICS	ICS	1
4688	Fluticasone 50microgram/actuation Pressurised inhalation	ICS	ICS	2
4759	Beclometasone 100microgram inhalation powder capsules	ICS	ICS	1
4801	Budesonide 500micrograms/2ml nebuliser liquid unit dose vials	ICS	ICS	1
4803	Beclazone 250microgram/actuation Inhalation powder (Actavis UK Ltd)	ICS	ICS	1
4926	Flixotide accuhaler 100 100microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)	ICS	ICS	2
4942	Budesonide 1mg/2ml nebuliser liquid unit dose vials	ICS	ICS	1
5143	Seretide 50 Evohaler (GlaxoSmithKline UK Ltd)	ICS	ICS/LABA	2
5161	Seretide 125 Evohaler (GlaxoSmithKline UK Ltd)	ICS	ICS/LABA	2
5172	Seretide 250 Evohaler (GlaxoSmithKline UK Ltd)	ICS	ICS/LABA	2
5223	Fluticasone 50micrograms/dose inhaler CFC free	ICS	ICS	2
5309	Flixotide 50micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
5521	Beclometasone 200micrograms/dose dry powder inhaler	ICS	ICS	1
5522	Beclometasone 100micrograms/dose dry powder inhaler	ICS	ICS	1
5551	Flixotide 0.5mg/2ml Nebules (GlaxoSmithKline UK Ltd)	ICS	ICS	2
5558	Salmeterol 50micrograms with fluticasone 500micrograms CFC free inhaler	ICS	ICS/LABA	2
5580	Flixotide accuhaler 50 50microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)	ICS	ICS	2
5683	Flixotide 250micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
5718	Flixotide 125micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
5804	Beclometasone 250micrograms/dose dry powder inhaler	ICS	ICS	1
5822	Fluticasone 250micrograms/dose inhaler CFC free	ICS	ICS	2
5864	Salmeterol 25micrograms with fluticasone 250micrograms CFC free inhaler	ICS	ICS/LABA	2

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
5885	Fluticasone propionate 100micrograms/dose dry powder inhaler	ICS	ICS	2
5942	Salmeterol 50micrograms with fluticasone 250micrograms CFC free inhaler	ICS	ICS/LABA	2
5975	Fluticasone 125micrograms/dose inhaler CFC free	ICS	ICS	2
5992	Beclometasone 50micrograms/dose dry powder inhaler	ICS	ICS	1
6050	Spiriva 18 microgram Capsule (Boehringer Ingelheim Ltd)	Non-ICS	LAMA	
6325	Symbicort 200/6 Turbohaler (AstraZeneca UK Ltd)	ICS	ICS/LABA	1
6526	Formoterol 12microgram inhalation powder capsules with device	Non-ICS	LABA	
6569	Salmeterol 25micrograms with fluticasone 125micrograms CFC free inhaler	ICS	ICS/LABA	2
6616	Salmeterol 25micrograms with fluticasone 50micrograms CFC free inhaler	ICS	ICS/LABA	2
6746	Budesonide 400micrograms/dose / Formoterol 12micrograms/dose dry powder inhaler	ICS	ICS/LABA	1
6780	Symbicort 400/12 Turbohaler (AstraZeneca UK Ltd)	ICS	ICS/LABA	1
6796	Budesonide 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler	ICS	ICS/LABA	1
6839	Alvesco 160 inhaler (Takeda UK Ltd)	ICS	ICS	2.5
6938	Salmeterol 50micrograms with fluticasone 100micrograms dry powder inhaler	ICS	ICS/LABA	2
7013	Symbicort 100/6 Turbohaler (AstraZeneca UK Ltd)	ICS	ICS/LABA	1
7133	Formoterol 12micrograms/dose dry powder inhaler	Non-ICS	LABA	
7268	Serevent 25micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)	Non-ICS	LABA	
7270	Salmeterol 25micrograms/dose inhaler CFC free	Non-ICS	LABA	
7356	Ciclesonide 80micrograms/dose inhaler CFC free	ICS	ICS	2.5
7602	Fluticasone 50microgram Disc	ICS	ICS	2
7638	Fluticasone 250microgram Disc	ICS	ICS	2
7653	Beclometasone 400microgram inhalation powder capsules	ICS	ICS	1
7724	Betamethasone valerate 100micrograms/actuation inhaler	ICS	ICS	1
7788	Budesonide 100micrograms/dose dry powder inhaler	ICS	ICS	1
7891	Fluticasone 500microgram Disc	ICS	ICS	2
7948	Fluticasone propionate 250micrograms/dose dry powder inhaler	ICS	ICS	2
7964	Beclometasone 50micrograms/ml nebuliser suspension	ICS	ICS	1
8111	Becloforte vm 250microgram/actuation VM pack (Allen & Hanburys Ltd)	ICS	ICS	1
8433	Budesonide 100micrograms/actuation inhaler	ICS	ICS	1
8635	Flixotide 50microgram Disc (Allen & Hanburys Ltd)	ICS	ICS	2
9164	Fluticasone propionate 50micrograms/dose dry powder inhaler	ICS	ICS	2
9233	Beclometasone 200microgram inhalation powder capsules	ICS	ICS	1
9477	Asmabec 100microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	ICS	ICS	1
9571	Beclometasone 250micrograms/actuation vortex inhaler	ICS	ICS	1
9577	Asmabec 50 Clickhaler (Focus Pharmaceuticals Ltd)	ICS	ICS	1
9599	Beclazone 50microgram/actuation Inhalation powder (Actavis UK Ltd)	ICS	ICS	1
9711	Formoterol 6micrograms/dose dry powder inhaler	Non-ICS	LABA	
9921	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	ICS	ICS	1

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
10090	Beclometasone 50micrograms/actuation extrafine particle cfc free inhaler	ICS	ICS	1
10102	Ciclesonide 160micrograms/dose inhaler CFC free	ICS	ICS	2.5
10218	Budesonide 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler	ICS	ICS/LABA	1
10254	Mometasone 400micrograms/dose dry powder inhaler	ICS	ICS	1
10321	Budesonide 400microgram inhalation powder capsules	ICS	ICS	1
10968	Foradil 12microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)	Non-ICS	LABA	
11198	Beclometasons 50 micrograms/actuation vortex inhaler	ICS	ICS	1
11307	Salbutamol 100micrograms/dose / Beclometasone 50micrograms/dose inhaler	ICS	ICS	1
11410	Fluticasone propionate 500micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler	ICS	ICS/LABA	2
11478	Fluticasone 2mg/2ml nebuliser liquid unit dose vials	ICS	ICS	2
11497	Beclometasone 400micrograms/dose dry powder inhaler	ICS	ICS	1
11588	Fluticasone 125micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free	ICS	ICS/LABA	2
11618	Fluticasone 250micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free	ICS	ICS/LABA	2
11732	Beclometasone 50micrograms/dose breath actuated inhaler CFC free	ICS	ICS	1
12994	Fluticasone 50micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free	ICS	ICS/LABA	2
13037	Pulvinal Beclometasone Dipropionate 200micrograms/dose dry powder inhaler (Chiesi Ltd)	ICS	ICS	1
13040	Fluticasone propionate 250micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler	ICS	ICS/LABA	2
13273	Fluticasone propionate 100micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler	ICS	ICS/LABA	2
13290	Clenil Modulite 100micrograms/dose inhaler (Chiesi Ltd)	ICS	ICS	1
13815	Beclazone 100microgram/actuation Inhalation powder (Actavis UK Ltd)	ICS	ICS	1
14294	Qvar 50micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)	ICS	ICS	2
14306	Formoterol 12micrograms/dose inhaler CFC free	Non-ICS	LABA	
14321	Beclometasone 200micrograms/dose inhaler CFC free	ICS	ICS	1
14524	Bdp 250microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	ICS	ICS	1
14561	Salbutamol 400microgram / Beclometasone 200microgram inhalation powder capsules	ICS	ICS	1
14567	Asmabec 250 Clickhaler (Focus Pharmaceuticals Ltd)	ICS	ICS	1
14590	Asmabec 250microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	ICS	ICS	1
14700	Budesonide 400micrograms/actuation inhaler	ICS	ICS	1
14736	Pulvinal Beclometasone Dipropionate 400micrograms/dose dry powder inhaler (Chiesi Ltd)	ICS	ICS	1
14757	Pulvinal Beclometasone Dipropionate 100micrograms/dose dry powder inhaler (Chiesi Ltd)	ICS	ICS	1
15326	Beclometasone 100micrograms/dose inhaler CFC free	ICS	ICS	1
15706	Beclometasone 100 micrograms/actuation vortex inhaler	ICS	ICS	1
16018	Mometasone 200micrograms/dose dry powder inhaler	ICS	ICS	1
16054	Budesonide 200micrograms/actuation breath actuated powder inhaler	ICS	ICS	1

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
16148	Clenil Modulite 250micrograms/dose inhaler (Chiesi Ltd)	ICS	ICS	1
16151	Clenil Modulite 200micrograms/dose inhaler (Chiesi Ltd)	ICS	ICS	1
16158	Clenil Modulite 50micrograms/dose inhaler (Chiesi Ltd)	ICS	ICS	1
16305	Flixotide 2mg/2ml Nebules (GlaxoSmithKline UK Ltd)	ICS	ICS	2
16433	Asmanex 200micrograms/dose Twisthaler (Merck Sharp & Dohme Ltd)	ICS	ICS	1
16584	Beclometasone 50micrograms/dose inhaler CFC free	ICS	ICS	1
16625	Ventide Rotacaps (GlaxoSmithKline UK Ltd)	ICS	ICS	1
17465	Fluticasone 500micrograms/2ml nebuliser liquid unit dose vials	ICS	ICS	2
17590	Asmanex 400micrograms/dose Twisthaler (Merck Sharp & Dohme Ltd)	ICS	ICS	1
17654	Easyhaler Beclometasone 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)	ICS	ICS	1
17670	Easyhaler Budesonide 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)	ICS	ICS	1
17691	QVAR CFC FREE	ICS	ICS	2
17695	QVAR AUTOHALER	ICS	ICS	2
17702	QVAR AUTOHALER	ICS	ICS	2
17726	QVAR CFC FREE	ICS	ICS	2
18394	Bdp 50microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	ICS	ICS	1
18456	Salbutamol 200microgram / Beclometasone 100microgram inhalation powder capsules	ICS	ICS	1
18484	Ventide Paediatric Rotacaps (GlaxoSmithKline UK Ltd)	ICS	ICS	1
18537	Budesonide 200microgram inhalation powder capsules	ICS	ICS	1
18848	Qvar 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)	ICS	ICS	2
19031	Bdp 100microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	ICS	ICS	1
19121	Beclometasone 100micrograms with Salbutamol 200micrograms inhalation capsules	ICS	ICS	1
19376	Beclometasone 200micrograms with Salbutamol 400micrograms inhalation capsules	ICS	ICS	1
19389	Asmabec 50microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	ICS	ICS	1
19401	Beclometasone 250micrograms/actuation inhaler and compact spacer	ICS	ICS	1
20825	Spacehaler BDP 250microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	ICS	ICS	1
21005	Beclometasone 250micrograms/dose inhaler CFC free	ICS	ICS	1
21224	Alvesco 80 inhaler (Takeda UK Ltd)	ICS	ICS	2.5
21482	Beclometasone 100micrograms/dose inhaler (Generics (UK) Ltd)	ICS	ICS	1
23741	Novolizer budesonide 200microgram/actuation Pressurised inhalation (Meda Pharmaceuticals Ltd)	ICS	ICS	1
24898	Spacehaler BDP 100microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	ICS	ICS	1
25204	Beclometasone 100micrograms/dose inhaler (A A H Pharmaceuticals Ltd)	ICS	ICS	1
25784	Atimos Modulite 12micrograms/dose inhaler (Chiesi Ltd)	Non-ICS	LABA	
26063	Beclometasone 100micrograms/dose inhaler (Teva UK Ltd)	ICS	ICS	1
27188	Easyhaler Budesonide 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)	ICS	ICS	1

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
27679	Beclometasone 100microgram/actuation Pressurised inhalation (Approved Prescription Services Ltd)	ICS	ICS	1
28073	Beclometasone 250microgram/actuation Pressurised inhalation (Approved Prescription Services Ltd)	ICS	ICS	1
28640	Beclometasone 100microgram/actuation Inhalation powder (Actavis UK Ltd)	ICS	ICS	1
28761	Spacehaler BDP 50microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	ICS	ICS	1
29325	Beclometasone 250micrograms/dose inhaler (Generics (UK) Ltd)	ICS	ICS	1
30210	Beclometasone 250micrograms/dose inhaler (Teva UK Ltd)	ICS	ICS	1
30238	Beclometasone 50microgram/actuation Pressurised inhalation (Approved Prescription Services Ltd)	ICS	ICS	1
30649	Easyhaler Budesonide 400micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)	ICS	ICS	1
31774	Beclometasone 50micrograms/dose inhaler (Generics (UK) Ltd)	ICS	ICS	1
32874	Beclometasone 50microgram/actuation Inhalation powder (Actavis UK Ltd)	ICS	ICS	1
33258	Beclometasone 250micrograms/dose inhaler (A A H Pharmaceuticals Ltd)	ICS	ICS	1
33849	Beclometasone 100microgram/actuation Inhalation powder (Neo Laboratories Ltd)	ICS	ICS	1
34315	Beclometasone 250microgram/actuation Inhalation powder (Actavis UK Ltd)	ICS	ICS	1
34428	Beclometasone 50microgram/actuation Inhalation powder (Neo Laboratories Ltd)	ICS	ICS	1
34739	Beclometasone 50micrograms/dose inhaler (Teva UK Ltd)	ICS	ICS	1
34794	Beclometasone 200micrograms/dose inhaler (A A H Pharmaceuticals Ltd)	ICS	ICS	1
34859	Beclometasone 250microgram/actuation Inhalation powder (Neo Laboratories Ltd)	ICS	ICS	1
34919	Beclometasone 50micrograms/dose inhaler (A A H Pharmaceuticals Ltd)	ICS	ICS	1
34995	Spiriva 18microgram inhalation powder capsules with HandiHaler (Boehringer Ingelheim Ltd)	Non-ICS	LAMA	
35000	Spiriva 18microgram inhalation powder capsules (Boehringer Ingelheim Ltd)	Non-ICS	LAMA	
35011	Tiotropium bromide 18microgram inhalation powder capsules	Non-ICS	LAMA	
35014	Tiotropium bromide 18microgram inhalation powder capsules with device	Non-ICS	LAMA	
35071	Becodisks 200microgram (GlaxoSmithKline UK Ltd)	ICS	ICS	1
35106	Becodisks 100microgram with Diskhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	1
35107	Beclometasone 400microgram inhalation powder blisters with device	ICS	ICS	1
35113	Beclometasone 200microgram inhalation powder blisters	ICS	ICS	1
35118	Becodisks 400microgram with Diskhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	1
35165	Serevent 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)	Non-ICS	LABA	
35225	Flixotide 100microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
35288	Beclometasone 400microgram inhalation powder blisters	ICS	ICS	1

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
35293	Beclometasone 200microgram inhalation powder blisters with device	ICS	ICS	1
35299	Becodisks 400microgram (GlaxoSmithKline UK Ltd)	ICS	ICS	1
35374	Flixotide 500microgram disks (GlaxoSmithKline UK Ltd)	ICS	ICS	2
35392	Flixotide 500microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
35408	Becodisks 100microgram (GlaxoSmithKline UK Ltd)	ICS	ICS	1
35430	Becodisks 200microgram with Diskhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	1
35461	Flixotide 250microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
35503	Salmeterol 50microgram inhalation powder blisters	Non-ICS	LABA	
35510	Budesonide 200micrograms/dose dry powder inhalation cartridge with device	ICS	ICS	1
35542	Salmeterol 50microgram inhalation powder blisters with device	Non-ICS	LABA	
35580	Beclometasone 100microgram inhalation powder blisters with device	ICS	ICS	1
35602	Budesonide 200micrograms/dose dry powder inhalation cartridge	ICS	ICS	1
35611	Flixotide 250microgram disks (GlaxoSmithKline UK Ltd)	ICS	ICS	2
35631	Budelin Novolizer 200micrograms/dose inhalation powder (Meda Pharmaceuticals Ltd)	ICS	ICS	1
35638	Fluticasone propionate 100microgram inhalation powder blisters with device	ICS	ICS	2
35652	Beclometasone 100microgram inhalation powder blisters	ICS	ICS	1
35700	Fluticasone propionate 500microgram inhalation powder blisters with device	ICS	ICS	2
35724	Budelin Novolizer 200micrograms/dose inhalation powder refill (Meda Pharmaceuticals Ltd)	ICS	ICS	1
35725	Formoterol Easyhaler 12micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)	Non-ICS	LABA	
35772	Fluticasone propionate 100microgram inhalation powder blisters	ICS	ICS	2
35825	Serevent 50microgram disks (GlaxoSmithKline UK Ltd)	Non-ICS	LABA	
35905	Fluticasone propionate 250microgram inhalation powder blisters	ICS	ICS	2
35986	Flixotide 50microgram disks (GlaxoSmithKline UK Ltd)	ICS	ICS	2
36021	Fluticasone propionate 50microgram inhalation powder blisters with device	ICS	ICS	2
36090	Flixotide 100microgram disks (GlaxoSmithKline UK Ltd)	ICS	ICS	2
36290	Flixotide 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
36401	Fluticasone propionate 250microgram inhalation powder blisters with device	ICS	ICS	2
36462	Fluticasone propionate 500microgram inhalation powder blisters	ICS	ICS	2
36864	Tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device CFC free	Non-ICS	LAMA	
36869	Spiriva Respimat 2.5micrograms/dose solution for inhalation cartridge with device (Boehringer Ingelheim Ltd)	Non-ICS	LAMA	
37432	Fostair 100micrograms/dose / 6micrograms/dose inhaler (Chiesi Ltd)	ICS	ICS/LABA	2.5

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
37447	Fluticasone propionate 50microgram inhalation powder blisters	ICS	ICS	2
37470	Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free	ICS	ICS/LABA	2.5
39099	Pulmicort 100micrograms/dose inhaler CFC free (AstraZeneca UK Ltd)	ICS	ICS	1
39102	Budesonide 100micrograms/dose inhaler CFC free	ICS	ICS	1
39200	AeroBec Forte 250 Autohaler (Meda Pharmaceuticals Ltd)	ICS	ICS	1
39879	Budesonide 200micrograms/dose inhaler CFC free	ICS	ICS	1
40057	Pulmicort 200micrograms/dose inhaler CFC free (AstraZeneca UK Ltd)	ICS	ICS	1
41269	Beclometasone 400 Cyclocaps (Teva UK Ltd)	ICS	ICS	1
41412	Beclometasone 400micrograms/actuation inhaler	ICS	ICS	1
42928	Flixotide 100micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
42985	Flixotide 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
42994	Flixotide 250micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
43074	Flixotide 500micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)	ICS	ICS	2
43738	Indacaterol 150microgram inhalation powder capsules with device	Non-ICS	LABA	
43893	Onbrez Breezhaler 150microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)	Non-ICS	LABA	
44064	Onbrez Breezhaler 300microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)	Non-ICS	LABA	
45610	Indacaterol 300microgram inhalation powder capsules with device	Non-ICS	LABA	
46157	Beclometasone 200 Cyclocaps (Teva UK Ltd)	ICS	ICS	1
47638	Neovent 25micrograms/dose inhaler CFC free (Kent Pharmaceuticals Ltd)	Non-ICS	LABA	
47943	Beclazone easi-breathe (roi) 100microgram/actuation Pressurised inhalation (Ivax Pharmaceuticals Ireland)	ICS	ICS	1
48340	Clenil Modulite 100micrograms/dose inhaler (Mawdsley-Brooks & Company Ltd)	ICS	ICS	1
48666	Flutiform 250micrograms/dose / 10micrograms/dose inhaler (Napp Pharmaceuticals Ltd)	ICS	ICS/LABA	2
48709	Qvar 100micrograms/dose Easi-Breathe inhaler (Sigma Pharmaceuticals Plc)	ICS	ICS	2
48739	Seretide 250 Evohaler (DE Pharmaceuticals)	ICS	ICS/LABA	2
49000	Seretide 250 Evohaler (Waymade Healthcare Plc)	ICS	ICS/LABA	2
49114	Symbicort 100/6 Turbohaler (Sigma Pharmaceuticals Plc)	ICS	ICS/LABA	1
49227	Aclidinium bromide 375micrograms/dose dry powder inhaler	Non-ICS	LAMA	
49228	Eklira 322micrograms/dose Genuair (Almirall Ltd)	Non-ICS	LAMA	
49367	Clenil Modulite 50micrograms/dose inhaler (Mawdsley-Brooks & Company Ltd)	ICS	ICS	1
49412	Clenil Modulite 200micrograms/dose inhaler (Mawdsley-Brooks & Company Ltd)	ICS	ICS	1
49711	Pulmicort 200micrograms/dose inhaler (AstraZeneca UK Ltd)	ICS	ICS	1
49772	Fluticasone 250micrograms/dose Evohaler (Sigma Pharmaceuticals Plc)	ICS	ICS	2

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
49868	Fluticasone 250micrograms/dose / Formoterol 10micrograms/dose inhaler CFC free	ICS	ICS/LABA	2
50036	Flutiform 125micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)	ICS	ICS/LABA	2
50037	Pulmicort 0.5mg Respules (Waymade Healthcare Plc)	ICS	ICS	1
50051	Serevent 25micrograms/dose Evohaler (Waymade Healthcare Plc)	Non-ICS	LABA	
50103	Spiriva 18microgram inhalation powder capsules with HandiHaler (Waymade Healthcare Plc)	Non-ICS	LAMA	
50129	Qvar 100micrograms/dose Easi-Breathe inhaler (DE Pharmaceuticals)	ICS	ICS	2
50287	Qvar 100 inhaler (DE Pharmaceuticals)	ICS	ICS	2
50292	Spiriva 18microgram inhalation powder capsules (Sigma Pharmaceuticals Plc)	Non-ICS	LAMA	
50560	Seretide 250 Accuhaler (Sigma Pharmaceuticals Plc)	ICS	ICS/LABA	2
50577	Spiriva 18microgram inhalation powder capsules with HandiHaler (DE Pharmaceuticals)	Non-ICS	LAMA	
50689	Flutiform 50micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)	ICS	ICS/LABA	2
50739	Symbicort 400/12 Turbohaler (Mawdsley-Brooks & Company Ltd)	ICS	ICS/LABA	1
50886	Seretide 250 Evohaler (Stephar (U.K.) Ltd)	ICS	ICS/LABA	2
50945	Symbicort 100/6 Turbohaler (Mawdsley-Brooks & Company Ltd)	ICS	ICS/LABA	1
51027	Seretide 125 Evohaler (DE Pharmaceuticals)	ICS	ICS/LABA	2
51151	Seretide 125 Evohaler (Lexon (UK) Ltd)	ICS	ICS/LABA	2
51209	Fluticasone 125micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free	ICS	ICS/LABA	2
51234	Qvar 100 inhaler (Waymade Healthcare Plc)	ICS	ICS	2
51270	Fluticasone 50micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free	ICS	ICS/LABA	2
51394	Seretide 500 Accuhaler (Waymade Healthcare Plc)	ICS	ICS/LABA	2
51415	Qvar 50 inhaler (Mawdsley-Brooks & Company Ltd)	ICS	ICS	2
51480	Qvar 100 Autohaler (DE Pharmaceuticals)	ICS	ICS	2
51570	Symbicort 200/6 Turbohaler (DE Pharmaceuticals)	ICS	ICS/LABA	1
51593	Seretide 500 Accuhaler (DE Pharmaceuticals)	ICS	ICS/LABA	2
51681	Qvar 100 inhaler (Sigma Pharmaceuticals Plc)	ICS	ICS	2
51759	Symbicort 200/6 Turbohaler (Mawdsley-Brooks & Company Ltd)	ICS	ICS/LABA	1
51815	Flixotide 250micrograms/dose Evohaler (Waymade Healthcare Plc)	ICS	ICS	2
51861	Seretide 500 Accuhaler (Mawdsley-Brooks & Company Ltd)	ICS	ICS/LABA	2
51909	Seretide 250 Evohaler (Necessity Supplies Ltd)	ICS	ICS/LABA	2
51967	Spiriva 18microgram inhalation powder capsules (Mawdsley-Brooks & Company Ltd)	Non-ICS	LAMA	
52732	Pulmicort 0.5mg Respules (Necessity Supplies Ltd)	ICS	ICS	1
52806	Qvar 100 Autohaler (Lexon (UK) Ltd)	ICS	ICS	2
53057	Flixotide 50micrograms/dose Evohaler (Lexon (UK) Ltd)	ICS	ICS	2
53230	Seretide 250 Accuhaler (DE Pharmaceuticals)	ICS	ICS/LABA	2
53237	Symbicort 400/12 Turbohaler (DE Pharmaceuticals)	ICS	ICS/LABA	1
53283	Seretide 100 Accuhaler (Waymade Healthcare Plc)	ICS	ICS/LABA	2
53480	Qvar 100 Autohaler (Stephar (U.K.) Ltd)	ICS	ICS	2
53491	Symbicort 200/6 Turbohaler (Sigma Pharmaceuticals Plc)	ICS	ICS/LABA	1

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
53761	Glycopyrronium bromide 55microgram inhalation powder capsules with device	Non-ICS	LAMA	
53982	Seebri Breezhaler 44microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)	Non-ICS	LAMA	
54207	Qvar 50 inhaler (DE Pharmaceuticals)	ICS	ICS	2
54399	Qvar 100 Autohaler (Sigma Pharmaceuticals Plc)	ICS	ICS	2
54742	Salmeterol 25micrograms/dose inhaler CFC free (A A H Pharmaceuticals Ltd)	Non-ICS	LABA	
55677	Seretide 500 Accuhaler (Lexon (UK) Ltd)	ICS	ICS/LABA	2
56462	Becodisks 400microgram (Waymade Healthcare Plc)	ICS	ICS	1
56471	Becodisks 200microgram (Mawdsley-Brooks & Company Ltd)	ICS	ICS	1
56474	Flixotide 125micrograms/dose Evohaler (DE Pharmaceuticals)	ICS	ICS	2
56475	Flixotide 50micrograms/dose Accuhaler (Sigma Pharmaceuticals Plc)	ICS	ICS	2
56477	Flixotide 100micrograms/dose Accuhaler (Waymade Healthcare Plc)	ICS	ICS	2
56478	Serevent 50micrograms/dose Accuhaler (DE Pharmaceuticals)	Non-ICS	LABA	
56482	Oxis 12 Turbohaler (Waymade Healthcare Plc)	Non-ICS	LABA	
56484	Flixotide 250micrograms/dose Accuhaler (Waymade Healthcare Plc)	ICS	ICS	2
56493	Qvar 50micrograms/dose Easi-Breathe inhaler (Sigma Pharmaceuticals Plc)	ICS	ICS	2
56498	Pulmicort 200 Turbohaler (Waymade Healthcare Plc)	ICS	ICS	1
56499	Flixotide 500micrograms/dose Accuhaler (Waymade Healthcare Plc)	ICS	ICS	2
57525	Flixotide 250micrograms/dose Accuhaler (Stephar (U.K.) Ltd)	ICS	ICS	2
57544	Serevent 50micrograms/dose Accuhaler (Waymade Healthcare Plc)	Non-ICS	LABA	
57555	Flixotide 125micrograms/dose Evohaler (Dowelhurst Ltd)	ICS	ICS	2
57558	Oxis 6 Turbohaler (Lexon (UK) Ltd)	Non-ICS	LABA	
57579	Flixotide 50micrograms/dose Accuhaler (DE Pharmaceuticals)	ICS	ICS	2
57589	Becloforte 250micrograms/dose inhaler (Dowelhurst Ltd)	ICS	ICS	1
57694	Vertine 25micrograms/dose inhaler CFC free (Teva UK Ltd)	Non-ICS	LABA	
59638	Spiriva 18microgram inhalation powder capsules with HandiHaler (Sigma Pharmaceuticals Plc)	Non-ICS	LAMA	
60937	Pulmicort 200 Turbohaler (Dowelhurst Ltd)	ICS	ICS	1
61176	Anoro Ellipta 55micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)	Non-ICS	LAMA/LABA	
61280	Seretide 250 Accuhaler (Waymade Healthcare Plc)	ICS	ICS/LABA	2
61490	Umeclidinium bromide 65micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler	Non-ICS	LAMA/LABA	
61582	Spiriva Respimat 2.5micrograms/dose solution for inhalation cartridge with device (Waymade Healthcare Plc)	Non-ICS	LAMA	
61644	Fostair NEXThaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (Chiesi Ltd)	ICS	ICS/LABA	2.5
61664	Clenil Modulite 250micrograms/dose inhaler (Waymade Healthcare Plc)	ICS	ICS	1
61666	DuoResp Spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (Teva UK Ltd)	ICS	ICS/LABA	1
61782	DuoResp Spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (Teva UK Ltd)	ICS	ICS/LABA	1
61879	Incruse Ellipta 55micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)	Non-ICS	LAMA	

Product Code	Product Name	ICS/ Non-ICS	Drug Class	ICS Eq.
61975	Budesonide 500micrograms/2ml nebuliser liquid unit dose vials (Almus Pharmaceuticals Ltd)	ICS	ICS	1
62030	Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler	ICS	ICS/LABA	2.5
62109	Umeclidinium bromide 65micrograms/dose dry powder inhaler	Non-ICS	LAMA	
62126	Seretide 100 Accuhaler (DE Pharmaceuticals)	ICS	ICS/LABA	2

Oral steroid prescriptions

All codes were included as part of the exclusion definition (if 3 or more prescriptions in year prior to study entry). Those marked 'Cat' E were also included as part of the exacerbation outcome definition.

Product Code	Product Name	Cat
44	Prednisolone 5mg gastro-resistant tablets	E
95	Prednisolone 5mg tablets	E
186	Dexamethasone 500micrograms/5ml oral solution	
229	Cortisone 25mg tablets	
557	Prednisolone 2.5mg gastro-resistant tablets	E
578	Prednisolone 1mg tablets	E
955	Prednisolone 5mg soluble tablets	E
1063	Prednesol 5mg Tablet (Sovereign Medical Ltd)	E
1280	Dexamethasone 2mg tablets	
1380	Entocort CR 3mg capsules (AstraZeneca UK Ltd)	
1971	Betnesol 500microgram soluble tablets (Focus Pharmaceuticals Ltd)	
2044	PREDNISONE 2.5 MG TAB	E
2130	Methylprednisolone 4mg tablets	
2368	Prednisolone 2.5mg tablet	E
2390	PREDNISOLONE E/C 1 MG TAB	E
2434	Florinef 100microgram tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)	
2439	Fludrocortisone 100microgram tablets	
2704	Prednisolone 25mg tablets	E
2799	PREDNISOLONE 10 MG TAB	E
2949	Prednisone 5mg tablets	E
3059	PREDNISOLONE 50 MG TAB	E
3345	Sintisone Tablet (Pharmacia Ltd)	E
3418	Hydrocortisone 10mg tablets	
3557	Prednisone 1mg tablets	E
3898	Budesonide 3mg gastro-resistant modified-release capsules	
3992	Deflazacort 6mg tablets	
4535	Hydrocortisone 20mg tablets	
4779	Dexamethasone 500microgram tablets	
4943	Dexamethasone 2mg/5ml oral solution sugar free	
5157	Dexamethasone 2mg/5ml oral solution	
5490	Deltacortril 5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)	E
5913	Deltacortril 2.5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)	E
6095	Budesonide 3mg gastro-resistant capsules	
6098	Hydrocortone 10mg tablets (Auden McKenzie (Pharma Division) Ltd)	
7286	Betamethasone 500microgram soluble tablets sugar free	
7548	Cortisone 5mg capsules	
7584	PREDNISOLONE 4 MG TAB	E

Product Code	Product Name	Cat
7710	PREDNISOLONE 15 MG TAB	E
7934	PREDNISONE 30 MG TAB	E
8261	Medrone 16mg tablets (Pfizer Ltd)	
9375	Deflazacort 1mg tablets	
9727	Prednisolone 50mg tablets	E
9994	Decadron 500microgram tablets (Merck Sharp & Dohme Ltd)	
10552	Methylprednisolone 16mg tablets	
10574	Cortisone acetate 5mg tablets	
10683	Medrone 2mg tablets (Pfizer Ltd)	
10684	Methylprednisolone 2mg tablets	
10754	Hydrocortistab 20mg Tablet (Waymade Healthcare Plc)	
10864	Betamethasone 500microgram tablets	
11149	Betnelan 500microgram tablets (Focus Pharmaceuticals Ltd)	
12398	Cortelan 25mg Tablet (Glaxo Laboratories Ltd)	
12400	Cortisyl 25mg Tablet (Aventis Pharma)	
13043	Hydrocortone 20mg tablets (Auden McKenzie (Pharma Division) Ltd)	
13522	PREDNISOLONE 2 MG TAB	E
13615	PREDNISONE 10 MG TAB	E
14076	Hydrocortisone 5mg/5ml Oral solution	
14172	Methylprednisolone 100mg tablets	
15555	Medrone 4mg tablets (Pfizer Ltd)	
15617	Ledercort 4mg Tablet (Wyeth Pharmaceuticals)	
16525	Budenofalk 3mg gastro-resistant capsules (Dr. Falk Pharma UK Ltd)	
16724	PREDNISONE 50 MG TAB	E
18042	Medrone 100mg tablets (Pfizer Ltd)	
18637	Cortistab 25mg Tablet (Waymade Healthcare Plc)	
19141	Prednisolone 5mg soluble tablets (AMCo)	E
20095	Precortisyl forte 25mg Tablet (Aventis Pharma)	E
20577	Calcort 6mg Tablet (Shire Pharmaceuticals Ltd)	
20670	PREDNISOLONE E/C	E
21218	Dexsol 2mg/5ml oral solution (Rosemont Pharmaceuticals Ltd)	
21417	Prednisolone 5mg tablets (A A H Pharmaceuticals Ltd)	E
21833	Decortisyl 5mg Tablet (Roussel Laboratories Ltd)	E
21903	Oradexon-organon 2mg Tablet (Organon Laboratories Ltd)	
22555	Calcort 1mg tablets (Shire Pharmaceuticals Ltd)	
23210	Cortistab 5mg Tablet (Waymade Healthcare Plc)	
23512	Precortisyl 5mg Tablet (Hoechst Marion Roussel)	E
24014	Ledercort 2mg Tablet (Wyeth Pharmaceuticals)	
24716	PREDNISOLONE E/C	E
25272	Precortisyl 1mg Tablet (Hoechst Marion Roussel)	E
27889	PREDNISOLONE	E
27959	PREDNISOLONE	E
27962	Deltastab 1mg Tablet (Waymade Healthcare Plc)	E
28375	Prednisolone 2.5mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	E
28376	Prednisolone 2.5mg Gastro-resistant tablet (Biorex Laboratories Ltd)	E
28859	Deltastab 5mg Tablet (Waymade Healthcare Plc)	E
29333	Prednisolone 5mg tablets (Actavis UK Ltd)	E
30390	DELTASTAB 2 MG TAB	E
30971	DECORTISYL 25 MG TAB	E
31327	Prednisolone steaglate 6.65mg tablet	E
31532	Prednisolone 5mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	E
32803	Prednisolone 5mg gastro-resistant tablets (Actavis UK Ltd)	E

Product Code	Product Name	Cat
32835	Prednisolone 5mg tablets (Wockhardt UK Ltd)	E
33691	Prednisolone 5mg Gastro-resistant tablet (Biorex Laboratories Ltd)	E
33988	Prednisolone 5mg Tablet (Co-Pharma Ltd)	E
33990	Prednisolone 5mg Tablet (IVAX Pharmaceuticals UK Ltd)	E
34109	Prednisolone 5 mg gastro-resistant tablet	E
34393	Prednisolone 5mg gastro-resistant tablets (Teva UK Ltd)	E
34404	Prednisolone 1mg tablets (Actavis UK Ltd)	E
34452	Prednisolone 1mg tablets (A A H Pharmaceuticals Ltd)	E
34461	Prednisolone 2.5mg gastro-resistant tablets (Actavis UK Ltd)	E
34631	Prednisolone 1mg Tablet (Co-Pharma Ltd)	E
34660	Prednisolone 1mg tablets (Kent Pharmaceuticals Ltd)	E
34748	Prednisolone 1mg tablets (Teva UK Ltd)	E
34781	Prednisolone 5mg tablets (Kent Pharmaceuticals Ltd)	E
34801	Dexamethasone 0.5mg/5ml Oral solution (Rosemont Pharmaceuticals Ltd)	
34880	Dexamethasone 2mg tablets (Aspen Pharma Trading Ltd)	
34914	Prednisolone 1mg Tablet (Celltech Pharma Europe Ltd)	E
34915	Dexamethasone 500microgram tablets (Organon Laboratories Ltd)	
34978	Prednisolone 1mg tablets (Wockhardt UK Ltd)	E
36055	Dexamethasone 2mg Tablet (Hillcross Pharmaceuticals Ltd)	
37203	Beclometasone 5mg gastro-resistant modified-release tablets	
37622	Fludrocortisone Capsule	
37870	Fludrocortisone Liquid	
38022	Hydrocortisone 10mg/5ml oral suspension	
38054	Hydrocortisone Tablet	
38407	Prednisolone 20mg tablet	E
39067	Clipper 5mg gastro-resistant modified-release tablets (Chiesi Ltd)	
41335	Calcort 6mg tablets (Sanofi)	
41515	Prednisolone 5mg tablets (Teva UK Ltd)	E
41745	Prednisolone 25mg tablets (Zentiva)	E
43544	Prednisone 5mg Tablet (Knoll Ltd)	E
44380	Prednisone 1mg modified-release tablets	E
44723	Prednisone 5mg modified-release tablets	E
44802	Lodotra 5mg modified-release tablets (Napp Pharmaceuticals Ltd)	E
44803	Lodotra 2mg modified-release tablets (Napp Pharmaceuticals Ltd)	E
45234	Dexamethasone 100microgram capsules	
45302	Prednisolone 5mg Tablet (Biorex Laboratories Ltd)	E
46711	Prednisone 2mg modified-release tablets	E
47142	Prednisolone 5mg Soluble tablet (Amdipharm Plc)	E
50225	Betnesol 500microgram soluble tablets (Waymade Healthcare Plc)	
51722	Hydrocortisone 5mg/5ml oral suspension	
51753	Prednisolone 1mg tablets (Co-Pharma Ltd)	E
51824	Hydrocortisone 5mg/5ml oral suspension sugar free	
51872	Hydrocortisone 2.5mg capsules	
51997	Budesonide 9mg gastro-resistant granules sachets	
52396	Dexamethasone 1mg/5ml oral solution	
52472	Fludrocortisone 50micrograms/5ml oral suspension	
53143	Cortisone 25mg tablets (A A H Pharmaceuticals Ltd)	
53207	Dexamethasone tablets	
53313	Prednisolone 20mg/5ml oral suspension	E
53336	Prednisolone 25mg tablets (A A H Pharmaceuticals Ltd)	E
53705	Cortisone acetate 5mg Capsule (Martindale Pharmaceuticals Ltd)	
54118	Prednisolone 25mg/5ml oral suspension	E

Product Code	Product Name	Cat
54432	Lodotra 1mg modified-release tablets (Napp Pharmaceuticals Ltd)	E
54434	Prednisolone 2.5mg/5ml oral suspension	E
54793	Dexamethasone 2mg/5ml oral suspension	
55024	Prednisolone 5mg/5ml oral solution	E
55401	Dexamethasone 500microgram tablets (A A H Pharmaceuticals Ltd)	
55480	Prednisolone 2.5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)	E
56144	Budenofalk 9mg gastro-resistant granules sachets (Dr. Falk Pharma UK Ltd)	
56347	Dexamethasone 5mg/5ml oral solution	
56891	Prednisolone 1mg tablets (Waymade Healthcare Plc)	E
57931	Hydrocortisone 20mg tablets (Teva UK Ltd)	
58000	Prednisolone 5mg tablets (Almus Pharmaceuticals Ltd)	E
58061	Prednisone 50mg tablets	E
58234	Prednisolone 10mg/5ml oral solution	E
58369	Prednisolone 5mg tablets (Boston Healthcare Ltd)	E
58384	Prednisolone 1mg tablets (Almus Pharmaceuticals Ltd)	E
58474	Dexamethasone 2mg/5ml oral solution sugar free (A A H Pharmaceuticals Ltd)	
58987	Prednisolone 5mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)	E
59229	Dilacort 5mg gastro-resistant tablets (Auden McKenzie (Pharma Division) Ltd)	E
59283	Dilacort 2.5mg gastro-resistant tablets (Auden McKenzie (Pharma Division) Ltd)	E
59338	Prednisolone 1mg/5ml oral solution	E
59912	Prednisolone 5mg gastro-resistant tablets (Waymade Healthcare Plc)	E
60120	Dexamethasone 2mg tablets (Alliance Healthcare (Distribution) Ltd)	
60421	Prednisolone 5mg tablets (Co-Pharma Ltd)	E
60516	Fludrocortisone 50microgram capsules	
60946	Entocort CR 3mg capsules (Waymade Healthcare Plc)	
61132	Prednisolone 1mg tablets (Boston Healthcare Ltd)	E
61162	Prednisolone 5mg tablets (Waymade Healthcare Plc)	E
61689	Prednisolone 5mg soluble tablets (A A H Pharmaceuticals Ltd)	E

Outcomes

Exacerbations

Medical Code	Read Code	Read Term
Exacerbation		
1446	H312200	Acute exacerbation of chronic obstructive airways disease
7884	H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec
Lower Respiratory Tract Infection		
68	H06z011	Chest infection
312	H060.00	Acute bronchitis
556	H27..00	Influenza
1019	H061.00	Acute bronchiolitis
1382	H060w00	Acute viral bronchitis unspecified
2157	H27z.11	Flu like illness
2476	H07..00	Chest cold
2581	H06z000	Chest infection NOS
3358	H06z100	Lower resp tract infection
5947	H27z.12	Influenza like illness
5978	H060.11	Acute wheezy bronchitis
6124	H062.00	Acute lower respiratory tract infection
8980	16L..00	Influenza-like symptoms
9043	H060600	Acute pneumococcal bronchitis
11072	H060300	Acute purulent bronchitis
14791	H27y100	Influenza with gastrointestinal tract involvement
15774	H271000	Influenza with laryngitis
16388	H27z.00	Influenza NOS
17185	H061200	Acute bronchiolitis with bronchospasm
17359	H30..11	Chest infection - unspecified bronchitis
17917	H061z00	Acute bronchiolitis NOS
18451	H061500	Acute bronchiolitis due to respiratory syncytial virus
20198	H060z00	Acute bronchitis NOS
21061	H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn
21145	H060400	Acute croupous bronchitis
21492	H060800	Acute haemophilus influenzae bronchitis
23488	H271z00	Influenza with respiratory manifestations NOS
24316	H24..11	Chest infection with infectious disease EC
24800	H060x00	Acute bacterial bronchitis unspecified
29273	H060C00	Acute bronchitis due to parainfluenza virus
29617	H271100	Influenza with pharyngitis
29669	H06..00	Acute bronchitis and bronchiolitis
31363	H27yz00	Influenza with other manifestations NOS
37447	H06z112	Acute lower respiratory tract infection
41137	H06z.00	Acute bronchitis or bronchiolitis NOS
43362	H060700	Acute streptococcal bronchitis
43625	H271.00	Influenza with other respiratory manifestation
46157	H27y000	Influenza with encephalopathy
47472	H27y.00	Influenza with other manifestations
48593	H060D00	Acute bronchitis due to respiratory syncytial virus
49794	H060900	Acute neisseria catarrhalis bronchitis
63697	43jQ.00	Avian influenza virus nucleic acid detection

Medical Code	Read Code	Read Term
64890	H060E00	Acute bronchitis due to rhinovirus
65916	H060F00	Acute bronchitis due to echovirus
66397	Hyu1.00	[X]Other acute lower respiratory infections
69192	H061300	Acute exudative bronchiolitis
71370	H060200	Acute pseudomembranous bronchitis
73100	Hyu1000	[X]Acute bronchitis due to other specified organisms
91123	43jz.00	Parainfluenza type 3 nucleic acid detection
93153	H060B00	Acute bronchitis due to coxsackievirus
94130	43jx.00	Parainfluenza type 1 nucleic acid detection
94858	43jy.00	Parainfluenza type 2 nucleic acid detection
94930	H29..00	Avian influenza
96017	4JU5.00	Influenza B virus detected
96018	4JU2.00	Influenza H3 virus detected
96019	4JU0.00	Influenza H1 virus detected
96286	4JUF.00	Human parainfluenza virus detected
97062	4JU4.00	Influenza A virus, other or untyped strain detected
97279	Hyu0700	[X]Influenza+other manifestations, virus not identified
97605	Hyu0600	[X]Influenza+oth respiratory manifestatns,virus not identifd
97936	Hyu0500	[X]Influenza+other manifestations,influenza virus identified
98102	H2A..11	Influenza A (H1N1) swine flu
98103	1W0..00	Possible influenza A virus H1N1 subtype
98115	1J72.11	Suspected swine influenza
98125	1J72.00	Suspected influenza A virus subtype H1N1 infection
98129	H2A..00	Influenza due to Influenza A virus subtype H1N1
98143	4J3L.00	Influenza A virus H1N1 subtype detected
98156	4JU3.00	Influenza H5 virus detected
98257	Hyu0400	[X]Flu+oth respiratory manifestations,'flu virus identified
99214	Hyu1100	[X]Acute bronchiolitis due to other specified organisms
101775	H060100	Acute membranous bronchitis
102918	4JU1.00	Influenza H2 virus detected
Hospitalisations due to COPD		
Hospital admission with COPD or acute respiratory code as primary diagnosis of hospitalisation (ICD-10 J00, J06, J09-18, J20-22, J40-44, J96)		
COPD exacerbation code as any diagnosis within the episode of hospitalisation (ICD-10 J44.0, J44.1)		
Oral steroid prescription for 5-14 days		
See 'Oral steroid prescriptions' above, marked category 'E'		
Respiratory symptoms (cough, breathlessness of sputum		
92	171..00	Cough
292	1719	Chesty cough
735	R060D00	[D]Breathlessness
741	R060800	[D]Shortness of breath
1025	1719.11	Bronchial cough
1160	R062.00	[D]Cough
1234	1716	Productive cough NOS
1251	R064.00	[D]Abnormal sputum
1273	171..11	C/O - cough
1429	173..00	Breathlessness
2563	R060600	[D]Respiratory distress
2575	173C.00	Short of breath on exertion

Medical Code	Read Code	Read Term
2737	Q30..00	Respiratory distress syndrome
2931	1738	Difficulty breathing
3068	1717	Night cough present
3092	R060A00	[D]Dyspnoea
3645	1716.11	Coughing up phlegm
3727	4JF5.00	Sputum sent for C/S
4070	171C.00	Morning cough
4822	1739	Shortness of breath
4836	173B.00	Nocturnal cough / wheeze
4931	1712	Dry cough
5175	173..11	Breathlessness symptom
5349	173..13	Shortness of breath symptom
5896	173..12	Dyspnoea - symptom
6326	1732	Breathless - moderate exertion
7000	2322	O/E - dyspnoea
7534	2324	O/E - respiratory distress
7706	1713	Productive cough -clear sputum
7707	171Z.00	Cough symptom NOS
7708	1715	Productive cough-yellow sputum
7773	1714	Productive cough -green sputum
7932	1733	Breathless - mild exertion
8239	R063000	[D]Cough with haemorrhage
8287	41D4.00	Sputum sample obtained
8760	R153100	[D]Positive culture findings in sputum
9297	R060700	[D]Respiratory insufficiency
9807	171..12	Sputum - symptom
10013	172..11	Blood in sputum - symptom
11072	H060300	Acute purulent bronchitis
14269	4E...00	Sputum examination
14271	4E4..00	Sputum culture
14272	4E3..00	Sputum microscopy
14273	4E2A.00	Sputum appearance
14804	4E3Z.12	Sputum appears infected
15430	R064100	[D]Sputum abnormal - colour
16026	4E13.00	Sputum examination: abnormal
18116	173D.00	Nocturnal dyspnoea
18907	171F.00	Cough with fever
18964	Z691.11	Sputum clearance
20086	R064000	[D]Sputum abnormal - amount
21801	173Z.00	Breathlessness NOS
22094	173F.00	Short of breath dressing/undressing
22318	171H.00	Difficulty in coughing up sputum
23252	4E3Z.00	Sputum microscopy NOS
23582	R064z00	[D]Abnormal sputum NOS
24181	4E23.00	Sputum: mucopurulent
24889	173G.00	Breathless - strenuous exertion
29318	171D.00	Evening cough
30754	4E28.00	Yellow sputum
30904	4E11.00	Sputum sent for examination
31143	1734	Breathless - at rest
35577	4E1..00	Sputum examination - general
36515	R064300	[D]Abnormal sputum - tenacious

Medical Code	Read Code	Read Term
36880	4E29.00	Green sputum
40202	4E...11	Mucoid sputum - O/E
40813	173b.00	Unable to complete a sentence in one breath
43270	4E3Z.11	Sputum evidence of infection
43272	4EZ..00	Sputum examination NOS
44214	R064200	[D]Sputum abnormal - odour
49029	4E1Z.00	Sputum gen. exam. NOS
49144	4E36.00	Sputum: pus cells present
49694	4E37.00	Sputum: organism on gram stain
53771	173C.11	Dyspnoea on exertion
54177	4E22.00	Sputum: excessive - mucoid
55936	4E35.00	Sputum: blood cells present
56133	4E2..00	Sputum inspection
60903	1D87.00	Cough aggravates symptom
61079	4E2Z.00	Sputum inspection NOS
64096	4E24.00	Sputum: contains blood
91680	7459500	Expectoration of induced sputum from respiratory tract
100484	4E2E.00	Volume of sputum
100515	4I2G.00	Cough swab
100524	4E2E100	Moderate sputum
100629	4E2D.00	White sputum
100647	4E2E000	Copious sputum
100931	4E2C.00	Brown sputum
101782	4E2E011	Profuse sputum
102351	4E2G.00	Bloodstained sputum
103209	4E2F.00	Grey sputum
107359	4E29000	Dark green sputum
Exacerbation exclusions – entity code 394/395 OR one of the following codes:		
1491	8B65.00	Prophylactic antibiotic therapy
4799	8B6Z.00	Prophylactic drug therapy NOS
6118	5882	Spirometry
7181	8B6..00	Prophylactic drug therapy
7229	663W.00	Asthma prophylactic medication used
29015	745C100	Spirometry
29934	ZV07312	[V]Prophylactic antibiotic
100337	8B33.00	Advance supply of antibiotic medication
100459	8B32.00	Advance supply of steroid medication
101042	8BMW.00	Issue of chronic obstructive pulmonary disease rescue pack
102522	745D400	Post bronchodilator spirometry

Product Code	Product Name
Exacerbation-specific antibiotic prescription for 5-14 days	
9	Amoxicillin 250mg capsules
48	Amoxicillin 500mg capsules
62	Amoxicillin 125mg/5ml oral suspension
63	Erythromycin 250mg gastro-resistant tablets
77	Oxytetracycline 250mg tablets
103	Erythromycin 250mg gastro-resistant capsules

Product Code	Product Name
105	Erythroped 250mg/5ml Liquid (Abbott Laboratories Ltd)
121	Tetracycline 250mg capsules
132	Oxytetracycline 250mg capsules
133	Amoxil 250mg capsules (GlaxoSmithKline UK Ltd)
155	Cefalexin 250mg capsules
163	Ciproxin 250mg/5ml oral suspension (Bayer Plc)
192	Ceporex 250mg Capsule (Galen Ltd)
264	Doxycycline 50mg capsules
268	Vibramycin 100mg capsules (Pfizer Ltd)
281	Ciprofloxacin 250mg tablets
318	Erymax 250mg Capsule (Elan Pharma)
319	Distaclor 500mg Capsule (Dista Products Ltd)
327	Erythroped a 500mg Tablet (Abbott Laboratories Ltd)
331	Clarithromycin 125mg/5ml oral suspension
366	Cefaclor 250mg capsules
386	Tetracycline 250mg tablets
397	Erythromycin 125mg/5ml oral suspension
399	Augmentin 375mg tablets (GlaxoSmithKline UK Ltd)
400	Cefalexin 500mg capsules
401	Erythromycin 500mg ec gastro-resistant tablets
415	Augmentin 125/31 SF oral suspension (GlaxoSmithKline UK Ltd)
427	Amoxicillin 250mg/5ml oral suspension
438	Erythromycin stearate 250mg tablets
439	Amoxicillin with Clavulanic acid dispersible tablets
480	Erythrocin 250mg Tablet (Abbott Laboratories Ltd)
485	Amoxicillin 125mg/1.25ml oral suspension paediatric
498	Ciprofloxacin 100mg tablets
503	Amoxicillin 125mg/5ml oral suspension sugar free
509	Augmentin 625mg tablets (GlaxoSmithKline UK Ltd)
524	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free
532	Erythroped 250mg/5ml Oral suspension (Abbott Laboratories Ltd)
537	Clarithromycin 250mg tablets
545	Co-amoxiclav 250mg/125mg tablets
553	Erythromycin 250mg.5ml oral suspension
561	Ofloxacin 200mg tablets
566	Ofloxacin 400mg tablets
569	Augmentin 250/62 SF oral suspension (GlaxoSmithKline UK Ltd)
583	Ciprofloxacin 500mg tablets
585	Amoxicillin 250mg/5ml oral suspension sugar free
641	Co-amoxiclav 500mg/125mg tablets
681	Clarithromycin 500mg tablets
728	Ciproxin 500mg tablets (Bayer Plc)
733	Erythromycin ethyl succinate 500mg tablets
743	Azithromycin 500mg tablets
765	Clarithromycin 250mg granules sachets
825	Erythroped pi 125mg/5ml Oral suspension (Abbott Laboratories Ltd)
829	Co-amoxiclav 250mg/125mg dispersible tablets sugar free
830	Keflex 250mg tablets (Flynn Pharma Ltd)
847	Amoxil 500mg capsules (GlaxoSmithKline UK Ltd)
865	Cefalexin 500mg tablets
870	Amoxicillin 250mg sugar free chewable tablets
966	AMOXIL SF 125 MG/5ML SYR

Product Code	Product Name
970	Doxycycline (as hyclate) 100mg tablets
993	Erythroped forte 500mg/5ml Liquid (Abbott Laboratories Ltd)
997	Erythroped pi 125mg/5ml Liquid (Abbott Laboratories Ltd)
1037	ERYTHROMYCIN ETHYLSUCCINATE SF 125 MG/5ML SUS
1038	Cefaclor 125mg/5ml oral suspension
1046	Doxycycline 100mg capsules
1072	Erythrocin 500 500mg Tablet (Abbott Laboratories Ltd)
1140	Amoxicillin 3g oral powder sachets sugar free
1146	Cefalexin 250mg tablets
1202	Ciproxin 250mg tablets (Bayer Plc)
1306	Suprax 200mg tablets (Sanofi)
1376	ERYTHROMYCIN 100 MG SYR
1384	Cefalexin 125mg/5ml suspension
1391	Amoxicillin 250mg / Clavulanic acid 125mg tablets
1393	AMOXYCILLIN FIZTAB 250 MG TAB
1570	AMOXYCILLIN 500 MG TAB
1637	Amoxil fiztab 250mg Tablet (Bencard)
1638	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free
1693	Cefalexin 125mg/5ml oral suspension
1713	Cefalexin 250mg/5ml suspension
1722	Amoxicillin 500mg dispersible tablets
1812	Amoxil 250mg/5ml syrup sucrose free (GlaxoSmithKline UK Ltd)
1837	Ciprofloxacin 750mg tablets
1860	Cefalexin 250mg/5ml oral suspension
1969	ERYTHROMYCIN 250 MG MIX
2019	ERYTHROCIN 125 MG SYR
2153	Amoxil 125mg/5ml syrup sucrose free (GlaxoSmithKline UK Ltd)
2171	Amoxil 125mg/1.25ml paediatric oral suspension (GlaxoSmithKline UK Ltd)
2174	Amoxil 3g oral powder sachets sucrose free (GlaxoSmithKline UK Ltd)
2202	Vibramycin 50 capsules (Pfizer Ltd)
2225	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free
2226	Erythromycin ethyl succinate 500mg/5ml oral suspension
2227	Cefalexin 500mg/5ml oral suspension
2281	Amoxicillin 500mg sugar free chewable tablets
2304	ERYTHROCIN 250 250 MG TAB
2313	ERYTHROPED 250 MG TAB
2326	Erythromycin 500mg/5ml oral suspension
2350	Erythromycin stearate 500mg tablets
2376	Erythromycin ethyl succinate 250mg/5ml oral suspension
2428	Distaclor 125mg/5ml Liquid (Dista Products Ltd)
2429	Erythromycin ethyl succinate 125mg/5ml oral suspension
2458	OXYTETRACYCLINE 100 MG TAB
2507	Augmentin 375mg dispersible tablets (GlaxoSmithKline UK Ltd)
2636	TETRACYCLINE 500 MG CAP
2661	Ceporex 500mg Capsule (Galen Ltd)
2719	Klaricid 250mg tablets (Abbott Laboratories Ltd)
2726	Tarivid 400mg tablets (Sanofi)
2884	Doxycycline (as hyclate) 100mg dispersible tablets
2902	AMOXYCILLIN FIZTAB 125 MG TAB
2922	Tetracycline 250mg with nystatin 250000units tablets
2976	Cefaclor 500mg capsules
3025	OXYTETRACYCLINE 500 MG TAB

Product Code	Product Name
3042	Erythroped pi 125mg Sachets (Abbott Laboratories Ltd)
3152	Vibramycin 100mg Dispersible tablet (Pfizer Ltd)
3180	Cefaclor 375mg modified-release tablets
3209	Erythromid 250mg Tablet (Abbott Laboratories Ltd)
3408	ERYTHROMYCIN 500 MG CAP
3523	Distaclor 500mg Modified-release tablet (Dista Products Ltd)
3528	TETRACYCLINE 500 MG TAB
3572	Erythroped 250mg Powder (Abbott Laboratories Ltd)
3609	Ceporex 125mg/5ml Oral solution (Galen Ltd)
3669	Amoxymed 250mg Capsule (Medipharma Ltd)
3736	Klaricid 125mg/5ml Oral suspension (Abbott Laboratories Ltd)
3737	Cefaclor 250mg/5ml oral suspension
3742	Amoxicillin 125mg sugar free chewable tablets
3816	Tetrachel 250mg Tablet (Berk Pharmaceuticals Ltd)
3831	Suprax Paediatric 100mg/5ml oral suspension (Sanofi)
3907	ERYTHROMYCIN SF sach 250 MG
4010	Amoxil 750mg Sachets (GlaxoSmithKline UK Ltd)
4091	Ciprofloxacin 250mg/5ml oral suspension
4153	Erythrolar 250mg/5ml Liquid (Lagap)
4154	Amoxil fiztab 125mg Tablet (Bencard)
4165	Zithromax 250mg capsules (Pfizer Ltd)
4372	Erythroped forte 500mg Sachets (Abbott Laboratories Ltd)
4489	Erycen 250mg Tablet (Berk Pharmaceuticals Ltd)
4513	Tarivid 200mg tablets (Sanofi)
4576	Distaclor 250mg Capsule (Dista Products Ltd)
4582	Amoxicillin 750mg soluble tablets
4596	Erythroped a 1g Sachets (Abbott Laboratories Ltd)
4610	Erythroped forte 500mg/5ml Oral suspension (Abbott Laboratories Ltd)
4672	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free
4689	Cefaclor 500mg Capsule (Lagap)
5057	Azithromycin 200mg/5ml oral suspension
5116	Azithromycin 250mg capsules
5238	Levofloxacin 500mg tablets
5335	Zithromax 500mg tablets (Pfizer Ltd)
5341	Augmentin-Duo 400/57 oral suspension (GlaxoSmithKline UK Ltd)
5357	Clarithromycin 250mg/5ml oral suspension
5859	Ceporex 500mg/5ml Oral solution (Galen Ltd)
6121	Klaricid XL 500mg tablets (Abbott Laboratories Ltd)
6206	Tavanic 500mg tablets (Sanofi)
6295	Levofloxacin 250mg tablets
6306	Moxifloxacin 400mg tablets
6396	Doxycycline 100mg dispersible tablets sugar free
6623	Klaricid 500 tablets (Abbott Laboratories Ltd)
6651	Cefalexin 125mg/5ml oral suspension sugar free
6671	Cefalexin 250mg/5ml oral suspension sugar free
6687	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free
6803	Clarithromycin 500mg modified-release tablets
7364	Co-amoxiclav 250mg/62mg/5ml oral suspension
7430	Keflex 250mg Capsule (Eli Lilly and Company Ltd)
7455	Terramycin 250mg Capsule (Pfizer Ltd)
7485	Keflex 125mg/5ml Liquid (Eli Lilly and Company Ltd)
7519	Norfloxacin 400mg tablets

Product Code	Product Name
7526	Cefaclor 125mg/5ml oral suspension sugar free
7560	Ceporex 125mg/5ml Liquid (Galen Ltd)
7581	AMOXYCILLIN 125MG/62MG CLAVULANIC ACID SYR
7592	AMOXYCILLIN 125 MG CAP
7636	Amoxicillin 250mg / Clavulanic acid 62mg/5ml oral suspension
7737	Amoxil fiztab 500mg Tablet (Bencard)
7752	Ciproxin 750mg tablets (Bayer Plc)
7792	ERYTHROMYCIN 12 MG SYR
7881	Chlortetracycline 250mg capsules
7889	Distaclor 375mg Modified-release tablet (Dista Products Ltd)
8008	Ceporex 250mg/5ml Oral solution (Galen Ltd)
8019	Ceporex 250mg Tablet (Galen Ltd)
8051	Cefaclor 500mg modified-release tablets
8085	Ceporex 500mg Tablet (Galen Ltd)
8219	Tetrachel 250mg Capsule (Berk Pharmaceuticals Ltd)
8284	Tetracycline 125mg/5ml syrup
8285	OXYTETRACYCLINE 250 MG SYR
8582	AMOXIDIN 250 MG CAP
8625	Ceporex 250mg/5ml Liquid (Galen Ltd)
8724	Doxycycline (as hyclate) 50mg/5ml oral solution
8906	Amoxicillin 125mg / Clavulanic acid 31mg/5ml oral suspension
9014	Tetrabid-organon 250mg Capsule (Organon Laboratories Ltd)
9034	Oxytetracycline 125mg/5ml syrup
9148	Erythromid ds 500mg Tablet (Abbott Laboratories Ltd)
9154	Ciproxin 100mg tablets (Bayer Plc)
9157	Keflex 250mg Tablet (Eli Lilly and Company Ltd)
9219	Distaclor 250mg/5ml Liquid (Dista Products Ltd)
9243	Amoram 250mg capsules (LPC Medical (UK) Ltd)
9267	Vibramycin Acne Pack 50mg capsules (Pfizer Ltd)
9293	Cefaclor 250mg/5ml oral suspension sugar free
9343	Amoxicillin 750mg sugar free powder
9361	Oxymycin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)
9434	Erymin 250mg/5ml Oral suspension (Elan Pharma)
9520	Cefaclor 250mg Capsule (Lagap)
9583	Klaricid 250mg/5ml Oral suspension (Abbott Laboratories Ltd)
9603	Keflex 500mg Tablet (Eli Lilly and Company Ltd)
9664	Cefalexin 500mg capsules (IVAX Pharmaceuticals UK Ltd)
9689	Cefalexin 500mg tablets (Teva UK Ltd)
9690	Cefalexin 250mg capsules (Teva UK Ltd)
9698	Cefalexin 250mg tablets (Teva UK Ltd)
9903	Erythromycin estolate 250mg capsules
9925	Clavulanic acid 125mg with Amoxicillin 250mg tablets
10190	Erymax 250mg gastro-resistant capsules (Teva UK Ltd)
10200	Co-amoxiclav 125mg/31mg/5ml oral suspension
10326	Clarithromycin 125mg granules straws
10454	Vibramycin 50mg/5ml Oral solution (Pfizer Ltd)
10455	Keflex 250mg/5ml Liquid (Eli Lilly and Company Ltd)
10782	ERYMAX 500 MG CAP
11611	Rommix 250 EC tablets (Ashbourne Pharmaceuticals Ltd)
11613	Amix 250 capsules (Ashbourne Pharmaceuticals Ltd)
11634	Amix 125 oral suspension (Ashbourne Pharmaceuticals Ltd)
11989	Keflex 250mg capsules (Flynn Pharma Ltd)

Product Code	Product Name
11992	Baxan 500mg capsules (Bristol-Myers Squibb Pharmaceuticals Ltd)
12235	Ceporex 1g Tablet (Galen Ltd)
12248	Cefalexin 125mg/1.25ml paediatric drops
12252	ERYMAX 125 MG SYR
12276	Keflex 500mg Capsule (Eli Lilly and Company Ltd)
12327	AMOXIDIN 500 MG CAP
12330	Erythromycin ethylsuccinate 1g sachets
12378	Amoram 125mg/5ml oral suspension (LPC Medical (UK) Ltd)
12504	Clomocycline 170mg capsules
12541	Imperacin 250mg Tablet (AstraZeneca UK Ltd)
12987	Doxycycline (as hyclate) 50mg capsules with microgranules
13120	Erythromycin ethyl succinate 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
13167	Erythromycin ethyl succinate 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
13216	Amoxicillin 500mg / Clavulanic acid 125mg tablets
13239	Clavulanic acid 125mg with Amoxicillin 500mg tablets
13262	Amoxicillin 250mg / Clavulanic acid 62mg/5ml oral suspension
13285	Amoxicillin 125mg / Clavulanic acid 31mg/5ml oral suspension
13635	Erythromycin ethylsuccinate 250mg sachets
13848	Amoxicillin 125mg sugar free powder
13910	Cefaclor 125mg/5ml Liquid (Generics (UK) Ltd)
14171	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free
14371	Galenamox 250mg capsules (Galen Ltd)
14386	Galenamox 125mg/5ml oral suspension (Galen Ltd)
14396	Galenamox 500mg capsules (Galen Ltd)
14407	Galenamox 250mg/5ml oral suspension (Galen Ltd)
14429	Erythromycin 125mg sprinkle capsules
14511	Erymax sprinkle 125mg Capsule (Elan Pharma)
14514	Zithromax 200mg/5ml oral suspension (Pfizer Ltd)
14557	ERYMIN 250 MG/5ML SUS
14607	Cefaclor 125mg/5ml Liquid (Lagap)
14816	Klaricid Adult 250mg granules sachets (Abbott Laboratories Ltd)
14904	Vibramycin-D 100mg dispersible tablets (Pfizer Ltd)
15071	Nordox 100mg Capsule (Sankyo Pharma UK Ltd)
15148	Amoxil 500mg Dispersible tablet (SmithKline Beecham Plc)
15192	Amoxicillin 400mg / Clavulanic acid 57mg/5ml sugar free oral suspension
15713	Erythromycin ethylsuccinate 500mg sachets
16612	Clavulanic acid 62mg with amoxicillin 250mg/5ml sugar free suspension
16747	Erythroped 250mg Sachets (Abbott Laboratories Ltd)
17093	Bisolvomycin Capsule (Boehringer Ingelheim Ltd)
17150	Ceporex 125mg/1.25ml Drops (Glaxo Laboratories Ltd)
17207	Ilosone 250mg Capsule (Dista Products Ltd)
17226	Economycin 250mg Capsule (DDSA Pharmaceuticals Ltd)
17282	Almodan 125mg/5ml syrup (Teva UK Ltd)
17467	Terramycin 250mg tablets (Pfizer Ltd)
17645	Clarithromycin 250mg granules straws
17693	Tavanic 250mg tablets (Sanofi)
17703	Oxytetramix 250 tablets (Ashbourne Pharmaceuticals Ltd)
17711	Amopen 500mg Capsule (Yorkshire Pharmaceuticals Ltd)
17746	Amoxicillin 375mg soluble tablets
17798	ERYTHROCIN A 1 GM TAB
18243	Distaclor 500mg capsules (Flynn Pharma Ltd)
18451	Cefalexin 1g tablets

Product Code	Product Name
18643	Ilosone 500mg Tablet (Dista Products Ltd)
18652	ERYCEN 250 MG SUS
18682	Ilosone 125mg/5ml Liquid (Dista Products Ltd)
18703	ERYCEN 125 MG SUS
18786	Amix 500 capsules (Ashbourne Pharmaceuticals Ltd)
18930	Flemoxin 375mg Soluble tablet (Paines & Byrne Ltd)
19001	Megaclor 170mg Capsule (Pharmax Ltd)
19133	Cefalexin 250mg capsules (IVAX Pharmaceuticals UK Ltd)
19138	Cefalexin 500mg capsules (Actavis UK Ltd)
19144	Cefalexin 125mg/5ml oral suspension sugar free (Teva UK Ltd)
19152	Cefalexin 250mg capsules (Actavis UK Ltd)
19160	Cefalexin 250mg capsules (Generics (UK) Ltd)
19161	Cefalexin 500mg capsules (Ranbaxy (UK) Ltd)
19184	Cefalexin 500mg capsules (Generics (UK) Ltd)
19209	Co-amoxiclav 250mg/125mg tablets (Actavis UK Ltd)
19330	Ilosone 250mg/5ml Liquid (Dista Products Ltd)
19414	Co-amoxiclav 250mg/125mg tablets (Sandoz Ltd)
19593	AMOXIL PAED 125MG IN 1.25ML
19615	ERYTHROPED FORTE 500mg/5ml
19652	ERYTHROPED
19692	ERYTHROCIN 250
19693	Sustamycin 250mg Capsule (Boehringer Mannheim UK Ltd)
19795	AMOXYCILLIN 250MG/CLAVULANIC ACID 125MG
20409	Cefaclor 250mg/5ml Liquid (Lagap)
20420	Cefaclor 250mg/5ml Liquid (Generics (UK) Ltd)
20432	Clavulanic acid 57mg with amoxicillin 400mg/5ml sugar free suspension
20515	KEFLEX-C 250 MG TAB
20526	KEFLEX-C 125 MG TAB
20881	Cefaclor 375mg modified-release tablets (Ranbaxy (UK) Ltd)
20992	Distaclor MR 375mg tablets (Flynn Pharma Ltd)
21038	Doxatet 100mg Tablet (Manufacturer unknown)
21775	Clavulanic acid 31mg with amoxicillin 125mg/5ml sugar free oral suspension
21799	Almodan 250mg Capsule (Berk Pharmaceuticals Ltd)
21802	Berkmycen 250mg Tablet (Berk Pharmaceuticals Ltd)
21804	Tetracycline 125mg/5ml syrup
21808	Rommix 125mg/5ml Oral suspension sugar free (Ashbourne Pharmaceuticals Ltd)
21810	CYCLODOX CAP 100 mg
21817	DEMIX 100 MG CAP
21827	Almodan 500mg Capsule (Berk Pharmaceuticals Ltd)
21828	Demix 50 capsules (Ashbourne Pharmaceuticals Ltd)
21829	Zoxycil 250mg Capsule (Trinity Pharmaceuticals Ltd)
21835	Kiflone 250mg Capsule (Berk Pharmaceuticals Ltd)
21844	Amix 250 oral suspension (Ashbourne Pharmaceuticals Ltd)
21845	Almodan 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)
21860	Cyclodox 100mg Capsule (Berk Pharmaceuticals Ltd)
21877	KEFLEX
21878	Demix 100 capsules (Ashbourne Pharmaceuticals Ltd)
21902	KEFLEX
21956	DISTACLOR
21963	Almodan 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)
21979	Kiflone 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)
21982	AMOXYCILLIN TRIHYDRATE SACHET

Product Code	Product Name
22015	Respillin 125mg/5ml Oral solution (OPD Pharm)
22016	Almodan 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)
22017	Respillin 125mg/5ml Oral solution (OPD Pharm)
22029	Amiclav 250mg/125mg tablets (Ashbourne Pharmaceuticals Ltd)
22042	Distaclor 250mg/5ml oral suspension (Flynn Pharma Ltd)
22088	CEPOREX PAEDIATRIC 125MG IN 1.25ML
22293	AMOXYCILLIN TRIHYDRATE SACHET
22321	Cefalexin 500mg tablets (Generics (UK) Ltd)
22415	Amoram 500mg capsules (LPC Medical (UK) Ltd)
22438	Amoram 250mg/5ml oral suspension (LPC Medical (UK) Ltd)
22469	AMOXYCILLIN 125mg/31mg CLAVULANIC ACID
22632	ERYTHROCIN B-PACK 10 FILMTABS 500 MG TAB
22653	ERYTHROCIN 100 MG SYR
23017	Erycen 500mg Tablet (Berk Pharmaceuticals Ltd)
23185	ERYTHROPED SUGAR FREE SACHET
23238	Amoxicillin 125mg/5ml oral suspension (IVAX Pharmaceuticals UK Ltd)
23243	ERYTHROPED P.I.
23244	Ilotycin 250mg Tablet (Eli Lilly and Company Ltd)
23405	Doxylar 100mg capsules (Sandoz Ltd)
23432	Doxylar 50mg capsules (Sandoz Ltd)
23740	Amoxicillin 500mg capsules (Generics (UK) Ltd)
23819	Doxycycline (as hyclate) 50mg capsules with microgranules
23954	Erythrolar 500mg Tablet (Lagap)
23967	Amoxicillin 250mg capsules (Teva UK Ltd)
24006	Clavulanic acid 31mg with amoxcillin 125mg/5ml oral suspension
24090	Cefalexin 250mg capsules (PLIVA Pharma Ltd)
24093	Clavulanic acid with amoxicillin dispersible tablets
24097	Rondomycin 150mg Capsule (Pfizer Ltd)
24126	Doxycycline 100mg capsules (IVAX Pharmaceuticals UK Ltd)
24127	Erythromycin 250mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)
24129	Erythromycin 250mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)
24149	Doxycycline 100mg capsules (A A H Pharmaceuticals Ltd)
24150	Amoxicillin 125mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)
24200	Respillin 500mg Capsule (OPD Pharm)
24203	Respillin 250mg Capsule (OPD Pharm)
24220	Arpimycin 250mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)
24288	AMOXIL
24396	Flemoxin 750mg Soluble tablet (Paines & Byrne Ltd)
24618	Keflex 500mg capsules (Flynn Pharma Ltd)
25016	VIBRAMYCIN
25017	TETRACYCLINE
25034	AMOXYCILLIN 125mg/62mg CLAVULANIC ACID
25127	Avelox 400mg tablets (Bayer Plc)
25278	Rommix 500mg Tablet (Ashbourne Pharmaceuticals Ltd)
25280	Tiloryth 250mg gastro-resistant capsules (Tillomed Laboratories Ltd)
25370	Ranclav 375mg tablets (Ranbaxy (UK) Ltd)
25384	Distaclor 125mg/5ml oral suspension (Flynn Pharma Ltd)
25484	Amoxicillin 250mg capsules (A A H Pharmaceuticals Ltd)
25595	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)
25751	Erythromycin ethylsuccinate (coated) 250mg/5ml oral suspension sugar free
26059	Clarithromycin 187.5mg granules straws

Product Code	Product Name
26111	Economycin 250mg Tablet (DDSA Pharmaceuticals Ltd)
26157	Amoxicillin 500mg capsules (Actavis UK Ltd)
26207	Keftid 250mg capsules (Co-Pharma Ltd)
26233	Keftid 125mg/5ml oral suspension (Co-Pharma Ltd)
26236	Keftid 500mg capsules (Co-Pharma Ltd)
26262	Zoxycil 500mg Capsule (Trinity Pharmaceuticals Ltd)
26289	Bacticlor MR 375mg tablets (Ranbaxy (UK) Ltd)
26365	Erythromycin 500mg Tablet (IVAX Pharmaceuticals UK Ltd)
26392	Vibrox 100mg capsules (Kent Pharmaceuticals Ltd)
26519	AMOXIL
26658	AUGMENTIN DISPERSIBLE 250/125
26669	ERYMAX
26747	Doxycycline 100mg Tablet (Neo Laboratories Ltd)
26989	Kiflone 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)
26992	Kiflone 500mg Tablet (Berk Pharmaceuticals Ltd)
27016	CIPROFLOXACIN
27017	Kiflone 500mg Capsule (Berk Pharmaceuticals Ltd)
27072	Keflex 125mg/5ml oral suspension (Flynn Pharma Ltd)
27195	TERRAMYCIN SYR
27203	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Teva UK Ltd)
27254	Tenkorex 500mg Capsule (OPD Pharm)
27495	Arpimycin 125mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)
27504	Primacine 500mg/5ml Liquid (Pinewood Healthcare)
27681	Ranclav 125mg/31mg/5ml SF oral suspension (Ranbaxy (UK) Ltd)
27714	Amrit 250mg Capsule (BHR Pharmaceuticals Ltd)
27725	Amoxicillin 250mg/5ml oral suspension (Teva UK Ltd)
27768	Erythrolar 250mg Tablet (Lagap)
27886	AMOXYCILLIN 250/CLAVULANIC ACID 125 DISP
27897	AMOXYCILLIN
28130	Amoxicillin 3g oral powder sachets sugar free (Teva UK Ltd)
28349	Clarosip 125mg granules for oral suspension straws (Grunenthal Ltd)
28544	Ciprofloxaxin 400mg/200ml in glucose 5% infusion
28722	Keflex 250mg/5ml oral suspension (Flynn Pharma Ltd)
28870	Amoxicillin 125mg/5ml oral suspension (Teva UK Ltd)
28871	Co-amoxiclav 250mg/125mg tablets (IVAX Pharmaceuticals UK Ltd)
28872	Amoxicillin 125mg/5ml Mixture (Crosspharma Ltd)
28874	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)
28875	Amoxicillin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)
28882	Amoxicillin 250mg Capsule (Crosspharma Ltd)
29061	AMOXIL SF
29154	Erythromycin 250mg Capsule (Actavis UK Ltd)
29202	Cefalexin 500mg tablets (A A H Pharmaceuticals Ltd)
29281	Cefalexin 500mg capsules (Teva UK Ltd)
29337	Amoxicillin 125mg/5ml Oral solution (Neo Laboratories Ltd)
29343	Ciprofloxacin 250mg tablets (A A H Pharmaceuticals Ltd)
29344	Erythromycin 250mg gastro-resistant tablets (Actavis UK Ltd)
29353	Co-amoxiclav 500mg/125mg tablets (Teva UK Ltd)
29356	Co-amoxiclav 500mg/125mg tablets (IVAX Pharmaceuticals UK Ltd)
29458	Ciprofloxacin 500mg tablets (A A H Pharmaceuticals Ltd)
29463	Amoxicillin 500mg capsules (IVAX Pharmaceuticals UK Ltd)
29464	Cefalexin 250mg/5ml oral suspension (Generics (UK) Ltd)
29472	Ciprofloxacin 750mg tablets (A A H Pharmaceuticals Ltd)

Product Code	Product Name
29697	Amopen 125mg/5ml Liquid (Yorkshire Pharmaceuticals Ltd)
29748	Cefalexin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
29858	Amoxicillin 125mg/5ml oral suspension sugar free (Sandoz Ltd)
30177	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)
30234	Erythromycin ethylsuccinate 125mg sachets
30498	Amopen 250mg Capsule (Yorkshire Pharmaceuticals Ltd)
30520	Primacine 125mg/5ml Liquid (Pinewood Healthcare)
30528	Amoxicillin 250mg capsules (Kent Pharmaceuticals Ltd)
30705	Co-amoxiclav 500mg/125mg tablets (Generics (UK) Ltd)
30707	Ciprofloxacin 500mg tablets (Generics (UK) Ltd)
30739	Doxycycline 100mg capsules (Teva UK Ltd)
30743	Amoxicillin 250mg capsules (Ranbaxy (UK) Ltd)
30745	Amoxicillin 250mg capsules (Generics (UK) Ltd)
30771	Cefaclor 500mg capsules (Ranbaxy (UK) Ltd)
30772	Cefaclor 250mg capsules (Ranbaxy (UK) Ltd)
30783	Co-amoxiclav 250mg/125mg tablets (Ranbaxy (UK) Ltd)
30786	Co-amoxiclav 250mg/125mg tablets (A A H Pharmaceuticals Ltd)
30980	Erythromycin ethyl succinate 500mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
31014	Amoxicillin 125mg/5ml oral suspension sugar free (Generics (UK) Ltd)
31110	Keflex 500mg tablets (Flynn Pharma Ltd)
31286	Amoxymed 125mg/5ml Oral solution (Medipharma Ltd)
31379	Ketek 400mg tablets (Sanofi)
31423	Amopen 250mg/5ml Liquid (Yorkshire Pharmaceuticals Ltd)
31425	TETRACYCLINE HCL/PANCREATIC CONCENTRATE CAP
31428	Retcin 250mg Tablet (DDSA Pharmaceuticals Ltd)
31514	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)
31530	Erythromycin 250mg gastro-resistant tablets (Ranbaxy (UK) Ltd)
31535	Amoxicillin 250mg/5ml oral suspension sugar free (Generics (UK) Ltd)
31571	AMOXYCILLIN
31661	Amoxicillin 250mg Capsule (Co-Pharma Ltd)
31689	Clarosip 187.5mg granules for oral suspension straws (Grunenthal Ltd)
31690	Clarosip 250mg granules for oral suspension straws (Grunenthal Ltd)
31801	Amoxicillin 500mg capsules (Sandoz Ltd)
31825	Cefalexin 250mg tablets (IVAX Pharmaceuticals UK Ltd)
31827	Cefalexin 500mg tablets (IVAX Pharmaceuticals UK Ltd)
32066	Doxycycline 100mg capsules (Generics (UK) Ltd)
32112	Norfloxacin 400mg tablets (Genus Pharmaceuticals Ltd)
32181	Cefalexin 125mg/5ml oral suspension (Actavis UK Ltd)
32235	Cefaclor 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)
32419	Doxycycline 50mg capsules (Teva UK Ltd)
32505	AMOXYCILLIN
32622	Amoxicillin 125mg/5ml oral suspension (Generics (UK) Ltd)
32640	Amoxicillin 250mg/5ml oral suspension (IVAX Pharmaceuticals UK Ltd)
32642	Cefalexin 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
32643	Cefalexin 500mg capsules (A A H Pharmaceuticals Ltd)
32872	Amoxicillin 250mg Capsule (Mepra-Pharm)
32898	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
32902	Erythromycin ethyl succinate 250mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
32910	Co-amoxiclav 500mg/125mg tablets (Sandoz Ltd)
33109	Amrit 125mg/5ml Liquid (BHR Pharmaceuticals Ltd)

Product Code	Product Name
33110	Amrit 250mg/5ml Liquid (BHR Pharmaceuticals Ltd)
33112	Amrit 500mg Capsule (BHR Pharmaceuticals Ltd)
33165	Amoxicillin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
33222	Amoxicillin 250mg Capsule (Lagap)
33248	Erythromycin 125mg/5ml Liquid (IVAX Pharmaceuticals UK Ltd)
33304	Kerymax 250mg gastro-resistant capsules (Kent Pharmaceuticals Ltd)
33329	Cefalexin 125mg/5ml oral suspension (Teva UK Ltd)
33334	Cefalexin 250mg tablets (A A H Pharmaceuticals Ltd)
33343	Amoxicillin 250mg capsules (Actavis UK Ltd)
33383	Amoxicillin 3g oral powder sachets sugar free (A A H Pharmaceuticals Ltd)
33570	Amoxicillin 250mg/5ml Mixture (Crosspharma Ltd)
33671	Doxycycline 100mg capsules (Kent Pharmaceuticals Ltd)
33685	Erythromycin 250mg gastro-resistant tablets (Teva UK Ltd)
33686	Erythromycin 250mg gastro-resistant capsules (A A H Pharmaceuticals Ltd)
33689	Amoxicillin 250mg/5ml oral suspension (Generics (UK) Ltd)
33690	Amoxicillin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
33692	Amoxicillin 500mg capsules (A A H Pharmaceuticals Ltd)
33693	Co-amoxiclav 250mg/125mg tablets (Kent Pharmaceuticals Ltd)
33694	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Generics (UK) Ltd)
33695	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Generics (UK) Ltd)
33696	Amoxicillin 125mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
33697	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
33699	Amoxicillin 250mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)
33701	Co-amoxiclav 500mg/125mg tablets (A A H Pharmaceuticals Ltd)
33703	Erythromycin 250mg gastro-resistant tablets (Abbott Laboratories Ltd)
33705	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Teva UK Ltd)
33706	Amoxicillin 500mg capsules (Kent Pharmaceuticals Ltd)
33707	Ofloxacin 400mg tablets (Teva UK Ltd)
33802	Cefalexin 250mg Capsule (Berk Pharmaceuticals Ltd)
33888	Azithromycin 250mg tablets
33989	Ciprofloxacin 250mg tablets (Generics (UK) Ltd)
34001	Amoxicillin 500mg capsules (Teva UK Ltd)
34011	Tetracycline 250mg capsules
34040	Oxytetracycline 250mg tablets (Actavis UK Ltd)
34042	Amoxicillin 250mg capsules (IVAX Pharmaceuticals UK Ltd)
34044	Oxytetracycline 250mg tablets (A A H Pharmaceuticals Ltd)
34133	Cefalexin 250mg/5ml oral suspension sugar free (Teva UK Ltd)
34141	Oxytetracycline 250mg tablets (Teva UK Ltd)
34175	Doxycycline 50mg capsules (A A H Pharmaceuticals Ltd)
34189	Erythromycin 250mg Tablet (C P Pharmaceuticals Ltd)
34231	Erythromycin 125mg/5ml Liquid (Berk Pharmaceuticals Ltd)
34232	Amoxicillin 250mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
34234	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Teva UK Ltd)
34253	Cefalexin 250mg capsules (A A H Pharmaceuticals Ltd)
34297	Co-amoxiclav 250mg/125mg tablets (Generics (UK) Ltd)
34300	Doxycycline 100mg capsules (Actavis UK Ltd)
34308	Ciprofloxacin 250mg tablets (Actavis UK Ltd)
34322	Ciprofloxacin 500mg Tablet (Niche Generics Ltd)
34334	Erythromycin 250mg gastro-resistant tablets (Generics (UK) Ltd)
34336	Oxytetracycline 250mg tablets (IVAX Pharmaceuticals UK Ltd)
34384	Amoxicillin 125mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)

Product Code	Product Name
34391	Ofloxacin 400mg tablets (Sandoz Ltd)
34394	Clarithromycin 250mg tablets (Generics (UK) Ltd)
34423	Doxycycline 100mg Capsule (PLIVA Pharma Ltd)
34435	Amoxicillin 250mg Capsule (DDSA Pharmaceuticals Ltd)
34448	Ciprofloxacin 250mg tablets (Niche Generics Ltd)
34478	Ciprofloxacin 250mg tablets (Teva UK Ltd)
34479	Erythromycin 250mg gastro-resistant tablets (Sovereign Medical Ltd)
34493	Co-amoxiclav 500mg/125mg tablets (Ranbaxy (UK) Ltd)
34494	Ciprofloxacin 500mg tablets (Wockhardt UK Ltd)
34512	Erythromycin 250mg gastro-resistant capsules (Teva UK Ltd)
34523	Ofloxacin 200mg tablets (Sandoz Ltd)
34533	Clarithromycin 250mg tablets (Teva UK Ltd)
34541	Ofloxacin 200mg tablets (Teva UK Ltd)
34559	Ciprofloxacin 250mg tablets (Sandoz Ltd)
34594	Doxycycline 100mg Capsule (Neo Laboratories Ltd)
34605	Ciprofloxacin 500mg tablets (Actavis UK Ltd)
34608	Clarithromycin 500mg tablets (Generics (UK) Ltd)
34638	Amoxicillin 125mg/5ml oral suspension sugar free (Teva UK Ltd)
34647	Ciprofloxacin 250mg Tablet (Neo Laboratories Ltd)
34650	Clarithromycin 250mg tablets (A A H Pharmaceuticals Ltd)
34655	Ciprofloxacin 250mg tablets (Wockhardt UK Ltd)
34679	Amoxicillin 125mg/5ml oral suspension sugar free (Actavis UK Ltd)
34680	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Ranbaxy (UK) Ltd)
34694	Ciprofloxacin 250mg tablets (PLIVA Pharma Ltd)
34714	Amoxicillin 250mg Capsule (Neo Laboratories Ltd)
34734	Co-amoxiclav 250mg/125mg tablets (Teva UK Ltd)
34760	Amoxicillin 250mg/5ml oral suspension (Actavis UK Ltd)
34765	Doxycycline 50mg capsules (Generics (UK) Ltd)
34775	Amoxicillin 250mg/5ml oral suspension sugar free (Teva UK Ltd)
34779	Erythromycin ethyl succinate 125mg/5ml oral suspension (Sandoz Ltd)
34795	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)
34811	Clarithromycin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)
34819	Ofloxacin 400mg tablets (Generics (UK) Ltd)
34837	Erythromycin 250mg Gastro-resistant tablet (Co-Pharma Ltd)
34838	Cefaclor 375mg modified-release tablets (A A H Pharmaceuticals Ltd)
34852	Amoxicillin 500mg capsules (Ranbaxy (UK) Ltd)
34853	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Teva UK Ltd)
34855	Amoxicillin 250mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)
34857	Amoxicillin 125mg/5ml oral suspension (Actavis UK Ltd)
34869	Erythromycin 500mg Tablet (C P Pharmaceuticals Ltd)
34873	Erythromycin 250mg Tablet (Berk Pharmaceuticals Ltd)
34885	Amoxicillin 500mg Capsule (DDSA Pharmaceuticals Ltd)
34888	Oxytetracycline 250mg Tablet (C P Pharmaceuticals Ltd)
34912	Amoxicillin 500mg Capsule (Neo Laboratories Ltd)
34913	Cefaclor 125mg/5ml Oral suspension (Genus Pharmaceuticals Ltd)
34972	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Sandoz Ltd)
34973	Ciprofloxacin 750mg Tablet (Niche Generics Ltd)
34974	Clarithromycin 500mg tablets (Teva UK Ltd)
35570	Amoxicillin 500mg Capsule (Crosspharma Ltd)
36054	Amoxicillin 125mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)
36330	Cefalexin 250mg tablets (Actavis UK Ltd)

Product Code	Product Name
36514	Arpimycin 250mg/5ml Oral suspension (Rosemont Pharmaceuticals Ltd)
36544	Arpimycin 125mg/5ml Oral suspension (Rosemont Pharmaceuticals Ltd)
36569	Cefalexin 500mg capsules (Kent Pharmaceuticals Ltd)
36578	Cefalexin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)
36599	Cefalexin 250mg capsules (Ranbaxy (UK) Ltd)
36689	CHLORTETRACYCLINE HCl SYR
36701	Cefalexin 250mg tablets (Generics (UK) Ltd)
37022	Arpimycin 500mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)
37304	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)
37694	Erythromycin estolate 500mg tablets
37755	Amoxicillin 250mg/5ml Oral suspension (Sandoz Ltd)
37796	Erythromycin estolate 125mg/5ml suspension
38163	Clarithromycin 500mg tablets (A A H Pharmaceuticals Ltd)
38684	Amoxicillin 500mg Capsule (C P Pharmaceuticals Ltd)
38997	Klaricid Paediatric 125mg/5ml oral suspension (Abbott Laboratories Ltd)
39010	Klaricid Paediatric 250mg/5ml oral suspension (Abbott Laboratories Ltd)
39118	Primacine 250mg/5ml Liquid (Pinewood Healthcare)
39417	Cefalexin 125mg/5ml oral suspension (Generics (UK) Ltd)
39613	Erythrocin 500 tablets (AMCo)
39616	Erythrocin 250 tablets (AMCo)
39623	Erythroped PI SF 125mg/5ml oral suspension (AMCo)
39632	Erythroped A 500mg tablets (AMCo)
39642	Erythroped Forte SF 500mg/5ml oral suspension (AMCo)
39669	Erythroped SF 250mg/5ml oral suspension (AMCo)
39703	Cefaclor 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
39913	Ciprofloxacin 100mg tablets (Sandoz Ltd)
40073	Erythromycin estolate 250mg/5ml suspension
40148	Co-amoxiclav 500mg/125mg tablets (Kent Pharmaceuticals Ltd)
40168	Amoxicillin 3g oral powder sachets sugar free (Kent Pharmaceuticals Ltd)
40218	Azithromycin 500mg tablets (Teva UK Ltd)
40238	Amoxicillin 250mg/5ml Mixture (Mepra-Pharm)
40243	Amoxicillin 250mg/5ml oral suspension sugar free (Actavis UK Ltd)
40320	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Ranbaxy (UK) Ltd)
40391	Doxycycline 50mg capsules (IVAX Pharmaceuticals UK Ltd)
40483	Oxytetracycline 250mg tablets (Sandoz Ltd)
40747	Cefalexin 250mg chewable tablets
40784	Clarithromycin 500mg tablets (Sandoz Ltd)
40884	Ceporex 250mg capsules (Co-Pharma Ltd)
40914	Ceporex 500mg tablets (Co-Pharma Ltd)
40915	Ceporex 500mg capsules (Co-Pharma Ltd)
40945	Ceporex 250mg/5ml syrup (Co-Pharma Ltd)
41049	Ceporex 250mg tablets (Co-Pharma Ltd)
41090	Amoxicillin 250mg/5ml oral suspension (Almus Pharmaceuticals Ltd)
41106	Ceporex 125mg/5ml syrup (Co-Pharma Ltd)
41192	Cefalexin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)
41230	Ceporex 500mg/5ml syrup (Co-Pharma Ltd)
41389	Erythoden 250mg/5ml Liquid (Stevenden Healthcare)
41453	Clarithromycin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)
41547	Tetracycline 250mg Capsule (Berk Pharmaceuticals Ltd)
41560	Doxycycline 100mg Capsule (IVAX Pharmaceuticals UK Ltd)
41561	Ciprofloxacin 250mg tablets (IVAX Pharmaceuticals UK Ltd)
41584	Erythromycin 250mg/5ml Liquid (IVAX Pharmaceuticals UK Ltd)

Product Code	Product Name
41604	Erythromycin 500mg Tablet (Hillcross Pharmaceuticals Ltd)
41605	Doxycycline 100mg Capsule (Sandoz Ltd)
41636	Tetracycline 250mg tablets (Actavis UK Ltd)
41734	Amoxicillin 3g Powder (Actavis UK Ltd)
41736	Cefalexin 250mg capsules (Kent Pharmaceuticals Ltd)
41818	Amoxicillin 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)
41825	Cefalexin 250mg/5ml Oral solution (C P Pharmaceuticals Ltd)
41835	Amoxicillin 125mg Powder (IVAX Pharmaceuticals UK Ltd)
41853	Keftid 250mg/5ml oral suspension (Co-Pharma Ltd)
41968	Cefalexin 250mg/5ml oral suspension (Teva UK Ltd)
42008	Cefalexin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
42174	Ciprofloxacin 500mg tablets (IVAX Pharmaceuticals UK Ltd)
42227	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
42240	Amoxicillin 125mg/5ml Oral solution (Co-Pharma Ltd)
42296	Erythromycin 250mg gastro-resistant tablets (Dr Reddy's Laboratories (UK) Ltd)
42485	Clavulanic acid 62mg with amoxicillin 250mg/5ml oral suspension
42507	Ciprofloxacin 100mg tablets (A A H Pharmaceuticals Ltd)
42545	Amoxicillin 125mg/5ml oral suspension (Almus Pharmaceuticals Ltd)
42659	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)
42661	Erythromycin 250mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)
42732	Amoxicillin 250mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)
42809	Amoxicillin 250mg Capsule (C P Pharmaceuticals Ltd)
42815	Amoxicillin 250mg/5ml Mixture (Celltech Pharma Europe Ltd)
42822	Amoxicillin 125mg/5ml Mixture (Celltech Pharma Europe Ltd)
43229	Amoxicillin 125mg/5ml Oral suspension (Sandoz Ltd)
43400	Clamelle 500mg tablets (Actavis UK Ltd)
43425	Cefaclor 500mg capsules (A A H Pharmaceuticals Ltd)
43517	Ciprofloxacin 750mg tablets (Actavis UK Ltd)
43538	Tetracycline 250mg tablets (A A H Pharmaceuticals Ltd)
43548	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
43557	Ciprofloxacin 500mg tablets (PLIVA Pharma Ltd)
43797	Ciprofloxacin 500mg tablets (Sandoz Ltd)
43814	Ciprofloxacin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)
44154	Co-amoxiclav 500mg/125mg tablets (Zentiva)
44755	Cefalexin 500mg Capsule (Berk Pharmaceuticals Ltd)
44854	Amoxicillin 500mg Capsule (Lagap)
45221	Cefalexin 250mg/5ml oral suspension (Actavis UK Ltd)
45263	Ofloxacin 400mg tablets (A A H Pharmaceuticals Ltd)
45267	Amoxicillin 250mg Capsule (Regent Laboratories Ltd)
45271	Tetracycline 250mg Tablet (Numark Management Ltd)
45285	Ciprofloxacin 500mg tablets (Teva UK Ltd)
45317	Amoxicillin 250mg/5ml Oral solution (Neo Laboratories Ltd)
45341	Ciprofloxacin 500mg Tablet (Neo Laboratories Ltd)
45591	Clarie XL 500mg tablets (Teva UK Ltd)
45795	Clarithromycin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
45870	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Pinewood Healthcare)
46154	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)
46488	Clarithromycin 500mg tablets (Ranbaxy (UK) Ltd)
46695	Azithromycin 500mg Tablet (Hillcross Pharmaceuticals Ltd)
46696	Erythromycin ethyl succinate 250mg/5ml oral suspension (Sandoz Ltd)
46807	Doxycycline 100mg capsules (Almus Pharmaceuticals Ltd)

Product Code	Product Name
46915	Co-amoxiclav 250mg/125mg tablets (Zentiva)
46918	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Sandoz Ltd)
46973	Cefaclor 250mg/5ml Oral suspension (Genus Pharmaceuticals Ltd)
47126	Erythromycin ethyl succinate 125mg/5ml oral suspension (Pinewood Healthcare)
47163	Cefalexin 250mg tablets (Arrow Generics Ltd)
47242	Erythromycin 250mg/5ml Liquid (C P Pharmaceuticals Ltd)
47582	Clarithromycin 250mg tablets (Sandoz Ltd)
47640	Amoxicillin 500mg capsules (Almus Pharmaceuticals Ltd)
47676	Erythromycin 500mg/5ml Liquid (C P Pharmaceuticals Ltd)
48006	Amoxicillin 250mg capsules (Sandoz Ltd)
48017	Erythoden 125mg/5ml Liquid (Stevenden Healthcare)
48023	Clarithromycin 500mg tablets (Actavis UK Ltd)
48025	Cefaclor 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)
48031	Ciprofloxacin 100mg tablets (Almus Pharmaceuticals Ltd)
48038	Amoxicillin 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
48095	Doxycycline 50mg capsules (Actavis UK Ltd)
48100	Tetracycline 250mg tablets (Teva UK Ltd)
48101	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Focus Pharmaceuticals Ltd)
48147	Co-amoxiclav 250mg/125mg tablets (Almus Pharmaceuticals Ltd)
48163	Clarithromycin 250mg tablets (Actavis UK Ltd)
48683	Augmentin 375mg tablets (Lexon (UK) Ltd)
49048	Augmentin 375mg tablets (Waymade Healthcare Plc)
49063	Augmentin 375mg tablets (DE Pharmaceuticals)
49065	Amoxicillin 250mg/5ml oral suspension sugar free (Bristol Laboratories Ltd)
49301	Erythrolar 500mg tablets (Ennogen Pharma Ltd)
49321	Augmentin 625mg tablets (Sigma Pharmaceuticals Plc)
49374	Augmentin 375mg tablets (Mawdsley-Brooks & Company Ltd)
49445	Ciprofloxacin 500mg tablets (Almus Pharmaceuticals Ltd)
49530	Azithromycin 200mg/5ml oral suspension (Sandoz Ltd)
49590	Amoxil 500mg capsules (Lexon (UK) Ltd)
49610	Co-amoxiclav 500mg/125mg tablets (Medreich Plc)
49656	Augmentin 625mg tablets (Lexon (UK) Ltd)
49683	Augmentin 625mg tablets (Waymade Healthcare Plc)
49737	Doxycycline 100mg capsules (Alliance Healthcare (Distribution) Ltd)
49839	Ciproxin 500mg tablets (Waymade Healthcare Plc)
49939	Clarithromycin 500mg tablets (Alliance Healthcare (Distribution) Ltd)
49952	Erythromycin 250mg gastro-resistant capsules (Phoenix Healthcare Distribution Ltd)
49978	Erythromycin ethyl succinate 125mg/5ml oral suspension (Focus Pharmaceuticals Ltd)
50002	Amoxicillin 125mg/5ml oral suspension (Bristol Laboratories Ltd)
50055	Ciprofloxacin 500mg tablets (DE Pharmaceuticals)
50205	Erythrolar 250mg tablets (Ennogen Pharma Ltd)
50223	Erythrocin 500 tablets (Stephar (U.K.) Ltd)
50279	Augmentin 625mg tablets (DE Pharmaceuticals)
50341	Co-amoxiclav 500mg/125mg tablets (Alliance Healthcare (Distribution) Ltd)
50446	Co-amoxiclav 250mg/125mg tablets (Phoenix Healthcare Distribution Ltd)
50580	Erythromycin 250mg gastro-resistant capsules (Actavis UK Ltd)
50595	Augmentin 125/31 SF oral suspension (Mawdsley-Brooks & Company Ltd)
50601	Ciprofloxacin 250mg tablets (Accord Healthcare Ltd)
50693	Erythrocin 500 tablets (Sigma Pharmaceuticals Plc)
50694	Erythromycin 250mg gastro-resistant capsules (Alliance Healthcare (Distribution) Ltd)
50742	Co-amoxiclav 500mg/125mg tablets (Actavis UK Ltd)

Product Code	Product Name
50946	Clarithromycin 250mg tablets (Sigma Pharmaceuticals Plc)
50948	Erythromycin ethyl succinate 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)
51154	Clarithromycin 250mg tablets (Kent Pharmaceuticals Ltd)
51164	Augmentin 125/31 SF oral suspension (Waymade Healthcare Plc)
51194	Augmentin-Duo 400/57 oral suspension (Sigma Pharmaceuticals Plc)
51382	Amoxicillin 250mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)
51426	Clarithromycin 500mg tablets (Accord Healthcare Ltd)
51436	Amoxil 500mg capsules (Mawdsley-Brooks & Company Ltd)
51536	Amoxicillin 250mg capsules (Milpharm Ltd)
51537	Ciprofloxacin 250mg tablets (Alliance Healthcare (Distribution) Ltd)
51623	Co-amoxiclav 250mg/125mg tablets (Alliance Healthcare (Distribution) Ltd)
51637	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
51678	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)
51831	Clarithromycin 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)
51984	Erythrocin 500 tablets (Mawdsley-Brooks & Company Ltd)
52029	Zithromax 250mg capsules (Mawdsley-Brooks & Company Ltd)
52058	Amoxicillin 500mg capsules (Medreich Plc)
52099	Ciprofloxacin 750mg tablets (Bristol Laboratories Ltd)
52122	Amoxicillin 125mg/5ml oral suspension sugar free (Bristol Laboratories Ltd)
52158	Clarithromycin 250mg tablets (Alliance Healthcare (Distribution) Ltd)
52177	Ciproxin 500mg tablets (Sigma Pharmaceuticals Plc)
52207	Augmentin 625mg tablets (Mawdsley-Brooks & Company Ltd)
52282	Cefalexin 250mg capsules (Milpharm Ltd)
52283	Cefalexin 250mg capsules (Arrow Generics Ltd)
52309	Ciprofloxacin 100mg tablets (Sigma Pharmaceuticals Plc)
52353	Ciproxin 250mg tablets (DE Pharmaceuticals)
52411	Klaricid 250mg tablets (Necessity Supplies Ltd)
52428	Erythromycin 250mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)
52501	Ciprofloxacin 500mg tablets (Accord Healthcare Ltd)
52616	Ciprofloxacin 500mg tablets (Arrow Generics Ltd)
52666	Augmentin 250/62 SF oral suspension (Sigma Pharmaceuticals Plc)
52685	Amoxicillin 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)
52719	Clarithromycin 250mg tablets (Apotex UK Ltd)
52771	Amoxicillin 500mg capsules (Bristol Laboratories Ltd)
52807	Ciproxin 500mg tablets (Mawdsley-Brooks & Company Ltd)
52820	Amoxicillin 500mg capsules (Alliance Healthcare (Distribution) Ltd)
52851	Cefalexin 500mg capsules (Alliance Healthcare (Distribution) Ltd)
52857	Amoxicillin 125mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)
52860	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
52906	Erythromycin 250mg gastro-resistant tablets (Alliance Healthcare (Distribution) Ltd)
52952	Erythromycin 250mg gastro-resistant tablets (Co-Pharma Ltd)
52967	Vibramycin-D 100mg dispersible tablets (Stephar (U.K.) Ltd)
53004	Erythrocin 500 tablets (Necessity Supplies Ltd)
53078	Amoxicillin 125mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
53086	Clarithromycin 250mg tablets (DE Pharmaceuticals)
53088	Ciprofloxacin 500mg tablets (Dr Reddy's Laboratories (UK) Ltd)
53109	Clarithromycin 500mg tablets (Somex Pharma)
53117	Tetracycline 250mg tablets (Almus Pharmaceuticals Ltd)
53135	Vibramycin-D 100mg dispersible tablets (Waymade Healthcare Plc)
53144	Clarithromycin 250mg tablets (Wockhardt UK Ltd)
53153	Clarithromycin 250mg tablets (Phoenix Healthcare Distribution Ltd)

Product Code	Product Name
53168	Clarithromycin 125mg/5ml oral suspension (Sandoz Ltd)
53179	Clarithromycin 250mg/5ml oral suspension (Sandoz Ltd)
53310	Doxycycline 100mg capsules (Sigma Pharmaceuticals Plc)
53449	Erythrocin 500 tablets (Lexon (UK) Ltd)
53519	Ciproxin 250mg tablets (Lexon (UK) Ltd)
53609	Co-amoxiclav 500mg/125mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)
53627	Amoxicillin 500mg capsules (Accord Healthcare Ltd)
53641	Ciprofloxacin 500mg tablets (Co-Pharma Ltd)
53688	Clarithromycin 250mg tablets (Ranbaxy (UK) Ltd)
53703	Clarithromycin 500mg tablets (Kent Pharmaceuticals Ltd)
53715	Clarithromycin 500mg tablets (Almus Pharmaceuticals Ltd)
53776	Clarithromycin 500mg tablets (DE Pharmaceuticals)
53850	Azithromycin 200mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
53875	Clarithromycin 500mg tablets (Tillomed Laboratories Ltd)
53878	Ciprofloxacin 500mg tablets (Ranbaxy (UK) Ltd)
53924	Amoxicillin 250mg/5ml oral suspension (Sigma Pharmaceuticals Plc)
53942	Amoxicillin 125mg / Clavulanic acid 62.5mg/5ml oral suspension
53945	Cefalexin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)
53973	Doxycycline 50mg capsules (Alliance Healthcare (Distribution) Ltd)
53986	Erythromycin 250mg gastro-resistant tablets (Medreich Plc)
53996	Co-amoxiclav 500mg/125mg tablets (Aurobindo Pharma Ltd)
54052	Co-amoxiclav 125mg/31mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
54098	Erythroped A 500mg tablets (Lexon (UK) Ltd)
54185	Amoxicillin 250mg capsules (Wockhardt UK Ltd)
54208	Clarithromycin 250mg/5ml oral suspension (Sigma Pharmaceuticals Plc)
54214	Tetracycline 250mg tablets (Alliance Healthcare (Distribution) Ltd)
54222	Amoxicillin 250mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
54241	Clarithromycin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
54269	Clarithromycin 250mg tablets (Somex Pharma)
54271	Amoxicillin 250mg capsules (Mawdsley-Brooks & Company Ltd)
54302	Ciprofloxacin 250mg tablets (Medreich Plc)
54324	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Actavis UK Ltd)
54393	Ciprofloxacin 250mg tablets (Arrow Generics Ltd)
54452	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
54472	Clarithromycin 250mg tablets (Accord Healthcare Ltd)
54491	Amoxicillin 250mg capsules (Bristol Laboratories Ltd)
54529	Clarithromycin 500mg Modified-release tablet (Hillcross Pharmaceuticals Ltd)
54555	Ciprofloxacin 100mg tablets (DE Pharmaceuticals)
54591	Co-amoxiclav 500mg/125mg tablets (Phoenix Healthcare Distribution Ltd)
54674	Ciprofloxacin 100mg tablets (Phoenix Healthcare Distribution Ltd)
54701	Ciprofloxacin 250mg tablets (Bristol Laboratories Ltd)
54708	Co-amoxiclav 250mg/62mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
54725	Amoxicillin 500mg capsules (Milpharm Ltd)
54732	Co-amoxiclav 125mg/31mg/5ml oral suspension (Generics (UK) Ltd)
54780	Co-amoxiclav 250mg/62mg/5ml oral suspension (Generics (UK) Ltd)
54796	Amoxicillin 250mg capsules (Boston Healthcare Ltd)
54808	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)
54864	Cefalexin 250mg capsules (Alliance Healthcare (Distribution) Ltd)
54882	Clarithromycin 250mg tablets (Almus Pharmaceuticals Ltd)
54897	Clarithromycin 250mg tablets (Tillomed Laboratories Ltd)
54903	Clarithromycin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)

Product Code	Product Name
54955	Cefalexin 500mg capsules (Milpharm Ltd)
55018	Amoxicillin 250mg/5ml oral suspension (Bristol Laboratories Ltd)
55047	Amoxicillin 125mg/5ml oral suspension (Sandoz Ltd)
55133	Erythromycin 250mg gastro-resistant capsules (Kent Pharmaceuticals Ltd)
55148	Clarithromycin 250mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)
55211	Cefaclor 500mg capsules (Kent Pharmaceuticals Ltd)
55300	Erythromycin 500mg Tablet (Teva UK Ltd)
55312	Co-amoxiclav 250mg/125mg tablets (Waymade Healthcare Plc)
55394	Amoxicillin 500mg capsules (Wockhardt UK Ltd)
55397	Erythromycin 250mg gastro-resistant capsules (Waymade Healthcare Plc)
55428	Clarithromycin 250mg/5ml oral suspension (Waymade Healthcare Plc)
55483	Erythromycin 250mg gastro-resistant tablets (Milpharm Ltd)
55499	Amoxicillin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)
55519	Doxycycline 100mg capsules (Waymade Healthcare Plc)
55527	Amoxicillin 500mg capsules (Boston Healthcare Ltd)
55589	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
55626	Amoxicillin 125mg/5ml oral suspension sugar free (Waymade Healthcare Plc)
55708	Levofloxacin 250mg tablets (Actavis UK Ltd)
55917	Ciprofloxacin 500mg tablets (Medreich Plc)
56012	Levofloxacin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)
56044	Tetracycline 125mg/5ml oral solution
56181	Tetracycline 250mg Tablet (Celltech Pharma Europe Ltd)
56198	Vibramycin-D 100mg dispersible tablets (Mawdsley-Brooks & Company Ltd)
56203	Erythroped A 500mg tablets (Sigma Pharmaceuticals Plc)
56223	Amoxicillin 250mg/5ml oral suspension (Sandoz Ltd)
56381	Ciprofloxacin 250mg tablets (Co-Pharma Ltd)
56561	Amoxicillin 125mg/5ml oral suspension (Waymade Healthcare Plc)
56578	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Waymade Healthcare Plc)
56591	Augmentin-Duo 400/57 oral suspension (Lexon (UK) Ltd)
56610	Cefaclor 125mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)
56700	Amoxil 500mg capsules (Necessity Supplies Ltd)
56789	Ciprofloxacin 500mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)
56856	Ciprofloxacin 750mg tablets (Ranbaxy (UK) Ltd)
56884	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)
57081	Co-amoxiclav 500mg/125mg tablets (Waymade Healthcare Plc)
57118	Ciprofloxacin 250mg tablets (Kent Pharmaceuticals Ltd)
57178	Amoxicillin 3g oral powder sachets sugar free (Mawdsley-Brooks & Company Ltd)
57267	Clarithromycin 125mg/5ml oral suspension (Waymade Healthcare Plc)
57660	Clarithromycin 250mg tablets (Almus Pharmaceuticals Ltd)
57833	Amoxil 500mg capsules (Waymade Healthcare Plc)
57886	Amoxil 500mg capsules (Stephar (U.K.) Ltd)
57960	Ciprofloxacin 500mg tablets (Tillomed Laboratories Ltd)
57966	Amoxicillin 250mg capsules (Medreich Plc)
58021	Ciprofloxacin 100mg tablets (Dr Reddy's Laboratories (UK) Ltd)
58037	Clarithromycin 500mg tablets (Almus Pharmaceuticals Ltd)
58053	Amoxicillin 250mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)
58057	Amoxicillin 250mg/5ml oral suspension sugar free (Sandoz Ltd)
58076	Tetracycline 250mg tablets (Kent Pharmaceuticals Ltd)
58097	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)
58175	Clarithromycin 500mg tablets (Wockhardt UK Ltd)
58206	Azithromycin 250mg tablets (Teva UK Ltd)

Product Code	Product Name
58235	Ciprofloxacin 250mg tablets (DE Pharmaceuticals)
58323	Ciprofloxacin 100mg tablets (Alliance Healthcare (Distribution) Ltd)
58326	Doxycycline 50mg capsules (Waymade Healthcare Plc)
58345	Levofloxacin 250mg tablets (Generics (UK) Ltd)
58426	Azithromycin 500mg tablets (Sandoz Ltd)
58494	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Colorama Pharmaceuticals Ltd)
58608	Ciprofloxacin 100mg tablets (Bristol Laboratories Ltd)
58756	Erythromycin ethyl succinate 125mg/5ml oral suspension (Waymade Healthcare Plc)
58760	Erythroped A 500mg tablets (Necessity Supplies Ltd)
58771	Amoxicillin 250mg capsules (DE Pharmaceuticals)
58803	Co-amoxiclav 250mg/125mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)
58824	Erythromycin 250mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)
58841	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)
58902	Clarithromycin 500mg tablets (Phoenix Healthcare Distribution Ltd)
58940	Levofloxacin 250mg tablets (A A H Pharmaceuticals Ltd)
58988	Doxycycline 100mg capsules (Phoenix Healthcare Distribution Ltd)
59036	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Pinewood Healthcare)
59042	Amoxicillin 250mg capsules (Alliance Healthcare (Distribution) Ltd)
59069	Cefalexin 250mg tablets (Phoenix Healthcare Distribution Ltd)
59100	Erythromycin 250mg gastro-resistant tablets (Waymade Healthcare Plc)
59112	Amoxicillin 125mg/5ml oral suspension sugar free (DE Pharmaceuticals)
59126	Erythromycin ethyl succinate 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
59153	Amoxicillin 250mg capsules (Waymade Healthcare Plc)
59269	Cefalexin 250mg capsules (DE Pharmaceuticals)
59391	Amoxicillin 125mg/5ml oral suspension (DE Pharmaceuticals)
59406	Cefalexin 500mg tablets (Waymade Healthcare Plc)
59432	Amoxicillin 250mg capsules (Accord Healthcare Ltd)
59441	Erythromycin ethyl succinate 125mg/5ml oral suspension (DE Pharmaceuticals)
59481	Amoxicillin 250mg capsules (Phoenix Healthcare Distribution Ltd)
59542	Vibramycin-D 100mg dispersible tablets (Sigma Pharmaceuticals Plc)
59572	Ciprofloxacin 500mg tablets (Sigma Pharmaceuticals Plc)
59588	Co-amoxiclav 125mg/31mg/5ml oral suspension (Waymade Healthcare Plc)
59592	Amoxicillin 500mg capsules (Pfizer Ltd)
59740	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)
59879	Amoxicillin 500mg capsules (DE Pharmaceuticals)
59908	Co-amoxiclav 500mg/125mg tablets (DE Pharmaceuticals)
59937	Ciprofloxacin 750mg tablets (Accord Healthcare Ltd)
60027	Amoxicillin 250mg/5ml oral suspension sugar free (DE Pharmaceuticals)
60034	Co-amoxiclav 250mg/125mg tablets (DE Pharmaceuticals)
60039	Cefalexin 250mg capsules (Waymade Healthcare Plc)
60134	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)
60159	Doxycycline 100mg capsules (DE Pharmaceuticals)
60190	Erythromycin 250mg gastro-resistant tablets (Waymade Healthcare Plc)
60202	Cefalexin 250mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
60263	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
60267	Amoxicillin 250mg/5ml oral suspension (DE Pharmaceuticals)
60281	Co-amoxiclav 125mg/31mg/5ml oral suspension (CST Pharma Ltd)
60308	Erythromycin ethyl succinate 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)
60382	Azithromycin 250mg capsules (DE Pharmaceuticals)

Product Code	Product Name
60436	Ciprofloxacin 250mg tablets (Almus Pharmaceuticals Ltd)
60577	Tetracycline 250mg tablets (Almus Pharmaceuticals Ltd)
60805	Clarithromycin 500mg tablets (Waymade Healthcare Plc)
60814	Azithromycin 500mg tablets (DE Pharmaceuticals)
60817	Levofloxacin 500mg tablets (Actavis UK Ltd)
60828	Erythromycin 250mg gastro-resistant tablets (Bristol Laboratories Ltd)
61001	Clarithromycin 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
61207	Amoxicillin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)
61264	Erythromycin 250mg gastro-resistant tablets (DE Pharmaceuticals)
61299	Co-amoxiclav 125mg/31mg/5ml oral suspension (Mawdsley-Brooks & Company Ltd)
61302	Ciprofloxacin 100mg tablets (Almus Pharmaceuticals Ltd)
61355	Doxycycline 50mg capsules (Chanelle Medical UK Ltd)
61407	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Colorama Pharmaceuticals Ltd)
61561	Erythromycin ethyl succinate 250mg/5ml oral suspension (Waymade Healthcare Plc)
61612	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Waymade Healthcare Plc)
61661	Cefalexin 125mg/5ml oral suspension (Waymade Healthcare Plc)
61783	Ciprofloxacin 250mg tablets (Waymade Healthcare Plc)
61810	Azithromycin 500mg tablets (A A H Pharmaceuticals Ltd)
61830	Clarithromycin 125mg/5ml oral suspension (Sigma Pharmaceuticals Plc)
61850	Levofloxacin 500mg tablets (A A H Pharmaceuticals Ltd)
61869	Ciproxin 250mg/5ml oral suspension (Waymade Healthcare Plc)
61906	Amoxicillin 500mg capsules (Mawdsley-Brooks & Company Ltd)
62008	Doxycycline 50mg capsules (DE Pharmaceuticals)
62025	Doxycycline 100mg capsules (Chanelle Medical UK Ltd)
62074	Amoxicillin 250mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)
62102	Amoxicillin 250mg/5ml oral suspension (Waymade Healthcare Plc)
62143	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (DE Pharmaceuticals)
62188	Cefalexin 250mg capsules (Phoenix Healthcare Distribution Ltd)

Pneumonia

Medical Code	Read Code	Read Term
Hospital admission with a pneumonia code (ICD-10 J10.0, J11.0, J12-18, J85.1) (any diagnosis within that admission)		
Death certificate with a pneumonia code as underlying or reported cause (ONS) (ICD-10 J10.0, J11.0, J12-18, J85.1)		
Or one of the following codes:		
68	H06z011	Chest infection
572	H26..00	Pneumonia due to unspecified organism
886	H25..00	Bronchopneumonia due to unspecified organism
1576	H231.00	Pneumonia due to mycoplasma pneumoniae
1849	H21..00	Lobar (pneumococcal) pneumonia
2581	H06z000	Chest infection NOS
3683	H261.00	Basal pneumonia due to unspecified organism
4899	H06z200	Recurrent chest infection
5202	H20..00	Viral pneumonia
5324	H28..00	Atypical pneumonia
5612	H224.00	Pneumonia due to staphylococcus
6094	H2z..00	Pneumonia or influenza NOS
6124	H062.00	Acute lower respiratory tract infection

Medical Code	Read Code	Read Term
9389	H20..11	Chest infection - viral pneumonia
9639	H260.00	Lobar pneumonia due to unspecified organism
10086	H2...00	Pneumonia and influenza
10992	H47..11	Aspiration pneumonitis
11202	H530z00	Abscess of lung NOS
11849	H2y..00	Other specified pneumonia or influenza
12061	H22y200	Pneumonia - Legionella
12423	H223.00	Pneumonia due to streptococcus
13563	SP13100	Other aspiration pneumonia as a complication of care
13573	H270000	Influenza with bronchopneumonia
14976	H20z.00	Viral pneumonia NOS
15308	A3A4.00	Legionella
15912	H270.00	Influenza with pneumonia
16287	H25..11	Chest infection - unspecified bronchopneumonia
17025	H233.00	Chlamydial pneumonia
17359	H30..11	Chest infection - unspecified bronchitis
19400	H26..11	Chest infection - pnemonia due to unspecified organism
21185	H53..00	Abscess of lung and mediastinum
22795	H22..11	Chest infection - other bacterial pneumonia
23095	H22z.00	Bacterial pneumonia NOS
23333	H540000	Hypostatic pneumonia
23546	H220.00	Pneumonia due to klebsiella pneumoniae
23726	H24y700	Pneumonia with varicella
24316	H24..11	Chest infection with infectious disease EC
24356	H540100	Hypostatic bronchopneumonia
24425	A310000	Pulmonary mycobacterium avium-intracellulare infection
25054	H470312	Aspiration pneumonia due to vomit
25694	H23..00	Pneumonia due to other specified organisms
26287	A3BXB00	Klebsiella pneumoniae/cause/disease classifd/oth chapters
27519	H24y200	Pneumonia with pneumocystis carinii
28634	H22..00	Other bacterial pneumonia
29005	H530.00	Abscess of lung
29166	H21..11	Chest infection - pneumococcal pneumonia
29457	H270.11	Chest infection - influenza with pneumonia
30437	H243.00	Pneumonia with whooping cough
30509	SP13200	Post operative chest infection
30591	H221.00	Pneumonia due to pseudomonas
30653	H23..11	Chest infection - pneumonia organism OS
31024	A3BXA00	Mycoplasma pneumoniae [PPLO] cause/dis classifd/oth chaptr
31269	H201.00	Pneumonia due to respiratory syncytial virus
31886	H060A00	Acute bronchitis due to mycoplasma pneumoniae
32172	A551.00	Postmeasles pneumonia
32223	A310.00	Pulmonary mycobacterial infection
33478	H20y.00	Viral pneumonia NEC
33730	H530000	Single lung abscess
34251	H23z.00	Pneumonia due to specified organism NOS
34274	H246.00	Pneumonia with aspergillosis
34300	H262.00	Postoperative pneumonia
34659	H53z.00	Abscess of lung and mediastinum NOS
35082	H243.11	Pneumonia with pertussis
35189	H530300	Abscess of lung with pneumonia
35745	H270z00	Influenza with pneumonia NOS

Medical Code	Read Code	Read Term
36675	H202.00	Pneumonia due to parainfluenza virus
37447	H06z112	Acute lower respiratory tract infection
37711	H530100	Multiple lung abscess
37881	H222.00	Pneumonia due to haemophilus influenzae
40299	AB24.11	Pneumonia - candidal
40498	H24..00	Pneumonia with infectious diseases EC
41015	H471000	Lipoid pneumonia (exogenous)
41034	H240.00	Pneumonia with measles
43286	H241.00	Pneumonia with cytomegalic inclusion disease
43884	H22yz00	Pneumonia due to bacteria NOS
45425	H22y100	Pneumonia due to proteus
47295	A205.00	Pneumonic plague, unspecified
47973	A54x400	Herpes simplex pneumonia
48481	AB24.00	Candidiasis of lung
48804	H222.11	Pneumonia due to haemophilus influenzae
49398	H24y600	Pneumonia with typhoid fever
50408	A730.00	Ornithosis with pneumonia
50867	H22y.00	Pneumonia due to other specified bacteria
52071	H247000	Pneumonia with candidiasis
52384	H22yX00	Pneumonia due to other aerobic gram-negative bacteria
52520	Hyu0800	[X]Other viral pneumonia
53753	Hyu0H00	[X]Other pneumonia, organism unspecified
53947	Hyu0D00	[X]Pneumonia in viral diseases classified elsewhere
53969	H247z00	Pneumonia with systemic mycosis NOS
57667	H530200	Gangrenous pneumonia
58896	A022200	Salmonella pneumonia
60119	H230.00	Pneumonia due to Eaton's agent
60299	H22y011	E.coli pneumonia
60482	H24y300	Pneumonia with Q-fever
61623	H24y000	Pneumonia with actinomycosis
62623	H242.00	Pneumonia with ornithosis
62632	H270100	Influenza with pneumonia, influenza virus identified
63763	Hyu0A00	[X]Other bacterial pneumonia
63858	H223000	Pneumonia due to streptococcus, group B
65419	H22y000	Pneumonia due to escherichia coli
66362	H24z.00	Pneumonia with infectious diseases EC NOS
67836	H200.00	Pneumonia due to adenovirus
67901	H24y100	Pneumonia with nocardiasis
69782	H24y.00	Pneumonia with other infectious diseases EC
70559	H24yz00	Pneumonia with other infectious diseases EC NOS
70710	A203.00	Primary pneumonic plague
72182	H24y400	Pneumonia with salmonellosis
73735	H232.00	Pneumonia due to pleuropneumonia like organisms
96583	AyuKA00	[X]Klebsiella pneumoniae/cause/disease classifd/oth chapters
98381	Hyu0B00	[X]Pneumonia due to other specified infectious organisms
98782	H24y500	Pneumonia with toxoplasmosis
101204	H470.11	Aspiration pneumonia
101292	AB41500	Histoplasma duboisii with pneumonia
101507	AB40500	Histoplasma capsulatum with pneumonia
103404	H247100	Pneumonia with coccidioidomycosis
104121	H2B..00	Community acquired pneumonia
104264	H2C..00	Hospital acquired pneumonia

Medical Code	Read Code	Read Term
106031	AyuK900	[X]Mycoplasma pneumoniae [PPLO]cause/dis classifd/oth chaptr
106300	H203.00	Pneumonia due to human metapneumovirus
106908	H244.00	Pneumonia with tularaemia

Deaths

Death due to any cause

Death due to COPD as underlying cause (ICD-10 J40-44)

Death due to pneumonia as underlying cause (ICD10 J10.0, J11.0, J12-18, J85.1)

Hospitalisations

Hospitalisation due to any cause

Hospital admission with a pneumonia code (ICD-10 J10.0, J11.0, J12-18, J85.1) (any diagnosis within that admission)

Hospital admission with COPD or acute respiratory code as primary diagnosis of hospitalisation ((ICD-10 J00, J06, J09-18, J20-22, J40-44, J96)

Non-elective hospitalisations

Other variables

Asthma

Medical Code	Read Code	Read Term
78	H33..00	Asthma
185	H333.00	Acute exacerbation of asthma
1555	H33..11	Bronchial asthma
2290	H330.11	Allergic asthma
3018	663V100	Mild asthma
3366	663V300	Severe asthma
4442	H33z.00	Asthma unspecified
4606	H33zz11	Exercise induced asthma
4892	H33z000	Status asthmaticus NOS
5267	H331.00	Intrinsic asthma
5627	H330011	Hay fever with asthma
5867	173A.00	Exercise induced asthma
6707	H330111	Extrinsic asthma with asthma attack
7058	8H2P.00	Emergency admission, asthma
7146	H330.00	Extrinsic (atopic) asthma
7731	H330.14	Pollen asthma
10487	663j.00	Asthma - currently active
11370	1O2..00	Asthma confirmed
13065	663V200	Moderate asthma
14777	H330000	Extrinsic asthma without status asthmaticus
15248	H330.13	Hay fever with asthma
16070	H33zz00	Asthma NOS
18323	H331111	Intrinsic asthma with asthma attack
21232	H33zz12	Allergic asthma NEC
22752	173c.00	Occupational asthma
24479	663d.00	Emergency asthma admission since last appointment
25796	H332.00	Mixed asthma
27926	H330100	Extrinsic asthma with status asthmaticus
29325	H331000	Intrinsic asthma without status asthmaticus
40823	H334.00	Brittle asthma
45073	H331z00	Intrinsic asthma NOS
45782	H330z00	Extrinsic asthma NOS
47337	663m.00	Asthma accident and emergency attendance since last visit
58196	H331100	Intrinsic asthma with status asthmaticus
73522	173d.00	Work aggravated asthma

Atopy

Medical Code	Read Code	Read Term
121	H170.11	Hay fever - pollens
175	H17..00	Allergic rhinitis
230	M12z100	Eczema NOS
334	M128.00	Allergic contact dermatitis
610	M112.00	Infantile eczema
775	H172.00	Allergic rhinitis due to unspecified allergen
788	F4C1411	Allergic conjunctivitis

Medical Code	Read Code	Read Term
964	H17z.00	Allergic rhinitis NOS
1240	M113.00	Flexural eczema
1424	M12z200	Infected eczema
1741	M111.00	Atopic dermatitis/eczema
1838	H170.00	Allergic rhinitis due to pollens
1930	H171.16	House dust mite allergy
2011	F4C0600	Acute atopic conjunctivitis
2372	H171.00	Allergic rhinitis due to other allergens
2859	14F1.00	H/O: eczema
3162	H171.15	House dust allergy
3699	M12z300	Hand eczema
3798	H172.11	Hay fever - unspecified allergen
5391	M12..12	Contact eczema
5627	H330011	Hay fever with asthma
5869	M114.00	Allergic (intrinsic) eczema
6180	M11z.00	Atopic dermatitis NOS
6399	M12..00	Contact dermatitis and other eczemas
6400	M280.00	Allergic urticaria
6728	M102.00	Infectious eczematoid dermatitis
7426	M128200	Allergic contact dermatitis due drugs in contact with skin
7731	H330.14	Pollen asthma
8994	M12z400	Erythrodermic eczema
9302	14B1.00	H/O: hay fever
10840	M117.00	Neurodermatitis - atopic
11132	M128000	Allergic contact dermatitis due to adhesives
13223	M11..00	Atopic dermatitis and related conditions
15248	H330.13	Hay fever with asthma
15879	F4D3112	Contact eczema - eyelids
16134	H171.14	Hay fever - other allergen
16676	F4C0611	Acute allergic conjunctivitis
16685	F4D3111	Allergic dermatitis - eyelid
16832	F4D3100	Contact or allergic eyelid dermatitis
17204	M128400	Allergic contact dermatitis due to other chemical products
18572	H17..12	Allergic rhinosinusitis
22764	Myu2200	[X]Exacerbation of eczema
29779	F4D3000	Eczematous eyelid dermatitis
30664	M128500	Allergic contact dermatitis due to food in contact with skin
32385	M128100	Allergic contact dermatitis due to cosmetics
38383	M128300	Allergic contact dermatitis due to dyes
39721	Myu2.00	[X]Dermatitis and eczema
41618	M128600	Allergic contact dermatitis due to plants, except food
47599	Hyu2100	[X]Other allergic rhinitis
72490	Hyu2000	[X]Other seasonal allergic rhinitis

Short-acting bronchodilator prescriptions

Product Code	Product Name
8	Salbutamol 100micrograms/dose inhaler
17	Salbutamol 100micrograms/dose inhaler CFC free
31	Ventolin 100microgram/inhalation Inhalation powder (Glaxo Wellcome UK Ltd)
235	Bricanyl 250micrograms/dose inhaler (AstraZeneca UK Ltd)

Product Code	Product Name
534	Atrovent 20micrograms/dose inhaler (Boehringer Ingelheim Ltd)
556	Combivent inhaler (Boehringer Ingelheim Ltd)
862	Salbulin Inhalation powder (3M Health Care Ltd)
882	Salbutamol 200microgram inhalation powder capsules
898	Ventolin evohaler 100 100microgram/inhalation Pressurised inhalation (Glaxo Wellcome UK Ltd)
907	Bricanyl turbohaler 500 500microgram Turbohaler (AstraZeneca UK Ltd)
942	Aerolin 100micrograms/dose Autohaler (3M Health Care Ltd)
957	Salamol easi-breathe 100microgram/actuation Pressurised inhalation (IVAX Pharmaceuticals UK Ltd)
958	Ventolin easi-breathe 100microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)
1087	Asmasal 95micrograms/dose Clickhaler (Focus Pharmaceuticals Ltd)
1093	Salamol 100microgram/actuation Inhalation powder (IVAX Pharmaceuticals UK Ltd)
1409	Ipratropium bromide 20micrograms/dose inhaler
1619	Terbutaline 500micrograms/dose dry powder inhaler
1620	Terbutaline 250micrograms/dose inhaler
1628	Terbutaline 250micrograms/actuation refill canister
1697	Atrovent 20micrograms/dose Autohaler (Boehringer Ingelheim Ltd)
1698	Salbutamol 100micrograms/dose breath actuated inhaler
1741	Salbutamol 100micrograms/dose breath actuated inhaler CFC free
1801	Ventide inhaler (GlaxoSmithKline UK Ltd)
1882	Ventodisks 200microgram/blister Disc (Allen & Hanburys Ltd)
1950	Ventodisks 400microgram/blister Disc (Allen & Hanburys Ltd)
1952	Ventolin 400microgram Rotacaps (GlaxoSmithKline UK Ltd)
2152	Ipratropium bromide with salbutamol 20mcg + 100mcg
2655	Airomir 100micrograms/dose inhaler (Teva UK Ltd)
2722	Duovent inhaler (Boehringer Ingelheim Ltd)
2758	Bricanyl Refill canister (AstraZeneca UK Ltd)
2850	Salbutamol 400microgram inhalation powder capsules
2851	Ventolin 200microgram Rotacaps (GlaxoSmithKline UK Ltd)
2862	Duovent Autohaler (Boehringer Ingelheim Ltd)
2978	Salbutamol 200micrograms/dose dry powder inhaler
2994	Atrovent aerocaps 40microgram Inhalation powder (Boehringer Ingelheim Ltd)
3163	Salbutamol 200micrograms disc
3306	Atrovent Forte 40micrograms/dose inhaler (Boehringer Ingelheim Ltd)
3443	Salbutamol 100microgram/inhalation Spacehaler (Celltech Pharma Europe Ltd)
3556	Beclometasone 50micrograms with salbutamol 100micrograms/inhalation inhaler
3763	TERBUTALINE RESPULES INH
3838	SALBUTAMOL 400MCG/BECLOMETH.100MCG R/CAP INH
4268	Ipratropium bromide 40micrograms/dose inhaler
4497	Ventolin accuhaler 200 200microgram/actuation Inhalation powder (Glaxo Wellcome UK Ltd)
4665	Salbulin 100micrograms/dose inhaler (3M Health Care Ltd)
5170	Salamol 100micrograms/dose inhaler CFC free (Teva UK Ltd)
5516	Salamol 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
5740	Airomir 100micrograms/dose Autohaler (Teva UK Ltd)
5753	Salbutamol 400micrograms disc
5889	Salamol 100microgram/inhalation Inhalation powder (Kent Pharmaceuticals Ltd)
6081	Ipratropium bromide 20micrograms/dose breath actuated inhaler
6462	Salbutamol 95micrograms/dose dry powder inhaler
6512	Atrovent 20micrograms/dose inhaler CFC free (Boehringer Ingelheim Ltd)
6522	Ipratropium bromide 20micrograms/dose inhaler CFC free

Product Code	Product Name
7017	Salbutamol 100micrograms/dose dry powder inhaler
7711	Terbutaline 250micrograms/dose inhaler with spacer
7935	Maxivent 100microgram/inhalation Inhalation powder (Ashbourne Pharmaceuticals Ltd)
7954	Bricanyl 250micrograms/dose spacer inhaler (AstraZeneca UK Ltd)
8267	Sodium cromoglicate 1mg/dose / Salbutamol 100micrograms/dose inhaler
8333	Ipratropium bromide 40microgram inhalation powder capsules
9651	Asmasal 100microgram/inhalation Spacehaler (Celltech Pharma Europe Ltd)
9681	Atrovent aerohaler 40microgram Inhalation powder (Boehringer Ingelheim Ltd)
10360	Aerocrom inhaler (Castlemead Healthcare Ltd)
11307	Salbutamol 100micrograms/dose / Beclometasone 50micrograms/dose inhaler
11779	Ipratropium bromide 40microgram inhalation powder capsules with device
12808	Fenoterol 100micrograms/dose / Ipratropium bromide 40micrograms/dose breath actuated inhaler
12909	Salbutamol 100micrograms/dose / Ipratropium 20micrograms/dose inhaler
13038	Pulvinal Salbutamol 200micrograms/dose dry powder inhaler (Chiesi Ltd)
13181	Easyhaler Salbutamol sulfate 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
13996	Salamol 100microgram/inhalation Inhalation powder (Sandoz Ltd)
14525	Salbutamol 100micrograms/inhalation vortex inhaler
14561	Salbutamol 400microgram / Beclometasone 200microgram inhalation powder capsules
16577	Easyhaler Salbutamol sulfate 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
16625	Ventide Rotacaps (GlaxoSmithKline UK Ltd)
18314	Aerocrom Syncroner with spacer (Castlemead Healthcare Ltd)
18456	Salbutamol 200microgram / Beclometasone 100microgram inhalation powder capsules
18484	Ventide Paediatric Rotacaps (GlaxoSmithKline UK Ltd)
19121	Beclometasone 100micrograms with Salbutamol 200micrograms inhalation capsules
19376	Beclometasone 200micrograms with Salbutamol 400micrograms inhalation capsules
21859	Asmaven 100microgram Inhalation powder (Berk Pharmaceuticals Ltd)
22225	BECLOMETHASONE /SALBUTAMOL
22430	Spacehaler salbutamol 100microgram/inhalation Spacehaler (Celltech Pharma Europe Ltd)
22512	SALBUTAMOL INHALER
24380	Sodium cromoglicate 1mg/dose / Salbutamol 100micrograms/dose inhaler with spacer
25020	IPRATROPIUM BROMIDE (FORTE)
25073	SALBUTAMOL
25218	SALBUTAMOL CFC/FREE B/A
26616	Ipratropium bromide with fenoterol hydrobromide 0micrograms + 100micrograms/actuation
27505	Ipratropium bromide with fenoterol hydrobromide 40micrograms + 100micrograms/actuation
27793	Salbutamol cyclohaler type 5 insufflator Inhalation powder (Bristol-Myers Squibb Pharmaceuticals Ltd)
28508	Salbutamol 100microgram/inhalation Inhalation powder (IVAX Pharmaceuticals UK Ltd)
30118	Salbutamol 100micrograms/dose inhaler CFC free (Teva UK Ltd)
30204	Salbutamol 200micrograms inahalation capsules
30212	Salbutamol cyclohaler
30230	Salbutamol 100micrograms/actuation breath actuated inhaler
30240	Aerolin autohaler 100microgram/actuation Pressurised inhalation (3M Health Care Ltd)
31933	Salbutamol 100micrograms/dose inhaler (A A H Pharmaceuticals Ltd)
32050	Salbutamol 400 Cyclocaps (Teva UK Ltd)
33089	Salbutamol 100micrograms/dose inhaler (Kent Pharmaceuticals Ltd)
33373	Salbutamol 200 Cyclocaps (Teva UK Ltd)
33588	Salbutamol 100micrograms/dose inhaler (Generics (UK) Ltd)
33817	Salbutamol 100micrograms/dose inhaler CFC free (Actavis UK Ltd)

Product Code	Product Name
34029	Salbutamol 400micrograms inahalation capsules
34134	Aerolin 400 100microgram/actuation Inhalation powder (3M Health Care Ltd)
34310	Salbutamol 100micrograms/dose inhaler CFC free (A A H Pharmaceuticals Ltd)
34311	Salbutamol 100microgram/inhalation Inhalation powder (Berk Pharmaceuticals Ltd)
34619	Salbutamol 100microgram/inhalation Inhalation powder (Kent Pharmaceuticals Ltd)
34702	Salbutamol 100microgram/inhalation Inhalation powder (C P Pharmaceuticals Ltd)
38079	Salbutamol 100micrograms/dose dry powder inhalation cartridge with device
38097	Salbutamol cyclocaps 200microgram Inhalation powder (DuPont Pharmaceuticals Ltd)
38136	Salbulin Novolizer 100micrograms/dose inhalation powder (Meda Pharmaceuticals Ltd)
38214	Salbutamol 100micrograms/dose dry powder inhalation cartridge
38226	Salbulin Novolizer 100micrograms/dose inhalation powder refill (Meda Pharmaceuticals Ltd)
38416	Salbutamol cyclocaps 400microgram Inhalation powder (DuPont Pharmaceuticals Ltd)
40655	Salbuvent 100microgram/actuation Inhalation powder (Pharmacia Ltd)
42830	Ventolin 100micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
42858	Ventolin 200micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
42886	Bricanyl 500micrograms/dose Turbohaler (AstraZeneca UK Ltd)
43090	Atrovent 40microgram Aerocaps (Boehringer Ingelheim Ltd)
43105	Atrovent 40microgram Aerocaps with Aerohaler (Boehringer Ingelheim Ltd)
44713	Salbutamol 100microgram/inhalation Inhalation powder (Celltech Pharma Europe Ltd)
46551	Salbutamol 100microgram/inhalation Inhalation powder (Neo Laboratories Ltd)
48490	Ventolin 100micrograms/dose Evohaler (DE Pharmaceuticals)
48519	Ventolin 100micrograms/dose Evohaler (Waymade Healthcare Plc)
48547	Salamol 100micrograms/dose inhaler CFC free (Arrow Generics Ltd)
48741	Ventolin 100micrograms/dose Evohaler (Mawdsley-Brooks & Company Ltd)
48742	Ventodisks 400microgram (GlaxoSmithKline UK Ltd)
48809	Ventodisks 400microgram with Diskhaler (GlaxoSmithKline UK Ltd)
49368	Ventodisks 200microgram with Diskhaler (GlaxoSmithKline UK Ltd)
49369	Salbutamol 200microgram inhalation powder blisters
49370	Ventodisks 200microgram (GlaxoSmithKline UK Ltd)
49591	Salbutamol 100micrograms/dose inhaler CFC free (Sandoz Ltd)
50315	Salbutamol 200microgram inhalation powder blisters with device
50503	Ventolin 200micrograms/dose Accuhaler (Mawdsley-Brooks & Company Ltd)
50557	Ventolin 200micrograms/dose Accuhaler (Lexon (UK) Ltd)
50810	Atrovent 20micrograms/dose inhaler CFC free (DE Pharmaceuticals)
50956	Ventolin 200micrograms/dose Accuhaler (DE Pharmaceuticals)
52410	Bricanyl 500micrograms/dose Turbohaler (Necessity Supplies Ltd)
52543	Salbutamol 400microgram inhalation powder blisters
52799	Salbutamol 400microgram inhalation powder blisters with device
53297	Ventolin 200micrograms/dose Accuhaler (Sigma Pharmaceuticals Plc)
57249	Asmavent 100micrograms/dose inhaler CFC free (Kent Pharmaceuticals Ltd)
57524	Ventolin 200micrograms/dose Accuhaler (Dowelhurst Ltd)
57557	Atrovent 20micrograms/dose inhaler CFC free (Lexon (UK) Ltd)
58269	AirSalb 100micrograms/dose inhaler CFC free (Sandoz Ltd)
59409	Salbutamol 100micrograms/dose inhaler CFC free (Waymade Healthcare Plc)
60920	Atrovent 20micrograms/dose inhaler CFC free (Sigma Pharmaceuticals Plc)
60923	Salamol 100micrograms/dose Easi-Breathe inhaler (DE Pharmaceuticals)
61591	Salbutamol 100micrograms/dose inhaler CFC free (Phoenix Healthcare Distribution Ltd)

Theophylline prescriptions

Product Code	Product Name
218	AMINOPHYLLINE 100 MG CAP
273	THEOPHYLLINE 200 MG CAP
555	Aminophylline 225mg modified-release tablets
590	Phyllocontin Continus 225mg tablets (Napp Pharmaceuticals Ltd)
863	Slo-phyllin 125mg Capsule (Lipha Pharmaceuticals Ltd)
879	Theophylline 125mg modified-release capsules
880	Theophylline 60mg modified-release capsules
1097	Slo-phyllin 60mg Capsule (Lipha Pharmaceuticals Ltd)
1423	Uniphyllin Continus 200mg tablets (Napp Pharmaceuticals Ltd)
1832	Theograd 350mg Tablet (Abbott Laboratories Ltd)
1833	Theophylline 200mg modified-release tablets
1834	Theophylline 400mg modified-release tablets
2147	Theophylline 250mg modified-release capsules
2609	Franol tablets (Sanofi)
2757	Slo-phyllin 250mg Capsule (Lipha Pharmaceuticals Ltd)
2995	Nuelin SA 175mg tablets (Meda Pharmaceuticals Ltd)
3187	Choledyl 62.5mg/5ml Oral solution (Parke-davis Research Laboratories)
3388	Theophylline 175mg modified-release tablets
4514	Aminophylline 350mg modified-release tablets
4591	Choledyl 100mg Tablet (Parke-davis Research Laboratories)
4592	Choledyl 200mg Tablet (Parke-davis Research Laboratories)
4593	Theophylline 125mg tablets
5261	Nuelin SA 250 tablets (Meda Pharmaceuticals Ltd)
5453	Uniphyllin Continus 400mg tablets (Napp Pharmaceuticals Ltd)
5941	Uniphyllin Continus 300mg tablets (Napp Pharmaceuticals Ltd)
6315	Slo-Phyllin 250mg capsules (Merck Serono Ltd)
6988	Aminophylline hydrate 100mg modified-release tablets
7477	Franol Plus tablets (Sanofi)
7730	Theo-Dur 300mg tablets (AstraZeneca UK Ltd)
7731	Theo-Dur 200mg tablets (AstraZeneca UK Ltd)
7732	Theophylline 300mg modified-release tablets
7733	Theophylline 250mg modified-release tablets
7832	Choline theophyllinate 200mg tablets
7841	Nuelin 125mg tablets (3M Health Care Ltd)
8056	Aminophylline 100mg tablets
8057	Aminophylline 100mg modified-release tablets
8470	AMINOPHYLLINE 225 MG SUP
8610	AMINOPHYLLINE 1 GM SUP
8653	AMINOPHYLLINE 360 MG SUP
8705	EPHEDRINE HCL 24MG/THEOPHYLLINE 120MG MG TAB
8806	Phyllocontin continus 350mg Tablet (Napp Pharmaceuticals Ltd)
8955	THEOPHYLLINE 100 MG TAB
9092	Theophylline 350mg modified release tablets
10289	AMINOPHYLLINE 200 MG SUP
10331	Nuelin 60mg/5ml liquid (3M Health Care Ltd)
10407	Phyllocontin Paediatric Continus 100mg tablets (Napp Pharmaceuticals Ltd)
10432	THEOPHYLLINE 300 MG SUP
10433	Theophylline 60mg/5ml oral solution
10561	Aminophylline 250mg/ml injection
10723	Theophylline 125mg/5ml syrup

Product Code	Product Name
10744	THEOPHYLLINE 80 MG ELI
10831	Biophylline 125mg/5ml Oral solution (Lorex Synthelabo Ltd)
11719	Slo-Phyllin 60mg capsules (Merck Serono Ltd)
11993	Pro-vent 300mg Capsule (Wellcome Medical Division)
12240	Theophylline 300mg modified release capsules
12274	Tedral Tablet (Parke-davis Research Laboratories)
12699	Pecram 225mg Modified-release tablet (Novartis Consumer Health UK Ltd)
13529	Amnivent-225 SR tablets (Ashbourne Pharmaceuticals Ltd)
14739	Norphyllin SR 225mg tablets (Teva UK Ltd)
14991	Aminophylline 250mg/10ml injection
15025	AMINOPHYLLINE 25 MG SUP
15153	Theophylline 120mg / Ephedrine hydrochloride 11mg tablets
15284	Slo-Phyllin 125mg capsules (Merck Serono Ltd)
15365	Theophylline 10mg/5ml SF elixir
15409	THEOPHYLLINE 3 MG SOL
15561	EPHEDRINE 11MG/THEOPHYLLINE 120MG 11 MG TAB
16994	Aminophylline hydrate 350mg modified-release tablets
17002	Aminophylline hydrate 225mg modified-release tablets
17140	Aminophylline 200mg tablets
18288	Choline theophyllinate 100mg tablets
18308	AMINOPHYLLINE 100 MG SUP
18988	Choline theophyllinate 62.5mg/5ml oral solution
19350	AMINOPHYLLINE 62.5 MG SUP
19953	Theophylline with ephedrine & caffeine tablets
20171	AMINOPHYLLINE 180 MG SUP
20225	AMINOPHYLLINE 500 MG INJ
21769	Lasma 300mg Tablet (Pharmax Ltd)
22080	AMINOPHYLLINE 20 ML INJ
23572	Aminophylline sr 225mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)
24023	Theodrox Tablet (3M Health Care Ltd)
24035	EPHEDRINE 15MG/THEOPHYLLINE 120MG 15 MG TAB
24117	AMINOPHYLLINE 300 MG SUP
24207	AMINOPHYLLINE PAED 50 MG SUP
24418	Biophylline 350mg Tablet (Lorex Synthelabo Ltd)
24674	Biophylline 500mg Tablet (Lorex Synthelabo Ltd)
25022	AMINOPHYLLINE 150 MG SUP
25093	THEOPHYLLINE S/R
25125	Aminophylline 360mg suppositories
25937	AMINOPHYLLINE INTRAMUSCULAR 500 MG INJ
26724	EPHEDRINE HCL/AMINOPHYLLINE E/C TAB
26860	Theophylline 120mg / Ephedrine sulfate 15mg tablets
27249	Do-Do ChestEze tablets (Novartis Consumer Health UK Ltd)
27593	AMINOPHYLLINE 350 MG SUP
27842	AMINOPHYLLINE 2 ML INJ
27944	Tedral Oral solution (Parke-davis Research Laboratories)
28241	Aminophylline 250mg/10ml solution for injection Minijet pre-filled syringes (UCB Pharma Ltd)
28786	EPHEDRINE HCL 25MG/AMINOPHYLLINE 130MG MG CAP
29273	Aminophylline 225mg Modified-release tablet (Hillcross Pharmaceuticals Ltd)
29395	PROXYPHYLLINE 300 MG TAB
30596	Aminophylline 225mg Modified-release tablet (Actavis UK Ltd)
32893	THEOPHYLLINE 100MG/LYSINE 74MG MG TAB

Product Code	Product Name
38120	Theophylline 500mg modified release tablets
39040	Phyllocontin Forte Continus 350mg tablets (Napp Pharmaceuticals Ltd)
42511	Aminophylline 25mg/ml Injection (Celltech Pharma Europe Ltd)
42910	Aminophylline 250mg/10ml solution for injection ampoules (Martindale Pharmaceuticals Ltd)
48484	Theophylline 250mg/5ml oral suspension
50018	Aminophylline 250mg/10ml solution for injection ampoules
51430	Theophylline 60mg/5ml oral suspension
57228	Aminophylline 250mg/10ml solution for injection ampoules (A A H Pharmaceuticals Ltd)
58600	Aminophylline 250mg/10ml solution for injection ampoules (AMCo)
61346	Aminophylline 360mg suppositories (Special Order)

Oxygen use

Medical Code	Read Code	Read Term
5211	8771	Oxygen therapy
6877	877..11	Oxygen therapy
8417	6639.12	Oxygen at home
9238	Z6J4.00	Long-term oxygen therapy
18115	Z6J4.11	LTOT - Long-term oxygen therapy
21855	6639	Home oxygen supply
22924	66Yj.00	Home oxygen supply - cylinder
26435	66Yk.00	Home oxygen supply - concentrator
32889	8776	LTOT - Long-term oxygen therapy
32961	7L1Q.00	Oxygen therapy
34472	6639.11	Home oxygen supply started
37030	663E.00	Home oxygen supply stopped
39149	7.45E+02	Home oxygen support
47121	745E.00	Oxygen therapy support
50699	9Nd6.00	Patient consent given for supply of home oxygen
51415	8777	SBOT - Short-burst oxygen therapy
52661	8778	Ambulatory oxygen therapy
53500	Z6J5.00	Humidified oxygen therapy
55888	Z6J..00	Oxygen therapy
61127	66Yl.00	Home oxygen supply - liquid oxygen
91276	7L1Qz00	Oxygen therapy NOS
94628	745Ez00	Oxygen therapy support NOS
96533	745Ey00	Other specified oxygen therapy support
97768	7L1Qy00	Other specified oxygen therapy
103481	7L1Q100	Humidified oxygen therapy
103773	6AJ..00	Home oxygen therapy review
104525	Z6J5.11	Humidified oxygen
107422	877C.00	Number of hours oxygen therapy prescribed per day
108142	877B.00	Number of hours oxygen therapy required per day
108950	877C000	Number of hours long-term oxygen therapy prescribed per day

Nebulised therapies

Product Code	Product Name
510	Ventolin 5mg/ml respirator solution (GlaxoSmithKline UK Ltd)
674	Ventolin 2.5mg Nebules (GlaxoSmithKline UK Ltd)
1148	Spacer/holding chamber device 750ml Nebuliser (AstraZeneca UK Ltd)
1269	Becotide 50microgram/ml Nebuliser liquid (Allen & Hanburys Ltd)
1410	Ipratropium bromide 0.25mg/ml
1411	Ipratropium bromide 250micrograms/ml
1414	Salamol 5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
1415	Steri-neb ipratropium 250microgram/ml Nebuliser liquid (IVAX Pharmaceuticals UK Ltd)
1630	Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials
1711	Salbutamol 5mg/2.5ml nebuliser liquid unit dose vials
1956	Pulmicort 1mg Respules (AstraZeneca UK Ltd)
1957	Ventolin 5mg Nebules (GlaxoSmithKline UK Ltd)
1959	Pulmicort 0.5mg Respules (AstraZeneca UK Ltd)
1962	Atrovent udv 0.25mg/ml Nebuliser liquid (Boehringer Ingelheim Ltd)
3305	Combivent nebuliser liquid 2.5ml UDVs (Boehringer Ingelheim Ltd)
4222	Bricanyl 10mg/ml respirator solution (AstraZeneca UK Ltd)
4634	Salamol 2.5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
4640	Bricanyl 5mg/2ml Nebuliser liquid (AstraZeneca UK Ltd)
4801	Budesonide 500micrograms/2ml nebuliser liquid unit dose vials
4942	Budesonide 1mg/2ml nebuliser liquid unit dose vials
5308	Terbutaline 5mg/2ml nebuliser liquid unit dose vials
5551	Flixotide 0.5mg/2ml Nebules (GlaxoSmithKline UK Ltd)
5837	Salamol steri-neb 5mg/2.5ml Nebuliser liquid (Numark Management Ltd)
5898	Salamol steri-neb 2.5mg/2.5ml Nebuliser liquid (Numark Management Ltd)
6719	Ipratropium bromide 500micrograms/2ml nebuliser liquid unit dose vials
6758	Ipratropium 250micrograms/1ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
6772	Ipratropium bromide 250micrograms/1ml nebuliser liquid unit dose vials
6911	Atrovent 250micrograms/1ml nebuliser liquid UDVs (Boehringer Ingelheim Ltd)
7140	Atrovent 500micrograms/2ml nebuliser liquid UDVs (Boehringer Ingelheim Ltd)
7964	Beclometasone 50micrograms/ml nebuliser suspension
7965	Salbutamol 5mg/ml nebuliser liquid
8676	Terbutaline 10mg/ml nebuliser liquid
9270	Ipratropium bromide with fenoterol hydrobromide 500micrograms + 1.25mg/4ml
9555	Spacer/holding chamber device 750ml Nebuliser (Allen & Hanburys Ltd)
11046	Ipratropium bromide with salbutamol 500micrograms + 2.5mg/2.5ml
11478	Fluticasone 2mg/2ml nebuliser liquid unit dose vials
12822	Salbutamol 2.5mg with ipratropium bromide 500micrograms/2.5ml unit dose nebuilser solution
13365	Berotec 5mg/ml Nebuliser liquid (Boehringer Ingelheim Ltd)
13757	Tropiovent steripoule 250microgram/ml Nebuliser liquid (Ashbourne Pharmaceuticals Ltd)
16207	Duovent UDVs nebuliser liquid 4ml (Boehringer Ingelheim Ltd)
16305	Flixotide 2mg/2ml Nebules (GlaxoSmithKline UK Ltd)
17465	Fluticasone 500micrograms/2ml nebuliser liquid unit dose vials
18140	Respontin 500micrograms/2ml Nebules (GlaxoSmithKline UK Ltd)
18299	Fenoterol 1.25mg/4ml / Ipratropium 500micrograms/4ml nebuliser liquid unit dose vials
18421	Respontin nebules 250microgram/ml Nebuliser liquid (Glaxo Wellcome UK Ltd)
19876	Sidestream disposable adult 4446 Nebuliser (R L Dolby)
20781	SALBUTAMOL U.DOSE NEBULISING 2.5MG/2.5ML
20803	IPRATROPIUM BROMIDE NEBULISER SOLUTION

Product Code	Product Name
23269	Maxivent 2.5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
23567	Respontin 250micrograms/1ml Nebules (GlaxoSmithKline UK Ltd)
23709	Ipratropium 500micrograms/2ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
23961	Ipratropium bromide 250microgram/ml Inhalation vapour (Galen Ltd)
23969	Spacer/holding chamber device 750ml Nebuliser (Rpr / Fisons)
25339	Maxivent 5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
27107	Sidestream disposable angled mouthpiece 4448 Nebuliser (R L Dolby)
30229	Ipratropium bromide 250microgram/ml Nebuliser liquid (Galen Ltd)
31050	Jet nebuliser Nebuliser liquid
31082	Salbuvent 5mg/ml Respirator solution (Pharmacia Ltd)
31963	Cirrus nebuliser [inter] 1493 Nebuliser (Intersurgical Ltd)
33097	Inspiron minineb nebuliser Nebuliser (A A H Pharmaceuticals Ltd)
34018	Salbutamol 5mg/2.5ml Nebuliser liquid (Galen Ltd)
34162	Salbutamol 2.5mg/2.5ml Nebuliser liquid (Galen Ltd)
35557	Ipramol nebuliser solution 2.5ml Steri-Neb unit dose vials (Teva UK Ltd)
37612	Terbutaline 5mg/2ml nebuliser liquid unit dose vials (Galen Ltd)
37791	Ipratropium bromide 250microgram/ml
40177	Ipratropium bromide 250microgram/ml Nebuliser liquid (Hillcross Pharmaceuticals Ltd)
40599	Salbutamol 5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
40637	Ipratropium 250micrograms/1ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
40709	Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials (A A H Pharmaceuticals Ltd)
40832	Ipratropium 500micrograms/2ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
42279	Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
43046	Salipraneb 0.5mg/2.5mg nebuliser solution 2.5ml ampoules (Arrow Generics Ltd)
43085	Bricanyl 5mg/2ml Respules (AstraZeneca UK Ltd)
45863	Salbutamol 5mg/2.5ml Nebuliser liquid (Generics (UK) Ltd)
48410	Salbutamol 2.5mg/2.5ml / Ipratropium bromide 500micrograms/2.5ml nebuliser liquid ampoules
48607	Salbutamol 2.5mg/2.5ml / Ipratropium bromide 500micrograms/2.5ml nebuliser liquid unit dose vials
49904	Combivent nebuliser liquid 2.5ml UDVs (Lexon (UK) Ltd)
50037	Pulmicort 0.5mg Respules (Waymade Healthcare Plc)
51903	Combivent nebuliser liquid 2.5ml UDVs (DE Pharmaceuticals)
52732	Pulmicort 0.5mg Respules (Necessity Supplies Ltd)
53019	Ventolin 2.5mg Nebules (Mawdsley-Brooks & Company Ltd)
53174	Ipratropium bromide 500micrograms/2ml nebuliser liquid unit dose vials (A A H Pharmaceuticals Ltd)
55132	Atrovent 500micrograms/2ml nebuliser liquid UDVs (Waymade Healthcare Plc)
60601	Salbutamol 5mg/2.5ml nebuliser liquid unit dose vials (Alliance Healthcare (Distribution) Ltd)
61330	Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials (Alliance Healthcare (Distribution) Ltd)
61975	Budesonide 500micrograms/2ml nebuliser liquid unit dose vials (Almus Pharmaceuticals Ltd)

Influenza vaccination

Medical Code	Read Code	Read Term
6	65E..00	Influenza vaccination
10821	68NV.00	Influenza vacc consent given
12104	9OX..11	Flu vaccination administration

Medical Code	Read Code	Read Term
12105	9k7..00	Influenza immunisation - enhanced services administration
12336	ZV04800	[V]Influenza vaccination
18330	9OX1.00	Has 'flu vaccination at home
18684	9OX3.00	Has 'flu vaccination at hosp.
21123	ZV04811	[V]Flu - influenza vaccination
32942	9OX8.00	Has influenza vaccination at work
35655	9OXZ.00	Influenza vacc.administrat.NOS
44555	9OX2.00	Has'flu vaccination at surgery
94301	65E0.00	First pandemic influenza vaccination
95092	65E1.00	Second pandemic influenza vaccination
97941	65E2.00	Influenza vaccination given by other healthcare provider
98047	68Nr.00	Consent given for pandemic influenza vaccination
98217	65E3.00	1st pandemic influenza vacc give by other healthcare providr
98306	65E4.00	2nd pandemic influenza vacc give by other healthcare providr
104688	65ED.00	Seasonal influenza vaccination
104958	68NV000	Consent given for seasonal influenza vaccination
105077	65E2000	Seasonal influenza vaccin given by other healthcare provider
105195	65ED000	Seasonal influenza vaccination given by pharmacist
106994	65EE000	Administration of first intranasal influenza vaccination
106995	65EE100	Administration of second intranasal influenza vaccination
107156	65EE.00	Administration of intranasal influenza vaccination
107297	65ED100	Administration of first intranasal seasonal influenza vacc
107315	6.50E+01	Administration of first intranasal pandemic influenza vacc
107352	65ED300	Administration of second intranasal seasonal influenza vacc
107413	65E2100	First intranasal seasonal flu vacc gvn by othr hlthcare prov
107573	65ED200	Seasonal influenza vaccination given while hospital inpt
107646	65E1000	Administration of second intranasal pandemic influenza vacc
107730	65E2200	Secnd intranasal seasonal flu vacc gvn by othr hlthcare prov

Product Code	Product Name
398	Influenza inactivated split virion Vaccination (Aventis Pasteur MSD)
639	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes
922	Influenza inactivated surface antigen Vaccination
24779	Influenza inactivated split virion Paediatric vaccination
30198	Influenza inactivated split virion Vaccination (sanofi pasteur MSD Ltd)
32391	Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)
38421	Influenza inactivated split virion Vaccination (Evans Vaccines Ltd)
40760	Influenza vaccine (split virion, inactivated) 15microgram strain suspension for injection 0.1ml pre-filled syringes
40876	Influenza vaccine (split virion, inactivated) 9microgram strain suspension for injection 0.1ml pre-filled syringes
41168	Influenza H1N1 vaccine (split virion, inactivated, adjuvanted) emulsion and suspension for emulsion for injection
41240	Influenza H1N1 vaccine (whole virion, Vero cell derived, inactivated) suspension for injection
44759	INFLUENZA PRE-FILLED SYRINGE
45661	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)
48085	Influenza inactivated split virion Vaccination (Chiron UK Ltd)

Product Code	Product Name
48658	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (sanofi pasteur MSD Ltd)
48740	Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes
49716	Influenza vaccine (surface antigen, inactivated, virosome) suspension for injection 0.5ml pre-filled syringes
51289	Influenza vaccine (live attenuated) nasal suspension 0.2ml unit dose
57140	Influenza vaccine (live attenuated) nasal suspension 0.2ml unit dose
61580	Influenza vaccine (split virion, inactivated) suspension for injection 0.25ml pre-filled syringes
61898	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (A A H Pharmaceuticals Ltd)

Pneumococcal vaccination

Medical Code	Read Code	Read Term
5764	7L19700	Subcutaneous injection of Pneumovax II
10713	68Ne.00	Consent given for pneumococcal vaccine
11363	6572	Pneumococcal vaccination
30411	9Oo..00	Pneumococcal vaccination administration
36826	6572000	Pneumococcal vaccination given
53198	657K.00	Booster pneumococcal vaccination
61504	657M.00	Second pneumococcal conjugated vaccination
61505	657N.00	Third pneumococcal conjugated vaccination
71121	657L.00	First pneumococcal conjugated vaccination
97759	657P.00	Pneumococcal vaccination given by other healthcare provider

Product Code	Product Name
821	Pneumococcal polysaccharide conjugated vaccine (adsorbed) suspension for injection 0.5ml vials
832	Pneumococcal polysaccharide vaccine solution for injection 0.5ml vials
930	Pneumovax II vaccine solution for injection 0.5ml vials (sanofi pasteur MSD Ltd)
1327	PNEUMOVAX VAC
3684	Pnu-Imune vaccine solution for injection 0.5ml vials (Wyeth Pharmaceuticals)
5757	Prevenar Vaccination (Wyeth Pharmaceuticals)
15482	PNEUMOVAC PLUS VACCINE VAC
42602	Prevenar 13 vaccine suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)
42612	Pneumococcal polysaccharide conjugated vaccine (adsorbed) suspension for injection 0.5ml pre-filled syringes
42991	Pneumococcal 10-valent saccharide conjugated absorbed vaccine
50264	Pneumovax II vaccine solution for injection 0.5ml pre-filled syringes (sanofi pasteur MSD Ltd)
50267	Prevenar vaccine suspension for injection 0.5ml vials (Wyeth Pharmaceuticals)
50338	Prevenar vaccine suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)
53159	Synflorix vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)

MRC breathlessness score

Medical Code	Read Code	Read Term
19426	173J.00	MRC Breathlessness Scale: grade 3
19427	173I.00	MRC Breathlessness Scale: grade 2
19429	173L.00	MRC Breathlessness Scale: grade 5
19430	173K.00	MRC Breathlessness Scale: grade 4
19432	173H.00	MRC Breathlessness Scale: grade 1

Laboratory results

Medical Code	Read Code	Read Term
Blood eosinophils – entity code 168 or one of the following codes if associated with value:		
22	42K..00	Eosinophil count
5495	D403.00	Eosinophilia
18531	42K3.00	Eosinophil count raised
19760	42b9.00	Percentage eosinophils
26905	42KZ.00	Eosinophil count NOS
26906	42K1.00	Eosinophil count normal
55214	D403z00	Eosinophilia NOS
Total white cell count – entity code 207 or one of the following codes if associated with value:		
15	42H.00	Total white cell count
13817	42H..11	White blood count
26946	42HZ.00	Total white cell count NOS
26947	42H7.00	Total white blood count
38198	42MG.00	Leucocyte count
Blood neutrophils – entity code 184 or one of the following codes if associated with value:		
18	42J..00	Neutrophil count
13777	42JZ.00	Neutrophil count NOS
15725	42J3.00	Neutrophilia
17622	42b0.00	Percentage neutrophils
23112	42J1.00	Neutrophil count normal
31382	42J4.00	Neutrophil count abnormal
C-reactive protein – entity code 280 or one of the following codes if associated with value:		
14066	44CC.00	Plasma C reactive protein
14067	44CC000	C reactive protein normal
14068	44CS.00	Serum C reactive protein level
19809	44CC100	C reactive protein abnormal

Appendix E: COMET study protocol

Study Title: Near-patient testing to guide COPD MaintenancE Treatment in primary care (COMET): observational study to determine variability and accuracy of inflammatory biomarkers in stable state.

Internal Reference Number / Short title: COMET

Ethics Ref: 16/SS/0135

IRAS ID: 209326

Date and Version No: 5.0 27 June 2018

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Funder:	National Institute for Health Research

Chief Investigator Signature:

Conflicts of interest

There are no conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. SYNOPSIS

Study Title	Near-patient testing to guide COPD MaintenancE Treatment in primary care (COMET): observational study to determine variability and accuracy of inflammatory biomarkers in stable state.	
Internal ref. no. / short title	COMET: Near-patient testing to guide COPD MaintenancE Treatment in primary care HA/COMET/0015	
Study Design	Prospective observational cohort study	
Study Participants	ICS-naïve patients with COPD in primary care	
Planned Sample Size	100	
Planned Study Period	01 January 2017 – 31 May 2019)	
	Objectives	**Outcome Measures**
Primary	To describe biomarker levels (eosinophils, FeNO, CRP, periostin) including repeatability and interdependence	Within- and between-person mean and standard deviation, intra-class correlation coefficient and correlation of biomarkers, obtained from blood samples
Secondary	To investigate method comparison of near-patient eosinophils compared to laboratory eosinophils	Mean difference, Bland-Altman analysis, and diagnostic accuracy, obtained from the venous and capillary blood samples
Tertiary	To assess the feasibility of undertaking such measurements in a primary care setting	Acceptability to participants using survey methods, obtained through the final visit participant questionnaire

2. ABBREVIATIONS

CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRP	C-reactive protein
CTRG	Clinical Trials & Research Governance, University of Oxford
CTU	Clinical Trials Unit
FeNO	Fraction of Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form

ICS	Inhaled Corticosteroids
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NRES	National Research Ethics Service
OUH	Oxford University Hospitals
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PPI	Patient and Participant Involvement
POC	Point-of-care
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure

3. BACKGROUND AND RATIONALE

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory condition affecting 1 million people in the UK, predominantly caused by smoking.[1] It is characterised by airflow obstruction which is not fully reversible, and symptoms include breathlessness, cough and increased sputum. It accounts for more than £800 million in direct healthcare costs and causes an estimated 24 million lost working days per annum in the UK. Diagnosis is by a combination of clinical findings (history and examination), together with post-bronchodilator spirometry confirming airflow obstruction (forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.7). National Institute for Health and Clinical Excellence (NICE) guidance defines severity by degree of airflow obstruction using percentage of predicted FEV_1 (giving severity categories of mild, moderate, severe and very severe), and also by degree of breathlessness and frequency of exacerbations.[1] Reversibility (change in airflow limitation in response to salbutamol) is not recommended as part of routine diagnosis, but can be helpful where there is suspicion of asthma.[1]

COPD is commonly managed in primary care using inhaled medication, with therapies added when patients experience frequent exacerbations or persistent breathlessness. Current NICE guidelines recommend inhaled corticosteroids (ICS) for worsening symptoms or moderate or severe COPD (FEV_1 <50% predicted).[1] Although trials of long-term use of ICS for COPD have demonstrated some symptomatic benefit, their effects on rate of lung function decline and mortality are unclear, they can be associated with adverse effects including pneumonia and osteoporotic fractures,[2-6] and they are expensive to the NHS.[7]

Previous research has shown that higher blood and sputum eosinophils are associated with poorer outcomes in patients with COPD, including faster decline in lung function and mortality,[8,9] and increased risk of COPD exacerbations during follow-up.[10,11] Early studies have also shown that in patients with higher sputum eosinophil counts, treatment in stable state with both oral and inhaled steroids improved FEV_1, dyspnoea and quality of life,[12-15] and management by sputum eosinophil count resulted in a reduction in severe exacerbations.[16] Patients who respond to oral steroids in terms of improvements in FEV_1 had a raised blood and sputum eosinophil count at baseline.[17] Several retrospective post-hoc analyses have

incorporated stratification by blood eosinophil count at baseline and found that broadly there is a greater response to ICS-containing preparations in patients with a higher baseline eosinophil count,[18-20] and there is a dose-response relationship of both rate of exacerbations and ICS-responsiveness according to degree of eosinophilic inflammation.[20]

While eosinophilic airway and systemic inflammation characterises one subgroup of patients with COPD, there is also a subgroup of patients characterised by raised sputum neutrophils and serum C-reactive protein (CRP) at baseline.[21,22] Fraction of exhaled nitric oxide (FeNO) is a breath test which correlates with eosinophilic airway inflammation, and is becoming of increasing importance in management of asthma, particularly in targeting and adjusting ICS treatment.[23-25] It has not been so widely studied in the COPD population, however some studies have shown that it can be used to predict response to both oral and inhaled steroids.[26-28] Periostin is an extracellular matrix protein which has been shown to be a serum biomarker for eosinophilic airway inflammation in asthma.[29] In patients with COPD, it remains stable over time irrespective of disease severity and ICS use, and is correlated with blood eosinophil count, particularly in ex-smokers.[30]

The majority of the studies discussed above have been conducted in a secondary care and/or trial setting;[18-20] however studies in these settings are poorly representative of the primary care COPD population, which is generally older, with better lung function, better quality of life, and fewer exacerbations.[31] The proportion of patients found to have raised eosinophil count varies widely between studies, ranging from 10-40%,[10,11,18-21,32,33] most likely due to different cut-offs, methods, and populations used. Furthermore, many patients referred to secondary care will already have been using ICS, which reduces airway eosinophilic inflammation,[12,13] so findings from these studies may not be applicable to those patients in primary care who will be ICS-naïve at the point when step-up treatment is being considered. Easy-to-measure biomarkers of eosinophilic inflammation, including blood eosinophils, FeNO and periostin, have not been characterised in the primary care ICS-naïve population.

Although blood eosinophil count has been identified as a promising new biomarker in the management of COPD, concerns have been raised about the application to a primary care environment where results are not immediately available.[34] Point-of-care, or near-patient, testing, refers to any test taken at the time of consultation which produces results which can be used to make immediate decisions about patient treatment, and is associated with increased patient and GP satisfaction.[35,36] It is increasingly used in primary care, particularly in Scandinavia, where, for example, CRP-guided treatment for acute respiratory infections is common.[37] There is now a commercially available device for measuring blood eosinophils in a near-patient setting (the HemoCue WBC DIFF®), however there are no published studies assessing its use in the primary care COPD population. FeNO can be used to assess airway eosinophilic inflammation in a near-patient setting using a portable device such as the NIOX VERO®, but this has also not been studied in an ICS-naïve primary care COPD population.

This study will take 4 measurements of inflammatory biomarkers over a 6 month period (approximately 2-monthly) in a population of 100 ICS-naïve patients with COPD in primary care aiming to (1) establish biomarker levels and their variability, repeatability and interdependence; (2) investigate method comparison of near-patient blood eosinophils compared to laboratory eosinophils in a real patient setting and (3) assess the feasibility of undertaking such inflammatory biomarker measurements in a primary care setting. Characterising these biomarkers within a novel population is essential preliminary information required to establish threshold values in this patient group, whether a single value is appropriate and

whether near-patient testing can replace laboratory testing, all of which will inform future research, specifically in planning a future biomarker-directed randomised controlled trial. This would consist of using inflammatory biomarkers to guide initiation of ICS to those patients who may most benefit from treatment, while avoiding treatment in those who may experience side-effects.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To describe biomarker levels (eosinophils, FeNO, CRP, periostin) including repeatability and interdependence	Within- and between-person mean and standard deviation, intra-class correlation coefficient and correlation of biomarkers, obtained from blood samples	4 repeated measurements over a 6 month period
Secondary Objectives To investigate method comparison of near-patient eosinophils compared to laboratory eosinophils	Mean difference and Bland-Altman analysis, and diagnostic accuracy, obtained from the venous and capillary blood samples	As above
Tertiary Objectives To assess the feasibility of undertaking such measurements in a primary care setting	Acceptability to participants using survey methods, obtained through the final visit participant questionnaire	Survey of participants at end of study

5. STUDY DESIGN

The design is a prospective observational cohort study with a nested method comparison study and feasibility assessment. See Appendix A (study flow chart).

ICS-naïve patients with COPD will be identified from their primary care records and invited by post to take part in the study, after GPs have checked that they are appropriate for inclusion. Participants will attend for a baseline visit, at their GP surgery (home visits will be undertaken in exceptional circumstances if appropriate). At this visit the participant will be fully informed about the study, eligibility will be confirmed, consent taken, and information obtained on demographic and disease/medication characteristics, in conjunction with the participant's health record. Measurements will be taken including spirometry, FeNO, finger-prick blood test, and venous blood test (serum for periostin and saved serum, full blood count (which includes eosinophils) and CRP). Near-patient eosinophils will be tested immediately using the Hemocue® WBC DIFF machine, including both venous and capillary blood. Questionnaires on respiratory-related symptoms and quality of life will be completed. Potential participants will be asked to avoid smoking, drinking alcohol, doing vigorous exercise, having a heavy meal or using their reliever inhaler for the few hours before this visit.

A further three visits will take place over a 6-month period, at approximately 2-month intervals. At each of these visits, the same measurements will be taken (including questionnaires), and any exacerbations and changes to baseline characteristics will be recorded. This will be corroborated against the participant's health record at each visit and at the end of the study.

At the final visit, participants will be given a survey to complete about the acceptability of similar tests as part of their annual COPD review. The results of this will enable feasibility to be assessed as part of this study. However, they will also be asked as part of this if they would be willing to be contacted in future to ask if they would discuss their opinions in more detail (this would form the basis of future qualitative study with a separate consent process).

Information recorded which would be useful for ongoing patient care (such as spirometry) will be recorded by researchers directly in the participant's health record, however there will be no intervention and patient care will not be altered as a result of participation in the study.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Participants with COPD who are ICS-naïve, in a primary care setting

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 40 years or above.
- Have a diagnosis of COPD meeting spirometric criteria for diagnosis of COPD (FEV_1/FVC ratio <0.7) (as recorded in their primary care records)

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Any previous diagnosis of bronchiectasis, cystic fibrosis, interstitial lung disease, lung cancer, alpha-1 anti-trypsin deficiency or other chronic respiratory disease not related to COPD or asthma.
- Co-existent active diagnosis of asthma (reviewed in the last 2 years)
- Currently prescribed an ICS, or had a prescription for ICS in the last 2 years.
- Regularly takes oral steroids, or has been regularly taking oral steroids in the last 2 years. Regular use of oral steroids will in general be defined as a longer than 2 week course, although discrete short courses with tapering are acceptable for inclusion.
- Prior inclusion in a clinical trial of an investigational medicinal product for airways disease in the last 90 days or which may involve administration of oral or inhaled steroid treatment.

7. STUDY PROCEDURES

Please see Appendix A (study flow chart) and Appendix B (Schedule of Procedures) for summary.

7.1. Recruitment

A list of potentially eligible participants will be obtained using searches of the practice electronic record to find participants potentially matching the eligibility criteria. This list will be screened by a GP in the practice to ensure there are no participants who would be inappropriate for inclusion are invited (for example, due to a terminal diagnosis or social reasons – and record the reasons for excluding any participants). The practice will send a letter to all potentially eligible participants inviting them to take part in the study. This letter will include a cover letter, a participant information sheet, and a slip to return with a prepaid envelope if they would like to be involved, giving their contact details.

7.1. Screening and Eligibility Assessment

Over the telephone following receipt of their interest slip, a basic check of eligibility will be performed. If they pass the eligibility check the participant will be booked into a trial appointment at a research clinic (home visits will be arranged in exceptional circumstances if the participant cannot travel to the surgery). At this visit eligibility will be confirmed using the participant's electronic health record.

7.2. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent Form (ICF) before any study specific procedures are performed.

Written and verbal versions of the Participant Information Sheet (PIS) and ICF will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the recruiter, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant and a copy retained by the trial team and stored securely separate from any other study paperwork. The original signed form will be retained at the study site.

7.3. Baseline Assessments (Visit 1 – approximately one hour)

The following assessments will take place:

- Demographics – demographic details (date of birth and sex) and contact details will be confirmed
- Medical history – taken from the participant, and corroborated using the primary care records, ideally simultaneously, to include:

  - Information about COPD diagnosis and previous treatments, with previous spirometry recordings noted, and previous exacerbation history (timings, treatments and whether hospitalisation/respiratory support was required)
  - Other chronic medical conditions including: asthma, heart failure, hypertension, cancer, hay fever, eczema, autoimmune conditions and other chronic conditions.
  - Smoking history including exposure to passive smoking
  - Current COPD medications, and previous oral or inhaled steroids prescribed
- Respiratory questionnaires – including the COPD Assessment Test (CAT, http://www.catestonline.org/) and Clinical COPD Questionnaire (CCQ, http://www.ccq.nl/)
- MRC Dyspnoea score
- Oxygen saturations
- FeNO
- Height and weight
- Spirometry including reversibility (participants will be asked to bring their own salbutamol inhaler with them to the assessment)
- Venous blood sample – EDTA tube (for full blood count, with part of this sample used for testing in Hemocue® machine), serum tube (for periostin and saved serum) and lithium-heparin tube (for CRP)
- Fingerprick blood sample – for testing in Hemocue® machine

7.4. Subsequent Visits (Visits 2-4 – approximately 45 minutes each)

Visits 2-4 will take place at approximately 2, 4 and 6 months after the baseline visit (within a 2 week period allowable either side). Visits 2-4 will consist of identical assessments to visit 1, with the exception that details would be requested of any updates to medications or new diagnoses. Details of any exacerbations and prescriptions for oral or inhaled steroids will be recorded.

At the final visit 4, participants will be given a questionnaire to complete and place in a sealed envelope, which will ask for feedback on the acceptability of these tests being incorporated into the routine COPD annual review, as a process evaluation.

Participants will be given a £30 gift voucher to thank them for their time in participating and cover any incidental travel expenses. They will be asked to sign to confirm that they have received this.

7.5. Sample Handling

All samples will be taken on 4 occasions as detailed above.

1) Breath samples (spirometry and FeNO) are not kept long-term and results are available immediately, but will be entered into the participant's medical record.
2) Venous blood samples (up to 15ml total)
   a. EDTA tube for full blood count – this will be transported to the OUH NHS Trust using standard transport from practices, and processed in the standard way. They will be kept for the standard duration of time routine EDTA samples are kept by the lab (up to 72 hours). Results will be transferred back to the practice via the standard system for notifying laboratory results to practices, and will be checked in the normal way (coming

into the GP's electronic in-tray identical to all other tests requested as part of routine clinical practice). Research staff will then extract this data from practice records when returning to the practice for subsequent clinics, and/or at the end of the study. This will be to ensure that any unexpected abnormalities e.g. severe anaemia, are dealt with promptly by the participant's usual provider, and means the results will be available in the participant's notes for future use. A small amount of the blood from the EDTA tube will also be used for testing in the Hemocue® machine, but this will not be kept long-term.

b. Lithium-heparin sample for CRP – this will be transported to the OUH NHS Trust using standard transport from practices, and processed in the standard way. They will be kept for the standard duration of time routine lithium-heparin samples are kept by the lab (up to 6 days). Results will be transferred back to the practice as above.
c. Serum sample – this will be transported to the OUH NHS Trust using standard transport from practices. It will then be spun, transferred to 2ml aliquots and stored in freezers in the OUH Trust:
    i. Aliquots of serum will be transported as a frozen batch to Viapath Ltd, a lab based in Kings College London, for testing for periostin – this will use manual ELISA (enzyme-linked immunosorbent assay, a laboratory technique), and samples will then be returned to the OUH NHS Trust. Results will be obtained from Viapath electronically (no identifiable participant information will be transported with the samples).
    ii. Samples will be stored long-term on OUH NHS Trust premises for use in future ethically-approved studies. This will not include genetic studies as it will have been rendered acellular by the centrifuge process.
d. Capillary sample for full blood count using the Hemocue® machine – this will processed and results available and recorded immediately, with discarding of samples afterwards.

7.6. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening). N.B. Starting an ICS during the study will not result in withdrawal.
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up

If withdrawal from the study is due to loss to follow up, already collected data will be used in analysis where possible. If participants state a wish to withdraw, they will be asked to complete a discontinuation form when they can state if they wish their existing data to be excluded.

The reason for withdrawal will be recorded in the CRF.

7.7. Definition of End of Study

The end of the study is the last visit of the last participant.

8. SAFETY REPORTING

This is an observational study and so no AEs or SAEs will be recorded or reported. The research only includes collection of clinical information and specimens and therefore adverse event reporting is not applicable as there is no intervention.

9. STATISTICS AND ANALYSIS

Objective 1: repeatability of biomarkers

- 1) How do different biomarkers vary by different patient characteristics?

For each biomarker (venous blood eosinophil count, CRP, FeNO and periostin), the following will be calculated: mean, standard deviation (within and between individuals). As well as presenting results for the whole population, stratified analysis by subgroups will include NICE disease severity categories, maintenance treatment (LABA/LAMA/LAMA-LABA combination/no maintenance treatment), and smoking status (current/ex/never smokers).

- 2) What is the repeatability of different biomarkers?

Intra-class correlation co-efficient (ICC) will be calculated for each biomarker as above. A multilevel regression model allowing for clustering within individuals for each biomarker will assess the repeatability of different biomarkers.

- 3) How do different biomarkers correlate with each other?

For each biomarker, correlation coefficients (or equivalent if variable not continuous normal) with other biomarkers will be calculated, including respiratory symptom questionnaire scores, spirometry (disease severity categorised using NICE severity, and % predicted FEV_1 as a continuous measure) (within and between individuals).

- 4) Do patient characteristics impact on the repeatability of biomarkers?

A model will be developed for each biomarker to assess the effects of other variables (e.g. age, gender, disease severity, smoking status) and other biomarkers on the intra-class correlation co-efficient of the key biomarkers of interest.

Sensitivity analyses will exclude those with any history of asthma, history of atopy, recent exacerbation (within the month prior to assessment), recent prescription for oral or inhaled steroid (within the month prior to assessment).

It will be assumed for the purposes of the main repeatability analysis that variation can be attributed to the biomarker rather than a change in the participant's condition over this relatively short time period.

However, sensitivity analysis will exclude patients who have had a significant change in symptoms or disease severity between visits.

Objective 2: method comparison of near-patient blood eosinophils

Appropriate methods that account for non-independence of observations will be adopted. Results from the finger-prick and venous blood eosinophil count will be compared using mean difference and a Bland-Altman plot as the primary analysis, allowing for multiple measures per individual.[38,39] Additionally, as a secondary analysis, using the venous blood eosinophil count as the reference test, finger-prick blood eosinophil count will be the index test and sensitivity, specificity, positive and negative predictive value and positive and negative likelihood ratios will be calculated for different thresholds of venous blood eosinophil count (200, 300, 400 and 500 cells/mm^3, as no clinical threshold has yet been established), receiver operating characteristic for multiple threshold values and alternative methods for comparing continuous methods[40] and consideration of clustering. Using the Hemocue® machine but with blood from the venous sample (rather than fingerprick) will also be assessed as an index test.

Exploratory analyses will assess the effect on method comparison of different participant characteristics e.g. age, gender, smoking status.

Objective 3: Feasibility and acceptability of testing for participants

Quantitative survey questions will be analysed descriptively. Any free text data will be analysed using thematic analysis. This information will be used to inform feasibility and acceptability of a larger trial, and the potential to incorporate into future routine clinical practice. Answers to the survey may also be used to identify a wide variation sample in terms of participant answers for a potential future more in-depth qualitative interview (with separate consent and ethics process).

9.1. The Number of Participants

This is a preliminary study designed to gather further information on biomarkers of interest in a primary care population, where very little data currently exist, in order to inform future clinical studies. 100 participants with 4 visits has been selected as a pragmatic estimate which will be acceptable to participants (as discussed in PPI meetings) while obtaining sufficient data to inform future studies. Repeated measurements of blood eosinophil count in a secondary care population found an intra-class correlation co-efficient of 3-monthly samples of 0.79, but it is likely that results would be different in a primary care population.

10. DATA MANAGEMENT

10.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

10.2. Data Recording and Record Keeping

Data Management will be performed in accordance with PC-CTU Data Management SOPs. Study specific procedures will be detailed in a Data Management Plan (DMP) to ensure that high quality data are

produced for statistical analysis. The DMP is reviewed and signed by all applicable parties including the Trial Manager and the Trial Statistician prior to the first participant being enrolled.

Participant contact information will be sent in via the return slip sent to the PC-CTU by the participant. This information will be used to contact the participant to book all necessary study appointments. The contact details will be stored at the centre separately from all other study data.

All participants will be consented using pre-printed paper consent forms including the unique participant ID. These will be kept separately to other study paperwork and stored securely.

Data collection and management will be conducted using a secure, web-based, system developed in conjunction with the clinical trials unit. The system will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance. Data will be entered directly into the clinical database as preference. Parallel paper-based data capture forms will be available where this is not possible e.g. if a home visit is required. Data protection requirements will be embedded into the design of the web-based system and enforced by best practice trial management procedures. The Clinical Data Manager will oversee the process of electronic data validation and manual listings, sending out Data Clarification Forms (DCFs) when required and following these up until the queries are resolved.

Once the last participant is enrolled, a critical item review and database audit will be undertaken by the Information System Manager, and reviewed by a statistician prior to database lock. All critical data items are 100% checked against original Source Data Documents to ensure accuracy, an error rate is established across all fields to ensure a consistently accurate dataset.

At the conclusion of the study and after the database has been locked, all essential documents will be archived for at least 5 years in accordance with the PC-CTU's archiving SOPs.

11. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

12.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

12.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database (with the exception of contact details database which will be held separately and destroyed at the end of the study). All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

12.6. Expenses and Benefits

All participants will be given a £30 gift voucher as a thank you for their participation in the study and to cover any potential costs incurred.

12.7. Other Ethical Considerations

The study is only recruiting adults who are able to give consent. It is not anticipated that there will be a significant number of non-English speakers in this study, but translation services e.g. Language Line will be made available to participants if needed so that we can ensure they are giving informed consent.

If, when recruiting participants or during subsequent visits, members of staff need to visit a participants home this will be done according to the University of Oxfords lone working policy.

13. FINANCE AND INSURANCE

13.1. Funding

The study is funded by the National Institute for Health Research, as part of a Doctoral Research Fellowship awarded to Dr Helen Ashdown (DRF-2014-07-052). NHS service support costs will be met by the Thames Valley and South Midlands Clinical Research Network. The Hemocue® machine (excluding consumables) is being provided on loan free of charge by the company Radiometer who are responsible for UK sales. They will have no role or input into the data collection, analysis or write-up.

13.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

14. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute for Health Research, using the standard disclaimer as advised by the NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

We will include an optional section on the consent form for participants to write their contact details should they wish to be informed of the results of the study. We will also present it at PPI groups e.g. Breathe Easy meetings, which includes patients with COPD.

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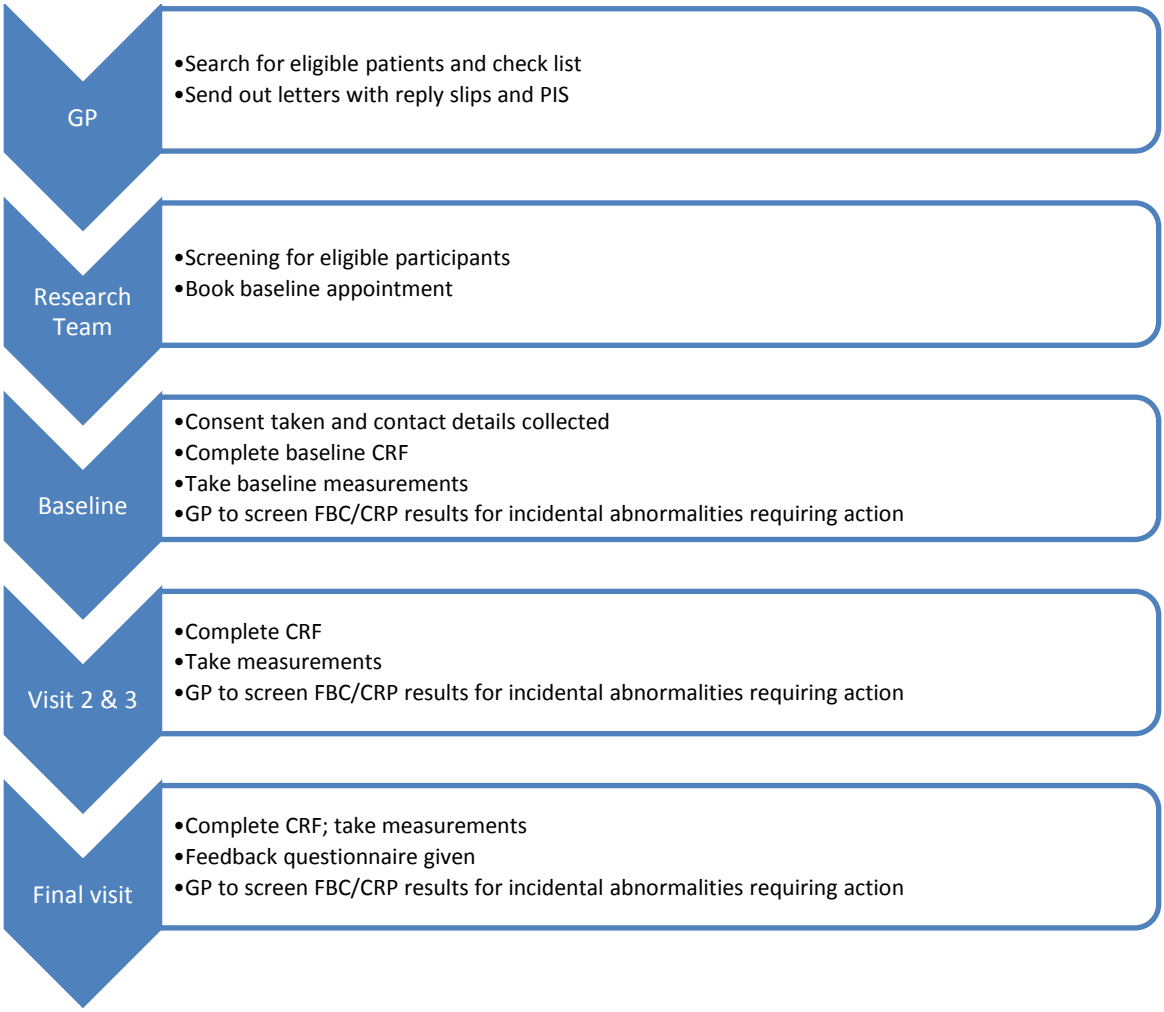
16. APPENDIX A: STUDY FLOW CHART



17. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

	Visit timing	**Week 0**	**Week 8**	**Week 16**	**Week 24**
	Screening and telephone contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Health record searches and recruitment letter	X				
Eligibility assessment	X	X			
Informed consent		X			
Demographics	X	X			
Contact Details		X	Check no changes	Check no changes	Check no changes
Medical history, smoking and medication history		X	Check no changes	Check no changes	Check no changes
Respiratory questionnaires		X	X	X	X
Physical examination (oxygen saturation only)		X	X	X	X
FeNO		X	X	X	X
Spirometry including reversibility		X	X	X	X
Venous blood tests (CRP, periostin, eosinophils – POC and laboratory)		X	X	X	X
Finger-prick test (POC eosinophils)		X	X	X	X
Survey about acceptability of tests					X

18. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	Study set up	N/a	File note in relation to HRA requesting PIS update – not officially an amendment but classed as 1 so bringing all documentation into line
2	3.0	30/01/2017	Helen Ashdown	Adding name of co-investigator; change of study dates
3	4.0	19/02/18	Helen Ashdown	Change of study dates
4	5.0	27/06/2018	Helen Ashdown	Change of study dates and removal of manual blood film analysis

Appendix F: COMET Research Information Sheet for Practices (RISP)

Study contacts:

Study Co-ordinator: Helen Ashdown **Tel:** 01865 289261 **E-mail:** helen.ashdown@phc.ox.ac.uk	**Primary Care Research Facilitator:** Ross Downes **Phone:** 07919553455 **Email:** ross.downes@oxfordhealth.nhs.uk **Former PCTs :** Oxfordshire

Research Information Sheet for Practices

Near-patient testing to guide COPD MaintenancE Treatment in primary care (COMET)

CSP number: TBC
UKCRN Study ID: TBC
Chief Investigator: Dr Helen Ashdown
Host Institution: Nuffield Department of Primary Care Health Sciences, University of Oxford
Funded By: National Institute for Health Research

The Study

Study Title: Near-patient testing to guide COPD MaintenancE Treatment in primary care (COMET): observational study to determine variability and accuracy of inflammatory biomarkers in stable state.
Type of study: Prospective observational cohort study
Aim of study:

1) To describe biomarker levels (eosinophils, fraction of exhaled nitric oxide (FeNO), CRP, periostin) in the primary care COPD population who have not yet been prescribed an inhaled steroid medication
2) To investigate method comparison of near-patient eosinophils compared to laboratory eosinophils
3) To assess the feasibility of undertaking such measurements in a primary care setting

Number of patients per practice screened: Approximately 50-100 depending on list size (electronic search)
Number of patients per practice invited: Approximately 40-80
Number of patients per practice recruited: Approximately 10-40
Number of practices in Thames Valley: 4-6
Study recruitment period: 1st September 2016 – 28th February 2018

Inclusion/Exclusion Criteria (Summary)

Inclusion Criteria (summary):

- Participant is willing and able to give informed consent for participation in the study.
- Aged 40 years or above.
- Has a diagnosis of COPD meeting spirometric criteria for diagnosis of COPD (FEV_1/FVC ratio <0.7) (as recorded in their primary care records)

Exclusion Criteria (summary):

- Previous diagnosis of chronic respiratory disease other than COPD or asthma
- Co-existent active diagnosis of asthma (reviewed in the last 2 years)
- Currently prescribed an inhaled corticosteroid (ICS) or had a prescription for ICS in the last 2 years
- Regularly takes oral steroids, or has been regularly taking oral steroids in the last 2 years

Practice Involvement in the Study – Summary

This would be a particularly good study for a practice with minimal research experience as there is not a great deal of input required from the surgery, lots of support is available and it is a small scale study.

By clinicians / practice:

GP

Recruitment

- search for eligible patients (using pre-defined search criteria) and briefly check the list to ensure there are no reasons patients should not be included e.g. dementia, palliative care

Follow-up

- After a study appointment, some blood results (FBC and CRP) will come back to the GP (via the normal system). GPs should screen and file these results on the system to ensure there are no incidental abnormalities requiring action.

Admin

Recruitment

- send out letters to eligible patients containing invitation letter, Participant Information Sheet and reply sheet (will be sent back to research team directly)

Study visits

- liaising with research team about when a room is available in the surgery for a researcher to use, and setting research team up with access to electronic patient records

By researchers:

Recruitment

- receive reply slips from participants and contact them to perform eligibility check
- arrange appointment with researcher at the surgery

Study visits

- Baseline appointment: consent taken and contact details collected; baseline CRF completed using medical records; take baseline measurements (including venous and capillary blood tests, FeNO, spirometry) N.B. We can record spirometry and other assessments needed for the COPD annual review in the medical records if requested by the practice (this may be useful for QOF)
- Appointments 2, 3, and 4 (at 2 month intervals) – repeat of measurements, including feedback questionnaire at appointment 4.

By participants:

- Give consent
- Respiratory questionnaires
- 2, 4 and 6 months after the baseline visit – repeat of measurements, including feedback questionnaire at appointment 4.
- Oxygen saturations
- FeNO
- Height and weight
- Spirometry including reversibility
- Venous blood sample (sent to lab along with other bloods from surgery)
- Fingerprick blood sample (analysed using portable machine which researcher will bring on site)

Reimbursement

Reimbursements have been agreed for the following activities. When the practice is initiated into the study, researchers will discuss the process for claiming these costs.

	Invoice Study Team	**Invoice CRN**
One-off costs: study set up, database search	£101.96	£43.92
Per-patient invited costs: Manual screening, telephone call, mail out	£1.16	£1.33
Per-patient recruited costs: miscellaneous equipment and review of blood results	£25	N/a

N.B. In addition, room hire at £15 per hour invoiced to the study team can be claimed but can only be paid if a clinic has had to be cancelled in order for the research clinic to go ahead and therefore the Practice have lost income.

Invoice to study team: Invoice 'COMET study, Nuffield Department of Primary Care Health Sciences' and sent to: Dr Helen Ashdown (COMET study), Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG

Invoice to CRN: Tracey Allen, Oxford University Hospitals NHS Trust, NIHR Clinical Research Network Block 8, Nuffield Orthopaedic Centre, Windmill Road, Headington, Oxford OX3 7HE

Potential Benefits for the Practice

- Opportunity for developing research at your practice
- GCP training available
- Opportunity for patients to engage in research
- Opportunity to raise practice profile
- Professional development for staff involved
- Measurements provided which are part of the COPD annual review which may save clinician time – we can also time our research clinic to coincide with a COPD nurse clinic if helpful

Advice on using DOCMAIL

Docmail is provided by CFH Docmail Ltd a secure print and mailing company who provide print and mailing services for Local Government, GP's, Dentists, Opticians, Medical Practices, Schools, Exam Boards and Banks etc. throughout the UK. The system can be found online at www.docmail.co.uk and requires a user name and password for businesses to send secure mailings via the website, print driver (www.docmail.co.uk/printdriver) or API (www.docmail.co.uk/api)

Docmail currently has over 50 health research studies and 3000 medical practices registered and using Docmail to send out their mailings.

Docmail, this is approved by the following:

- GP System of Choice – Lot 2 supporting services
- Crown Commercial Service for Hybrid Mail, which allows all government organisations to use Docmail.
- Health Trust Europe and London Procurement Programme for Outgoing Mail Solutions
- Caldicott Guardians across a number areas have approved the use of Docmail
- Ethics Committees have approved the use of Docmail by surgeries for use in medical studies.
- EMIS Partner Programme
- Connecting For Health - achieved a 100% rating when completing the Dept. of Health's Information Governance Toolkit Assessment for 2014-2015 and meets the terms and conditions of the DH Information Governance Assurance Statement. The assessments are available at:
  https://www.igt.connectingforhealth.nhs.uk/reportsnew.aspx?tk=401634495202720&cb=10%3a49%3a25&lnv=6&clnav=YES

For further information on the Docmail system please visit FAQs page at http://www.cfhdocmail.com/faqs.html.

If you do not wish to use Docmail, contact the study co-ordinator for alternatives.

Patient Confidentiality

Participant data will only be accessed upon notification of consent being obtained. Data collected will be securely stored in compliance with all national and local regulations. All Staff adhere to the principles of Good Clinical Practice (GCP) and the Data Protection Act, 1998. All study documents will be anonymised and patients will only be identified by unique Participant ID. Any documents holding Patient Identifiable Data (PID) are held securely with restricted access either electronically or in paper format and kept securely, and will be used only for patient follow-up, e.g. if a member of the research team needs to make a follow up phone call to a patient or recall them for a follow-up visit. In the event that the study team require access to PID as part of an agreed protocol, explanation of this will take place at the point of consent.

If you wish to take part in the study, what happens next?

Please e-mail your research facilitator or Tracey Allen with the following details:

Email to: tracey.allen@oxfordhealth.nhs.uk
Email subject heading: Expression of Interest – COMET study

GP name:
Practice manager/Research admin:
Practice Address:
Telephone Number:
Email address:

Thank you for your interest in this study. Please call the Study Co-ordinator if you would like to discuss this study further.

Appendix G: COMET Site Initiation Plan

TM110-A
SITE INITIATION PLAN template
COMET v2

The following points should be discussed at the initiation meeting (which may take place by e-mail/telephone).

N.B. More than one Site Initiation Plan may be required if different sites have different requirements – please adapt and highlight any changes if anything is not relevant/applicable to this site.

List all sites that this Site Initiation Plan is applicable to.	
Site	**Principle Investigator**

1. Ethics, R&D, MHRA (if relevant) approvals and agreements

All approvals are now in place, copies will be in ISF.

2. Study/trial discussion

Please see study protocol for further details on those items in italics

a) Background/objectives

b) Primary and secondary endpoints

c) Study design

d) Inclusion and exclusion criteria

e) Informed consent procedure

Research staff will be taking informed consent as part of the research visits.

f) Participant registration/randomisation procedure

Participants will contact the research team directly if they wish to take part in the study. There is no randomisation.

g) CRF completion / data management

This will all be completed by research staff.

h) Participant withdrawal

Participants may withdraw from the study at any time, and we will complete a 'Study discontinuation form' for these participants. We will inform you of any patients who have chosen to withdraw who are lost to follow-up.

i) Safety reporting requirements and responsibilities

We do not anticipate any adverse events taking place and so there will be no formal recording process. However we would let you know (through correspondence with the named PI) if anyone became significantly unwell during the testing process (and record this in the notes), or if we are concerned that clinical action may be needed due to an abnormal result or something else picked up on during our observation.

j) Ordering study supplies

See *Research visits* section below.

k) Other study specific procedures or arrangement
e.g. handling of samples/scans etc

See *Handling of samples* section below.

3. Provided Working Instructions

a) Searching for eligible participants

Please conduct searches as per inclusion and exclusion criteria, as suggested in the provided document 'COMET patient searches – guidance for GPs v1' and example EMIS search, particularly the suggested manual checks. An electronic EMIS search is also availabile for you to import directly (but please still perform manual checks). Please complete the spreadsheet 'COMET screening log v1' and record details of any deviation from suggested search strategy (or ask if queries), and any patients excluded, with reasons. A column is included for you to record patient identifiers in case this is helpful for you in conducting the search or sharing with colleagues to check suitability with colleagues, but please remove this column before returning the spreadsheet to us due to data security/confidentiality. A copy of the screening log should also be placed in the ISF.

b) Sending out invitation letters

Please let us know the number of potentially eligible participants, so that we can provide you with the correct number of study information packs. You will be provided with:

- Participant Information Sheet (COMET PIS V3.0)
- Participant Reply Slip (COMET Reply Slip V1.0) – these will be marked with individual screening IDs (so please don't photocopy)
- Pre-paid envelope with Nuffield Dept Primary Care address included

Please enclose these along with your site recruitment letter (as personalised for use by your practice), with individual patient details included on the letter, and send out to those patients identified as eligible in your search and marked as having been invited on the screening log above. You may wish to use MailMerge software to generate these letters and envelopes, as you prefer.

Participants will return their reply form directly to the study team. However, it is possible participants may contact the surgery directly with queries about the study or why they have been invited, as well as contacting the study team. Please pass them on to us if you are unable to answer their specific query.

c) Research visits

We will liaise with you over a mutually convenient time for us to do a research session at the surgery. We will ask you about your lab pick-up time, as it would be ideal to have concluded the session before the pick-up time in order that samples can reach the lab the same day (but this is not critical – see *Sample Handling* below).

At this visit we will require use of a clinical room in which to access EMIS and undertake clinical procedures – most rooms routinely used for GP or practice nurse consulting should be fine. Please see the spreadsheet 'equipment needed in practice v1' for a list of our IT and equipment requirements (these are all items which most practices should routinely have in stock, please discuss before ordering anything specially). Particularly, research staff will require access to EMIS and to be able to submit ICE requests and **this may need to be set up in advance** – names are Dr Helen Ashdown (Research GP) and Mrs Heather Rutter, Ms Pippa Whitbread and Ms Karen Madronal (Research Nurses). We do not anticipate needing Docman access but it would be helpful if we could use a practice generic login if this were needed.

We will use our own appointment booking system rather than the practice system, but can let you know in advance who we have arranged to see if this would be helpful. When we see patients we will enter in their consultation records that we have seen them for a research visit (recording this as 'Research admin'), and will record details of their height and weight, spirometry, MRC dyspnoea score and oxygen saturations (unless you ask us to do otherwise).

d) Handling of samples

We will request full blood count and CRP via the standard ICE system. The EDTA (purple) and lithium-heparin (green) tubes for these tests will be placed in an orange Oxford University Hospitals Trust sample bag, with the standard ICE label.

In addition, we will also be taking a serum sample (gold) tube which will go in a separate orange sample bag, with a special study label (see 'Label v1.1' for an example), which will also go to the same hospital lab, but will be processed differently.

We will label up samples and place in bags. Ideally samples will be transported to the laboratory the same day in the standard laboratory transport, and we will need to be told where to put samples so that they go in this, and the lab pick-up time.

In the event that samples cannot be transported to the laboratory the same day, the serum sample bag (gold tube) should be placed in the fridge overnight, and the other sample bag (green and purple tubes) should be kept at room temperature. We will need to be shown the location of the fridge and where samples should be stored to ensure they go in transport the next day. If you have access to a centrifuge, the lithium-heparin (green) tube should be centrifuged. There is a 'note to practice staff' on the special study label which gives a reminder of how the different bags and samples should be handled.

e) Follow-up of blood results

When requesting the full blood count and CRP on ICE, we will write the reason for test as 'COMET study' and set the research GP as the requesting clinician (unless you ask us to do otherwise).

The results for full blood count and CRP will then routinely come back to the practice in the standard way. This is in order that any abnormalities can be reviewed promptly by the patient's usual clinical care team who have access to all of their records and any previous results, and can determine the significance of any abnormal results. Although we are predominantly interested in the eosinophils, by virtue of taking full blood count it is possible that incidental abnormalities e.g. anaemia, low platelets, etc. may be detected. **The Principal Investigator (or delegated practice staff) are responsible for acting on any abnormal results and contacting patients if any clinical action is deemed necessary.** Please file results as you would normally – we will obtain the results from EMIS when we next visit the practice.

The serum sample will be processed separately for tests which are not routinely used in clinical practice and results will not be fed back to the practice.

f) Close of the study

The close of the study is the final visit of the final patient, although we will need to visit the practice one time after the study has closed to get the final visit blood results from EMIS.

4. Delegation and signature form

The ISF will contain a delegation log which includes research staff and the PI needs to confirm their agreement for research staff to conduct the study in the practice. Any additional staff performing research activities may be added to the delegation log (this is

not necessary for purely administrative tasks), and their CV and GCP certificate added to the ISF.

5. Location and Maintenance of the ISF

The ISF will be located at the practice. Please detail the exact location on the 'initiation training report'.

6. Monitoring

We will monitor recruitment and ongoing participation in the study throughout.

7. Archiving

We will be responsible for archiving of participant information. A copy of the informed consent form (ICF) will be retained by the practice for scanning into the patient medical record and then to be retained in the ISF. We will also give a copy to the patient.

8. GCP and CVs

GCP and CVs for Principal Investigator and all research staff will be in the ISF. Please add GCP and CVs for any additional study staff to whom research responsibilities are delegated.

9. Staffing levels and conflicting studies

Patients who are also taking part in the PACE or STARR-1 study are also eligible to take part in COMET, but not if they are taking part in STARR-2 (not yet started recruitment).

10. Copies of PIS/GP letter/ICF on site headed paper (as applicable)

Study packs will be provided as above once we know the number of potentially eligible patients identified. Copies of other study documents will be located in the ISF.

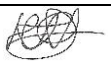
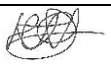
11. Explanation of Green Light Release process

Please do not send out study information to patients until you have received your Green Light letter.

12. Other

This is a relatively small scale study with flexibility to adapt the practicalities of recruitment to suit individual settings. Please ask if unsure or if anything else would be helpful.

Site initiation Plan approval:

Plan developed by:			
Name	**Role**	**Signature**	**Date**
Helen Ashdown	**Chief Investigator**		**21/10/16**
Plan approved by: (CI or delegate)			
Name	**Role**	**Signature**	**Date**
Helen Ashdown	**Chief Investigator**		**17/11/16**

Appendix H: COMET electronic search guidance for practices

COMET patient searches – guidance for GPs (version 1.0 26.09.16)

Many thanks for taking part in the COMET study. Inclusion and exclusion criteria are set out in the protocol and as copied below.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 40 years or above.
- Have a diagnosis of COPD meeting spirometric criteria for diagnosis of COPD (FEV1/FVC ratio <0.7) (as recorded in their primary care records)

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Any previous diagnosis of bronchiectasis, cystic fibrosis, interstitial lung disease, lung cancer, alpha-1 anti-trypsin deficiency or other chronic respiratory disease not related to COPD or asthma.
- Co-existent active diagnosis of asthma (reviewed in the last 2 years)
- Currently prescribed an ICS, or had a prescription for ICS in the last 2 years.
- Regularly takes oral steroids, or has been regularly taking oral steroids in the last 2 years. Regular use of oral steroids will in general be defined as a longer than 2 week course, although discrete short courses with tapering are acceptable for inclusion.
- Prior inclusion in a clinical trial of an investigational medicinal product for airways disease in the last 90 days or which may involve administration of oral or inhaled steroid treatment.

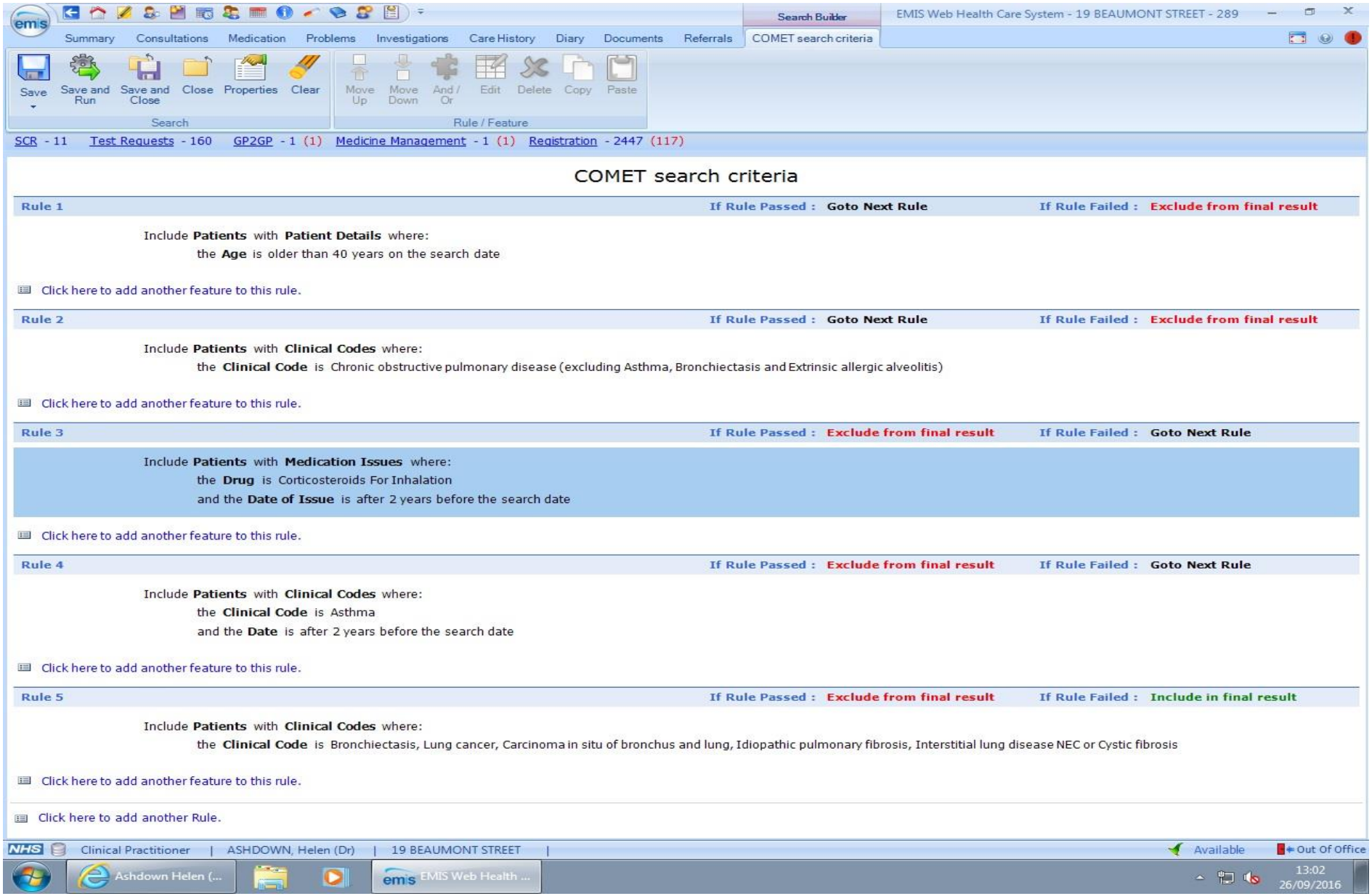
We would recommend EMIS searches as displayed in the screen shot at the end of this document (particularly N.B. to exclude asthma, bronchiectasis and extrinsic allergic alveolitis from the expanded list when searching for 'chronic obstructive pulmonary disease'. Asthma-COPD overlap syndrome can remain included).

Then please perform a brief manual screen to check the following:

- Patient has at least one FEV1/FVC ratio <0.7 (or 70%) [N.B. This refers to the absolute ratio, not the percentage predicted. This can be variably coded which makes it hard to reliably incorporate into search but feel free to add to search criteria if it is consistently recorded at your practice.]
- Patient does not regularly take oral steroids [it's fine if prednisolone is listed as one of their regular medications for use as short courses for exacerbations (which is why we cannot included it in EMIS search), but they should not be taking it regularly e.g. for polymyalgia.
- There is no reason they would be unsuitable to be invited for an unrelated reason e.g. unable to consent due to dementia, inappropriate due to palliative care, etc.

We will re-confirm eligibility over the phone and then in person but it would be helpful if we don't schedule visits with ineligible people, for their time and ours.

Helen Ashdown
September 2016


Search Builder
EMIS Web Health Care System - 19 BEAUMONT STREET - 289
Summary
Consultations
Medication
Problems
Investigations
Care History
Diary
Documents
Referrals
COMET search criteria
Save
Save and Run
Save and Close
Close
Properties
Clear
Search
Move Up
Move Down
And / Or
Edit
Delete
Copy
Paste
Rule / Feature
SCR - 11
Test Requests - 160
GP2GP - 1 (1)
Medicine Management - 1 (1)
Registration - 2447 (117)
COMET search criteria
Rule 1
If Rule Passed : Goto Next Rule
If Rule Failed : Exclude from final result
Include Patients with Patient Details where:
the Age is older than 40 years on the search date
Click here to add another feature to this rule.
Rule 2
If Rule Passed : Goto Next Rule
If Rule Failed : Exclude from final result
Include Patients with Clinical Codes where:
the Clinical Code is Chronic obstructive pulmonary disease (excluding Asthma, Bronchiectasis and Extrinsic allergic alveolitis)
Click here to add another feature to this rule.
Rule 3
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
Include Patients with Medication Issues where:
the Drug is Corticosteroids For Inhalation
and the Date of Issue is after 2 years before the search date
Click here to add another feature to this rule.
Rule 4
If Rule Passed : Exclude from final result
If Rule Failed : Goto Next Rule
Include Patients with Clinical Codes where:
the Clinical Code is Asthma
and the Date is after 2 years before the search date
Click here to add another feature to this rule.
Rule 5
If Rule Passed : Exclude from final result
If Rule Failed : Include in final result
Include Patients with Clinical Codes where:
the Clinical Code is Bronchiectasis, Lung cancer, Carcinoma in situ of bronchus and lung, Idiopathic pulmonary fibrosis, Interstitial lung disease NEC or Cystic fibrosis
Click here to add another feature to this rule.
Click here to add another Rule.
Clinical Practitioner | ASHDOWN, Helen (Dr) | 19 BEAUMONT STREET |
Available
Out Of Office
Ashdown Helen (...
EMIS Web Health ...
13:02
26/09/2016

Appendix I: COMET recruitment letter

GP Practice Headed Paper

Patient address

Dear Mr/Mrs xxxxxxxxxxxxxx,

COMET: Near-patient testing to guide COPD MaintenancE Treatment in primary care

xxxxxxxxxxxxxxMedical Practice is working together with the University of Oxford in carrying out a research study in patients who have COPD (Chronic Obstructive Pulmonary Disease). We are investigating whether new blood and breath tests could help improve the treatment of COPD. We are particularly looking for people who have not been prescribed a steroid inhaler for their COPD.

We are writing to you to let you know about the study because we think you would be eligible to take part. Taking part in the study would involve four appointments at our surgery with one of the researchers (a doctor or nurse) over a 6 month period for some blood and breath tests. The first appointment would last about an hour, and follow-up appointments about half an hour each. The diagram on the back of this letter summarises what is involved for you, and the enclosed information leaflet has been written by the research team to give further details about the study and what is involved.

If after reading the leaflet, you think you might be willing to take part, please complete the enclosed reply slip and return in the pre-paid envelope. You will then be contacted by telephone by one of the research team from the University of Oxford to arrange an appointment with them at our surgery, when you will be asked if you agree to take part. Returning the reply slip does not commit you to taking part in the study.

There are no direct benefits to you of taking part, although we hope that this study will benefit other patients with COPD in future. You will also be offered a £30 gift voucher to thank you for your time in participating. If you do not wish to take part, you do not need to do anything further and your decision will not affect the care you receive from our team.

If you have received this letter and don't think you should have been invited (for example, if you don't think you have COPD), please contact us to discuss further. If you have queries about the study, please contact the research team using the contact details on the enclosed leaflet.

Many thanks for considering taking part in this study.

Yours sincerely

Dr X X, on behalf of Dr X and partners

COMET
Near-patient testing to guide COPD MaintenancE Treatment in primary care

What is involved in this study?

1

We have sent you this information pack and invitation. To start you need to:

- You return reply slip using the pre-paid envelope
- You will then be contacted by a researcher from the University of Oxford to discuss the study and answer any questions you may have
- They will confirm that you are eligible for the study
- They will arrange an appointment with them at your local surgery

2

At the first appointment

- The research team will answer any further questions and ask you to sign a consent form
- You will answer some questions about your medical history (for example previous illnesses and medications)
- You will also complete a questionnaire about your chest symptoms
- We will measure your height and weight, and place a clip on your finger to measure oxygen saturations
- We will do a spirometry (lung function test) - before and after using your blue inhaler
- We will also measure your fraction of exhaled nitric oxide (FeNO) - another type of lung function test
- We will then take a finger prick blood sample and a venous blood sample (a normal blood test, from a vein)
- *This appointment will take approximately one hour, you will also be given a gift voucher*

3

At your second appointment:

- We will check if any details have changed compared to Appointment 1
- All other tests are identical to Appointment 1
- *This appointment will take approximately half an hour*

4

At your third appointment:

- We will check if any details have changed compared to Appointment 1
- All other tests are identical to Appointment 1
- *This appointment will take approximately half an hour*

5

At your last appointment

- We will check if any details have changed compared to earlier appointments
- All other tests are identical to earlier appointments
- You will complete a short questionnaire survey about your experience of having these tests, and ask your permission to be contacted about other research studies in future
- *This appointment will take approximately half an hour*

Appendix J: COMET Participant Information Sheet (PIS)

N.B. Pages appear out of order because this was designed to be folded into an A5 booklet

How have patients and the public been involved in this study?

Patients with COPD helped develop the research topic and what research questions should be asked, and in designing the study we have taken into account patient opinions on the frequency of participant appointments and the tests that we will carry out. Patients with COPD have been involved in reviewing and improving this Participant Information Sheet and other documents.

Who is organising and funding the study?

The researchers are from the University of Oxford. The Chief Investigator is Dr Helen Ashdown, who is a GP in Oxford. The funding for this research comes from the National Institute for Health Research (NIHR). Your GP surgery is being paid for including you in this study.

Who has reviewed the study?

This study has been reviewed and given a favourable opinion by South East Scotland Research Ethics Committee 2 (reference 16/SS/0135).

Do you have any further questions or concerns?

If you want to discuss the study, please contact the COMET team on 01865 617966 or e-mail comet@phc.ox.ac.uk, or return your contact sheet using the pre-paid envelope provided and we will contact you to discuss the study further. If you would like to discuss the study with somebody else, you can also talk to your GP.

Thank you for taking the time to read this information sheet

Further information and contact details are listed below

COMET Study

Nuffield Dept of Primary Care Health Sciences

University of Oxford

Radcliffe Observatory Quarter, Oxford, OX2 6GG

comet@phc.ox.ac.uk

Tel: (01865) 617966

COMET

Near-patient testing to guide COPD MaintenancE Treatment in primary care

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

UNIVERSITY OF OXFORD

Primary Care Clinical Trials Unit

PARTICIPANT INFORMATION SHEET

We'd like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information, and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please ask us.

What is the purpose of the study?

Chronic obstructive pulmonary disease (COPD) is a disease which causes chest symptoms such as cough and breathlessness. It is often (but not always) caused by smoking. At the moment, patients who have COPD may be prescribed inhalers to help with these symptoms. There are several different types of inhalers which may be used, including one type which contains a steroid. However, this may not benefit all patients. Some recent studies have suggested that we might be able to tell which patients would most benefit from a steroid inhaler using some new blood and breath tests, which could be used at the yearly COPD check-up in addition to the tests already done.

These tests have so far only been looked at in patients attending hospital, and not in patients attending their GP or nurse for their COPD. We want to see whether these tests could be used in future at GP surgeries. To do this we want to see what the results of these tests are in patients who have COPD, and how the results change over time, before a steroid inhaler has been prescribed. We also want to find out what patients with COPD think about these new tests.

Why have I been invited to take part?

You have been invited to take part because you are over 40 and your medical records at your GP surgery suggest that you have a diagnosis of COPD, and have not been prescribed a steroid inhaler in the last 2 years. We are looking to involve 100 patients with these characteristics in our research study. You can take part if you are involved in another research study, as long as it does not involve taking steroids or steroid inhalers.

Do I have to take part?

No. You are free to decide whether or not to take part. If you decide to take part, you are still free to withdraw at any time, without giving a reason. A decision not to take part or to withdraw will not affect the standard of care you receive from your healthcare team.

What will happen if I don't want to carry on with the study?

Participation in the study is voluntary and you can change your mind at a later stage, without giving a reason. Withdrawal will not affect the care you receive from your GP surgery and the NHS. If you withdraw from the study, unless you state otherwise, any data or samples which have been collected whilst you have been in the study will be used for research as detailed in this participant information sheet. If you were to lose your capacity (ability to give permission) during the study we would use information and samples you have already provided but not collect further information. Once your data has been anonymised and combined with others' it will not be possible to withdraw it from the study. You are free to request that your blood or tissue samples are destroyed at any time during or after the study.

What will happen to the results of the study?

We will combine data collected about you with that from other participants for analysis, and publish the findings in journals and at conferences. Some of the research being undertaken will also contribute to the fulfilment of an educational requirement (a doctoral thesis). You would not be identified from any report or publication placed in the public domain. There will be a space on the consent form where you can tell us if you would like to be informed of the results of the study.

What if you find something unexpected?

It is possible that one of the blood tests may indicate an incidental abnormality. Your GP will be checking these results, and it is possible that you may need further investigation or tests to look into this further.

What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided. If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr Helen Ashdown (helen.ashdown@phc.ox.ac.uk or 01865 289261) or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, or the head of CTRG, email ctrg@admin.ox.ac.uk.

Are there any disadvantages or risks from taking part?

This study is observational, which means that we are not asking you to change any treatments as part of the study, only doing additional tests. We do not anticipate any serious risks from doing these tests. Taking blood samples may be uncomfortable and occasionally is associated with bruising or feeling faint. Breathing tests may require additional effort but should not be painful or uncomfortable. Testing will be done by a nurse or doctor trained in these procedures. Attending the surgery for these appointments will take up time (approximately three hours in total across all four appointments) and we are grateful for this.

Will the GP be informed of participation?

Your GP is aware that we have invited you to take part in this study. As mentioned above, we will use information in your medical records to find out about your previous medical problems, and will record some of the test results in your medical notes. Results of some tests will be sent back to your GP so that you can be followed up if there is any abnormality.

Will my taking part in the study be kept confidential?

Yes, all information collected about you during the research will be kept strictly confidential in accordance with the Data Protection Act. Only the research team will have access to the data. Responsible members of the University of Oxford and the Oxford University Hospital NHS Foundation Trust may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

Personal information which we have recorded about you will be stored in locked storage or password-protected electronic files. This will be securely destroyed after the study is complete, unless you have agreed that we can keep it for longer to be able to contact you again, in which case we would keep it for up to 3 years.

Will I be reimbursed for taking part?

We will offer you a £30 gift voucher (for Amazon and many high street stores) to thank you for your time in participating in the study, and to cover any travel expenses you might not otherwise have incurred. We will ask you to sign to say that you have received the gift voucher.

What will happen to me if I take part?

If we hear back from you that you are willing to take part, we will contact you to check that you are eligible to take part in the study, and arrange an appointment for you to be seen in our research clinic at your surgery. At this appointment, we will check that you understand what being in the study involves and ask you to sign a consent form, and then do take some measurements and tests as set out below. We estimate that this first appointment will take about an hour.

We will then ask you to come back to the surgery approximately every two months over the next six months (four appointments in total), when we will repeat these measurements. These other appointments will be shorter (approximately 45 minutes), as we will not need to ask you as many questions as on the first appointment. We can work around any holidays or plans you may have to be away.

These appointments are as part of the research study and would be in addition to your normal COPD appointments with your GP or practice nurse. However, some of the tests we are doing would be done routinely as part of your yearly COPD review and so these will be put on your records as they may be helpful for monitoring your COPD over time.

Before the tests

We will ask you to bring the inhalers you currently use (including your blue reliever inhaler (salbutamol) if you have one) to the appointment, and (if you can) to avoid smoking, drinking alcohol, doing vigorous exercise, having a heavy meal, or using your reliever inhaler in the few hours before the appointment.

Medical information

We will ask some questions about you and your medical history, including how much you have smoked. We will ask your permission to look at your GP records as well, so don't worry if you can't remember lots of detail. At the later appointments, we will just check that nothing has changed since your last appointment.

Questionnaires

We will ask you to complete some questionnaires about how good or bad your symptoms have been recently, and how these affect your life. The researcher can help you if you have difficulty with reading or writing.

Measurements

We will place a small clip on your finger to measure your oxygen levels. This is not uncomfortable and usually takes a few seconds. We will measure your height and weight.

Breathing Tests

Spirometry is a type of lung function test, and shows how well you breathe in and out. This is the same test that you may do at your yearly COPD review. A clip will be put on your nose to make sure that no air escapes from your nose. We will ask you to blow into a mouthpiece as fast and as far as you can until your lungs are completely empty. We will take three readings. We will then ask you to use your reliever (blue) inhaler, and repeat the spirometry after approximately 20 minutes. This is to test whether your breathing improves after using this inhaler (called 'reversibility'). We will do other tests while waiting for this time to pass. Fraction of exhaled nitric oxide (FeNO) is another breathing test, which is a guide to how much inflammation there is in the lungs. It is commonly used in hospital clinics, but is not yet used widely in GP surgeries. Doing the test involves blowing out into a mouthpiece keeping the breath steady. We will explain how to do this in more detail at the appointment.

Blood samples

We will prick your finger using a lancet, to obtain a drop of blood to test in a machine straight away. This measures the number and different types of white cells in the blood. This is a similar procedure used to when people with diabetes need to check their blood sugar. For a small number of participants, we will also put a drop of blood onto a glass slide to look at it under the microscope (to check how it matches the results from the machine). We will also take a sample of blood from a vein. This is the same procedure for a blood test that you would normally have done at your surgery. We will take 3 small bottles (15ml of blood, or about 3 teaspoons) in total each appointment and also use a drop to test in the machine above.

Feedback survey (final appointment only)

At the final appointment, we will ask you to complete a short questionnaire survey about your experience of having the tests above. This survey will also ask if you would be willing to be contacted in future to ask you in more detail about your thoughts and experiences of the tests, or other studies in future. We would ask your permission (consent) for other studies separately. Other than this, we will not contact you again after your final (fourth) appointment at six months.

What will happen to my test results and samples?

We will record the results of those tests which are normally done at your yearly COPD review in your GP records, as this may be useful for future reference. We will record the results of the questionnaires, FeNO breathing test and finger prick blood sample in a research database.

The blood sample taken from your veins will be processed by the laboratory. 2 of the small bottles will be sent for tests called 'full blood count' and 'C-reactive protein' (CRP). These are tests which might commonly be done by your GP, and the results will go back to your GP in a similar way to routine blood tests. Your GP would contact you directly if there was any serious abnormality with these tests. Otherwise, you can get the results in the normal way you would get the results of a blood test from your surgery (this varies between surgeries so we will discuss this with you at the appointment).

The third bottle will be processed for what is called 'saved serum'. This means it will be spun in a machine and then frozen to use for further tests in future. One of the tests we will do is called 'periostin' which is a new test of inflammation in COPD. However, we would like your permission to keep the sample we have frozen in order to do further tests in future. Your anonymised samples will be used mainly by local researchers, but ethically approved research projects may take place in hospitals, universities, non-profit institutions or commercial laboratories worldwide. The process of spinning the blood destroys all genetic material, so the sample could never be used for genetic testing or identify who you are.

What are the possible benefits of taking part?

There are no direct benefits to you of taking part. However, we hope this study will benefit patients with COPD in future by providing information about whether these tests can help guide whether steroid inhalers are beneficial for individual patients. However, we do not know what the outcome will be, which is why we are conducting this research.

Appendix K: COMET Informed Consent Form

Study Title: **Near-patient testing to guide COPD MaintenancE Treatment in primary care**

REC Ref: 16/SS/0135

		PLEASE INITIAL
1	I confirm I have read and understood the information sheet version number V2.0 dated 15th August 2016 for the above study and have had the opportunity to ask questions.	
2	I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.	
3	I consent to being contacted by the research team for the purposes of study follow up and I understand that this will require me to provide the research team with my contact details	
4	I understand that my medical notes will be reviewed and data collected by the research team. I permit these individuals access to my clinical records.	
5	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Oxford, from regulatory authorities [and from the NHS Trust(s)], where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
6	I understand that a blood sample will be taken to be used and stored by the research team for further research and analysis, and that I will not receive the result of this analysis.	
7	I consider these samples a gift and I understand I will not gain any direct personal benefit from this.	
8	I understand that the information collected about me may be used in an anonymous form to support other research in the future. It will not be possible for me to be identified by it.	
9	I agree to take part in the above study.	
10	**ADDITIONAL:** I agree to be contacted about ethically approved research studies for which I may be suitable, if I compete these details on the final visit survey. This information will be held for a maximum of 3 years. I understand that agreeing to be contacted does not oblige me to participate in any further studies.	
11	I agree for my anonymised samples to be used in future research, in hospitals, universities, non-profit institutions or commercial laboratories, here or abroad, which has ethics approval.	

Person taking consent:

Signed: _____ Name: _____ Date: __ __ / __ __ __ / __ __ __ __

Volunteer:

Signed: _____ Name: _____ Date: __ __ / __ __ __ / __ __ __ __

**1 copy for participant; 1 copy kept in medical notes, I copy returned to PC_CTU*

Appendix L: COMET Case Report Forms (CRFs)

CRFs formed the basis for the online CRF platform using OpenClinica. CRFs include:

- Eligibility CRF
- Baseline CRF
- Visit 2 CRF (Visit 3 and 4 CRFs are the same as Visit 2 CRF and are therefore not duplicated here)
- Blood Results CRF
- Study Discontinuation CRF

Participant ID: __ __ __ __ __

Screening ID: __ __ __ __ __ __ Date: __ __ / __ __ __ / __ __ __ __ Site ID: __ __

		Telephone Screening		Baseline Appt. Check	
Inclusion		**Yes**	**No**	**Yes**	**No**
1	Participant is willing and able to give informed consent for participation in the study.				
2	Male or Female, aged 40 years or above				
3	Have a diagnosis of COPD meeting spirometric criteria for diagnosis of COPD (FEV_1/FVC ratio <0.7) (as recorded in their primary care records)				
Exclusion		**Yes**	**No**	**Yes**	**No**
1	Any previous diagnosis of bronchiectasis, cystic fibrosis, interstitial lung disease, lung cancer, alpha-1 anti-trypsin deficiency or other chronic respiratory disease not related to COPD or asthma.				
2	Currently prescribed an ICS, or had a prescription for ICS in the last 2 years.				
3	Regularly takes oral steroids, or has been regularly taking oral steroids in the last 2 years. Regular use of oral steroids will in general be defined as a longer than 2 week course, although discrete short courses with tapering are acceptable for inclusion				
4	Prior inclusion in a clinical trial of an investigational medicinal product for airways disease in the last 90 days or which may involve administration of oral or inhaled steroid treatment.				
	Do not check during telephone screening				
5	Co-existent active diagnosis of asthma (reviewed in the last 2 years)				

TELEPHONE SCREENING: If inclusion criteria are all YES and relevant exclusion criteria are all NO the participant is eligible to be booked in for a baseline appointment, please continue with booking

BASELINE APPOINTMENT: If inclusion criteria are all YES and relevant exclusion criteria are all NO the participant is eligible to continue on to complete the informed consent

Full eligibility completed by:

Signed: _____ Name: _____ Date: __ __ / __ __ __ / __ __ __ __

Date: __ __ / __ __ __ / __ __ __ __

Demographic Information		
1	Date of Birth:	__ __ / __ __ __ / __ __ __ __
2	Sex:	Male: ☐ Female: ☐

Medical History		
1	Asthma	Yes: ☐ No: ☐
2	Heart Failure	Yes: ☐ No: ☐
3	Hypertension	Yes: ☐ No: ☐
4	Cancer	Past: ☐ Current: ☐ Never: ☐
		Site of cancer: _____
5	Hay fever	Yes: ☐ No: ☐
6	Eczema	Yes: ☐ No: ☐
7	Autoimmune condition	Yes: ☐ No: ☐
		If yes please state: _____
8	Other chronic condition	Yes: ☐ No: ☐
		If yes please state: _____
		If yes please state: _____
		If yes please state: _____
9	Previous steroid use:	Yes: ☐ No: ☐
		If yes: Date: __ __ / __ __ __ / __ __ __ __
		Reason: _____

COPD History

1 Date of COPD Diagnosis: __ __ / __ __ __ / __ __ __ __

2i Data of eligibility spirometry (FEV1/FVC ratio <0.7): __ __ / __ __ __ / __ __ __ __

If more than one eligible spirometry, please use the most recent result

ii Value of FEV1/FVC ratio __ . __ __

iii FEV1 % predicted __ __ __ %

3 Date of last Exacerbation: __ __ / __ __ __ / __ __ __ __

4 How many exacerbations in the last year: _____

Details of exacerbations in the last year

i. Date: __ __ __ / __ __ __ __

Details unknown: ☐

Treatment: Home: ☐ Hospital: ☐

Treatment with: Steroids: ☐ Antibiotics: ☐ Nebulisers: ☐ Respiratory Support: ☐

5 How many exacerbations in the last 2 years: _____
Including the total above

6 MRC Dyspnoea Score: _____

MRC Dyspnoea guide	
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after about 100 m or after a few minutes on the level
5	Too breathless to leave the house, or breathless when dressing or undressing

Smoking History				
1	Current Smoker:	Yes: ☐	No: ☐	
1b	If no, ever smoked:	Yes: ☐	No: ☐	Passive: ☐
1c	If yes, start date:	__ __ / __ __ __ / __ __ __ __		
4	Quit date	__ __ / __ __ __ / __ __ __ __		
5	Number of years	_____ years		
6	Smoked what:	_____		
7	Number smoked per day:	_____		
8				

Medication History – Respiratory Medications (including O2)

Name	Formulation (oral/inhaler /nebuliser)	Dose – no. of puffs	Frequency	Strength	Date Started	Continued?	If no: stop date	*For inhalers only:* Last time taken
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	

Concomitant Medication – non respiratory, current only and considered medically relevant

Name	Dose	Started	Frequency
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	

For more medications see spare pages

Physical Examination			
1	Oxygen Saturation:	__ __ __	%
2	Weight:	__ __ __	Kg
3	Height:	__ __ __	cm

FeNO Test

FeNO: 10s successfully completed Yes ☐ No ☐

Number of attempt made:
Including successful attempt _____

6s successfully completed
only if 10s unsuccessful Yes ☐ No ☐

Number of attempt made:
Including successful attempt _____

FeNO Result: __ __ ppb

Please remember to give the participant the CAT and CCQ so that they can complete them in the rest periods of the spirometry

Spirometry				
Date: **Venue:**	**YES**	**NO**	**N/A**	**COMMENTS**
Contraindications: Haemoptysis of unknown origin; Pneumothorax; unstable cardiovascular status including recent MI or PE; pain; recent cerebral-vascular event; thoracic-abdominal or aortic aneurism; recent eye surgery or detached retina; recent thoracic or abdominal surgery; nausea and vomiting; ear infection; pregnancy				
Patient sat in a chair with arms on both sides?				
The patient has dentures?				
Dentures were removed for the test?				
The patient is wearing loose clothing?				
The patient has had a large meal in last 2hrs?				
The patient has had any alcoholic in last 4hrs?				
Patient has completed vigorous exercise in last 30mins?				
The patient smoke?				
Time of their last cigarette: __ __ : __ __ am / pm				

Last inhalers:

Name: _____ Dose: _____ Time: __ __ : __ __ am / pm

Name: _____ Dose: _____ Time: __ __ : __ __ am / pm

Name: _____ Dose: _____ Time: __ __ : __ __ am / pm

Spirometry			
Relaxed Vital Capacity results (exhale in a relaxed breath)			
Pre: Time: __ __ : __ __ 24Hr		**Post: Time: __ __ : __ __ 24Hr**	
1st	__ . __ __	1st	__ . __ __
2nd	__ . __ __	2nd	__ . __ __
3rd	__ . __ __	3rd	__ . __ __
Forced Expiratory Capacity Results (short sharp puff)			
Pre: Time: __ __ : __ __ 24Hr		**Post: Time: __ __ : __ __ 24Hr**	
1st	__ . __ __	1st	__ . __ __
2nd	__ . __ __	2nd	__ . __ __
3rd	__ . __ __	3rd	__ . __ __
Patient felt unwell during spirometry? Yes: ☐ No: ☐			
FEV 1: __ . __ __		FEV 1: __ . __ __	
FVC: __ . __ __		FVC: __ . __ __	
Ratio (FEV 1/ FVC) : __ __		Ratio (FEV 1/ FVC) : __ __	
FEV 1 % Predicted: __ __ __ %		FEV 1 % Predicted: __ __ __ %	

POCT Result			
- Take a the capillary sample first and record the results with as many decimal points as given - Take the venous sample second - If there was a problem taking either sample please comment here: _____ _____			
		Capillary Sample	Venous Sample
1	Eosinophil count:	x10^9/L	x10^9/L
2	Total WCC	x10^9/L	x10^9/L
3	Neutrophils	x10^9/L	x10^9/L
4	Lymphocytes	x10^9/L	x10^9/L
Make sure that all samples to be sent to the lab are labelled and in the correct shipment material			

Signed: _____ Name: _____ Date: __ __ / __ __ __ / __ __ __ __

Exacerbations extra page	
Please complete when participant has had more than 2 exacerbations within the last 2 years. Put most recent exacerbation at the top	
1	Date: __ __ __ / __ __ __ __ Details unknown: Treatment: Home: ☐ Hospital: ☐ Treatment with: Steroids: ☐ Antibiotics: ☐ Nebulisers: ☐ Respiratory Support: ☐
2	Date: __ __ __ / __ __ __ __ Details unknown: Treatment: Home: ☐ Hospital: ☐ Treatment with: Steroids: ☐ Antibiotics: ☐ Nebulisers: ☐ Respiratory Support: ☐
3	Date: __ __ __ / __ __ __ __ Details unknown: Treatment: Home: ☐ Hospital: ☐ Treatment with: Steroids: ☐ Antibiotics: ☐ Nebulisers: ☐ Respiratory Support: ☐

Medication History – Respiratory Medications (including O2) – Extra sheet								
Name	Formulation (oral/inhaler /nebuliser)	Dose – no. of puffs	Frequency	Strength	Date Started	Continued?	If no: stop date	*For inhalers only:* Last time taken
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	

Concomitant Medication – non respiratory, current only and considered medically relevant			
Name	Dose	Started	Frequency
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	

Date: __ __ / __ __ __ / __ __ __ __

Update questions			
1	Have there been any changes to their medication since the last visit:	☐ Yes	☐ No
2	Have there been any new diagnoses since their last visit:	☐ Yes	☐ No
3	Have there been any changes to their contact details since their last visit:	☐ Yes	☐ No

COPD History

1 How many exacerbations since last visit: _____

Details of exacerbations :

Most recent:

Date: __ __ / __ __ __ / __ __ __ __

Details unknown: ☐

Treatment:
- Home: ☐
- Hospital: ☐

Treatment with:
- Steroids: ☐
- Antibiotics: ☐
- Nebulisers: ☐
- Respiratory Support: ☐

Previous: *where more than 2 please complete the additional page*

Date: __ __ / __ __ __ / __ __ __ __

Treatment:
- Home: ☐
- Hospital: ☐

Treatment with:
- Steroids: ☐
- Antibiotics: ☐
- Nebulisers: ☐
- Respiratory Support: ☐

Physical Examination				
1	Oxygen Saturation:	_____	%	Please record to nearest kg and cm
2	Weight:	_____	Kg	
3	Height:	_____	cm	

FeNO Test

FeNO: 10s successfully completed Yes ☐ No ☐

Number of attempt made:
Including successful attempt _____

6s successfully completed
only if 10s unsuccessful Yes ☐ No ☐

Number of attempt made:
Including successful attempt _____

FeNO Result: __ __ ppb

1 MRC Dyspnoea Score: _____

MRC Dyspnoea guide	
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after about 100 m or after a few minutes on the level
5	Too breathless to leave the house, or breathless when dressing or undressing

Please remember to give the participant the CAT and CCQ so that they can complete them in the rest periods of the spirometry

Spirometry				
Date: **Venue:**	**YES**	**NO**	**N/A**	**COMMENTS**
Contraindications: Haemoptysis of unknown origin; Pneumothorax; unstable cardiovascular status including recent MI or PE; pain; recent cerebral-vascular event; thoracic-abdominal or aortic aneurism; recent eye surgery or detached retina; recent thoracic or abdominal surgery; nausea and vomiting; ear infection; pregnancy				
Patient sat in a chair with arms on both sides?				
The patient has dentures?				
Dentures were removed for the test?				
The patient is wearing loose clothing?				
The patient has had a large meal in last 2hrs?				
The patient has had any alcoholic in last 4hrs?				
Patient has completed vigorous exercise in last 30mins?				
The patient smoke?				
Time of their last cigarette: __ __ : __ __ am / pm				

Last inhalers:

Name: _____ Dose: _____ Time: __ __ : __ __ am / pm

Name: _____ Dose: _____ Time: __ __ : __ __ am / pm

Name: _____ Dose: _____ Time: __ __ : __ __ am / pm

Spirometry			
Relaxed Vital Capacity results (exhale in a relaxed breath)			
Pre: Time: __ __ : __ __ 24Hr		**Post: Time: __ __ : __ __ 24Hr**	
1st	__ . __ __	1st	__ . __ __
2nd	__ . __ __	2nd	__ . __ __
3rd	__ . __ __	3rd	__ . __ __
Forced Expiratory Capacity Results (short sharp puff)			
Pre: Time: __ __ : __ __ 24Hr		**Post: Time: __ __ : __ __ 24Hr**	
1st	__ . __ __	1st	__ . __ __
2nd	__ . __ __	2nd	__ . __ __
3rd	__ . __ __	3rd	__ . __ __
Patient felt unwell during spirometry? Yes: ☐ No: ☐			
FEV 1: __ . __ __		FEV 1: __ . __ __	
FVC: __ . __ __		FVC: __ . __ __	
Ratio (FEV 1/ FVC) : __ __		Ratio (FEV 1/ FVC) : __ __	
FEV 1 % Predicted: __ __ __ %		FEV 1 % Predicted: __ __ __ %	

POCT Result

- Take a the capillary sample first and record the results with as many decimal points as given
- Take the venous sample second
- If there was a problem taking either sample please comment here: _____

_____

		Capillary Sample	Venous Sample
1	Eosinophil count:	x10^9/L OR %	x10^9/L OR %
2	Total WCC	x10^9/L	x10^9/L
3	Neutrophils	x10^9/L OR %	x10^9/L OR %
4	Lymphocytes	x10^9/L OR %	x10^9/L OR %

Make sure that all samples to be sent to the lab are labelled and in the correct shipment material

Signed: _____ Name: _____ Date: __ __ / __ __ __ / __ __ __ __

Exacerbations extra page		
Please put most recent exacerbation at the top		
1	Date:	__ __ __ / __ __ __ __
	Details unknown:	☐
	Treatment:	Home: ☐ Hospital: ☐
	Treatment with:	Steroids: ☐ Antibiotics: ☐ Nebulisers: ☐ Respiratory Support: ☐
2	Date:	__ __ __ / __ __ __ __
	Details unknown:	☐
	Treatment:	Home: ☐ Hospital: ☐
	Treatment with:	Steroids: ☐ Antibiotics: ☐ Nebulisers: ☐ Respiratory Support: ☐
3	Date:	__ __ __ / __ __ __ __
	Details unknown:	☐
	Treatment:	Home: ☐ Hospital: ☐
	Treatment with:	Steroids: ☐ Antibiotics: ☐ Nebulisers: ☐ Respiratory Support: ☐

Medication History – Respiratory Medications (including O2) – Extra sheet								
Name	Formulation (oral/inhaler /nebuliser)	Dose – no. of puffs	Frequency	Strength	Date Started	Continued?	If no: stop date	*For inhalers only:* Last time taken
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	
					M M/ Y Y	Y / N	M M/ Y Y	

Concomitant Medication – non respiratory, current only and considered medically relevant			
Name	Dose	Started	Frequency
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	
		M M/ Y Y	

Signed: _____ Name: _____ Date: __ __ / __ __ __ / __ __ __ __

Date: __ __ / __ __ __ / __ __ __ __

Blood Results			
1	Haemoglobin	gms/dl	Standardised unit Please mark as many decimal points as are given
2	Total White Cell count	x10^9/L	
3	Eosinophil Count	x10^9/L	
4	Neutrophil Count	x10^9/L	
5	Lymphocyte Count	x10^9/L	
6	CRP	mg/L	
Any comments *e.g. results of blood film*		_____	

Blood Results – collected from London lab at later date		
1	Periostin	µg/L

Signed: _____ Name: _____ Date: __ __ / __ __ __ / __ __ __ __

STUDY DISCONTINUATION FORM

Participant ID:

Date of last scheduled visit participant attended: | d | d | m | m | 2 | 0 | y | y |

PLEASE COMPLETE WITHDRAWAL SECTION OR LOSS TO FOLLOW UP SECTION AS APPLICABLE

WITHDRAWAL

Please indicate how the participant was withdrawn (tick one box) & specific reason if known

A. WITHDRAWAL BY RESPONSIBLE INVESTIGATOR ☐	**SPECIFIC REASON(S) FOR WITHDRAWAL:** ☐ Non adherence to study procedures ☐ Due to safety concerns ☐ Ineligibility ☐ Non-compliance ☐ Withdrawal of consent ☐ Significant protocol deviation ☐ Other Further Details: _____ _____ _____
B. WITHDRAWAL BY PARTICI-PANT ☐	

Please indicate below:

☐ Withdrawal from follow up visits only—no further involvement but participant allows continued use of samples already collected.

OR

LOST TO FOLLOW-UP

☐ The loss or lack of continuation of a subject to follow-up

Signature_____ Date_____

Appendix M: Respiratory questionnaires

Respiratory questionnaires include:

- COPD Assessment Test (CAT)
- Clinical COPD Questionnaire (CCQ)

Your name:	Today's date:

COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

Last Updated: February 24, 2012

CLINICAL COPD QUESTIONNAIRE

Diary

Information:
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Internet: www.ccq.nl

Patient number:_____
Date:_____

CLINICAL COPD QUESTIONNAIRE

Please **circle** the number of the response that best describes how you have been feeling during the **past 24 hours**. (Only **one** response for each question).

On average, **during the past 24 hours**, how often did you feel:	never	hardly ever	a few times	several times	many times	a great many times	almost all the time
1. Short of breath **at rest**?	0	1	2	3	4	5	6
2. Short of breath **doing physical activities**?	0	1	2	3	4	5	6
3. **Concerned** about getting a cold or your breathing getting worse?	0	1	2	3	4	5	6
4. **Depressed (down)** because of your breathing problems?	0	1	2	3	4	5	6
In general, **during the past 24 hours**, how much of the time:							
5. Did you **cough**?	0	1	2	3	4	5	6
6. Did you **produce phlegm**?	0	1	2	3	4	5	6
On average, **during the past 24 hours**, how limited were you in these activities **because of your breathing problems**:	not limited at all	very slightly limited	slightly limited	moderately limited	very limited	extremely limited	totally limited /or unable to do
7. **Strenuous physical activities** (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
8. **Moderate physical activities** (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
9. **Daily activities at home** (such as dressing, washing yourself)?	0	1	2	3	4	5	6
10. **Social activities** (such as talking, being with children, visiting friends/ relatives)?	0	1	2	3	4	5	6

Appendix N: COMET working instructions

Work Instructions

COMET - Near-patient testing to guide COPD MaintenancE Treatment in primary care

An observational study to determine variability and accuracy of inflammatory biomarkers in stable state

CONTENTS

OVERVIEW

Study Design:	Prospective observational cohort study GP surgery based
Study Participants:	ICS-naïve patients with COPD in primary care
Planned Sample Size:	100 patients
Planned Study Period:	18 months (January 2017 – June 2018)
Objectives:	**Primary** - to describe biomarker levels (eosinophils, FeNO, CRP, periostin) including repeatability and interdependence. **Secondary** - to investigate method comparison of near-patient eosinophils compared to laboratory eosinophils. **Tertiary** - to assess the feasibility of undertaking such measurements in a primary care setting.

MAIN CONTACTS

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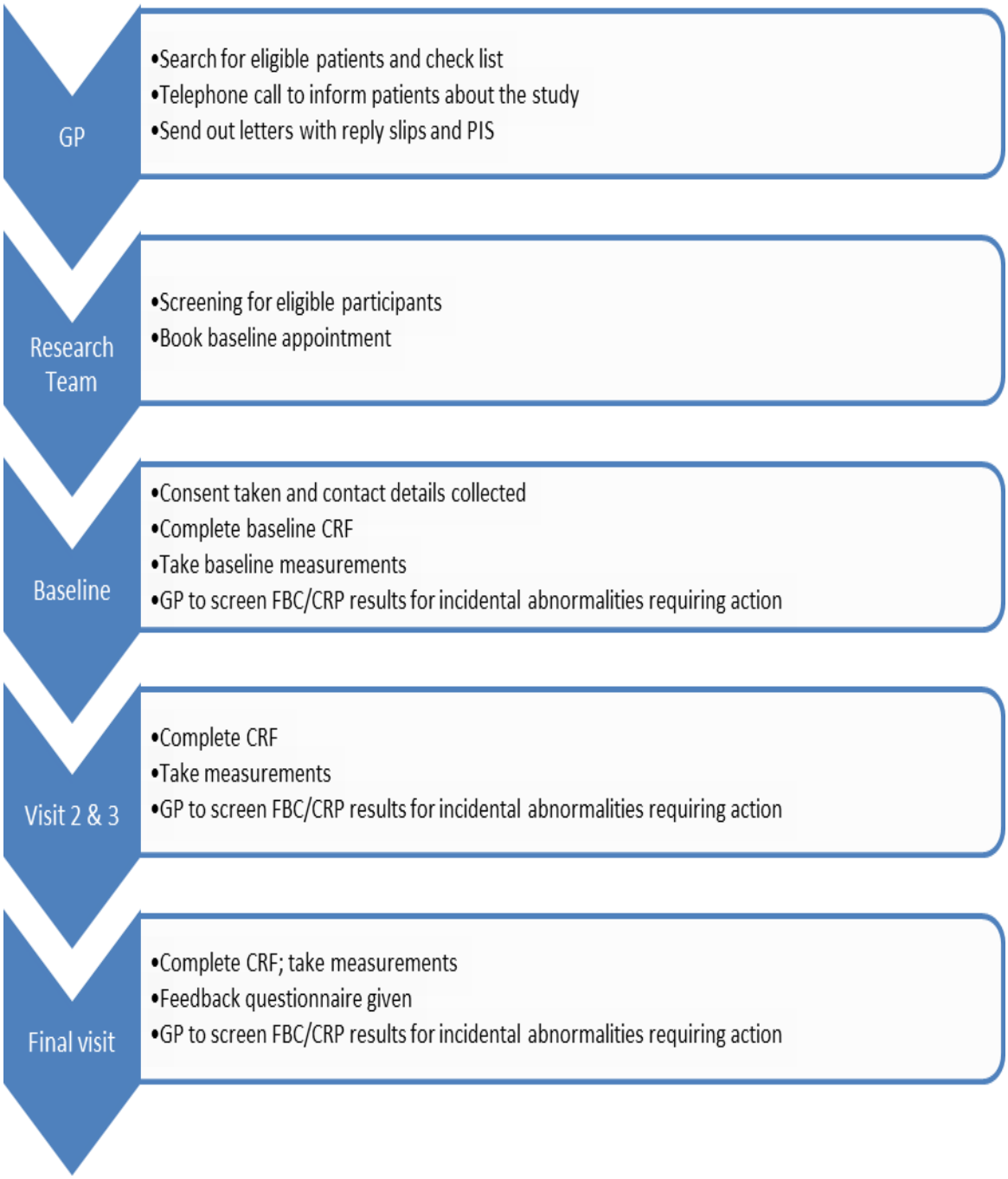
E-mail: heather.rutter@phc.ox.ac.uk

STUDY PROCEDURES

Study flow chart



Schedule of Study Procedures

	Visit timing	**Week 0**	**Week 8**	**Week 16**	**Week 24**
	Screening and telephone contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Health record searches, GP phone call and recruitment letter	X				
Eligibility assessment	X	X			
Informed consent		X			
Demographics	X	X			
Contact Details		X	Check no changes	Check no changes	Check no changes
Medical history, smoking and medication history		X	Check no changes	Check no changes	Check no changes
Respiratory questionnaires		X	X	X	X
Physical examination (oxygen saturation only)		X	X	X	X
FeNO		X	X	X	X
Spirometry including reversibility		X	X	X	X
Venous blood tests (CRP, periostin, eosinophils – POC and laboratory)		X	X	X	X
Finger-prick test (POC eosinophils)		X	X	X	X
Survey about acceptability of tests					X

Booking Appointments

Use the password-protected database to record patient details. Go through the eligibility checklist using Open Clinica over the phone with the patient (or e-mail if preferred). Use the password-protected spreadsheet to record appointment times. Appointments should be scheduled before the final lab pick-up time for the practice.

When booking patient in for their appointment, please remind them:

1. To bring all their inhalers, including their salbutamol or other reliever inhaler, with them to the appointment
2. Inhalers should be taken as normal
3. No alcohol/heavy meal/vigorous exercise in the two hours prior to the appointment
4. No smoking in the half hour before the appointment
5. To bring reading glasses for completing forms and questionnaires

After times have been agreed with patients and practice, shortly before the visit, the practice should be e-mailed from a secure NHS account with details of patient names for the appointment system. It is also helpful to arrange appointment times for the follow-up visits to be able to arrange this with the patient.
Ideally phone patients a few days beforehand to remind them about the appointment.

Equipment and paperwork to take with you to clinic

Equipment:

- Niox Vero monitor (FeNO machine) and mouthpiece (attached)
- FeNO disposable filters
- HemoCue machine
- HemoCue cuvettes (Blood slides)
- HemoCue lancets
- HemoCue cleaning solution (just in case)
- DiffSafe blood dispensers ("Supplier GP Supplies, London Ordering code 366005 Description BD 366005 Vacutainer DIFF-SAFE Blood Dispenser Quantity Pack of 100 Cost £13.32 per pack")
- Spirometer (in carry case with power source and extension lead)
- Syringe (no need to take if able to calibrate the afternoon/evening beforehand)
- Alcohol gel
- Checklist and paper work (see below)
- Clenil wipes (or if clenil wipes are not available then an approved antibacterial wipe)
- Spirometry nose clips
- Spirometry one way mouth piece
- Spare paper for spirometry machine
- Pulse oximeter

- Spare batteries for oximeter (2xAAA)
- Marker pen to anonymise blood results printed (visits 2-4)

Paperwork:

- PIS (visit 1 only, in case pt wants to refer to it)
- Consent form (visit 1 only)
- CCQ
- CAT
- Punch pockets (to organise above into pre-visit)
- Appointment cards
- Labels for blood form
- Back-up printed CRF
- Gift voucher (visit 4 only)
- Voucher receipt form (visit 4 only)
- Survey (visit 4 only)
- A5 envelopes for survey (visit 4 only)

Check in room on arrival that the following are available:

- Access/ID card if needed
- EMIS log in
- ICE linkage
- Generic Docman login
- Connection to printer
- Plain paper
- ICE sheets (labels)
- Orange biochemistry/haematology forms
- Spare electric socket

Phlebotomy (N.B. This should be standard equipment)

- Gloves
- Butterfly needles - blue/green
- Butterfly vacutainer connectors
- Vacutainers
- Green vacutainer needles
- EDTA tubes (purple)
- Lithium heparin tubes (green)
- Serum (SST) tubes (gold)
- Cotton wool
- Micropore tape
- Plasters
- Disposable tourniquets
- Appropriate clinical waste disposal (yellow bin and sharps bin)
- Paper towel

Other equipment

- Weighing scales (access to these, not necessarily in clinical room used although this would be ideal)
- Height measurer (access, not necessarily in clinical room used although this would be ideal)

Baseline Assessments

CRF Completion

- Eligibility CRF [view other diagnoses on 'problems' tab, medications] and consent, before proceeding to baseline CRF
- Demographics – demographic details (date of birth and sex) and contact details will be confirmed
- Medical history – taken from the participant, and corroborated using the primary care records, ideally simultaneously, to include:
    - Information about COPD diagnosis and previous treatments, with previous spirometry recordings noted, and previous exacerbation history (timings, treatments and whether hospitalisation/respiratory support was required)
    - Previous spirometry recorded can usually be found in the investigations tab (uncheck 'latest only' at the top).
    - Other chronic medical conditions including: asthma, heart failure, hypertension, cancer, hay fever, eczema, autoimmune conditions and other chronic conditions.
    - Smoking history including exposure to passive smoking
    - Current medications, current and past respiratory medications, and previous oral or inhaled steroids prescribed (view easiest by selecting Sort by 'EMIS drug group' from within 'medications' tab, and changing between current and past medications – oral steroids are listed under GI medications. Start date can be found by right clicking on medication and selecting 'drug history'. 'Previous oral steroids' in CRF refers to regular use of oral steroids (a long-term prescription, rather than one-off courses)). Remember to scroll to the right on the page. If inhaler has not been used that day, enter 00:00 and add an annotation detailing when last taken e.g. 6 months ago.

- MRC Dyspnoea score (record the highest score which the patient fits)
- Oxygen saturations (see operational details below)
- FeNO (see operational details below)
- Height and weight – remove shoes/heavy clothing
- Spirometry including reversibility (see operational details below)
- Respiratory questionnaires – the COPD Assessment Test (CAT) and Clinical COPD Questionnaire (CCQ), remember to add study and visit number e.g. A-005-1 to forms
- Capillary blood sample – Hemocue® machine (see operational details below)
- Venous blood sample – Gold, Green and Purple topped bottles. EDTA tube (for full blood count, with part of this sample used for testing in Hemocue® machine), serum tube (for periostin and saved serum) and lithium-heparin tube (for CRP)

FeNO

This should be done before spirometry. Start the instrument from power save mode If NIOX VERO ® is in standby or sleep mode simply touch the display to activate it.

Please note: Patient filters are for single use only and that the instrument must NOT be switched OFF during measurement procedure.

Preparation for measurement

1. Lift the breathing handle from the holder and remove the handle cap.
2. Obtain a new patient filter. Attach the patient filter to the breathing handle. Make sure to twist the patient filter in place until it clicks into place.
3. Give the breathing handle to the patient and guide the patient to provide a breath sample as described in the next section. Go through it using the demo first of all – use colour scale as example.

Measurement

1. Empty the lungs by breathing out thoroughly.
2. Close the lips around the mouthpiece on the patient filter so that no air leakage occurs.
3. Inhale deeply through the patient filter to total lung capacity. During inhalation, the cloud on the display moves upwards.

Please note: The procedure is activated by inhaling air from the handle or by pressing the start measurement button

4. Exhale slowly through the filter while keeping the cloud within the limits as indicated on the display (the white lines).
5. The instrument display and audio signals guide the user to the correct exhalation pressure.

Please note: A continuous sound indicates correct pressure with a frequency proportional to the pressure. An intermittent high frequency sound - too strong pressure. An intermittent low frequency sound - too weak pressure. Exhalation with: Pressure correct, Pressure too strong, Pressure too weak.

6. Exhale until the cloud has passed the flag.
7. The instrument will analyse the sample and generate a result in approximately one minute.
8. The result is then displayed.

Please note: Do not exhale or inhale through the patient filter during the analysis process

Try up to 3 times with the 10 second measurement before proceeding to the 6 second measurement. Patients may try more than 3 times if they wish at the 6 second measurement but this should be stopped if they are tiring/unwell, or if there is no suggestion that their technique is improving after the 2x3 attempts.
Perform 6s NO measurement

Change to 6s Measurement mode by selecting the 10s button (green man symbol) on the main menu
1. The button changes to 6 s measurement mode (orange, small child symbol).
2. The 6s measurement mode is illustrated with an orange start button.
3. Perform measurement as instructed in the Measurement section.
5. Wait for the result.
6. The result screen displays the icon for 6s measurement.

Please note: The device will always return to the default 10s mode after a 6s measurement – **this needs to be selected each time before a 6s measurement.**

Spirometry

Calibration

Calibration to be conducted at the beginning of each clinic unless the temperature of the clinic room changes or the Spirometry is dropped then re-calibration should be carried out. This can be done the day before in primary care to avoid carrying the syringe, if no major change in conditions are expected.

- Check the Spirometer for damage e.g. marks, scratches or bumps; ensure the mouth piece is clear from debris. If damage found document in calibration check file and contact contractors who complete annual servicing for advice.
- Turn the Spirometry on, check that date and time are correct.
- Connect the three litre syringe to the mouth piece with the manufactures adapter (white plastic tube, kept in box with syringe).
- On the machine screen click on the calibration icon and follow the instructions for calibration.
- Complete three blows with the calibration syringe by pulling out and pushing handle in and out of the syringe. The first blow medium, the second slow and the third fast, aiming to keep within the grey shading shown on the Spirometry screen.
- If not within 3% repeat, if problem persists discontinue use of Spirometer.
- Print calibration report and sign (in black ink).
- Place report in the calibration folder in the COMET file, which is kept with trial documents in the cupboard in the senior trial managers' room.

Please note: when using any function on the Spirometer, the again button takes you onto the next step, the reject button will delete the last blow recorded and the done button will take you to either the main screen menu or the results.

Cleaning

- Clean outer case and machine with clenil wipes (or if clenil wipes are not available then an approved antibacterial wipe) on a daily basis. Ensuring wipes are disposed of in a bin or yellow bag if in clinic setting.
- Clean transducer after every 10th patient, to clean the transducer, remove from the Spirometer and place in approximately 500mls of water for a maximum of 10 minutes.
- Remove transducer and leave to air dry in a safe place over night.
- When re-inserting transducer to the Spirometer review turbine for cracks or damage.
- If damage seen do not use and document in the cleaning file, and contact the contractors who complete annual servicing for advice.

Errors in Spirometry Testing

When conducting Spirometry look out for the following errors:-

- Poor seal around mouthpiece
- Hesitation or false start
- Early termination on exhalation
- Poor intake of breath
- Poor forced expiratory effort
- Cough during procedure
- Incorrect data into the spirometer prior to testing

If any of these errors occur, demonstrate and explained again to the patient what you are asking them to do.

Performing Spirometry

- Complete trial documentation. Enter patient details as study/visit number (e.g. A-005-1), DOB, sex, height/weight.
- Explain the Spirometry test to the patient and answer any questions they may have. Check exclusion criteria as per CRF – not a problem if patient wearing dentures but should check they are correctly fitting and make sure do the same for subsequent spirometry.
- If the patient feels unwell at any point throughout the Spirometry test stop immediately and ensure patient is back to their original health state before letting them leave the appointment.
- Use single use one way mouth piece and for relaxed blows disposable nose clip.
- Give patients clear instructions and demonstrate what you are asking of them.
- Carry out relaxed Vital Capacity (VC) by asking patient to take a full inspiration and then to perform a full expiration in a steady manoeuvre, 2 tests should be within 5% (Note if patient leans forward place hand on shoulder to discourage as this will compromise the result).
- Carry out three Forced Vital Capacity (FVC) without nose clips by asking the patient to take full inspiration and then to exhale fully using forced manoeuvre (2 blows should be within 5% of each other).
- A maximum of 8 attempts is acceptable in any one session. If the patient is unable to perform the test, document as missing on the CRF.
- The patient is to then self-administration their own salbutamol inhaler (2 puffs), wait 20 minutes before repeating as post-bronchodilator (machine will need to be left plugged in during this time). Other tests (except FeNO) and questionnaires can be done in this time.
- Print out numerical and graphical Spirometry results.
- Document Spirometry results in trial documentation as per CRF.

- Wear gloves to remove mouth piece from the Spirometry machine and then dispose of mouth piece and nose clip in patients' waste bin.
- Using clenil wipes (or if clenil wipes not available an antibacterial wipe) clean outer casing of the turbine vain, Spirometry machine and carry case.

Capillary blood sample - Hemocue® machine

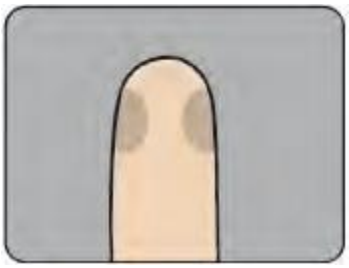
Please note: The microcuvette is for single use only.

1. Make sure the patient's hand is warm and relaxed. Use only the middle or ring finger for sampling. Avoid fingers with rings on.

2. Clean fingertip with disinfectant and allow to dry completely or wipe off with a dry, lint-free wipe.

3. Using your thumb, lightly press the finger from the top of the knuckle towards the tip.

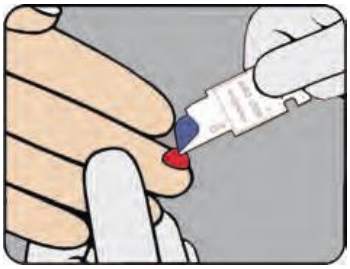
4. Sample at the side of the fingertip.



5. While applying light pressure towards the fingertip, puncture the finger using a lancet.

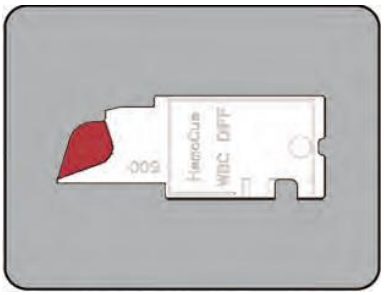
6. Wipe away the first two or three drops of blood.

7. Re-apply light pressure towards the fingertip until another drop of blood appears.



8. When the blood drop is large enough, fill the microcuvette in one continuous process. Do NOT refill!
NOTE: Make sure that the microcuvette is filled from the tip, forming an angle (about 45 °) with the blood drop.

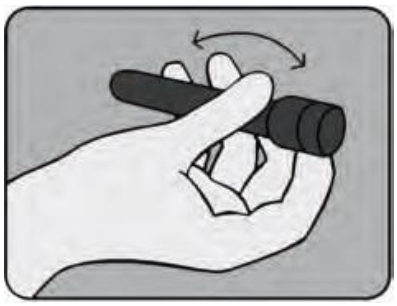
9. Wipe off excess blood from the outside of the microcuvette with a clean, lint-free wipe e.g. paper towel. Do not touch the open end of the microcuvette.

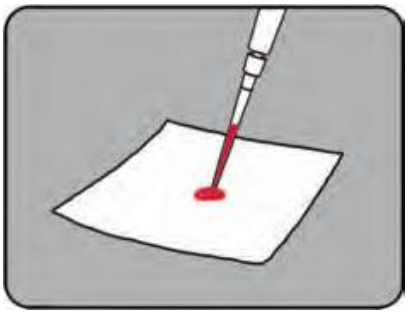


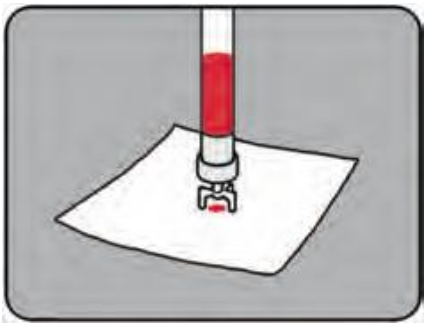
10. Look for air bubbles in the filled microcuvette. If present, discard the microcuvette and fill a new microcuvette from a new drop of blood.

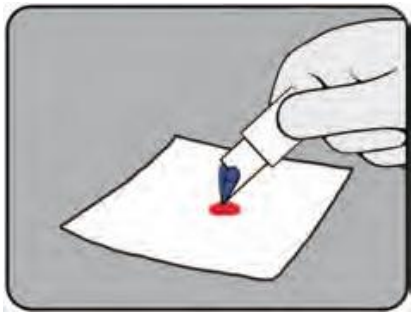
Please note: If a second sample is to be taken, it is important that this is done after the measurement of the first sample is completed. Wipe away the remains of the drop of blood and fill the second microcuvette from a new drop of blood as per steps 8–10 above.
NOTE: HemoCue WBC DIFF is not validated for heel stick.

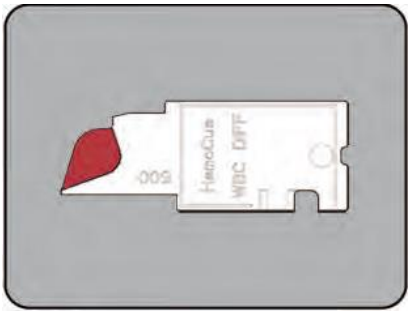
Blood Collection Venous Sample and Control Material – use EDTA (purple) tube











For the measuring procedure see *Routine Use/QC Test* or *Routine Use/Patient Test*. Control material shall always be measured using QC test procedure.

1. Venous blood samples shall be stored at room temperature (18–30 °C, 64–86°F) and analyzed within eight hours after sample collection. Mix the venous sample tubes thoroughly using a roller mixer for 1-2 minutes or invert the tube 10–20 times by hand. Samples may not be diluted. For control material always follow instructions for use provided by the manufacturer.
2. Place a drop of blood or control material onto a hydrophobic surface e.g. a glove, on a hard surface, using a pipette (2a) or other suitable transfer device (2b).
3. Fill the microcuvette in one continuous process. Do NOT refill!

NOTE: Make sure that the microcuvette is filled from the tip, forming an angle (about 45 °) with the blood drop.

4. Wipe off excess blood from the outside of the microcuvette with a clean, lint-free wipe. Do not touch the open end of the microcuvette.
5. Look for air bubbles in the filled microcuvette. If present, discard the microcuvette and fill a new microcuvette from a new drop of blood.

Patient Test stands for performing tests on samples from patients

1. Start the analyzer as described in *Start-Up* section. Place the cuvette moving arm in loading position.
2. The display will show the main menu. Take a microcuvette from the package (HemoCue WBC DIFF Microcuvette or HemoCue WBC Microcuvette). For single packaged microcuvettes; open the inner wrapping and take out the microcuvette.
3. Press the button below Patient Test symbol.
4. Enter required data (selected in settings) e.g. Operator ID, Patient ID, Lab ID, and Site ID. To enter data see *Data Entry* section.
5. If data has been entered the data confirmation window is shown. Press right button to confirm. To change information, press left button until the desired window is shown.


HemoCue
WBC DIFF


HemoCue
WBC DIFF

6. Insert cuvette symbol is shown.
7. Take a sample according to *Blood Collection Capillary Sample* or *Blood Collection Venous Sample and Control Material* sections. Place the microcuvette into the cuvette holder (7a) and start measurement as soon as possible but no later than 1 minute after filling the microcuvette by gently pushing the cuvette holder to its measuring position (7b).
8. During measurement the measuring window is shown.

More pics 9a, 9b, 9c

9. The results are displayed within < 5 minutes,
9a. WBC DIFF result window
9b. WBC result window
9c. Entered data

The result windows may differ due to data entered and choice of microcuvette. To jump between the result and data entered windows press button below the Switch symbol.
Confirm result by pressing button below the Accept symbol. Reject result by pressing button below the Reject symbol. A rejected result will be saved but marked with a flag as rejected. The display shows the main menu.
NOTE: Do not remeasure the filled microcuvette.
10. Always handle blood specimens with care, they might be infectious. Consult local environmental authorities for proper disposal. Always wear protective gloves when handling blood specimens. The microcuvette is for single use only.

Enter data on CRF for both capillary and venous samples. Enter the absolute values (on the left hand side), not the % figures.

Expected Values (Dacie and Lewis Practical Haematology)

White Blood Cell values for normal adults expressed as a mean ±2SD (95% Range)

	Adults (x109/L)	Adults (%)
White Blood Cell Count	4.0-10.0	NA
Neutrophils	2.0-7.0	40-80
Lymphocytes	1.0-3.0	20-40
Monocytes	0.2-1.0	2-10
Eosinophils	0.02-0.5	1-6
Basophils	0.02-0.1	<1-2

The values above may vary due to a wide range of factors, such as sex, diurnal variations, exercise, physical stress or trauma, pregnancy, indigestion of food, and cigarette smoking.

Venous blood sample

Venous samples should be taken in the order: gold tube, green tube, purple tube and inverted approx. 10 times after taking. The purple tube should be used for the sample for the Hemocue machine (as above).

Subsequent Visits (Visits 2-4)

Visits 2-4 will take place at approximately 2, 4 and 6 months after the baseline visit (within a 2 week period allowable either side). Visits 2-4 will consist of identical assessments to visit 1, with the exception that details would be requested of any updates to medications or new diagnoses. Details of any exacerbations and prescriptions for oral or inhaled steroids will be recorded.

At the final visit 4, participants will be given a questionnaire to complete and place in a sealed envelope, which will ask for feedback on the acceptability of these tests being incorporated into the routine COPD annual review, as a process evaluation.

At the final visit 4, participants will be given a £30 gift voucher to thank them for their time in participating and cover any incidental travel expenses. They will be asked to sign to confirm that they have received this using the receipt of voucher form.

At visits 2,3 and 4 the blood results from the previous visit should be printed off and anonymised using the marker pen with study number added, and returned to the CTU for data entry.

Sample Handling

All samples will be taken on 4 occasions as detailed above.

1) Breath samples (spirometry and FeNO) are not kept long-term and results are available immediately, but will be entered into the participant's medical record.

2) Venous blood samples (up to 15ml total)

Handling of samples and labelling

1.1. We will request full blood count and CRP via the standard ICE system (using the clinician name as agreed with the practice, usually the PI). The EDTA (purple) and lithium-heparin (green) tubes for these tests will be placed in an orange Oxford University Hospitals Trust sample bag, with the standard ICE label. ICE labels usually need to be placed in the printer facing downwards with the smaller labels towards the back of the printer.

1.2. In addition, we will also be taking a serum sample (gold) tube which will go in a separate orange sample bag, with a special study label, which will also go to the same hospital lab, but will be processed differently. This sample should be labelled on the bottle with the study and visit number e.g. A-005-1, date and 'COMET study'. Remember to also write the study and visit number and date on the special study label.

1.3. We will label up samples and place in bags. Ideally samples will be transported to the laboratory the same day in the standard laboratory transport, and we will need to be told where to put samples so that they go in this, and the lab pick-up time.

In the event that samples cannot be transported to the laboratory the same day, the serum sample bag (gold tube) should be placed in the fridge overnight, and the other sample bag (green and purple tubes) should be kept at room temperature. We will need to be shown the location of the fridge and where samples should be stored to ensure they go in transport the next day. If you have access to a centrifuge, the lithium-heparin (green) tube should be centrifuged. There is a 'note to practice staff' on the special study label which gives a reminder of how the different bags and samples should be handled.

Further details of sample processing:

a. EDTA tube for full blood count – this will be transported to the OUH NHS Trust using standard transport from practices, and processed in the standard way. They will be kept for the standard duration of time routine EDTA samples are kept by the lab (up to 72 hours). Results will be transferred back to the practice via the standard system for notifying laboratory results to practices, and will be checked in the normal way (coming into the GP's electronic in-tray identical to all other tests requested as part of routine clinical practice). Research staff will then extract this data from practice records when returning to the practice for subsequent clinics, and/or at the end of the study. This will be to ensure that any unexpected abnormalities e.g. severe anaemia, are dealt with promptly by the participant's usual provider, and means the results will be available in the participant's notes for future use. A small amount of the blood from the EDTA tube will also be used for testing in the Hemocue® machine, but this will not be kept long-term.

b. Lithium-heparin sample for CRP – this will be transported to the OUH NHS Trust using standard transport from practices, and processed in the standard way. They will be kept for the standard duration of time routine lithium-heparin samples are kept by the lab (up to 6 days). Results will be transferred back to the practice as above.

c. Serum sample – this will be transported to the OUH NHS Trust using standard transport from practices. It will then be spun, transferred to 2ml aliquots and stored in freezers in the OUH Trust:
    i. Aliquots of serum will be transported as a frozen batch to Viapath Ltd, a lab based in Kings College London, for testing for periostin – this will use manual ELISA (enzyme-linked immunosorbent assay, a laboratory technique), and samples will then be returned to the OUH NHS Trust. Results will be obtained from Viapath electronically (no identifiable participant information will be transported with the samples).
    ii. Samples will be stored long-term on OUH NHS Trust premises for use in future ethically-approved studies. This will not include genetic studies as it will have been rendered acellular by the centrifuge process.

d. Capillary sample for full blood count using the Hemocue® machine – this will processed and results available and recorded immediately, with discarding of samples afterwards.

A sample of twenty consecutive blood and capillary samples will be put on glass slides in addition for manual microscopic counts for validation (these will be transported by hand to the laboratory). Results will be obtained from the laboratory electronically (no identifiable participant information will be transported with the samples). Samples will be discarded after assessment. This will be sorted separately by the Chief Investigator.

Open Clinica guidance

CRFs should be completed via Open Clinica. However a back-up printed version should be taken in case of any problems accessing Open Clinica during the visit.

Website https://openclinica.phc.ox.ac.uk

HFA login [redacted]

For accessing patient contact details from the surgery, this can be done using https://netstorage.imsu.ox.ac.uk, selecting Netstorage3 and using Novell password. Patient contact details can be checked and changed if needed.

Documentation and paperwork

White consent form should go to patient, blue consent form to practice (for scanning to patient notes and placing in ISF), pink consent form to folder in cupboard in Julie Allen's office.

Questionnaires/surveys/spirometry printout should be returned to Chris Lovekin for data entry and storage. Spirometry results should be entered in Open Clinica in the surgery.

Add a consultation in the patient records (see screen shot):
Problem title: Research administration
History:

- COMET visit X [1-4]
- Smoking status [never smoked tobacco/ex smoker/current smoker]
- MRC breathlessness score

Examination:

- Height (from drop down)
- Weight (from drop down, can let it calculate BMI if offered)
- Oxygen saturation at periphery
- Postbronchodilation spirometry
- FEV1/FVC ratio [as whole number]
- Forced expired volume in 1 second
- Percent predicted FEV1

Comments:

- COPD severity [mild/moderate/severe/very severe COPD as per spirometry findings. If normal spirometry code as mild]
- Follow-up visit arranged for 8 weeks (date/time if available).

Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening). N.B. Starting an ICS during the study will not result in withdrawal.
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up

If withdrawal from the study is due to loss to follow up, already collected data will be used in analysis where possible. If participants state a wish to withdraw, they will be asked to complete a discontinuation form when they can state if they wish their existing data to be excluded.

The reason for withdrawal will be recorded in the CRF (study discontinuation CRF).

Appendix O: COMET participant survey

N.B. Pages appear out of order because this was designed to be folded into an A5 booklet. The last page (‘Future research studies’) was perforated so that it could be removed and stored separately to other study information, as it contained personal identifiers.

Future research studies

We would like to ask for your permission to contact you in future about a follow up interview study asking more detail about your experiences and opinions on having these tests (going into more detail on the answers given on this questionnaire). This would have a separate process of providing you with information about the study, and you giving your consent, and be ethically approved.

If you would be willing to be contacted, please provide your contact details below. Providing your details now doesn't commit you to taking part, and we would not use your details for any other purpose. If you would rather not provide your details, please just leave blank.

Name _____ Participant ID _ _ _ _ _

Gender M / F

Home address

_____

Telephone number (home)

_____

Telephone number (mobile)

_____

GP surgery

_____

Thank you for taking the time to complete this survey

COMET

Near-patient testing to guide COPD MaintenancE Treatment in primary care

PARTICIPANT SURVEY

Participant ID _ _ _ _ _

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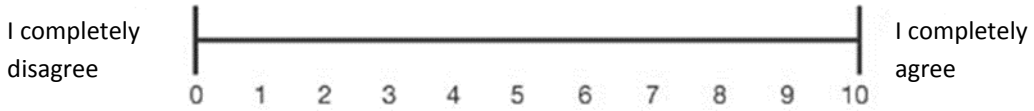
PLEASE CONTINUE TO THE NEXT PAGE

About being in this study

I have enjoyed being part of this study



What did you find worked well?

What did you find made it difficult?

What would have made it easier for you?

Please write here any additional comments you have about the study

Instructions

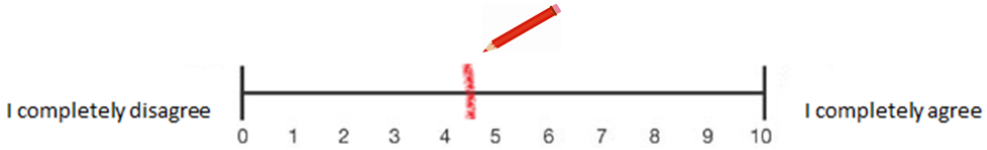
Many thanks for your participation in this research study about some new methods for monitoring and guiding treatment in COPD.

We would like to find out about your experiences of using these methods, and your opinion on whether they would work well at the COPD annual review. This is to help us find out whether they would acceptable for patients in future, and any improvements which could be made. Please be as honest as you can be.

Please mark on the scale how much you agree or disagree with the following statements.

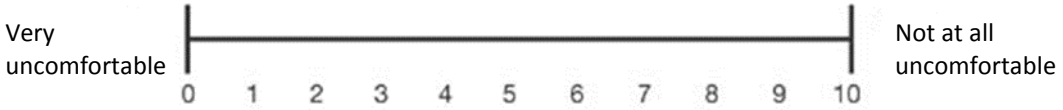
Example:

I enjoy eating brussel sprouts

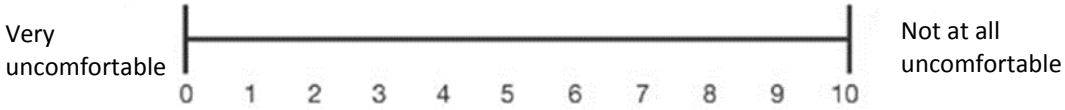


About the blood tests

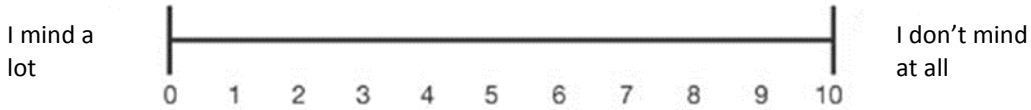
I found the blood test from my arm uncomfortable



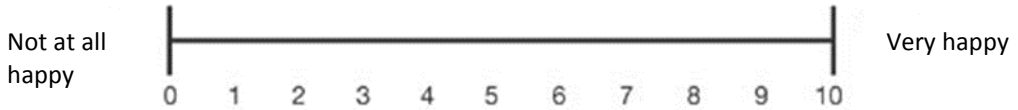
I found the blood test from my finger uncomfortable



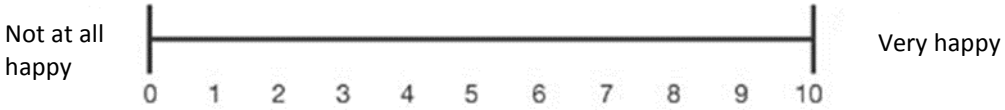
I don't mind putting up with the discomfort of a blood test if it helps with managing my COPD



I would be happy to have a fingerprick blood test as part of my COPD annual review



I would be happy to have a blood test from my arm as part of my COPD annual review

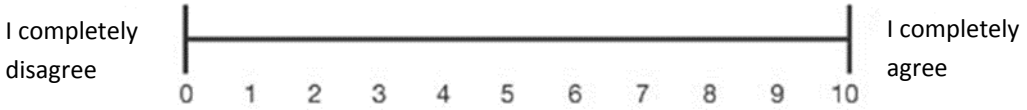


Please write here any thoughts or comments you have about the COPD annual review and extra testing in general.

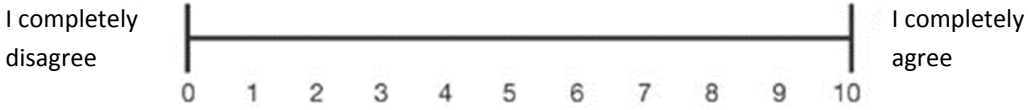
About the COPD annual review

I find the annual review helpful

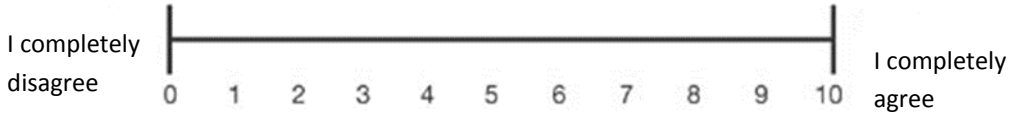
In general, I feel happier if I have had a lot of tests



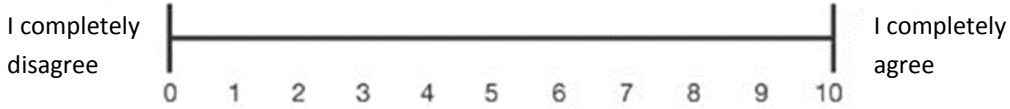
I would like to have instant feedback on my results (rather than having to wait for a result of a test)



I would be more motivated to look after my COPD because of additional testing



Having these tests regularly would strengthen my relationship with my GP or nurse



Please write here any thoughts or comments you have about the blood tests and the process of getting the blood tests (both arm and finger prick).

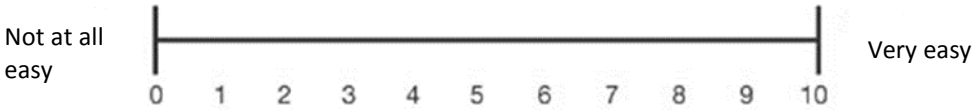
About the breathing tests

N.B. **Spirometry** refers to the test you usually have as part of your annual review which we have also been testing in this study (the one with the nose clip). **FeNO** (fraction of exhaled nitric oxide) refers to the additional blowing test into the white machine with the visual display.

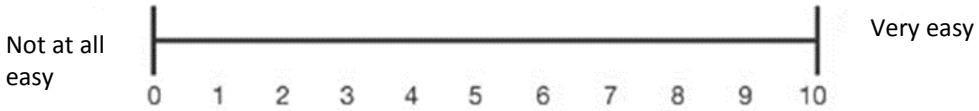
Spirometry

FeNO

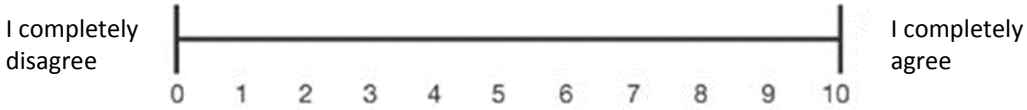
I find spirometry is easy to perform



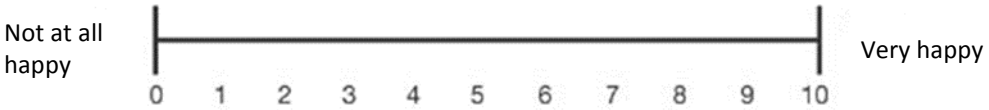
I find FeNO is easy to perform



The visual display made it easier for me to understand how to use the FeNO machine



I would be happy to have FeNO as part of my COPD annual review



Please write here any thoughts or comments you have about the breathing tests and the process of doing this.