Factors associated with the rate of FEV_1 decline in a primary care COPD population

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Declaration of Originality

I, Hannah R Whittaker, hereby certify that the work presented in this thesis is my own and all information presented from other works is properly referenced.

Hannah R Whittaker

Copyright Declaration

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Abstract

The purpose of this thesis was to describe the rate of forced expiratory volume in 1 second (FEV_1) decline in COPD patients seen in primary care and investigate factors associated with the rate to help identify COPD patients who might decline faster and who may benefit from interventions to slow the rate of FEV_1 decline.

The aims of this research were:

i. To describe and explore the rate of FEV_1 decline in a primary care COPD population,
ii. To investigate the relationship between inhaled corticosteroids (ICS) and rate of FEV_1 decline in a primary care COPD population, and
iii. To investigate the relationship between the rate of FEV_1 decline and future risk of CVD in a primary care COPD population.

Firstly, other than increasing age, COPD patients who were current smokers, had low BMI, high mMRC dyspnoea, low baseline FEV_1 percent predicted, and more frequent or severe AECOPD were more likely to have accelerated FEV_1 decline. Secondly, a systematic review revealed that COPD patients enrolled in randomised control trials (RCTs) treated with ICS had reduced rates of FEV_1 decline compared to patients not treated with ICS over short follow-up periods. However, over longer follow-up periods the rate of FEV_1 decline in patients in ICS and non-ICS trial arms were similar. In addition, using primary care data, COPD patients who initiated ICS showed an increase in FEV_1, notably in patients with high blood eosinophils, compared to patients who were not prescribed ICS however, prevalent ICS users had a clinically similar rate of FEV_1 decline compared to those not prescribed ICS, regardless of blood eosinophil level, echoing the findings of the systematic review. Similarly, COPD patients who withdrew from ICS (from triple therapy) showed a similar mean rate of FEV_1 decline compared to patients who remained on triple therapy. Thirdly, the rate of FEV_1 decline, including accelerated FEV_1 decline, was not associated with future risk of CVD disease and mortality in CVD naïve COPD patients.

These results suggest that rate of FEV_1 decline is heterogeneous and both patient related and disease related characteristics should be monitored to identify COPD patients with faster disease progression earlier. Whilst these patients may not have an increased risk of CVD, it is still important to identify these patients to intervene with better treatments or other possible interventions to reduce the risk of all-cause mortality and other potential morbidities. ICS treatment is a common intervention used to slow the progression of COPD however, results suggest that its long-term use does not significantly slow down the rate of FEV_1 decline compared to non-ICS medications, but initiation of ICS treatment does improve FEV_1 in the short-term. Proactive identification of fast FEV_1 decliners and the implementation of effective interventions in COPD patients by primary care providers may help to improve patient outcomes.

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List of Abbreviations

A&E - Accident and Emergency 36
ACE - Angiotensin-converting enzyme 84
AECOPD - Acute Exacerbation of Chronic Obstructive Pulmonary Disease 22
AF - Atrial fibrilation 81
ARIC - Athlerosclerosis Risk in Communities 34
ATS - American Thoracic Society 63
BMI - Body Mass Index 29
BODE - Body mass index, degree of airflow obstruction and dyspnoea, and exercise capacity 27
CAD - Coronary Artery Disease 81
CI - Confidence Interval 31
COPD - Chronic Obstructive Pulmonary Disease 20
COSMIC - COPD and Seretide: a Multi-centre Intervention and Characterisation study 190
CPRD - Clinical Practice Research Datalink 19
CRD - Current Registration Date 70
CVD - Cardiovascular Disease 22
ECLIPSE - Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints 27
EHR - Electronic Healthcare Record 35
EOS - eosinophils 80
ERS - European Respiratory Society 29
FEF - Forced Expiratory Flow 23
FEV_1 - Forced Expiratory Volume in 1 Second 20
FVC - Forced Vital Capacity 23
GOLD - Global Initiative for Chronic Obstructive Lung Disease 24
GORD - Gastro-Oesophageal Reflux Disease 84
GP - General Practitioner 66
GPRD - General Practice Research Datalink 66
HES - Hospital Episode Statistics 37
HF - Heart Failure 59
HR - Hazard Ratio 89
ICD - International Classification of Diseases 77
ICS - Inhaled Corticosteroid 29
IMD - Index of Multiple Deprivation 78
IMPACT- Informing the Pathway of COPD Treatment 61
IQR - Interquartile Range 94
ISAC - Independent Scientific Advisory Committee 78
ISOLDE - Inhaled Steroids in Obstructive Lung Disease in Europe 27
KOCOSS - Korean COPD Subtype Study 160
LABA - Long Acting Beta Agonist 29
LAMA - Long Acting Muscarinic Antagonist 29
LCD - Last Collection Date 70
LRTI - Lower Respiratory Tract Infection 59
MHRA - Medicines and Healthcare products Regulatory Agency 19
MI - Myocardial Infarction 59
mMRC - Modified Medical Research Council 83
NHS - National Health Service 19
NICE - National Institute for Health and Care Excellence 24

Ethnics, Support, and Data Disclosure Statement

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This work is based, in part, on data from the Clinical Practice Research Datalink (CPRD) obtained under license from the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA). The data are provided by patients and collected by the National Health Service (NHS) as part of their care and support. The interpretation and conclusions contained in these studies are those of the author alone.

Protocols for this research (Chapters IV-VI) were approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol numbers 18_006R2 and 18_074RARA2) and the approved protocol was made available to the journal in which this research is published and to the reviewers during peer review. Generic ethical approval for observational research using the CPRD with approval from ISAC has been granted by a Health Research Authority (HRA) Research Ethics Committee (East Midlands – Derby, REC reference number 05/MRE04/87).

Linked pseudonymised mortality data from the Office for National Statistics (ONS), socioeconomic data from the Index of Multiple Deprivation (IMD), and secondary care data from Hospital Episode Statistics (HES) were provided for these studies by CPRD for patients in England. Data were linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select general practices consent to this process at a practice level, with individual patients having the right to opt-out.

Data are available on request from the CPRD. Their provision requires the purchase of a license, and this license does not permit the authors to make them publicly available to all. This work used data from the January 2018 and the Methods sections for each Chapter have clearly specified the data selection process. To allow identical data to be obtained by others, via the purchase of a license, the code lists have been provided in Appendix III. Licenses are available from the CPRD (http://www.cprd.com): The Clinical Practice Research Datalink Group, The Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU.

Chapter 1
Background

This chapter defines Chronic Obstructive Pulmonary Disease (COPD) and forced expiratory volume in 1 second (FEV_1), summarises the epidemiological literature to date on rate of FEV_1 decline in COPD and introduces the use of electronic healthcare records and their importance in epidemiological research. The chapter will also contain a description of the rationale, aims, and objectives of this thesis.

1.1. Chronic Obstructive Pulmonary Disease

COPD is a term used to define a group of lung diseases including emphysema and chronic bronchitis, which develop due to chronic systemic inflammation from toxic particles such as cigarette smoke as well as occupational and environmental factors [1]. COPD is characterised by the obstruction of airways which is progressive and not fully reversible. The increased systemic inflammation can cause increased thickening of bronchiolar walls, increased mucus secretion, and destruction of alveolar walls leading to the narrowing of small airways and increased air trapping in the lungs [2]. Those with COPD often develop symptoms such as breathlessness, a chronic cough, and persistent wheeze.

1.1.1. Epidemiology of COPD

Globally, in 2019 COPD was the 4th leading cause of disability adjusted life years in people over the age of 50 [3]. In 2016, the Global Burden of Disease Study estimated that prevalence of COPD was over 250 million cases and approximately 3.2 million people die from COPD annually worldwide [4]. Smoking is the main cause of COPD [5]. It is estimated that approximately 75% of people with COPD have a history of smoking and 80% of COPD related deaths are due to smoking [6]. Other causes of COPD include occupational exposures to dust and chemicals, air pollution, and indoor pollution from biomass fuels which is common in low-income countries [7]. These exposures can lead to the development of COPD in people who have never smoked [7]. Further risk factors such as genetics, age, gender, and presence of comorbidities are also associated with the risk of developing COPD [8].

In the UK, it is estimated that 1.2 million people have COPD and approximately 115,000 people are diagnosed each year [9]. It is thought that there are many more people living with COPD in the UK who have not been diagnosed, often referred to as the “missing millions” [10]. In the UK, mortality rates in people with COPD has remained high, unlike similar countries where mortality rates have decreased [4, 11]. Overall, the prevalence of COPD in the UK is higher in men and in older people, and varies by region and socio-economic status, with a higher prevalence in northern regions and more economically deprived individuals [9].

1.1.2. COPD progression

COPD is a heterogeneous disease, with groups of clinical, pathophysiological, and demographic characteristics considered to be important in describing the natural history of disease. These may be useful in describing distinct phenotypes, targeting therapies, or predicting risk. It is common for COPD phenotypes to vary by symptom burden, frequency and severity of exacerbations of COPD (AECOPD), presence of comorbidities, and rate of lung function decline [12, 13]. For example, one study found that just over one third of people with airflow obstruction did not report any respiratory symptoms whilst the remaining population with airflow obstruction reported chronic cough and sputum production [14]. In addition, some patients may experience no AECOPD whilst others may experience multiple within one year. A previous study that investigated the frequency of AECOPD in the UK found that approximately 40% of patients did not exacerbate within a given year and 26% did not exacerbate over a 10 year follow-up period [12].

Comorbidities in people with COPD is common, notably in late disease progression. Cardiovascular disease (CVD) is the most common comorbidity in people with COPD and other common comorbidities include lung cancer, anxiety and depression, and obesity [15]. Patient related outcomes and COPD progression may vary between patients with differing comorbidities. Similarly, the rate at which lung function declines can also vary by COPD patients, contributing to the heterogeneity of COPD progression and the wide distribution of potential phenotypes within COPD [16, 17]. This will be discussed further in **section 1.2**.

1.2. Forced expiratory volume in one second in COPD

FEV_1 measures the amount of air that can be exhaled in a forced breath in 1 second. Specifically, FEV_1 is used to assess lung function and is measured using a spirometer device that measures the volume of expired air. FEV_1 naturally varies across the life course and across individuals. FEV_1 increases with age and reaches its peak in young adulthood. Thereafter, FEV_1 naturally declines with age (see **Figure 1.1**). After puberty men generally have larger values of FEV_1 compared to women due to a larger thorax and similarly, taller individuals are more likely to have larger lungs and increased FEV_1 [18].

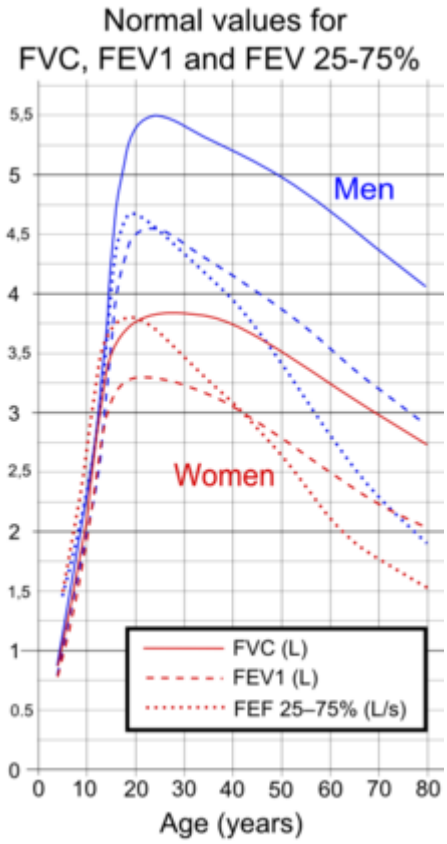


Figure 1.1: *Normal lung function with age. Reproduced from [19].*
Note: *Figure illustrates changes in FEV_1 with age, as well as change in forced vital capacity (FVC) and forced expiratory flow (FEF). See Appendix 1 for all copyrights and approved permissions for use of figures in this thesis.*

Studies have found that COPD can develop in individuals who reach a normal peak FEV_1 in young adulthood but who have an accelerated decline in FEV_1 in adulthood. In addition, patients who reach a lower than normal peak FEV_1 but who have a relatively normal decline in FEV_1 in adulthood are also more at risk of developing COPD (**figure 1.2**)[20].

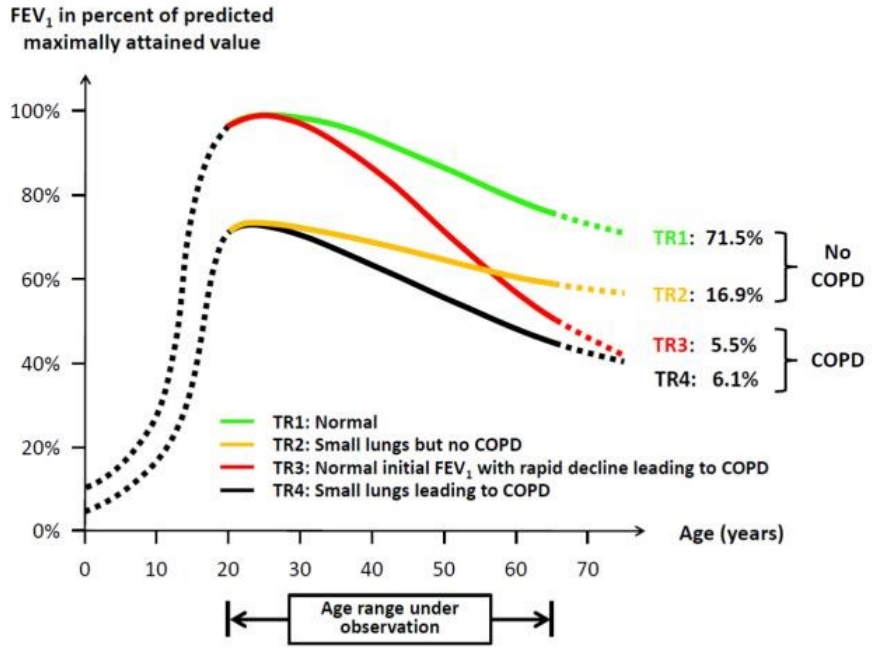


Figure 1.2: *FEV_1 trajectories and COPD. Reproduced from [20].*

1.2.1. Diagnosis of COPD in the UK

In primary care practices across the UK, FEV_1 is used in part to make a diagnosis of COPD. Following the National Institute for Health and Care Excellence (NICE) guidelines, a suspected diagnosis of COPD should be considered in people who are over the age of 35 who have a risk factor for COPD (such as a history of smoking), have at least one COPD-related symptom (breathlessness, chronic cough, sputum production, wheeze, or seasonal bronchitis), and who have confirmed airflow obstruction [21]. Airflow obstruction is defined as a post-bronchodilator FEV_1/FVC (forced vital capacity)<0.7. Thereafter, the severity of airflow obstruction can be assessed periodically using FEV_1 percent predicted, which is calculated using FEV_1, age and sex following the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and NICE 2010

guidelines [22] (**table 1.1**). More recently, the 2017 GOLD guidelines additionally request symptom burden and frequency of AECOPD to assess severity of COPD [1].

***Table 1.1**: GOLD 2011 grades to describe COPD severity using FEV_1.*

GOLD severity grade	FEV_1 predicted
Mild	≥80%
Moderate	50-80%
Severe	30-50%
Very severe	<30%

1.3. FEV_1 decline in COPD

FEV_1 naturally declines with age in COPD patients however, in 1977 Fletcher and Peto found that the rate of FEV_1 decline from adulthood was more rapid in individuals with airflow obstruction and in those who smoked using a cohort of working class men in London [23]. Additionally, those who stopped smoking had a slower FEV_1 decline than those who continued smoking however, those who stopped smoking never fully recovered the FEV_1 that was lost (**Figure 1.3**). Overall, this landmark study suggested that FEV_1 may decline at a faster rate in those with COPD than those without COPD as well as in COPD patients who smoked compared to those who stopped smoking.

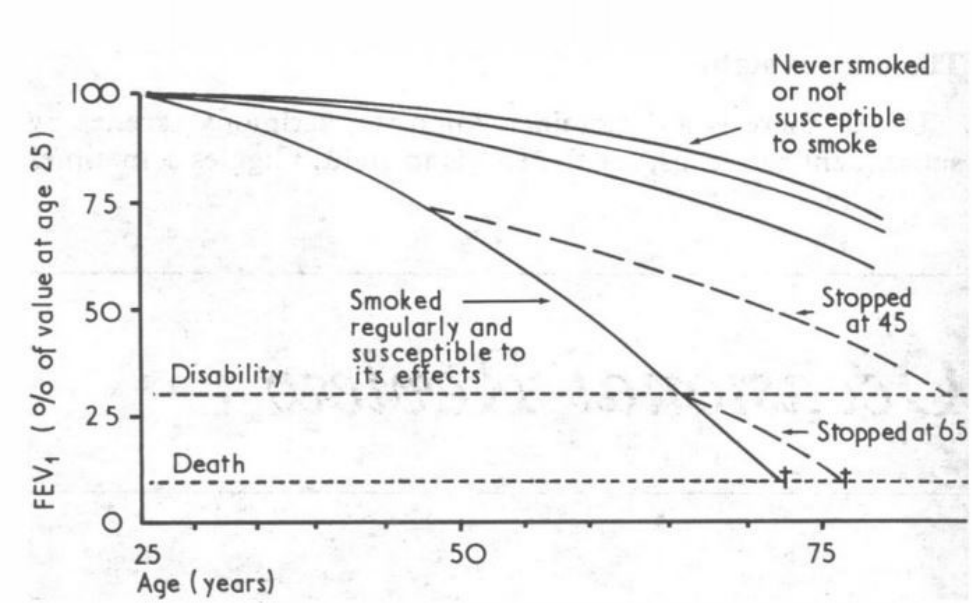


***Figure 1.3**: Observed FEV_1 decline in men by airflow obstruction (i.e., smoking susceptibility) and smoking status. Reproduced from [23].*
***Note**: Susceptible to smoke was defined as having airflow obstruction in this study.*

1.3.1. Heterogeneity of rate of FEV_1 decline

Since then, studies have found that the rate of FEV1 decline, even within COPD patients, is variable. A recent systematic review of randomised control trials (RCTs) that investigated rate of FEV_1 decline by medications found that the rate of FEV_1 decline fell between -42 ml/year and -59 ml/year in patients in placebo arms [24]. Specifically, the Understanding Potential Long-term Impacts on Function with Tiotropium trial (UPLIFT) reported a mean decline of -45.0 ml/year, the Study to Understand Mortality

and Morbidity in COPD trial (SUMMIT) reported a mean decline of -46.0 ml/year, and the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial reported a mean decline of -59.0 ml/year [25-27].

Observational studies generally report an attenuated mean rate of FEV_1 decline compared to those seen in RCTs. For example, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study reported a mean FEV_1 decline of -33.2 ml/year in COPD patients aged 40 to 75 with a history of smoking [17]. In addition, the body mass index, degree of airflow obstruction and dyspnoea, and exercise capacity (BODE) study found that 82% of 751 COPD patients had a non-significant mean decline of -28 ml/year (not significantly different from no decline) and further observational studies have found rates of decline ranging from -12.6 ml/year to -27 ml/year in people with COPD [28-30]. Differences in rate of FEV_1 decline reported in RCTs and observational studies is likely to differ due to differences in participant inclusion criteria and study designs. For example, it is common for RCTs to include patients with few or no comorbidities but with more severe COPD [31]. The differences in rates of FEV_1 decline seen within different types of studies suggests variation in the rate of decline exists in people with COPD.

Vestbo and colleagues investigated the variation in rate of FEV_1 decline in a COPD population who were enrolled in the ECLIPSE observational study. Patients were required to have spirometry confirmed COPD and have a history of smoking. The authors found that the mean rate of FEV_1 decline was -33.2 ml/year however, significant variation in the rate of change was observed as illustrated by the authors in **Figure 1.4**. In this study, 38% of participants had a mean FEV_1 decline greater than -40 ml/year, 31% have an FEV_1 decline between -21 ml/year and -40 ml/year, 23% had a change in FEV_1 between -21 ml/year and an increase of +20 ml/year, and 8% increased more than +20 ml/year [17]. This suggests that factors, such as patient characteristics, may influence an individual's rate of FEV_1 decline leading to a variation in FEV_1 decline within COPD patients.

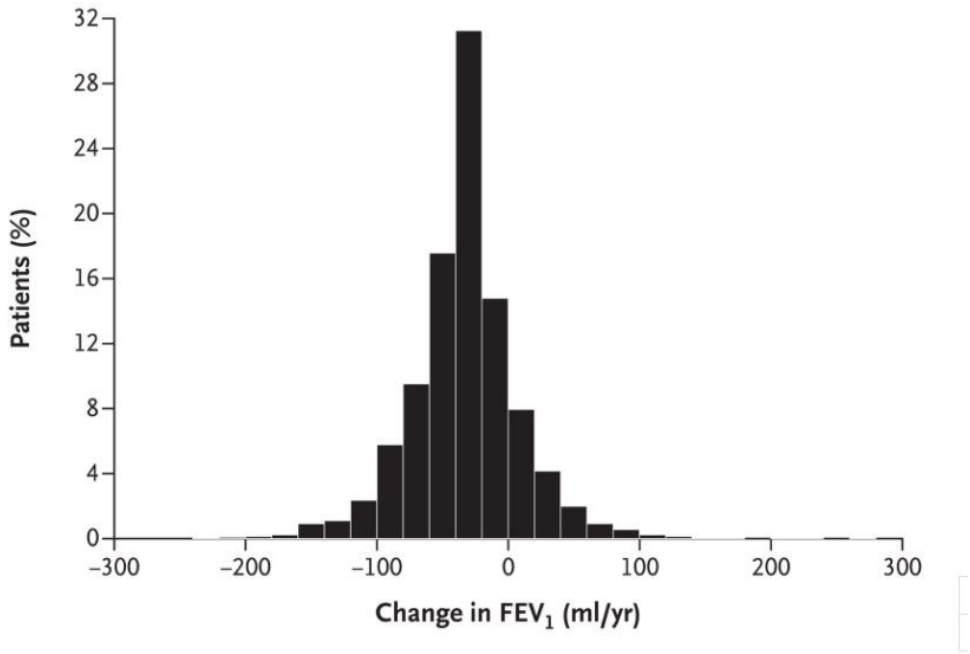


Figure 1.4: *Distribution of the rate of change in FEV_1 in COPD patients enrolled in the ECLIPSE study. Reproduced from [16].*

1.3.2. Known risk factors associated with FEV_1 decline in COPD

Much of the evidence for understanding patient related factors that are associated with an increased or decreased rate in FEV_1 decline comes from RCTs. The UPLIFT study found that a single moderate or severe AECOPD was associated with an increased rate in FEV_1 decline in patients with COPD when compared to patients' previous rate of FEV_1 decline, which was not seen in patients who did not experience any AECOPD [32]. Donaldson and colleagues found that patients with frequent AECOPD (defined as greater than approximately 3 per year) had faster rates of FEV_1 decline compared to those with infrequent AECOPD frequencies (-40.1 ml/year vs -32.1 ml/year, respectively) [33].

While FEV_1 decline is faster in frequent exacerbators, some COPD patients have more rapid FEV_1 decline irrespective of exacerbations, suggesting that other characteristics are important too. These individuals tend to have mild to moderate disease, be current smokers and have a more emphysematous phenotype [17]. Other studies have found that low body mass index (BMI) is associated with faster decline in FEV_1 in COPD patients, as is COPD disease severity [34-36]. Specifically, mild COPD disease has been associated

with accelerated decline in absolute FEV_1 which is explained by the amount of baseline lung function patients initially have [36].

1.3.3. Treatment of COPD and change in FEV_1

Treatment is one of the factors whose association with FEV_1 has been most studied in the literature. Common COPD maintenance treatments include the use of short and long-acting bronchodilators and inhaled corticosteroids (ICS). Specifically, bronchodilators used to treat COPD include short and long-acting beta agonist bronchodilators (SABA and LABAs) and short and long-acting muscarinic antagonists (SAMA and LAMAs). **Figure 1.5** describes the pathway for COPD maintenance therapy recommended by 2018 NICE and 2020 European Respiratory Society (ERS) guidelines [21, 37]. COPD patients are prescribed SAMA and SABA to alleviate breathlessness which can be used alongside long-acting bronchodilator therapies. If patients remain breathless or experience AECOPDs then LABA/ICS or LABA/LAMA should be prescribed depending on if patients are responsive to steroids or not. Asthmatic features suggesting steroid responsiveness can include a previous diagnosis of asthma and higher blood eosinophil levels [21]. If patients remain symptomatic on LABA/ICS or LABA/LAMA or experience at least two AECOPDs requiring oral corticosteroids and antibiotics, or an AECOPD requiring hospitalisation, patients should be prescribed triple therapy (LABA/LAMA/ICS). The addition of ICS to COPD therapy has been shown to reduce rate of FEV_1 decline compared to placebo or long-acting bronchodilator medication in many RCTs [38, 39]. More recent studies suggest that patients with higher blood eosinophils (greater than 2% of total white blood cell count) may be more responsive to ICS in term of change in FEV_1 [40].

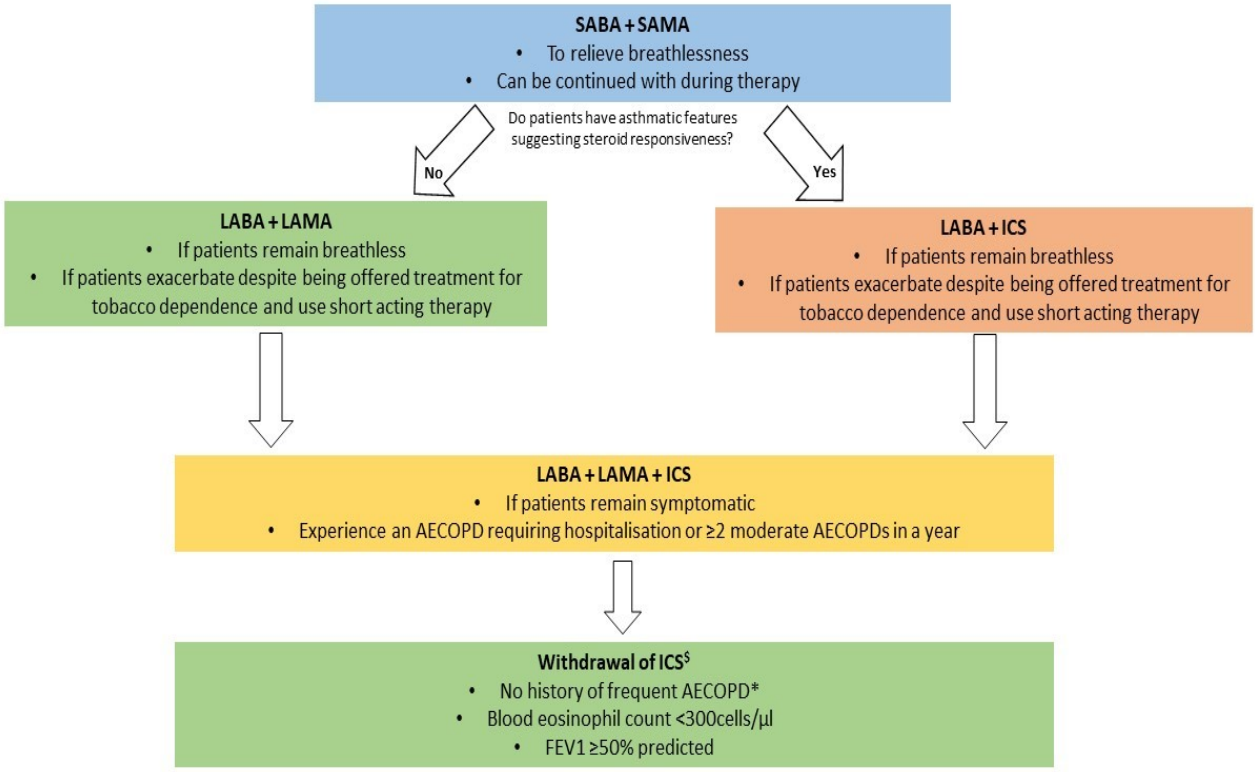


***Figure 1.5**: Summary of COPD therapy recommendations.*
***Note**: *Frequent AECOPD defined as ≥2 in one year, $ICS withdrawal recommended for low dose ICS or switch to low dose ICS at the first instance if patients are on high dose ICS prior to complete ICS withdrawal.*

Despite the benefits of using ICS, ICS has also been associated with increased risk of pneumonia and efforts have been made to understand the effects of withdrawal of ICS in COPD patients [41]. The Withdrawal of Inhaled Steroids during Optimised Bronchodilator Management (WISDOM) trial assessed the association between withdrawal of ICS in COPD patients on triple therapy and various outcomes including rate of FEV_1 decline. Patients who withdrew from ICS had a significantly faster annual decline in FEV_1 compared to patients who did not withdraw from ICS [42]. It is important to note that the WISDOM population has specific inclusion and exclusion criteria including no AECOPD 6 weeks prior to randomisation and FEV_1 less than 50% predicted. Whilst change in FEV_1 differed between WISDOM's two trial arms, other findings such as no difference in AECOPD rate led to new ERS guidelines that state that ICS should be withdrawn if patients do not have a history of frequent AECOPD and if patients have blood eosinophils less than 300cells/µl [37].

Despite the large amount of evidence around COPD treatment and the rate of FEV_1 decline, it is important to note that RCTs commonly exclude patients based on age, comorbidities, severity of disease, and often have shorter follow-up periods (of one year or less) [43]. One study found that as little as 2.3% to 46.7% of COPD patients in a French cohort would have met the eligibility criteria for 16 possible RCTs that aimed to investigate treatment on reducing AECOPD (mean eligibility rate 16.5% [95% confident interval (CI) 9.2 – 23.7]) [44]. In addition, one study compared the presence of comorbidities in patients recruited to 116 different RCTs compared to people with similar conditions in a general population of people in Wales. Results suggested that people in COPD related trials had approximately half the number of comorbidities than people with COPD in the community [31].

COPD clinical guidelines are largely informed by RCT results, but we do not know if findings, specifically related to lung function decline, apply to large patient populations not studied in trials. While RCTs will continue to be the gold standard for assessing the efficacy of medical interventions, they are expensive to conduct, and for practical and ethical reasons usually involve testing treatments in patient populations, and within contexts, which are sometimes very different to real life. For example, the patients that are most commonly seen in COPD outpatient clinics are those that would be excluded from clinical trials due to their comorbidities. As patient populations with chronic diseases such as COPD become more complex, the studies used to generate clinical evidence should reflect this by either running large scale open label pragmatic trials (such as the Salford Lung Study) or by extrapolating RCT findings to other COPD populations. However, large pragmatic trials can be very costly and time consuming, and therefore the use of observational data, specifically routinely collected data, is vital in understanding whether many outcomes seen in RCTs are also seen in routine practice [45]. In fact, national drug licensing authorities are now demanding better real-world evidence on which to make decisions. They have introduced legislation mandating studies of both effectiveness and risk to be conducted in routine clinical care rather than the narrow and optimal confines of most RCTs. However, the use of these studies to estimate treatment effectiveness is in its infancy [46, 47].

1.3.4. Importance of rate of FEV_1 decline in COPD

The rate at which FEV_1 declines in COPD patients is important because of the association between low FEV_1 and increased morbidity and mortality, not only in COPD populations but also in the general population [48-51]. Previous studies have reported an increased risk of death in people whose FEV_1 was faster than 50 ml/year, while other studies reported an increased risk of death in people whose FEV_1 was faster than 171 ml/year (the fastest quartile of decline) [34, 52]. Ultimately, the faster the rate of FEV_1

decline, the sooner the patient will reach a low FEV_1. Not only is low FEV_1 associated with increased risk of mortality and morbidity, but it is also associated with increased use of healthcare utilisation such as hospitalisations [53, 54]. In addition, patients with low FEV_1 have a greater risk of comorbidities and poorer prognosis, which also contributes to increased use of healthcare services [55]. Reducing the rate at which FEV_1 declines in COPD is important to improve these outcomes.

Interventions are needed to help reduce the rate of FEV_1 decline however, these are limited. As described in the previous section, treatments are used to relieve COPD related symptoms and improve lung function however, the extent to which treatments, notably ICS, improve lung function or slows down FEV_1 decline is not completely clear as much of the evidence originates from subpopulations of COPD patients recruited in RCTs. Therefore, it is important to investigate factors associated with FEV_1 decline to better identify COPD patients who might progress faster and target these people with better interventions, in addition to medications. For example, more effective smoking cessation programmes and better healthy lifestyle advice such as optimised weight management programmes for people with COPD.

1.4. Cardiovascular disease and COPD and rate of FEV_1 decline

One of the most prevalent comorbidities in COPD patients is CVD [56]. CVD defines a group of diseases that affect the heart and blood vessels [57]. The prevalence of CVD in COPD patients lies between 14% to 33% and 25-30% of COPD patients have CVD related causes as their underlying cause of death from death certificates [8, 58, 59]. Patients with COPD and CVD share common risk factors including aging and smoking [60, 61]. Patients who smoke are exposed to toxic particles that can cause increase systemic inflammation that characterises both COPD and CVD [62, 63]. It is not fully understood how COPD and CVD are linked beyond their shared risk factors however, mechanisms such as hypoxia and oxidative stress may be involved [56, 60]. **Figure 1.6** illustrates the relationship between COPD and CVD in more detail.

As with COPD, studies have shown that people with low lung function or increased airflow obstruction are more likely to develop CVD. Specifically, low FEV_1, FVC, and FEV_1/FVC ratio have all been associated with an increased risk of developing CVD as well as an increased risk of hospitalization from CVD and CVD mortality in both the general population and in COPD patients [64-70].

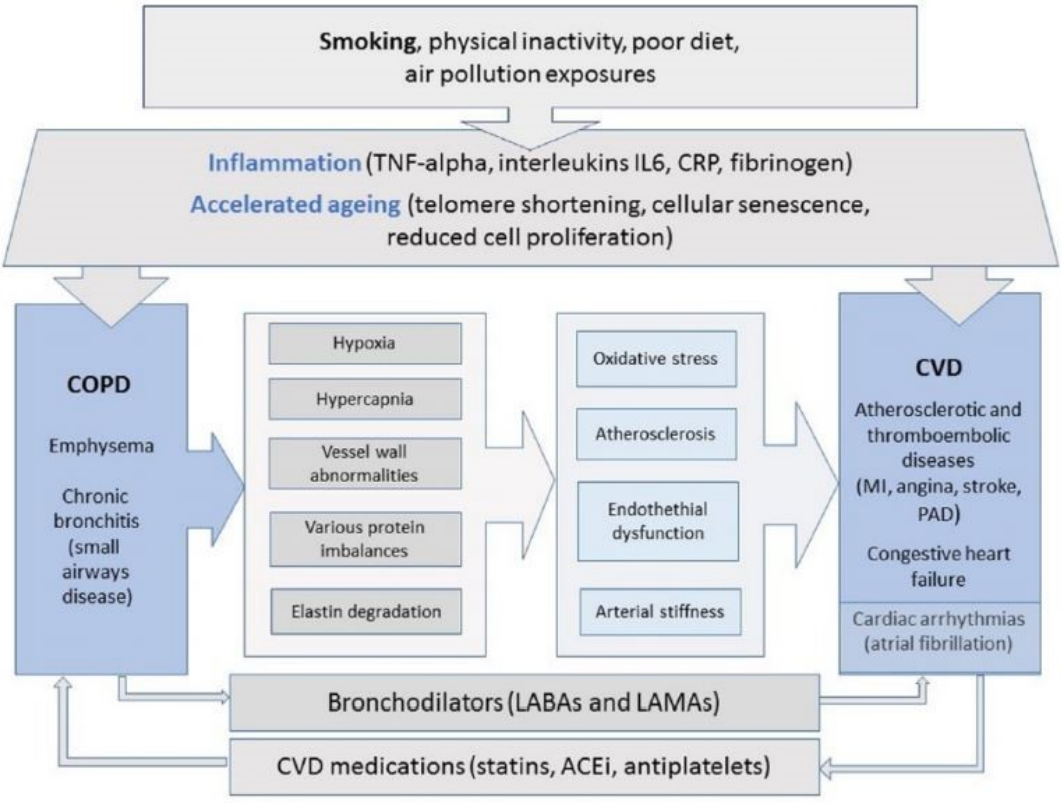


***Figure 1.6**: Pathophysiological mechanisms between COPD and CVD. Reproduced from [56]*

Several factors have been found to be associated with the rate of change in lung function in COPD patients including frequency and severity of acute AECOPD, smoking, and medication use [32, 33, 38, 71-73] however, little is known about the association between the rate of FEV_1 decline and CVD in COPD patients. Recently, the Atherosclerosis Risk in Communities (ARIC) study found that people who had accelerated FEV_1 decline had an increased risk of hospitalisation and death from heart failure and stroke [74]. The ARIC study is an observational study of a general population of people who live in America and to date, no studies have investigated the association between rate of FEV_1 decline and risk of CVD outcomes and mortality in patients with COPD, who are already at greater risk of CVD than the general population [56].

1.5. Electronic healthcare records

Electronic healthcare record (EHR) databases routinely collect and store healthcare data electronically. EHRs can exist in various forms and can contain data on routine processes in primary and secondary care, including information on prescriptions, procedures, and disease diagnoses. Examples of different types of EHR databases include primary and secondary care databases, medical insurance claims databases, and mortality databases. Other types of medical databases include more specific disease registries, for example the cancer registry in the UK. The way in which information is contained and coded in EHR and registries differs. One of the original purposes, certainly in the UK, was to store medical information digitally but EHRs are increasingly being used for research and population-based studies globally [75].

The strengths of EHR includes larger sample sizes and detailed coverage of the general population. EHR also allow for the identification of patients with disease, who are not necessarily studied in RCTs, whose data is captured in every day clinical practice. Therefore, results from studies using EHRs can be more generalisable to wider populations that populations used in RCTs, which makes EHRs increasingly useful to epidemiological research. EHRs can also be linked to additional databases which allows for more in-depth patient related information to allow for a more complete investigation and a wide breadth of study variables [75].

However, unlike databases that prospectively record data of a specific population, the original purpose of data collection in EHRs is not for research. For this reason, EHRs may include missing or inaccurately recorded data. Unlike EHRs, data for epidemiological studies are collected with an overarching research question in mind and data collection is as standardised as possible across all study participants. Participants may be actively followed-up with regular in-person appointments by healthcare technicians as part of longitudinal or cohort studies. EHRs, on the other hand, may contain data that is inaccurately recorded or missing because the purpose of EHRs is not primarily for research. For example, data (such as smoking status) that was once recorded may not be updated at a later date in the patient's medical history.

One controversy of the use of EHR is that data should be used for the purpose that it is collected, as stated by Van der Leir's 1st law of medical informatics [76]. It argues that data can be misinterpreted outside the context in which it was collected. This is largely due to issues with data quality such as lack of precise data recording, including potential recall bias and bias from selection of specific information that clinicians think is important. In addition, it is also important to understand why variables are recorded in EHRs as

there may be underlying reasons why data are or are not recorded in specific people, which can potentially lead to selection bias. For example, a clinician may request a blood test if patients are unwell and therefore patients with a recorded blood test in their EHR may differ from those who do not have a recorded blood test, even in patients with the same disease. A previous study investigated the relationship between having a record of a white blood cell (WBC) count test and three-year survival in patients who were hospitalised in America [77]. Authors found that patients with a WBC count had increased odds of mortality by 45% compared to patients who did not have a WBC count test recorded. It is crucial that researchers understand these healthcare processes and how they may affect studies using EHR.

Despite these limitations, there are incentives in place, for some EHR databases, to encourage more complete data recording such as the Quality and Outcome Framework (QOF) indicators used in primary care. If specific indicators related to the management of patients with chronic conditions, management of public health concerns, and providing of preventative measures related to disease within GP practices are met, GP practices are compensated financially [78]. There are also researcher level methods that can be used to ensure the quality of EHR data is high. One way is to use validated algorithms to identify specific healthcare processes such as diagnoses of conditions. It is good practice to use such algorithms because recorded events would have been validated against any additional clinical information supplied by the source provider and cross checked by trained healthcare practitioners who have specialised knowledge of the disease or event of interest.

There is a wide range of EHRs that exist on an international level that are utilised for research. For example, the Medicare and Medicaid databases in North America are insurance claims databases that contain information on national insurance programmes for elderly people, people living with disabilities, and people with low income. Despite large sample sizes and detailed information on factors such as medications, these databases do not contain information on lifestyle factors that are important when investigating COPD [79, 80]. In Europe, the Danish National Patient Registry contains information on secondary care events including inpatient and outpatient hospital appointments and accident and emergency (A&E) visits [81]. Whilst secondary care information is essential when investigating routine practice in COPD, the use of secondary care databases only will lead to the inclusion of more severe patients and events.

In the UK, there are some commonly used EHR databases such as The Health Improvement Network (THIN) and CPRD. These are similar databases and contain information on clinical information in primary care however, they vary in sample size and the possibility to link to other databases. Hospital Episode

Statistics (HES) is a secondary care database that is available for England and is the largest secondary care databases in the UK. HES contains detailed information on inpatient hospital admissions, outpatient appointments, and A&E visits.

In this thesis, CPRD data was used and was linked to HES data. CPRD contains detailed information on clinical diagnoses, tests, prescriptions, and lifestyle factors such as smoking status, all of which are important when investigating factors associated with lung function in COPD patients. The addition of HES allows for more detailed variables with varying degrees of severity. These databases will be described in further detail in Chapter 3.

1.6. Rationale

Low FEV_1 in COPD is associated with increased risk of mortality, morbidity and consequently, increased healthcare utilisation and costs to healthcare services. Therefore, the rate at which a patient's FEV_1 declines is important to identify patients with accelerated FEV_1 decline and who might benefit from interventions to minimise further outcomes. Much of the research to date on lung function decline in COPD has been conducted in RCTs and shows varying estimates of rate of FEV_1 decline. This suggests that different patient populations may decline at different rates, which is important to investigate to improve clinical care and management of COPD patients.

The main limitation of previous work investigating factors associated with rate of FEV_1 decline is that the COPD populations used were not representative of all COPD patients within the community. Therefore, little is known about the rate of FEV_1 decline and factors associated with it in a population of COPD patients who are routinely seen in primary care. It is important to understand what factors may be associated with faster decline in COPD patients so that healthcare practitioners can identify patients who will demonstrate faster COPD progression early in their disease course and target them with appropriate interventions. In addition, little is known about how the rate of FEV_1 decline in COPD patients could be associated with future comorbidity. Specifically, I will focus on CVD as it is the most common comorbidity in COPD and has a significant impact on mortality and healthcare costs in the UK [56, 59]. Accelerated FEV_1 decline has been associated with risk of CVD in a general population of America but no studies have looked at this relationship in COPD patients specifically. Overall, this thesis aims to fully investigate changes in FEV_1, factors that are associated with the decline, and how the decline itself may be associated with future comorbidity. This will help to better understand lung function and identify ways in which to manage COPD more effectively in patients who are seen in everyday clinical practice; a population who are rarely studied.

1.7. Aims and objectives

The overarching aim of this thesis is to describe the rate of FEV_1 decline in a primary care population of COPD patients and investigate the association between patient related factors and rate of FEV_1 decline. Specifically, I will describe the rate of FEV_1 decline in this population and investigate how patient characteristics, comorbidities, and ICS use are associated with the rate of FEV_1 decline. This thesis includes three overarching aims with more specific sub aims, all of which contribute to investigating the rate of FEV_1 decline in COPD patients in primary care and factors associated with the rate of decline in this population. **Figure 1.7** illustrates the structure of aims and corresponding chapters within this thesis.

1.7.1. Aim 1: Describe and explore the rate of FEV_1 decline in a primary care population of COPD patients.

Aim 1.1: Investigate the recording of FEV_1 in CPRD and ways to define longitudinal change in FEV_1.

The first part of aim one is to investigate the recording of FEV_1 in CPRD and ways to define longitudinal change in FEV_1. Spirometry has been validated in CPRD however, there is no validated definition for the longitudinal change in FEV_1 in CPRD. Spirometry recordings in RCTs and prospective cohort studies are usually measured at specific times and uniformly across COPD patients however, measurements recorded in EHR can be more sporadic. Measurements are often taken at varying times and for various reasons by healthcare practitioners. For this reason, it is important to understand longitudinal spirometry measurements in CPRD and how they can be used to accurately define longitudinal change in FEV_1. Methods developed will be used to define rate of FEV_1 decline in CPRD for the later chapters.

Aim 1.2: Describe the rate of FEV_1 decline in a primary care COPD population and investigate patient characteristics that are associated with the decline.

The second part of aim one is to describe the rate of FEV_1 decline in primary care COPD patients and understand baseline characteristics associated with accelerated decline. Rate of FEV_1 decline in COPD patients has primarily been described in RCTs or in COPD populations with specific inclusion criteria. Rate of FEV_1 decline has not been described in a more generalisable population of COPD patients in terms of patient characteristics, symptom burden, and presence of comorbidities.

1.7.2. Aim 2: Investigate the relationship between ICS and rate of FEV_1 decline in a primary care population of COPD patients.

Aim 2.1: Conduct a systematic review of the association between inhaled corticosteroid use and rate of FEV_1 decline in COPD.

Clinical guidelines on the use of ICS in COPD patients are based on findings from RCTs that have shown that ICS use is associated with reduced rate of FEV_1 decline however, these studies are often short in follow-up and are not generalisable to the wider population of COPD patients. The first part of this aim is to conduct a systematic review to understand the relationship between any ICS-containing medications compared to any non-ICS-containing medication comparators to better understand this relationship in more generalisable COPD patients.

Aim 2.2: Investigate the relationship between ICS use, eosinophil counts, and rate of FEV_1 decline.

Previous studies have found that ICS use is associated with slower decline in FEV_1 as seen primarily in RCTs [39]. Due to the potential risk of pneumonia associated with ICS use, the use of biomarkers to guide the use of ICS is needed and blood eosinophils have been shown to modify the relationship between ICS and FEV_1 decline however, no observational studies have investigated this relationship in generalisable COPD patients.

Aim 2.3: Investigate the relationship between withdrawal of ICS and rate of FEV_1 decline.

ERS guidelines now recommend withdrawing ICS from patients on triple therapy if patients do not exacerbate and have low blood eosinophil levels. These guidelines are based primarily on findings from the WISDOM trial, that had specific inclusion and exclusion criteria. The relationship between ICS withdrawal has not been investigated in a generalisable population of COPD patients or in patients with comorbidities who are commonly seen in clinical practice.

1.7.3. Aim 3: Investigate the relationship between the rate of FEV_1 decline and future risk of CVD.

The third aim is to investigate the potential association between rate of FEV_1 decline and future risk of CVD in a primary care population of COPD patients. Recently, rate of FEV_1 decline has been associated with increased risk of CVD in a general population from the ARIC study. No studies have investigated this

association in a COPD population, and it is important to know whether the rate at which FEV_1 declines is associated with the risk of developing further comorbidities specifically CVD, a common comorbidity of COPD.

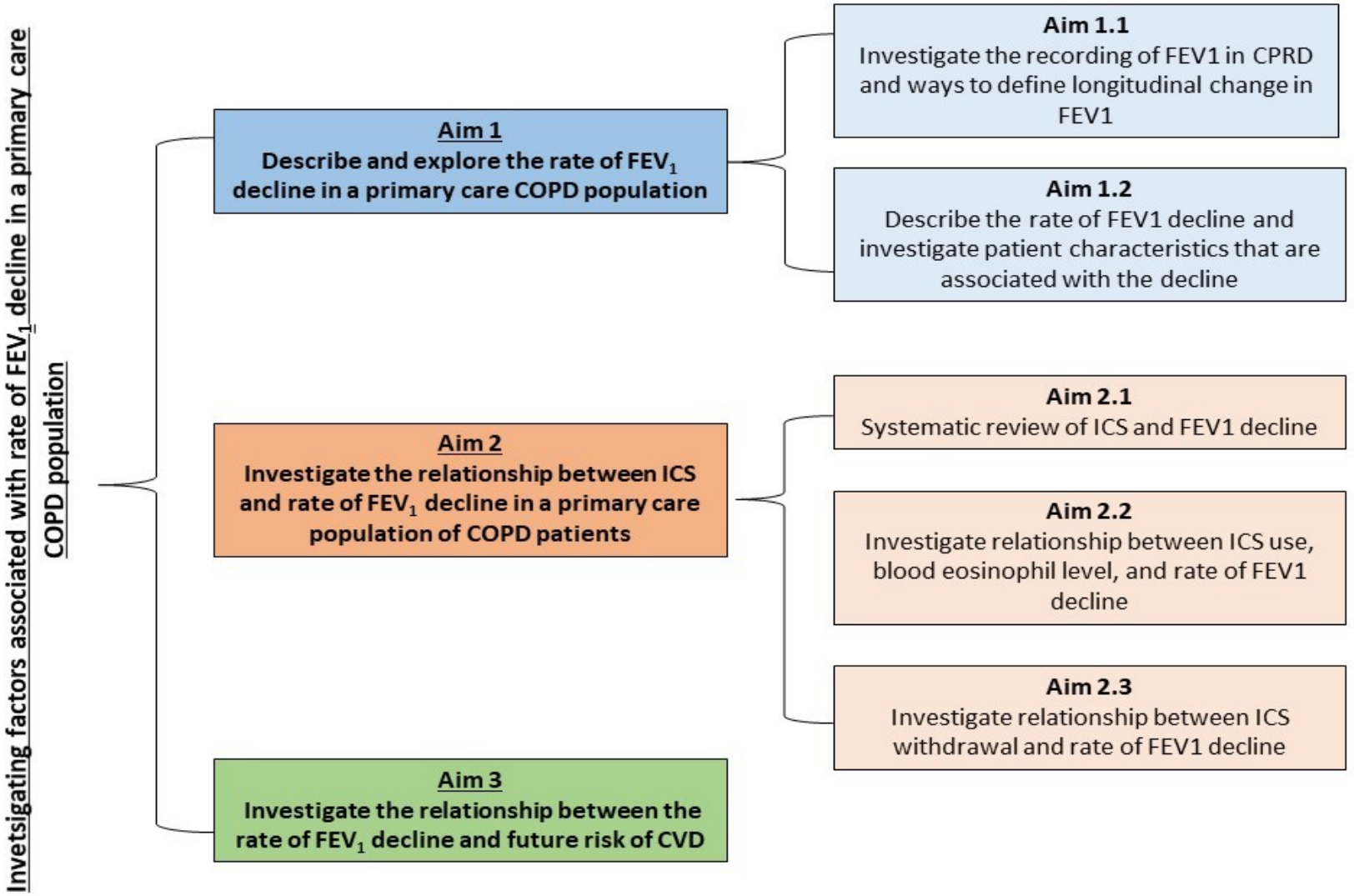


Figure 1.7: *Organization of aims within this thesis.*

Chapter 2
Inhaled corticosteroids and FEV_1 decline in chronic obstructive pulmonary disease: a systematic review

In the UK, ICS are prescribed to COPD patients (in combination with bronchodilators) if patients are symptomatic or experience AECOPD however, these guidelines are largely based off RCTs that have specific inclusion and exclusion criteria and can have a short follow-up of one year or less. ICS use has been associated with an increased risk of pneumonia and it is therefore important to understand the relationship between ICS and rate of FEV_1 decline over longer follow-ups and in different types of studies. Previous systematic reviews have included specific ICS and non-ICS comparators and no studies have reviewed the literature on all types of ICS and non-ICS comparisons. This chapter aims to summarise the existing literature on the association between ICS use and the rate of FEV_1 decline in a COPD population.

2.1 Introduction

Evidence based clinical NICE guidelines recommend the use of LABA or LAMA for COPD maintenance therapy [82, 83]. Currently, the addition of ICS is reserved for those who remain breathless or exacerbate despite taking SABAs following NICE guidelines [21]. GOLD guidelines suggest initial treatment of ICS should be reserved for patients in GOLD group D alongside LABA if blood eosinophil levels are greater than 300cells/µl. In addition, combination ICS (ICS/LABA) should be considered in patients who exacerbate if blood eosinophil levels are greater than 300, or 100 if they experience at least 2 moderate exacerbations or a hospitalization from AECOPD, or remain breathless [1]. However, the use of ICS for the treatment of COPD has been debated. Whilst it is well established that ICS use reduces the risk of AECOPD, the relationship with rate of lung function decline is not as clear cut [84, 85].

Previous large, RCTs have found that ICS reduce the rate of FEV_1 decline in people with COPD [86-89]. However, there are limitations to these studies. Firstly, RCTs have specific inclusion and exclusion criteria and commonly exclude participants based on age, comorbidities and severity of disease [43]. Therefore, the rates of decline associated with ICS use reported in many RCTs may not be generalisable to the wider population of COPD patients. Secondly, RCTs have short follow-up periods of generally less than 1 year. It is argued that this length of follow-up is not long enough to investigate the long-term rate of lung function decline [90]. Therefore, whilst most RCTs report an improvement in FEV_1 decline with ICS use in COPD, it is important to look at lung function decline in relation to studies with longer follow-up.

Previous literature reviews have consisted of pre-specified ICS and non-ICS comparators such as LAMA/LABA vs LABA/ICS or ICS, LAMA/LABA vs LABA, LAMA or LABA/ICS and more specific comparisons such as budesonide or beclomethasone vs placebo [91-96]. Since then, several large scale RCTs reporting associations between ICS and FEV_1 decline have taken place including SUMMIT and WISDOM trials, justifying the need to inform and summarise novel findings. This chapter aimed to investigate the association between ICS or ICS-containing medications and FEV_1 decline compared to non-ICS-containing medications in COPD populations and determine whether length of follow-up influences the difference in FEV_1 decline between ICS and non-ICS containing groups.

2.2 Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRIMSA-P) 2015 guidelines were used to outline the methodology [97]. This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42018090741.

2.2.1 Eligibility Criteria

Articles meeting the following eligibility criteria were included in this systematic review.

***Participants**:* People with a physician diagnosis of COPD or who had an FEV_1/FVC<70%, who were 35 years old or older and were smokers or ex-smokers.

***Study designs**:* Prospective observational studies and RCTs with at least 2 post-bronchodilator FEV_1 measurements recorded during follow-up. Length of follow-up was not restricted in the eligibility criteria.

Exposure: The exposure for this systematic review was ICS-containing medications. ICS-containing medications included ICS monotherapy, or combination ICS therapy. Combined ICS therapy included ICS combined with any other COPD specific medication such as LABAs and LAMAs.

***Comparisons**:* Articles must have compared people with COPD on an ICS-containing medication with people on a placebo or non-ICS-containing medication.

***Outcomes**:* The outcome of interest was rate of post-bronchodilator FEV_1 decline. Studies were considered if the outcome was expressed as change in FEV_1 over time. Units could include millilitres (ml) or litres (L) per year and absolute change in FEV_1 in ml or L from baseline.

***Exclusion criteria**:* Conference presentations available as an abstract but not as a full paper were excluded. In addition, review articles or other systematic reviews were excluded, articles that included asthma patients were excluded, and only English language papers were included.

2.2.2 Information sources

MEDLINE and EMBASE were searched using the journal database platform, OVID. MEDLINE and EMBASE are bibliographic databases of articles mainly within the field of biomedical research. In order to keep up to date with systematic reviews on ICS and FEV_1 decline in COPD, the Cochrane Database of Systematic Reviews and PROSPERO were regularly searched. MEDLINE and EMBASE were searched up until the 12th May 2020.

2.2.3 Search strategy

Medical subject headings and text words were used to identify literature related to COPD, ICS-containing medication, and rate of post-bronchodilator FEV_1 decline. These three concepts were combined using the Boolean operator "AND" to search for potentially relevant literature. Medical subject headings and text words used in the search are shown in **table 2.1.**

Table 2.1: *Literature search terms.*

Concept	Medical subject headings and text words
Concept 1: COPD	Pulmonary disease, chronic obstructive/
	COPD.mp
	COAD.mp
	Obstruct$ adj3 (airflow$ or airway$ or lung$ or pulmonary or respiratory or bronch$).mp
	Emphysema$.mp
	Chronic$ adj3 bronch$.mp
Concept 2: ICS	Inhal$ corticosteroid$.mp
	Inhal$ adj3 corticosteroid$.mp
	Ics.mp
	Inhal$ aj3 (budesonide or fluticasone or beclomethasone or mometasone or flunisolide or ciclesonide).mp
Concept 3: Lung function decline	Forced expiratory volume/
	Lung function/
	Respiratory function tests/
	FEV_1.mp
	(Chang$ or rate$ or declin$ or worse$ or reduc$ or decreas$ or slow$) adj3 ($FEV_1$ or lung$ function or lung$ volume$)

Note: *".mp" describes a text word. Text followed by "/" describes medical subject headings. "$" allows truncated search words. "adj3" allows the specific search terms to be 3 words away from each other.*

2.2.4 Study records

Articles that met the MEDLINE and EMBASE search were imported to the reference management software Endnote and duplicate articles were removed. Consequently, the selection of relevant literature was performed in two steps.

Firstly, all titles and abstracts were reviewed and sorted into those meeting the inclusion criteria and those not. Uncertain titles and abstracts were included to minimise the risk of rejecting a relevant article. Secondly, full texts of articles included in the first step were reviewed against the inclusion criteria. A second reviewer reviewed all full texts. Full texts that met the inclusion criteria were included in the systematic review and a list of rejected articles were recorded. Relevant data were extracted from included articles and managed using excel.

2.2.5 Data items

Specifically, data were extracted using the population, intervention, comparison and outcomes (PICO) framework [98]. Information on study populations, interventions, control groups, and outcomes were extracted. This included study design, length of study, population characteristics (such as number of people included, age and gender), inclusion and exclusion criteria of studies, study name and geographic location, ICS and non-ICS medications used as the exposure, outcome definition, and outcome data. Study information could be found in the full text or in the supplementary material. Data were extracted using an excel extraction tool which include all information listed above. The excel data extraction tool was piloted before it was used for all included articles.

2.2.6 Outcomes and prioritisation

The outcome of interest for this systematic review was rate of lung function decline, specifically post-bronchodilator FEV_1 decline, stratified by short- and long-term follow-up. Rate of FEV_1 decline measured in ml or L per year and absolute change in FEV_1 (ml or L) from baseline was used to determine rate or change in FEV_1. Short- and long-term follow-up were defined as follow-up of one year or less and greater than one year.

2.2.7 Risk of bias in individual studies

For RCTs the Cochrane Risk of Bias Tool was used to assess selection bias, reporting bias, performance bias, detection bias, and attrition bias. For observational studies, risk of bias was determined using the risk of bias in non-randomised studies of interventions (ROBINS-I) tool. ROBINS-I assesses pre-intervention

biases, such as confounding and selection bias, biases at intervention such as classification of interventions, and post-intervention biases, such as missing data, outcome measurements and reporting bias. All domains of bias were identified as high, moderate, low, or unclear.

2.2.8 Data synthesis

A descriptive synthesis was provided describing study characteristics, types of ICS and non-ICS comparisons, types of inclusion and exclusion criteria used in each study, and rates of post-bronchodilator FEV_1 decline in studies with follow-up less than one year and follow-up greater than one year. Treatment differences, if not reported, were calculated using t-tests based on information extracted from the specific article including sample sizes, mean rates of decline, and standard deviations [99]. Treatment differences were differences in the rate or change of FEV_1 between patients on ICS-containing medications and those on non-ICS-containing medications. A meta-analysis of the treatment differences was performed and stratified by study follow-up time. Between study heterogeneity was tested using the I^2 statistic. Heterogeneity (I^2) greater than 50% was considered as moderately to highly heterogeneous [100]. If high heterogeneity was detected a descriptive synthesis was performed.

2.3 Results

Overall, 4,454 studies were identified in MEDLINE (n=1,319) and EMBASE (n=3,135) following the electronic systematic search. After duplicate articles were excluded 3,353 article titles and abstracts were screened of which, 181 articles were selected for full text screening. Of 181 articles screened, 17 articles met the inclusion criteria as illustrated in the PRISMA flowchart (**figure 2.1**). 164 articles were excluded because they consisted of conferences abstracts, no change or rate of FEV_1 was reported, asthma patients were included, there was not an ICS vs no ICS-containing medication comparison, articles were systematic reviews, review articles or protocols, FEV_1 decline was reported in specific subgroups of COPD patients, or post-bronchodilator FEV_1 was not used.

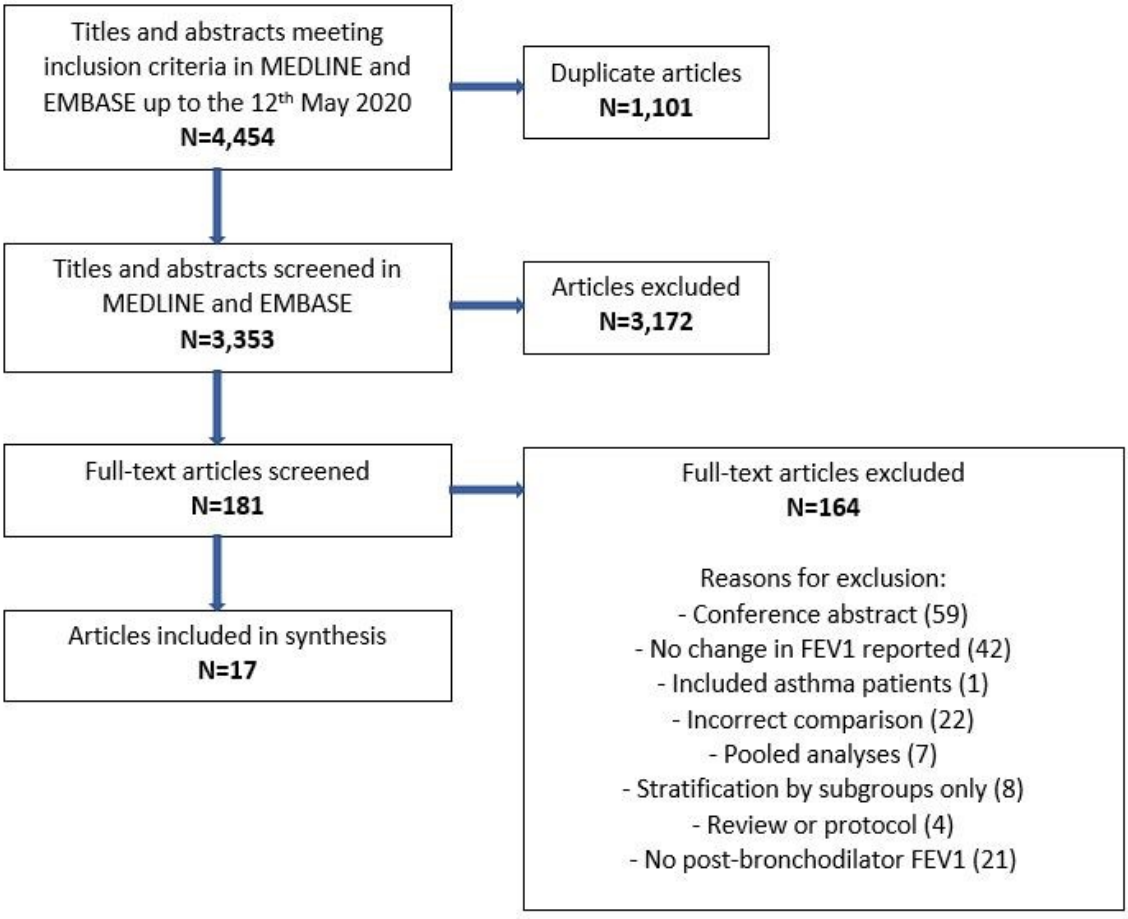


***Figure 2.1**: PRISMA flowchart illustrating selection process of articles.*

All studies that met the inclusion criteria were RCTs (**table 2.2**). Examples of RCTs that met the inclusion criteria included: ISOLDE, single inhaler extra fine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY), SUMMIT and Trial of Inhaled Steroids and long acting β_2 Agonists (TRISTAN). The included studies were published from 1991 to 2018, spanning a 27-year period. The number of patients included in studies ranged from 24 participants to 16,485 patients [38, 86, 101]. Most studies had high numbers of recruited males. The percentage of females in studies ranged from 0% to 46% and the median percentage of females included was 25.5% [102, 103]. The mean age of included participants ranged from around 53 years to 67 years [104, 105] and study follow-up ranged from 3 months to 4 years [38, 86, 101, 105, 106].

Table 2.2: *Articles included from literature search.*

Change in FEV_1 Definition	Authors	Study Name	Geographic location	Follow-up (months)	Patient N	Female (%)	Mean age years (SD)	Intervention (dose µg)	Change in post bronchodilator FEV_1 in ml (SD or 95%CI)
Mean change in FEV_1 (ml)	Auffarth et al 1991[101]	-	Netherlands	3	24	0.04	57.0 (8.2)	Placebo	-120 (230)
								Bud (1600)	15 (110)
	Cazzola et al 2000[106]	-	Italy	3	80	11.6	64.2 (6.3)	Sal (50)	163 (80 to 245)
								Sal/FP (50/250)	188 (89 to 287)
								Sal/FP (50/500)	239 (183 to 296)
	Lee et al 2016[105]	-	China, Hong Kong, Indonesia, South Korea, Thailand	3	577	4.3	66.8 (8.3)	Tio (18)	80 (27)
								Tio + bud/form (18 + 160/4.5)	160 (29)
	Bourbeau et al 1998 [107]	-	Canada	6	79	21.5	66.0 (8.0)	Placebo	0-3 months: -1(-65 to 62) 0-6 months:12(-61 to 85)
								Bud (400)	0-3 months: -13(-59 to 33) 0-6 months: 8(-51 to 68)
	Ohar et al 2014 [103]	-	United States, Argentina, Norway	6.5	639	46	62.9 (9.2)	Sal (50)	40 (342)
								FP/Sal (250/50)	140 (372)
	Vestbo et al 2005 [108]	TRISTAN	Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Lithuania, Netherlands, New Zealand, Norway, Poland, Russia, South Africa, Spain, Sweden, Switzerland, IK	12	1465	27.6	63.2 (8.6)	Placebo	-65 (-200 to 85)
								Sal (50)	0 (-130 to 140)
								FP (500)	0 (-160 to 160)
								Sal/FP (50/500)	80 (-50 to 250)

Rate of FEV_1 change (ml/year)	Vestbo et al 2017[109]	TRINITY	Argentina, Belarus, Bulgaria, Croatia, Germany, Hungary, Italy, Mexico, Poland, Romania, Russia, Slovakia, Turkey, UK, Ukraine	12	2,691	23.6	63.2 (8.6)	Tio (18)	21 (3 to 39)
								Fixed: Beclo/FP/gly bro (100/6/12.5)	82 (65 to 100)
								Open: Becl/FP/Tio (100/6/18)	85 (31 to 110)
	Wise et al 2000[110]	Lung Health Study	United States, Canada	12	1116	36.9	56.3 (6.8)	Placebo	-47 (70.8)
								Triamcinolone acetonide (600)	-44.2(69.8)
	Weir et al 1999[111]	-	UK	24	98	25.5	66.6 (7.0)	Placebo	-56.9(15)
								Becl (750)	-20.6(16)
	Renkema et al 1996[102]	-	Netherlands	24	59	0	56.0 (8.6)	Placebo	-60 (-570 to 140)
								Bud (800)	-30 (-180 to 870)
								Bud + oral prednisolone (800/5)	-40 (-340 to 60)
	Burge PS et al 2000[27]	ISOLDE	UK	36	751	25.4	63.7 (7.1)	Placebo	-59 (30.8)
								FP (500)	-50 (28.7)
	Calverley PM et al 2003 [112]	ISOLDE	UK	36	751	25.3	63.7 (7.1)	Placebo	-46
								FP (500)	-51
	Pauwels et al 1999[104]	-	Belgium, Denmark, Finland, Italy, Netherlands, Norway, Spain, Sweden, UK	36	1277	27.2	52.5 (7.6)	Placebo	0-6 months: -81 9-36 months: -69
								Bud (400)	0-6 months: 17 9-36 months: -57
	Vestbo 1999[113]	CCHS	Denmark	36	290	39.7	59.1 (9)	Placebo	-49.1
								Bud (400)	-46.0
	Calverley et al 2018 [38] & Vestbo et al 2016 [86]	SUMMIT	US, Argentina, Australia, Austria, Belarus, Belgium, Bosnia & Herzegovina, Bulgaria, Canada, Chile, China, Columbia, Croatia, Czech Republic, France, Georgia, Germany, Greece, Hungary, India, Indonesia, Israel, Italy, Japan, Korea, Latvia,	48	16,485	25.5	65.0 (8.0)	Placebo	-46(160.3)
								Vil (25)	-47(154.0)
								FF (100)	-38(154.3)
								FF/Vil (100/25)	-38(154.1)

			Malaysia, Macedonia, Mexico, Netherlands, Philippines, Poland, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Taiwan, Thailand, Turkey Ukraine, UK, Vietnam						
	Shaker et al 2009[114]	-	Denmark	48	254	42	63.6 (7.4)	Placebo	-56 (-72 to -40)
								Bud (400)	-54 (-69 to-40)

Notes: *2 included studies (Calverley 2018, Vestbo 2016) were analysed on the same population and reported the same change in FEV_1 estimates.*

Abbreviations: *FP; Fluticasone proprionate; FF: Fluticasone furoate; Sal: Salmeterol; Bud: Budesonide; Becl: Beclomethasone; TIO: Tiotropium; Vil: Vilanterol; Mom: mometasone; Form: formoterol.; UMEC: umeclidinium; Gly Br: glycopyyronium bromide; Ol: olodaterol*

Studies differed by types of ICS and non-ICS medications. The most common comparison was placebo vs ICS. Other comparisons included LABA vs LABA/ICS, placebo vs LABA/ICS, LABA vs ICS, and LAMA vs LAMA/ICS. **Table 2.2** & **table 2.3** illustrate all types of ICS and non-ICS comparisons in more detail.

***Table 2.3**: ICS and non-ICS-containing medication comparisons.*

Type of ICS-containing medication	Type of non-ICS containing medication	Number of studies
Placebo	**ICS**	**13**
	Fluticasone propionate	3
	Budesonide	6
	Fluticasone furoate	2
	Beclomethasone	1
	Triamicinolone acetonide	1
LABA	**LABA/ICS**	**5**
Salmeterol	Salmeterol/fluticasone proprionate	3
Vilanterol	Vilanterol/fluticasone furoate	2
Placebo	**LABA/ICS**	**3**
	Vilanterol/fluticasone furoate	2
	Salmeterol/fluticasone proprionate	1
LABA	**ICS**	**3**
Vilanterol	Fluticasone furoate	2
Salmeterol	Fluticasone proprionate	1
LAMA	**LAMA/ICS**	**2**
Tiotropium	Glycopyyronium/beclomethasone/fluticasone proprionate	1
Tiotropium	Tiotropium/beclothmethasone/fluticasone proprionate	1
LAMA	**LAMA /LABA/ICS**	**1**
Tiotopium	Tiotropium + formoterol/budesonide	1

***Notes**: numbers do not add up to the total number of studies included in the systematic review due to multiple ICS or non-ICS containing medications used in some studies.*

2.3.1 Change in post-bronchodilator FEV_1

Table 2.2 illustrates the change in FEV_1, by study and ordered by length of study follow-up, and shows a high degree of variation in change in FEV_1 between studies. A large proportion of the variation was dependent on study follow-up time and type of ICS and non-ICS comparison. Change in FEV_1 in studies that had less than one year of follow-up varied between -120 ml (SD 230) to +163 ml (95% CI 80 to 245) over 3 months with non-ICS containing medications and between -13 ml (95% CI -59 to 33) to +239ml (95% CI 183 to 296) over 3 months with ICS-containing medication [101, 106, 107]. Change in FEV_1 in studies that had more than one year of follow-up varied between -69 ml/year to 21 ml/year (95% CI 3 to 39) with non-ICS

containing medications and between -57 ml/year to 85 ml/year (95% CI 31 to 110) with ICS-containing medications [104, 109].

A meta-analysis was performed for all studies as well as for studies with short and long-term follow-up separately and between study heterogeneity (I^2) varied between 98.8% and 88.4%. These heterogeneity estimates are considered high and therefore, a descriptive synthesis of the relationship between ICS-containing medications and the rate of FEV_1 decline was reported.

2.3.2 Study follow-up time

Figure 2.2 illustrates change in FEV_1 in ICS and non-ICS-containing medications in studies with follow-up of one year or less. Most ICS point estimates show an increase in FEV_1 and 8 out of 10 studies showed that change in FEV_1 increased more or declined slower in ICS groups compared to non-ICS groups.

Figure 2.3 illustrates change in FEV_1 in ICS and non-ICS-containing medications in studies with follow-up greater than one year in ml/year. All studies showed a decline in FEV_1 in both ICS and non-ICS groups, of which there was little difference in FEV_1 decline between the two groups. All studies with greater than 1 year of follow-up were placebo vs ICS comparisons.

The general trend in change in FEV_1 with increasing follow-up time suggests that FEV_1 tends to increase with ICS-containing medications in the short term up to approximately one year. Longer studies with follow-up greater than one-year show that FEV_1 generally declines over time in both ICS and non-ICS groups, with little difference in rates of decline in some studies.

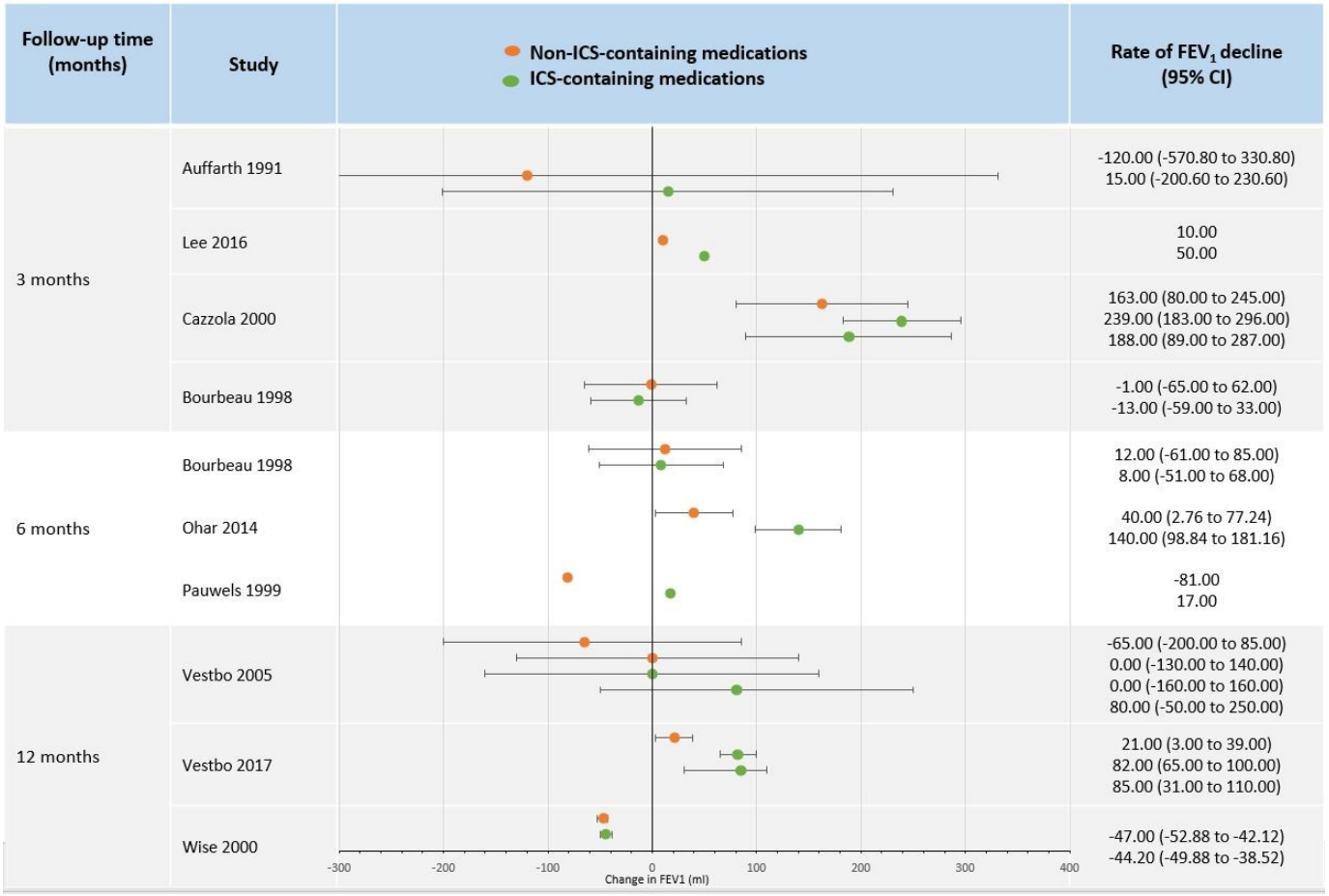


Figure 2.2: *Change in post-bronchodilator FEV_1 (ml) in studies with follow-up of one year or less.*
Note: *Confidence intervals were not shown if the study did not report them or they were unable to be calculated.*

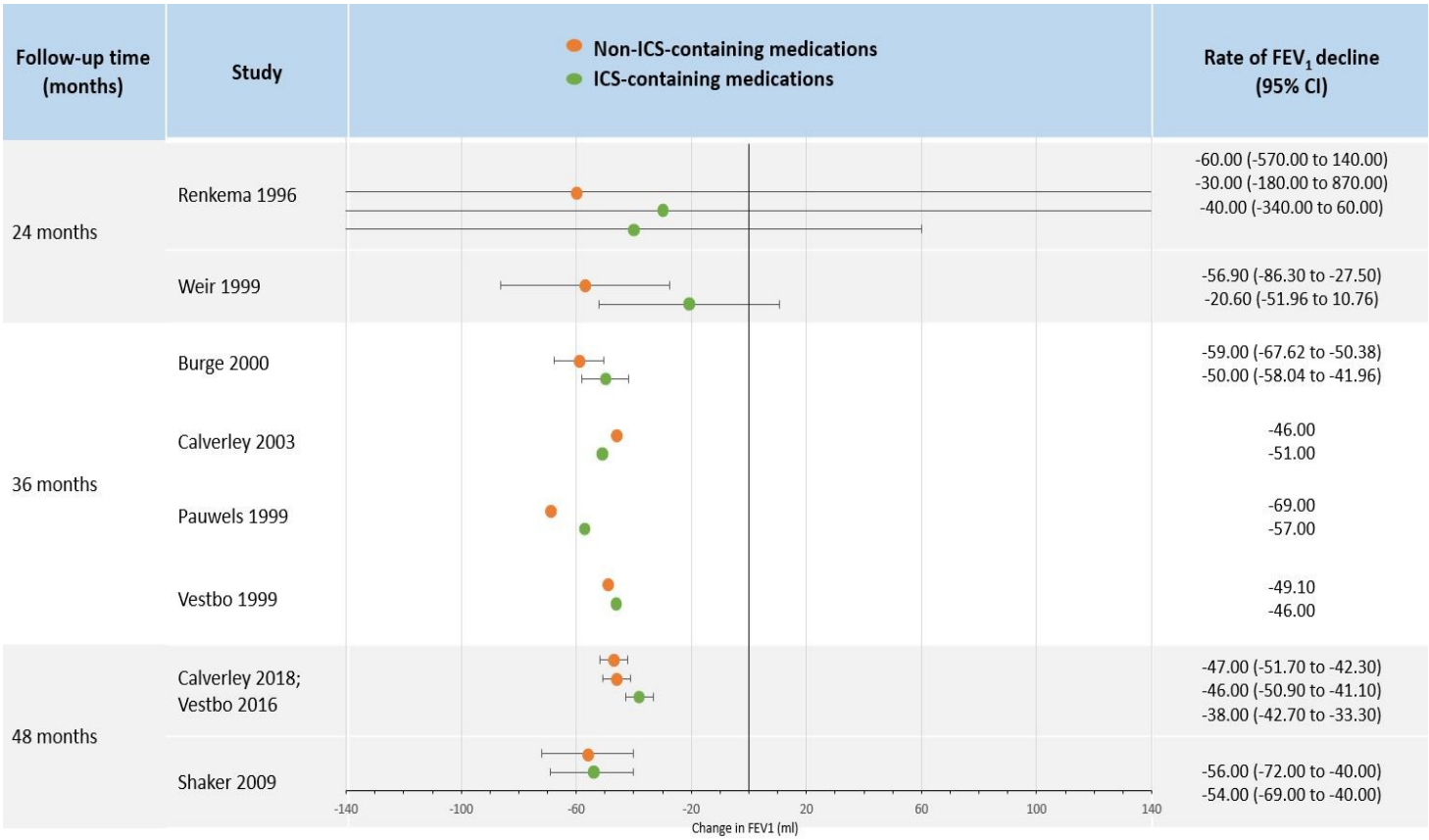


Figure 2.3: *Change in post-bronchodilator FEV_1 (ml/year) in studies with follow-up greater than one year.*
Note: *Confidence intervals were not shown if the study did not report them or they were unable to be calculated.*

2.3.3 Inclusion and exclusion criteria

Study inclusion and exclusion criteria are illustrated in **appendix 2**. Common inclusion criteria included specific criteria regarding age, smoking status and disease severity. Specifically, most studies included patients aged 40 years old or older. In terms of smoking status, most studies included current or ex-smokers with at least 10 pack years history smoking. FEV_1 % predicted criteria were commonly 30-70%. Three studies required patients to have severe or very severe COPD by GOLD 2011 definition.

Furthermore, 4 studies required at least one AECOPD prior to the start of follow-up. These included moderate or severe AECOPD requiring prescribed oral corticosteroids and/or antibiotics or have been hospitalised for AECOPD prior to the start of the study. One study specifically required no AECOPD prior to study start. Other inclusion criteria included MRC dyspnoea scores of 2 or more, FEV_1 reversibility, and risk or history of CVD.

The most common exclusion criteria were the presence of diagnosed comorbidities including other respiratory diseases (e.g., asthma, pneumonia, upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI)) and clinically significant diseases that could affect results and patient participation (e.g., myocardial infarction (MI), heart failure (HF), angina, and diabetes). Further exclusion criteria included long-term oxygen therapy, evidence of alcoholism or solvent abuse, AECOPD requiring prescription of oral corticosteroid, antibiotics, or hospitalisation prior to study start or moderate/severe AECOPDs.

2.3.4 Risk of bias assessment

The majority of studies were considered low risk in each of the bias domains as shown in **Figure 2.4.** Reasons for considering "random sequence and allocation concealment" unclear was due to no mention of a sequence generator in text or supplementary material. "Reporting bias" and "other biases" were low risk because all outcomes mentioned in the methods were reported in the results. "Performance and detection bias" were considered unclear in the study by Cazzola et al., 2000 because the authors failed to report whether and how the study participants and personnel were blinded during follow-up and outcome assessment [106]. "Performance and detection bias" was considered high risk in the study by Lee et al., 2016 and colleagues as participants or participants and personnel were not blinded during the study [105]. The study by Shaker et al., 2009 was considered to have unclear "attrition bias" because there was no indication whether only participants with complete follow-up were used to measure change in FEV_1 [114]. High risk "attrition bias" was observed in 4 studies. This was because only participants with complete follow-up (i.e., completed the study and did not dropout) were included in the analysis of change in FEV_1. See **appendix 2** for detailed risk of bias assessment for each study.

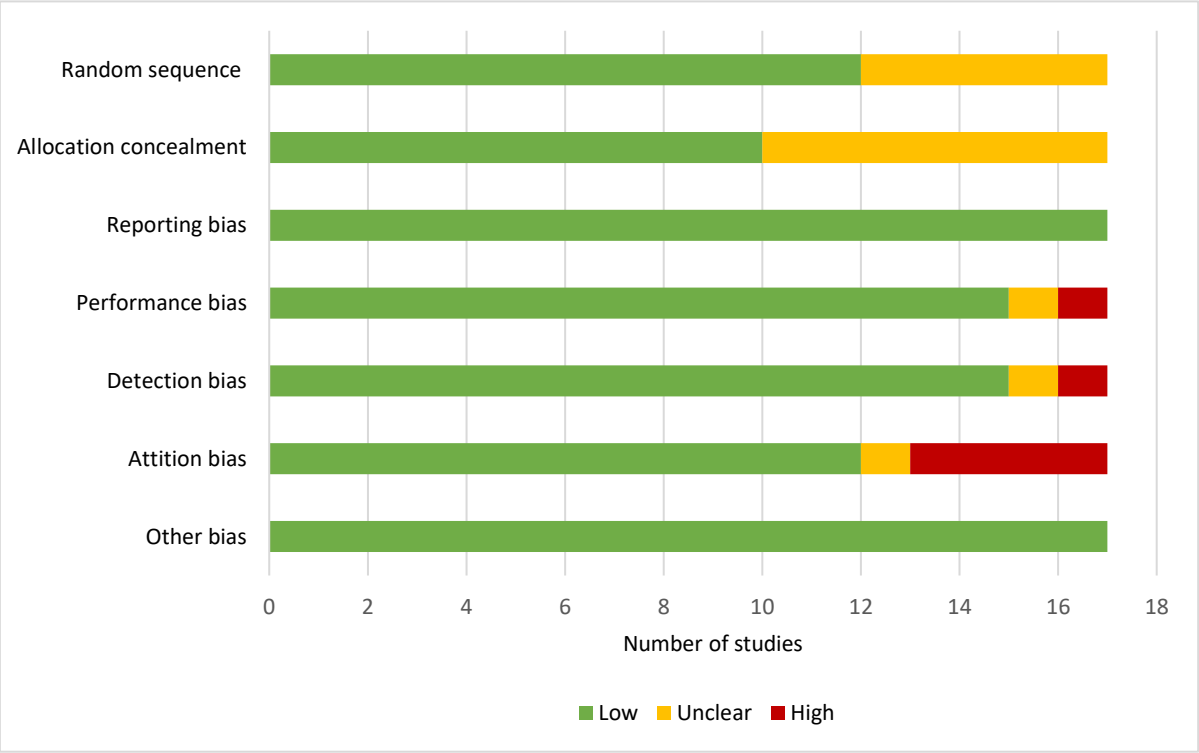


Figure 2.4:*Risk of bias assessment of included studies.*

2.4 Discussion

This systematic review investigated the change in post-bronchodilator FEV_1 with ICS-containing medications compared to non-ICS-containing medications in COPD patients over the short and long term. Of the 17 studies that met the inclusion criteria, all were RCTs. Overall, most studies with less than a year follow-up reported increases in FEV_1, with the general trend favouring ICS medications compared to non-ICS medications. Studies with more than a year follow-up generally reported a decline in FEV_1 with little evidence of a treatment difference between ICS and non-ICS containing medications.

This systematic review was published in December 2019 and has since been updated for the purpose of this thesis [115]. For the purpose of this discussion, the search was updated on the 20th May 2020 and only one additional article met the inclusion criteria. Kato et al., 2019 analysed data from the Informing the Pathway of COPD Treatment (IMPACT) study to compare outcomes between triple therapy LABA/LAMA/ICS (FF/UMEC/Vil), dual therapy LABA/ICS (FF/Vil) and a LABA/LAMA (UMEC/Vil) [116]. IMPACT was a multicentre study with locations in 37 countries. The study follow-up was 12 months, and 10,355 COPD patients were recruited, of which approximately 33% were female. In terms of FEV_1 decline they found that patients on LABA/LAMA/ICS (FF/UMEC/Vil) had a mean increase in FEV_1 of 14 ml (95%CI -24 to 54), patients on (LABA/ICS) FF/Vil had a mean decline in FEV_1 of -52 ml (95% CI -60 to -44), and patients on LABA/LAMA (UMEC/Vil) had a mean decline of -27 ml (95% CI -85 to 31). Here, interestingly patients randomised to LABA/ICS showed the fastest mean decline in FEV_1, however, the confidence intervals around the estimates for LABA/LAMA/ICS and LABA/LAMA are wide.

2.4.1 Length of study follow-up

The main finding suggests that initiating ICS medications improves lung function compared to non-ICS medications however, over long periods of time lung function declines at a similar rate in both ICS and non-ICS medications. This may be due to an initial acute bronchodilation, or subtle improvements in care in both arms shortly after recruitment [117]. FEV_1 decline in studies with more than a year of follow-up is observed in both ICS and non-ICS containing medications and raises the question of whether ICS-containing medications are similar to non-ICS medications over long periods of time with respect to their effect on lung function. In addition, the studies that reported a significant difference between the changes in FEV_1 favouring ICS-containing medications were studies that were less than 1 year in duration.

2.4.2 Type of ICS-containing medications and comparators

In this review most studies compared: i) placebos to monotherapy ICS; ii) LABA to LABA/ICS; iii) placebo to LABA/ICS; iv) LABA to monotherapy ICS; and v) LAMA to LAMA+LABA/ICS. Previous literature suggests that COPD patients on ICS/LABA have better outcomes compared to those on ICS monotherapy or LABA monotherapy. ICS/LABA is associated with reduced rate of AECOPD, improved FEV_1 and an improvement

in patient's health status compared to ICS and LABA separately [26]. Barnes and colleagues have previously showed that monotherapy ICS does not suppress inflammation in COPD and further studies have found that the anti-inflammatory effect of ICS is greater in the presence of beta agonists by increasing the number of beta-receptors to improve bronchodilation from LABA [118-121]. Four studies in this systematic review included both ICS/LABA and ICS monotherapy as the ICS comparison arms. In these studies, FEV_1 improved in ICS/LABA groups but declined in monotherapy ICS groups compared to their non-ICS comparators. In addition, all studies that compared ICS/LABA to LABA or ICS/LAMA to LAMA showed that FEV_1 improved more in ICS combination groups compared to LABA or LAMA. Whilst improvement in FEV_1 was seen in LABA and LAMA groups, the addition of ICS improved lung function further, highlighting the initial beneficial effect of ICS.

Furthermore, recently it has been suggested that the use of LAMA/LABA is preferential over ICS/LABA in COPD patients. This may be due to the synergistic effect of LABA and LAMA which activate both adrenergic and cholinergic pathways, maximizing bronchodilation [122, 123]. Recent systematic reviews have investigated the use of LAMA/LABA compared to ICS/LABA and found that patients on LAMA/LABA had improved health status, decreased moderate or severe AECOPD, and decreased use of rescue medications compared to patients on ICS/LABA [91, 94, 124, 125]. The study by Kato et al., 2019 compared LABA/ICS to LAMA/LABA and the rate of FEV_1 decline was faster in patients on LABA/ICS than those on LAMA/LABA, adding to the argument that LABA/LAMA may improve lung function compared to LABA/ICS [116].

Interestingly, the latest GOLD guidelines state that ICS/LABA use should be considered if blood eosinophils are greater than 300cells/µl in patients who exacerbate more frequently, severely, and who are more breathless [1]. Studies have shown that patients with high blood eosinophils who initiate ICS respond better in terms of lung function compared to those with low blood eosinophils [40]. Studies included in this review did not stratify by blood eosinophils however, a further literature review and meta-analysis on the relationship of ICS, eosinophils, and FEV_1 decline would help summarise short and long-term effect of ICS on FEV_1 decline by eosinophils.

In terms of triple therapy, NICE guidelines state that triple therapy might be more beneficial in patients previously on LABA/ICS than patients on LAMA/LABA in improving FEV_1 as well as reducing AECOPD [21]. Kato et al., 2019 found that FEV_1 in COPD patients on triple therapy improved compared to patients on ICS/LABA or LAMA/LABA [116]. Whilst these patients are all newly initiating users, findings indicate that triple therapy may be more beneficial than dual therapy.

2.4.3 Strengths and Limitations

This is an extensive literature update comparing the change in FEV_1 between ICS-containing medications and non-ICS containing medications over time. ICS-containing medications were compared with non-ICS-containing medications in order to be as inclusive as possible and highlight differences in ICS type as well as length of follow-up and other study characteristics. Most studies included in this review had few biases and were of good quality. In addition, clinical trials with large patient populations such as TRISTAN, TRINITY, ISOLDE, and SUMMIT were included in this review. Since this review was published an additional one study met the inclusion criteria which used data from the IMPACT trial.

One limitation of this systematic review is that ICS monotherapy was included even though it is not currently licensed in the UK [21, 126]. This is because long term use of ICS is less effective than LABA/ICS [1]. ICS monotherapy use is also associated with an increased risk of developing pneumonia, little improvement in lung function, and an increased risk of mortality compared to that of LABAs and LABA combinations [41, 127, 128]. Over time prescribing ICS monotherapy has decreased and it is advised by NICE that ICS monotherapy should not be used for treatment of COPD [126, 129]. Most studies reported a change in lung function in patients on ICS monotherapy, but 7 of the 12 studies were published in 2000 or earlier. The remaining studies that included ICS monotherapy were published between 2001 and 2018. These studies were either conducted in the United States or were multicentre studies that included centres in countries across Europe, Africa, and the Americas. Changes in FEV_1 reported in these studies should therefore be interpreted with caution depending on the prescribing location.

Furthermore, whilst differences in change in FEV_1 between ICS-containing medications and non-ICS-containing medications were seen, they were not always significant. This could have been due to small numbers of recruited patients in some studies. In addition, not all studies reported a treatment difference and it therefore unclear whether these differences are statistically significant as well as clinically significant. In those that did report statistical treatment differences, not all were clinically significant. It has previously been suggested by the American Thoracic Society (ATS) and the ERS that a minimal important difference in FEV_1 between two treatments ranges from 100ml to 140ml [130]. However, this is with regards to pharmacological trials and individual FEV_1 measurements rather than a rate of change. In addition, it is important to note that clinically important differences in the real world may be different to those seen from RCTs.

Moreover, the results from included studies consist of mostly crude changes in FEV_1. Whilst it is important to observe the range of crude changes with regards to ICS and non-ICS containing medications, they could be skewed by baseline FEV_1. Milder patients with a higher baseline FEV_1 may have more lung function to lose compared to a more severe patient with a lower baseline FEV_1 [131]. Using a measure of change that accounts for baseline FEV_1 may be more informative, such as percent change from baseline.

Many studies were excluded from this literature review because they used trough FEV_1 as the outcome. Trough FEV_1 is a measure of FEV_1 approximately 24 hours after the last administrated drug. This outcome is common in RCTs because it is needed for regulatory approval. Naturally, this is different to post-bronchodilator FEV_1, which is used in the clinical setting to assess lung function. To be consistent and more generalisable to the wider respiratory field, only post-bronchodilator FEV_1 measurements were used.

In addition, all studies included were RCTs and had many inclusion and exclusion criteria. All studies included patients with moderate to very severe COPD. Other common inclusion and exclusion criteria included specific pack year smoking history and no other significant comorbidity. Whilst RCTs are important due to their valuable methodological design, they are typically not representative of the wider population of COPD patients, many of whom have comorbidities. Therefore, the representativeness of the results included in this review should be noted [31, 44]. Observational and general practice studies are needed to identify changes in lung function in a more representative COPD population with a wider degree of disease severity and comorbid conditions. Lastly, a high level of heterogeneity between studies was observed and therefore, results from the meta-analysis should be interpreted with caution, if interpreted at all. This limited the ability to make conclusions on rate of change in FEV_1 by ICS and non-ICS comparisons.

2.5 Conclusion

The findings from this systematic review suggests that in COPD patients, initiating ICS medications improves post bronchodilator lung function compared to non-ICS medications. However, over long periods of time lung function declines at a similar rate for both ICS and non-ICS medications. Further studies that are more generalisable to the wider population of COPD patients are needed in order to investigate the association between ICS and FEV_1 decline further. Additionally, studies with a longer follow-up are needed to observe the long-term effect of ICS on lung function.

Chapter 3
Data Sources and Methodology

This chapter describes data sources used for the following chapters and outlines basic definitions of variables used, such as COPD and other variables. This chapter also describes the main statistical models used in the following chapters.

3.1 Data Sources

3.1.1 Introduction

EHR databases systematically and routinely collect and store healthcare data electronically. They exist in multiple forms and can include data on routine processes in primary and secondary care (disease codes, prescriptions, procedures, and tests), as well as being used for medical insurance claims, to collect mortality data, or for specific disease registries such as the cancer registry in the UK. The information contained and the way in which it is coded in these databases differ. The original purpose, certainly in the UK, was simply to store medical information digitally but increasingly, these databases are being used for other purposes. EHR have gained increasing recognition as a mechanism for research and are used for population-based studies globally, allowing inclusion of populations not necessarily routinely studied in randomised controlled trials and include large sample sizes, and offer a wide breadth of study variables.

The National Healthcare Service (NHS) is the largest publicly funded health service in the world providing healthcare to millions through primary care general practitioner (GP) staff and secondary care professionals in the UK. GPs are often the first point of care in managing medical treatment of patients, educating and advising patients, and caring for patients with long-term illness as most people in the UK are registered with a GP (98% of people in the UK) [132]. Patients needing secondary care can be referred by GPs, who act as a gatekeeper, to other healthcare services in the UK. The value of such comprehensive data led to the establishment of the Clinical Practice Research Datalink (CPRD) which has become a valuable source of data for health-related research [133].

CPRD is a non-profit service that has been providing anonymized patient data to health-related researchers for over 30 years. In 1987 general practices started using the first iteration of an electronic healthcare system to record patient data through the Value-Added Medical Products (VAMP) database. Following this, the general practice research datalink (GPRD) was established within the Department of Health with the aim of collecting and using anonymized patient data for research. In 2012, GPRD was expanded to CPRD which is more comprehensive and allowed access to other health care linkages [133]. CPRD is a centralised database that regularly collects data from general practices who agree to contribute and adds to its ever-growing database. General practices have the option to opt into the contribution of data to CPRD whereas individual patients have the option to opt out. The longitudinal nature of GP health records allows researchers to study diseases over a long period of time and its comprehensiveness has led to its use both globally and in the UK for epidemiological studies as well as pragmatic clinical trial studies.

CPRD contains two databases; CPRD GOLD and CPRD Aurum based on different software systems used to collect data at GP practices. CPRD GOLD currently contains information on patients at over 1,800 GP practices across the UK and holds patient data from 1987 to present day. Approximately 50 million patients across the UK have their anonymous data recorded within CPRD GOLD of which of which 14 million patients

(approximately 20% of the UK population) are currently alive. When compared to the 2011 census, patients included in CPRD GOLD were representative of the general UK population in terms of age, gender, and ethnicity [132, 133]. In October 2017, CPRD launched its second database based on a different general practice data collection software in England only; CPRD Aurum. As of September 2018, over 7 million patients were alive and included in CPRD Aurum (approximately 14% of the population of England). This number will continue to increase as practices switch software systems to those that will be included in CPRD Aurum. To date, patients included in CPRD Aurum are representative of the general UK population in terms of geographical spread, socioeconomical deprivation, age, and gender [132].

3.1.2 Structure and organization of CPRD

Patient data are available through CPRD and is recorded by GPs or other healthcare professionals during a consultation. GPs record patient data with the use of a software system that allows them to input details of the consultation. GPs across the UK use several different software systems to record patient data, but the two most popular systems are Vision and EMIS, which contribute data towards CPRD GOLD and Aurum, respectively. It is important to note that general practices opt in and individual patients can opt out of contributing data to CPRD if they wish.

Data collected using Vision and EMIS systems contribute to two databases within CPRD: CPRD GOLD and CPRD Aurum, respectively. Up until October 2017, CPRD GOLD was the only CPRD database available and contains general practices using Vision software in England, Scotland, Wales, and Northern Ireland. Since then, CPRD launched a new database, CPRD Aurum, which contains general practices using EMIS software in England. Vision and EMIS systems are used to record information on consultations, diagnoses, prescribed medications, requested tests and results, immunizations, and referrals to outpatient clinics; data which is all consequently available in CPRD databases.

All patient data in CPRD GOLD and CPRD Aurum is deidentified which means that personal identifiable information such as patient name, address, NHS number and full date of birth are not collected or seen by CPRD or researchers. Patients can opt out of contributing their data to CPRD for research purposes at any time. In this case the patient's entire medical record will be removed from CPRD and thus only patients who have not opted out will contribute data. Anonymised patient records recorded in CPRD GOLD and CPRD Aurum are continuously collected every month by CPRD from practices who have signed up to contribute data to CPRD. CPRD GOLD and Aurum are similar in the fact that they record the same details of any given consultation however, they differ in structure.

Both CPRD GOLD and Aurum databases use clinical codes to define clinical terms recorded during a consultation. GPs record these as read codes in CPRD GOLD and SNOMED CT codes in CPRD Aurum. Read codes were first created by Dr James Read in the 1980's and are a set of unique codes that are used to describe specific medical conditions. During a consultation, the GP will add a new consultation to a patient's

record using the "Consultation Manager" interface in the Vision and EMIS software systems (see **figure 3.1**). The GP can record symptoms or conditions that arise during the consultation as a new consultation event (an example using weight in the Vision software system is seen in **figure 3.2**)**.** Specific key words can be typed into the designated dialogue box which generates a list of potential codes that can be recorded to describe a clinical event. GPs can select the most specific code to the condition of that patient using the drop-down menu which includes the corresponding read term, a summary term used to describe a specific code. Free text can be entered into the system if additional information is warranted and data can be added retrospectively, for example to add events such as tests that might have been performed outside of the consultation, and update or amend events to enrich patient records.

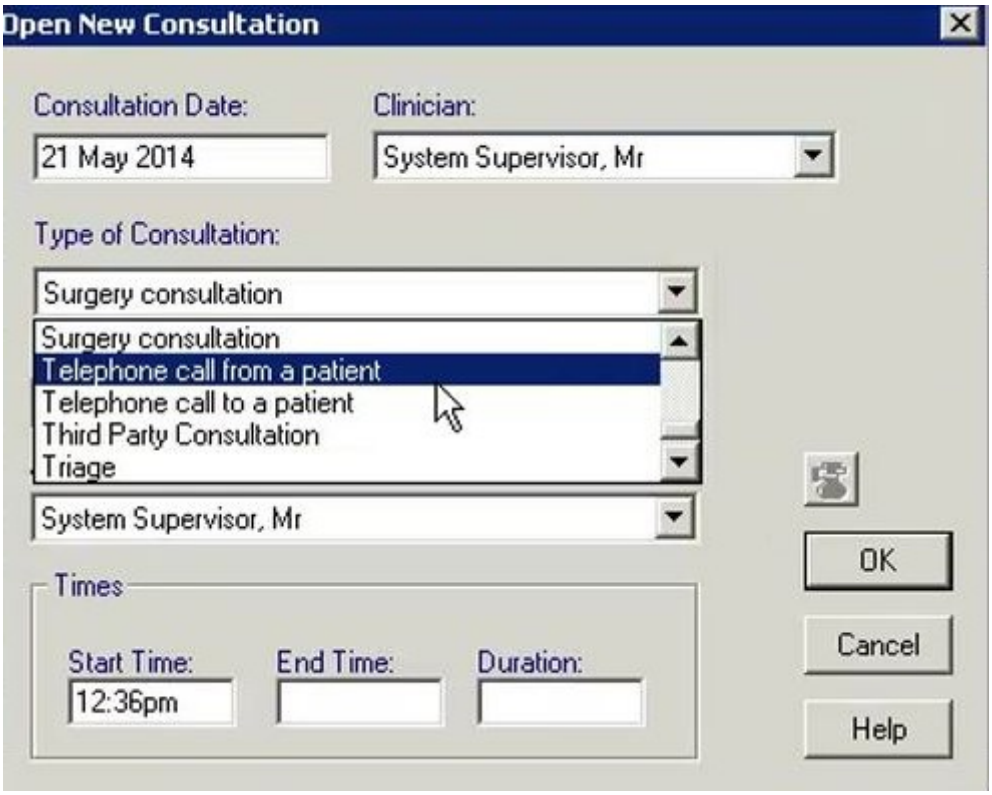


Figure 3.1: *Consultation manager. Reproduced from [134].*

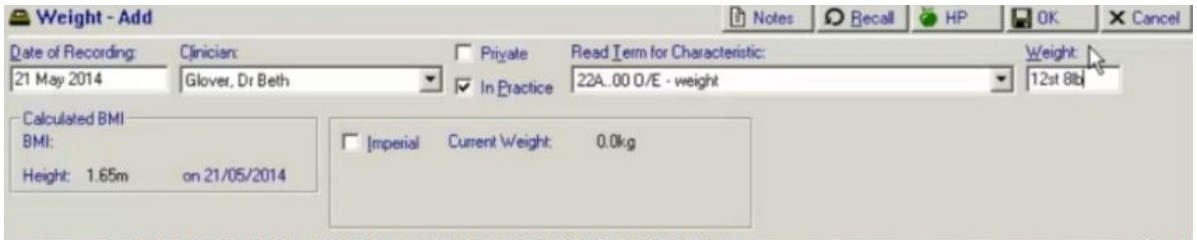


Figure 3.2*: Adding clinical event during consultation. Reproduced from [134].*

Patient records that are entered into Vision and EMIS are collected by CPRD every month and organised into files for researchers to use. These files contain information on patients complete medical history. Data from the Vision software (CPRD-GOLD) is organised into 10 files. The structure and organization of these files within CPRD-GOLD is illustrated in **figure 3.3.** Data from EMIS software (CPRD-Aurum) is organised into 8 files. The structure and organisation of these files within CPRD Aurum is illustrated in **figure 3.4**.

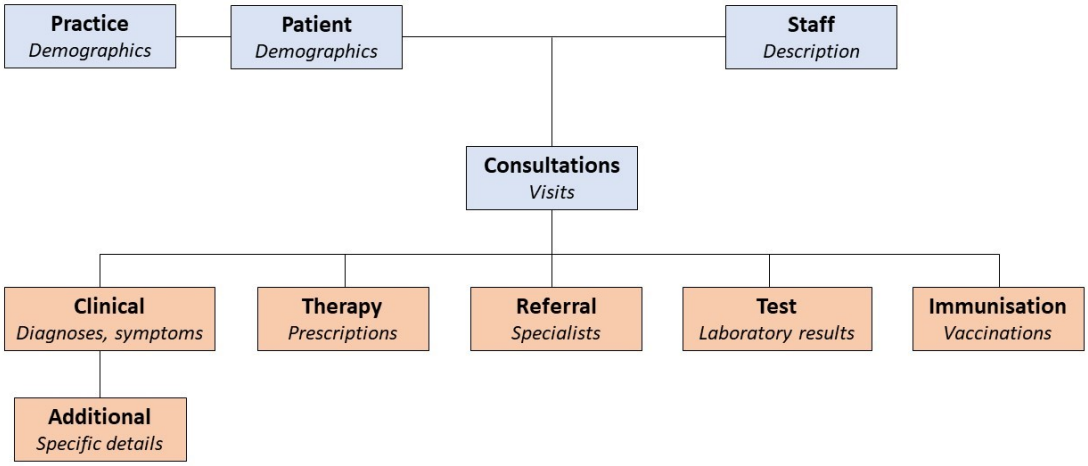


Figure 3.3: *Structure of files in CPRD GOLD. Adapted from [132].*

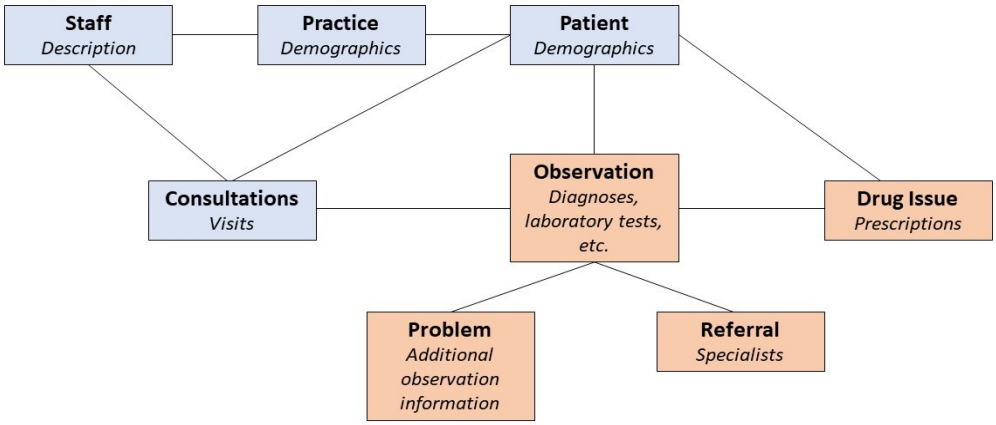


Figure 3.4*: Structure of files in CPRD Aurum. Adapted from [133].*

The patient file is the central file that contains patient demographic information and unique pseudonymised patient identifiers that are used to link the events files. Specifically, the patient file contains information on patient registration with the general practice, the date and reason for leaving the general practice where appropriate, and the date of death if a patient died. Important variables in this file include: i) a current registration date (CRD), which is the date at which the patient registered with their current general practice; ii) a transfer out date (TOD), which is the date at which a patient leaves a CPRD general practice, for example if they move away and joined a different general practice that does not contribute to CPRD or it is the date of a patient's death, and iii) the last collection date (LCD) which is the date that CPRD last collected data from general practices.

The practice file, which can be linked to the patient file, is used to identify a unique practice number, geographic location, and a data quality marker. The practice ID is the last three digits of the patient's unique pseudonymised identifier within CPRD. The geographic region of the practice is coded into 13 regions in CPRD GOLD including north east England, north west England, Yorkshire and the Humber, east midlands, west midlands, east of England, south west England, south central England, London, south east coast, Northern Ireland, Scotland, and Wales. CPRD Aurum only included regions based in England. Specific names and locations of practices are not available to CPRD or researchers to protect the anonymity of patients. Finally, an "up-to-standard (UTS) date" is provided which is a date at which the practice is deemed to be of research quality. Specifically, this is a practice-based quality measure based on the continuous recording of data and death recording within the general practice. CPRD monitors data recording every month and the UTS date is the first date whereby the recording of data and death data was acceptable [133].

The consultation file is limited in that it does not contain information on any records that were entered during the consultation however, it does contain information on the type of consultation, for example whether it was a GP practice appointment, telephone appointment or emergency visit. It also contains the date at which the consultation occurred. This file can be used alongside more detailed event files listed below to find records that were entered within a specific consultation.

Event files consist of a group of files that contain information on clinical diagnoses, prescriptions, referrals, tests performed, and immunisations that occurred within a consultation. In CPRD GOLD these files are called the clinical, additional, therapy, referral, test, and immunisation files (**figure 3.3**). In CPRD Aurum these files are called the observation, drug issue, problem, and referral files (**figure 3.4**). Clinical diagnoses, symptoms, and medical conditions can be identified in the clinical file in CPRD GOLD and in the observational file in CPRD Aurum. Events are coded using medcodes in CPRD GOLD and medcodeid codes in CPRD Aurum. These are CPRD's unique version of read codes and SNOMED CT codes, respectively. **Table 3.1** illustrates an example of how read terms, software related codes, and CPRD's medical codes relate in CPRD GOLD and CPRD Aurum. Clinical codes correspond to a specific clinical event recorded on a specific

date, otherwise known as the event date. In CPRD GOLD, additional clinical information such as height, weight, BMI, blood pressure and various lifestyle factors such as smoking status and alcohol consumption, can also be recorded in the additional file and linked via the event date.

Table 3.1: *Example of read terms, software codes, and CPRD codes used to define chronic cough.*

Read term	CPRD GOLD		CPRD Aurum	
	Vision Read code	Medcode	Emis SNOMED CT code	Medcodeid
Dry cough	1712.00	4931	11833005	20419011
Persistent cough	171B.00	3628	284523002	423230012
Chesty cough	1719.00	292	161929000	252359015
Chronic cough	171A.00	1612	68154008	113213012
Morning cough	171C.00	4070	161932002	252363010
Cough with fever	171F.00	18907	135883003	216653013
Bronchial cough	1719.11	1025	161929000	252360013
Night cough present	1717.00	3068	161927003	252357018

Information on medications and prescriptions can be found in the therapy file in CPRD GOLD and the drug issue file in CPRD Aurum. These files include unique CPRD codes used to identify types of medications prescribed by the GP, called prodcodes. Further information on the prescription length, number of packs, dosage, and the date on which the prescription was made by the GP can also be found in these files.

Lastly, information on referrals and tests can be found in the in the referral and test files in CPRD GOLD and in the referral and observation file in CPRD Aurum. Specific information includes the date and the specialty of the referral consultant, the type of test performed during a consultation (such as spirometry), laboratory tests performed (such as blood tests) and their results, and the date the tests were performed. All the files highlighted in **figure 3.3** and **figure 3.4** can be used to extract variables of interest for a research project.

3.1.3 Quality and completeness of CPRD

Every month CPRD collects data from general practices and add it to existing patient data. During this process quality checks are conducted to ensure the integrity of the data for research. CPRD check that all files have been collected (as demonstrated in **figure 3.3** and **figure 3.4**) and have the correct data structure. Lastly, CPRD replace text with codes, for example changing men to "1" and women to "2" and create lookup files that can be used by researchers to find out what each code represents. After these processes have

been performed by CPRD, a new release of the data is available to researchers to download every month. Monthly data releases include all previous data available in the CPRD databases as well as the additional new month.

One main process that CPRD conduct for each new monthly release of data is a data quality check. Errors can occur if GPs incorrectly input data and the quality of data can vary when software and recording practices evolve. In order to ensure data quality, CPRD creates data quality flags when processing the data to help maintain consistency of CPRD data. Data quality checks are specific to CPRD and consist of a patient and practice level quality marker. It is important to note that more comprehensive data quality checks such as checking completeness of data, value ranges, and consistency of data should be performed by the researcher.

The patient level quality flag is an "acceptability" flag which can be found in the patient file. This is coded as acceptable or not acceptable for each patient. In order for patients to be deemed acceptable patients must have: i) a valid gender and date of birth with no prior clinical events; ii) be less than 115 years old at the last collection date or transfer out date; iii) consistent and valid registration dates; iv) a valid transfer out date and reason for patients who have transferred to non-CPRD general practices or have died whereby the transfer out date must be after the registration date; and v) at least one valid event date in any of the CPRD files highlighted in **figure 3.3** and **figure 3.4**. Invalid event dates are those that are entered before the 1st January 1800 or after the current monthly data release.

The practice level quality marker is a UTS date. This is the date at which the data provided by the practice is of research quality. A practice is contributing good quality research if mortality rates for the practice are within expected ranges and there are no gaps in recorded data. Unlike the patient level quality marker, which is a binary flag, the practice level quality marker is a date that researchers should use to define their study period so that only data that is deemed research quality is used.

Whilst CPRD have processes in place to check the quality of data collected from the general practice, there are also schemes in place to ensure the recording of data by GPs is high at the first instance. QOF is a voluntary scheme that rewards good practice within general practices. It was first introduced in 2004 and it works by awarding payments and "achievement points" to practices based on two domains: clinical practice and public health. QOF encourages GPs to better record the management of patients with chronic diseases and preventative measures that are taken to reduce the risk of specific diseases. The implementation of QOF aims to improve the quality and detail of data recorded by GPs. **Table 3.2** highlights the QOF indicators for COPD.

Table 3.2: *Quality of Outcomes (QOF) indicators for COPD. Adapted from [135].*

Type of indicator	Indicator	Achievement threshold
Records	1. The contractor establishes and maintains a register of patients with COPD	
Initial diagnosis	2. The percentage of patients with COPD in whom the diagnosis has been confirmed by post bronchodilator spirometry between 3 months before and 12 months after entering on to the register	45-80%
Ongoing management	3. The percentage of patients with COPD who have had a review, undertaken by a healthcare professional, including an assessment of breathlessness using the MRC dyspnoea scale in the preceding 12 months	50-90%
	4. The percentage of patients with COPD with a record of FEV_1 in the preceding 12 months	40-75%
	5. The percentage of patients with COPD ad MRC dyspnoea scale ≥3 at any time in the preceding 12 months, with a subsequent record of an offer of referral to a PR rehabilitation programme	40-90%
	6. The percentage of patients with COPD who have had influenza immunisation in the preceding 1st August to 31st March	57-97%

3.1.4 Extracting CPRD data

CPRD collect data from general practices each month, process it, and combine it with pre-existing data to generate an up-to-date data build. This process is described in **figure 3.5.** After these processes, data is available to be downloaded by researchers. Only data that is required for a specific study of interest can be downloaded from CPRD. Therefore, prior to downloading CPRD data, researchers are required to define their study population of interest using a set of codes that can be used to identify patients with, for example, a specific disease such as COPD.

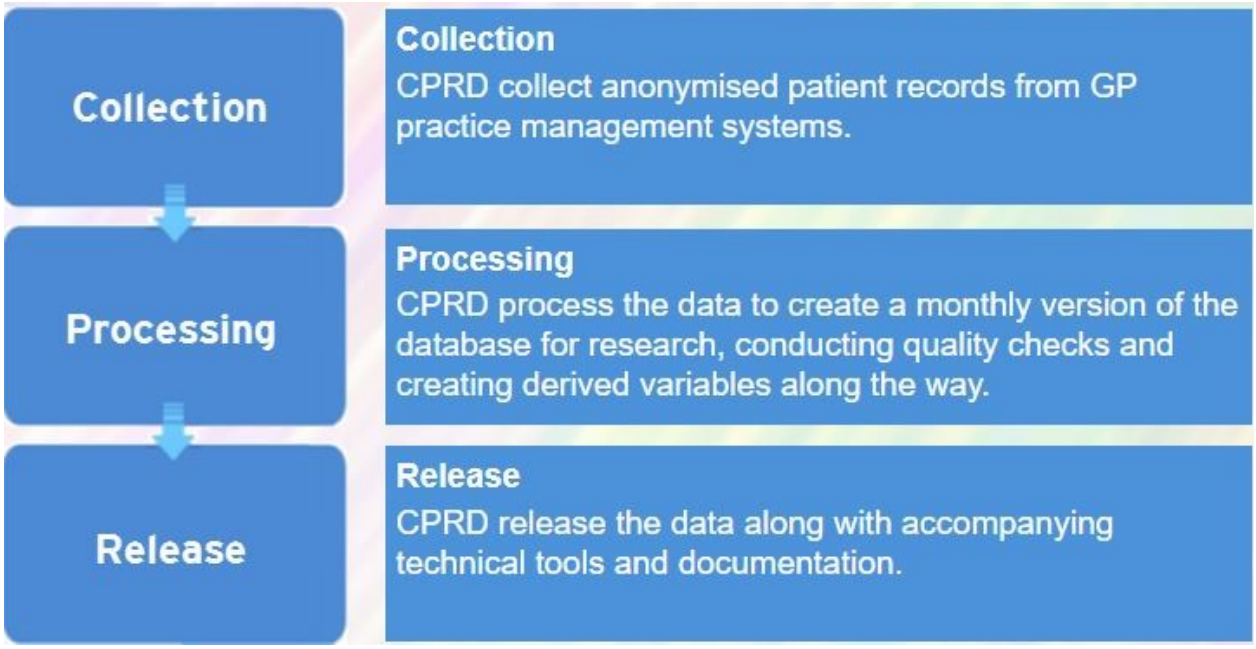


Figure 3.5: *CPRD data workflow. Reproduced from [134].*

To generate code lists used to define diseases in CPRD, a search tool called the code browser is given to researchers by CPRD to search for specific codes relating to a specific medical condition or medication. An example of a CPRD GOLD search performed in the code browser is illustrated in **figure 3.6.** Specific terms for a condition or medication were searched for and the code browser generated a list of potential medcodes or prodcodes that can be used to define clinical events and prescriptions. These codes were reviewed and codes which did not properly describe the event of interest were excluded from the list of codes. These were also reviewed by a clinically trained professional to ensure the correct codes were used.

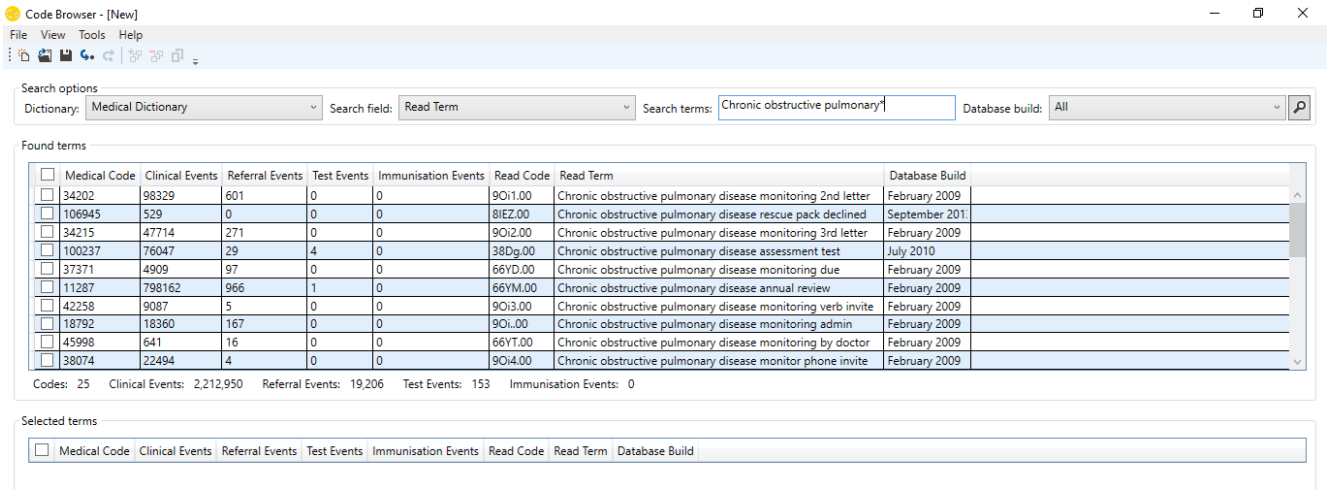


Figure 3.6: *CPRD Code Browser.*

Once a suitable code list was created, this was sent to CPRD who use this list to define a population based on codes provided. It is also possible to apply additional inclusion and exclusion criteria to the population prior to downloading the data however, in most cases it is easier to apply more specific criteria after the data has been downloaded. Once the study population was properly defined, CPRD data files were extracted and downloaded. **Figure 3.7** illustrates the workflow from generating code lists to extracting and downloading CPRD data.

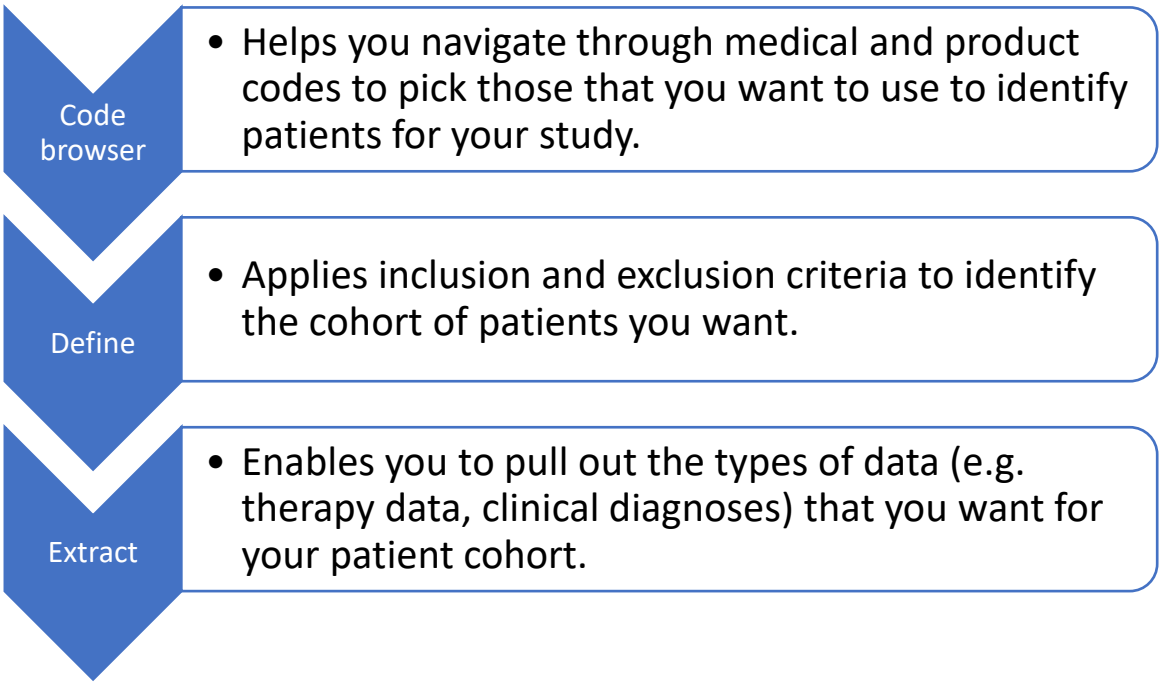


Figure 3.7: *Extracting CPRD data.*

3.1.5 Linked datasets

CPRD can be linked to other electronic healthcare databases including secondary care databases, mortality data, and specific disease registries. Linkages are helpful when GP data might lack detail. Using secondary care as an example, it is possible for GPs to input information about events requiring hospitalisation into their GP records however, the information around the hospitalisation can lack detail. In addition, studies have shown that not all hospital events are recorded in primary care. For example, Whittaker et al., found that only 5.7% of chest CT scans recorded in secondary care were also recorded in primary care in a population of COPD patients [136]. Therefore, linkage to secondary care is essential to gain additional details on events that occur in hospital. General practices opt in for their data to be linked to other databases and can opt out if they wish. Approximately 75% of general practices in England had agreed to the linkage scheme in 2015 [133].

CPRD can link their two databases, CPRD GOLD and CPRD Aurum, to other databases. They do this by working with a trusted third party, NHS digital, to keep the anonymity of patients within CPRD safe. Some databases are already anonymised and can be sent directly to CPRD for linkage with CPRD data but databases that include identifiable patient data must be linked to CPRD by NHS digital. Patient identifiers including patient name, address, NHS number, and date of birth are sent directly to NHS digital from the general practice without any clinical patient data. NHS digital then links the patient identifiers to other databases of interest, anonymises the data and sends the data to CPRD along with an indicator which identifies which anonymized patients from CPRD have linked data. **Figure 3.8** illustrates the linkage process between the general practice, the third party (NHS digital), and CPRD. The three main databases that can be linked with CPRD include Hospital Episode Statistics (HES), a secondary care database, the Office of National Statistics (ONS), mortality data, and the Index of Multiple deprivation (IMD), socioeconomic deprivation data. All these databases were used in the following chapters.

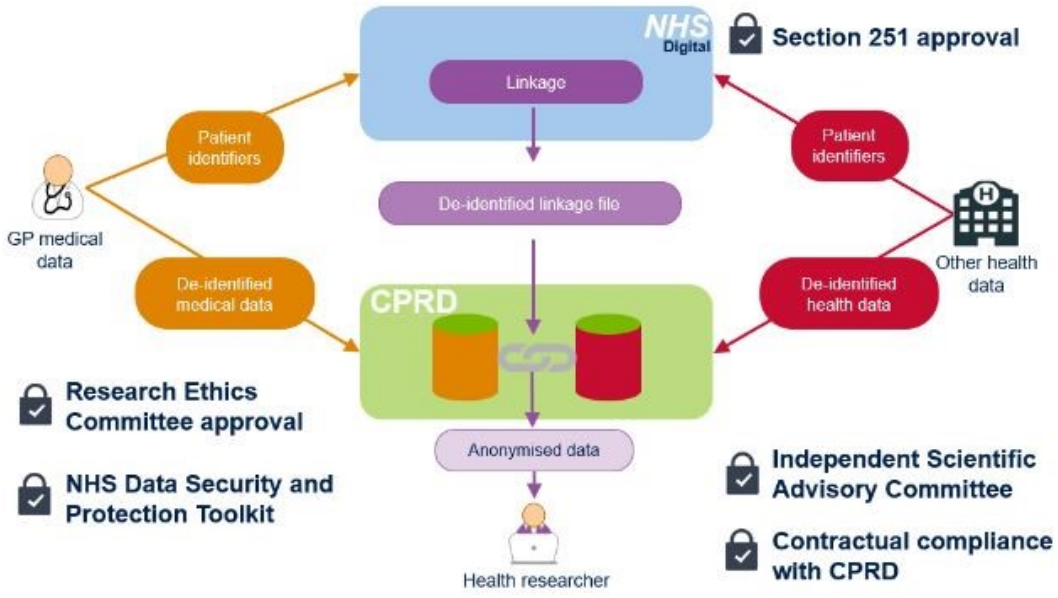


***Figure 3.8**: Linking CPRD data to other data sources. Reproduced from [137].*

3.1.5.1 Hospital Episode Statistics (HES)

HES contains records of all hospital events from NHS hospitals and private hospitals treating NHS patients in England. HES contains information on events such as diagnoses, procedures, admission dates, and hospitalizations. All events recorded within HES are coded using International Classification of Disease (ICD) 10 codes and are structured by hospitalizations. Within each hospitalization there can be multiple episodes which correspond to a specific type of care given. Clinical events such as diagnoses by consultants can be found within episodes of a hospitalization. **Figure 3.9** illustrates how hospitalizations and episodes are structure in HES.

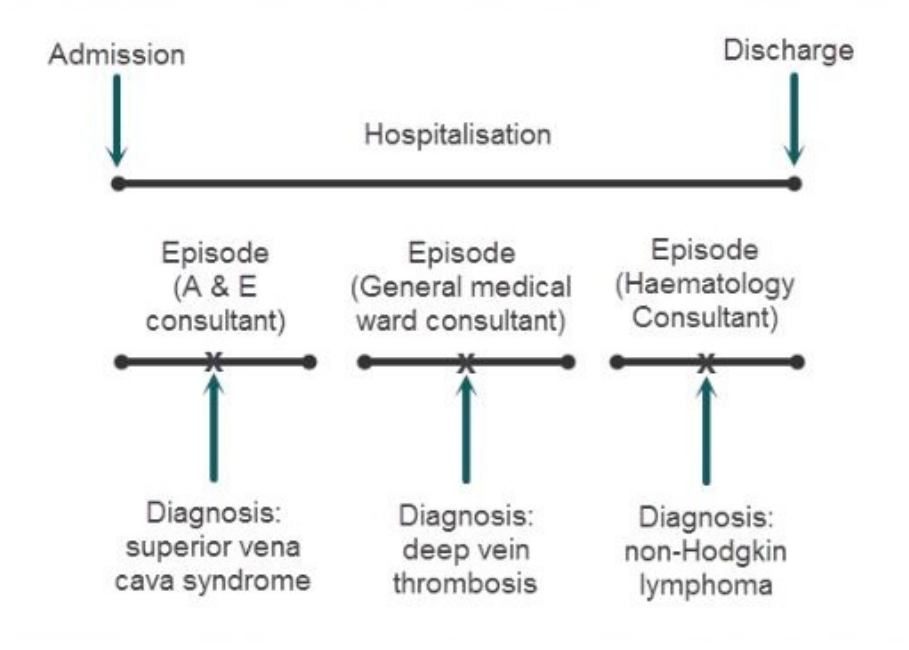


***Figure 3.9**: Structure of data within Hospital Episode Statistics (HES). Reproduced from [134].*

3.1.5.2 Office of National Statistics (ONS)

ONS is a mortality database that can also be linked to CPRD. Every death in the UK must be reported by the General Register Office and information is recorded by the ONS. A medical certificate is required upon death which lists the cause (or causes) of death. The certificate must be signed by a doctor and delivered to the general register office. All information recorded on death certificates is captured by ONS, which makes ONS more detailed than the death information recorded in CPRD directly. ONS contains the date of death recorded by the general register office, the underlying cause of death, and up to 15 contributory causes of death whereas death recorded in CPRD only includes a death date that is calculated by CPRD using an algorithm based on other patient information. This means that the death dates recorded in CPRD are not always exact. Therefore, studies that include death as a main outcome should link CPRD with ONS. Interestingly, a study investigating the accuracy of death recording in CPRD compared to ONS found that 69.7% of deaths were recorded on the same day in both databases. For those that were not, the majority

of CPRD death dates were recorded within one month of the ONS death date, notably within one month after the ONS date. This could be because of a delay in reporting death information to the GP, or a lack of incentive or urgency for GPs to record a patient's death in their GP records [138].

3.1.5.3 Index of Multiple Deprivation (IMD)

Lastly, socioeconomic deprivation data such as IMD can be linked to CPRD. IMD data includes deprivation indices at the practice level, which is a weighted deprivation score based on factors such as income, employment, education, health deprivation, crime, housing and living environment [139]. Deprivation scores are calculated for each small area in England and are ranked from the most deprived areas (decile 1) to the least deprived area (decile 10).

3.1.6 Governance and approval

CPRD is joint venture from the Medicines and Healthcare Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR). It is owned by the UK Department of Health and operates within the MHRA. CPRD itself has National Research Ethics Service Committee (NRES) ethnics approval for the collection and supply of CPRD data and established linked databases for observational research [133]. CPRD must meet UK and European laws of confidentiality to protect patient identities because patient consent has not been given. Therefore, patient identifiers are kept separate from any clinical data so that CPRD and researchers are unable to identify patients from the data.

Prior to extracting CPRD data, approval from an Independent Scientific Advisory Committee (ISAC) is required. Approval is needed because patient level data is being requested. To do this an ISAC form must be submitted. The form describes the research project, the funding source for the study, specific details on how and where the data will be accessed and processed and data linkages that will be required (see **appendix 3** for all ISAC approvals for the work performed in this thesis).

3.2 Study design

Once all data files were downloaded, data were cleaned in order to ensure good quality using the patient and practice level data quality markers described above. Consequently, a cohort of patients was created using the data that met specific study criteria.

Each chapter within this thesis shared a common study design foundation. The main inclusion criteria for each study required patients to 1) have a clinical diagnosis of COPD; 2) be current or ex-smokers; 3) be aged 35 or older; and 4) have linked HES data. For most chapters, patients were also required to have at least 2 FEV_1 measurements at least 6 months apart to estimate rate of FEV_1 decline. The inclusion criteria are based on the validated algorithm for COPD using CPRD data, the use of secondary care data to ensure detailed variable information and having spirometry data to measure rate lung function decline [140].

Each study included 2 key study design dates: the index date and the end of follow-up date. The index date was the date at which a patient's follow-up started. This was the date at which patients met the main inclusion criteria, a specific CPRD related criterion, a specific study related criterion, and had spirometry recorded (where relevant). As an example, the index date could be the last date that the following criteria were met: i) date of COPD diagnosis; i) current GP registration date, iii) UTS date; iv) date at which patient's turned 35; and v) had data recorded from the 1st January 2004. The 1st January 2004 was included as an inclusion criteria because this was the date at which QOF was introduced and therefore data recorded after this date (such as study outcomes) would be more reliable in terms of quality [141]. Where rate of FEV_1 was the outcome of interest, the index date was the date at which the first FEV_1 measurement was recorded after all other criteria were satisfied. It is important to note that the first FEV_1 measurement, that was recorded after the inclusion criteria was met, was not always the first FEV_1 recorded within the patient's historical data, but rather the first measurement included for analysis.

The end date was the date at which the study follow-up period ended. Data recorded after the patient's end date was not included for analysis. Patients were therefore censored at this date, at the latest, depending on the study outcome. Patients' end date was the first of the following dates: i) study end date, such as the 31st December 2017, or otherwise; ii) date at which the patient died (if they died); or iii) the date at which the patients transferred to a non-CPRD contributing GP practice. **Figure 3.10** illustrates an example of the basic study design used to investigate rate of FEV_1 decline as an outcome and how the index date and end date were defined.

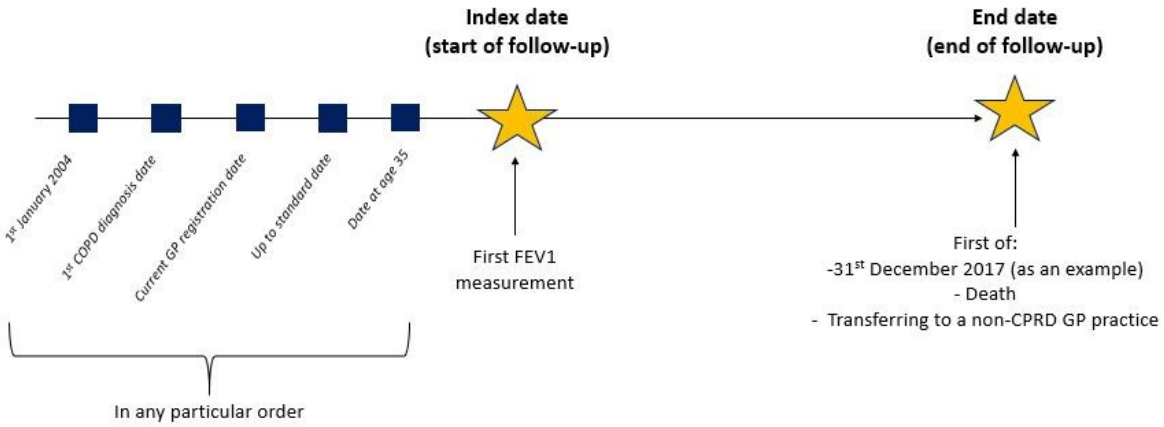


***Figure 3.10**: Basic study design elements.*

3.3 Study variables

In this thesis the main outcome and exposure variables included COPD, rate of FEV_1 decline, blood eosinophils (EOS), ICS use, and CVD outcomes. These were defined using data from various data files within CPRD as well as events recorded within HES and ONS where possible.

3.3.1 COPD

The COPD definition used in this thesis has been validated in CPRD GOLD and has been used to define COPD cohorts in many previous studies [136, 142]. The positive predictive value of detecting COPD patients in CPRD GOLD was 97.1% (95% CI 80.2 to 99.6) when using a clinical COPD diagnosis code in patients with a history of smoking over the age of 35 years old [140]. Following this validation study, COPD patients were defined as patients with a clinical code for COPD, being aged 35 or older, and having a history of smoking. See **appendix 3** for clinical COPD codes.

3.3.2 Rate of FEV_1 decline

Rate of FEV_1 decline, the variable of interest in this thesis, was determined through repeated measures of FEV_1 during a patient's follow-up. In order to include patients who, have a sufficient number of FEV_1 measurements, as well as follow-up time, patients were required to have at least 2 FEV_1 measurements at least 6 months apart. Two FEV_1 measurements were needed to calculate rate of FEV_1 decline and a minimum of 6 months of follow-up was required in order to estimate lung function decline over a substantial length of time.

FEV_1 measurements were identified through spirometry test results found in CPRD data. Measurements that were recorded in absolute units (ml or L) were identified. Over 75% of all FEV_1 measurements were recorded in these units. Other units included percentages and uninterpretable units. All measurements were transformed to ml to estimate ml/year for rate of lung function decline. Measurements that were higher than 7 litres were excluded as the measurement was likely to be measurement error (94.8% of all FEV_1 measurements over follow-up were below 7 litres). In addition, if more than one measurement was recorded on the same day, the highest value was identified and used.

3.3.3 EOS

EOS counts are recorded as part of the results from blood tests requested by GPs. EOS counts were identified if they were recorded in cells/microlitre (µl) or as a percentage of the total white blood cell count. EOS measurements recorded as a percentage of the total white blood cell count were converted to cells/µl by multiplying the percentage by the total WBC count. In addition, baseline EOS measurements were identified over a 2-year period prior to Index date. The closest EOS measurement to the index date was identified and used as the baseline EOS count. A 2-year period was chosen following previous studies that investigated the stability of EOS in CPRD GOLD. Studies found that EOS recorded in CPRD GOLD were relatively stable over a two-year period after excluding individual EOS measurements that were within 4 weeks of an OCS and antibiotic [143, 144]. In addition, of patients who had repeated EOS, 80% of those with an EOS less than 300cells/µl at baseline had an EOS less than 300cells/µl in the year after, further highlighting the stability of EOS over 2 years [145]. Therefore, EOS measurements that were within 4 weeks of a prescribed oral corticosteroid (OCS) or respiratory-related antibiotic (see **appendix 3**) were excluded because they could have influenced a patient's EOS level. OCS and respiratory-related antibiotic can be prescribed to patients during an AECOPD episode where EOS would increase. Measurements during these episodes were excluded to identify stable measurements.

3.3.4 CVD

A composite CVD outcome was used as the primary outcome for chapter 8. The individual components included: i) MI events; ii) HF events; iii) stroke events; iv) coronary artery disease (CAD) and angina events; and v) atrial fibrillation (AF) events. These were identified in CPRD, HES, and ONS relating to GP treated events, hospitalised events, and death from events, respectively. Events recorded within CPRD were found using clinical diagnosis codes (see **appendix 3**). Events recorded in HES were found using ICD10 codes in the first position for primary diagnosis of hospitalisation (**appendix 3**). Events recorded in ONS were found using ICD10 codes for the primary cause of death (**appendix 3**). Events that were within 14 days of one another were excluded because they were likely to be the same event. This is because HES and ONS events can be relayed back to GPs and recorded in CPRD, sometimes with a lag phase. Whilst these events can be

recorded in CPRD, the quality of these events within CPRD is poor and CPRD, HES, and ONS should be used together to better identify events [136].

3.3.5 Covariates

Further covariates were identified and used as potential confounders and effect modifiers in the following chapters. The following described how each of these variables were defined in CPRD, and where appropriate in HES.

Gender and age in CPRD

Gender was identified in CPRD and coded as "males" and "females". Age was defined at index date for each study by calculating patient's age at this date. Date of birth is not disclosed in CPRD because it is identifiable. Therefore, an artificial date of birth was defined as the 1st July of the patient's specific year of birth. Age at index date was calculated as: (index date – artificial date of birth)/365.25.

Smoking status in CPRD

Smoking status at index date was defined as the closest recorded smoking status to the index date using clinical codes for smoking status (see **appendix 3**) and prioritizes smoking status in the following order:

1) A smoking status recorded from one year prior to index date to one month after index date.

2) A smoking status recorded from one month to one year after index date.

3) A smoking status recorded any time before the index date to the year prior to index date.

4) A smoking status recorded from the year after the index date to any time after thereafter.

Smoking status was recorded as current or ex-smokers. Never smokers were not included following the validated definition of COPD [140].

IMD

IMD is a database that was linked to CPRD and includes a weighted deprivation score as described in section 3.1.5.3. IMD was grouped into 5 categories where 1 represented the most deprived and 5 represented the least deprived.

Ethnicity in HES

Ethnicity was identified in HES and was coded into the following groups: white, black, Asian, other.

AECOPD events in CPRD and HES

AECOPD events were identified in CPRD and HES using validated algorithms [146, 147]. The following algorithm provides a positive predictive value of 85.5% (95% CI 82.7 – 88.3) and sensitivity of 62.9% (95% CI 55.4 – 70.4) in CPRD [146]. In CPRD, AECOPD can be identified as one of the following:

1) a clinical code for an AECOPD event (found in Clinical file), which includes codes for lower respiratory tract infections (LRTI);
2) a prescription of an OCS and respiratory-related antibiotic for 14 days;
3) at least 2 of 3 symptoms relating to an AECOPD including breathlessness, cough, and sputum purulence.

AECOPD events that were within 14 days of one another were excluded because they were likely to be the same events. In addition, AECOPD events that occurred on the same day as an annual review were excluded to avoid duplication. It is important to note that using this algorithm alone would only identify moderate AECOPD that are treated at the GP. Therefore, HES data was linked to CPRD in order to identify more severe AECOPD that require hospitalisation. AECOPD events in HES have also been validated and AECOPD are identified using ICD10 codes for acute lower respiratory tract infections, exacerbations of COPD, and acute bronchiectasis (see **appendix 3).** Following this, any AECOPD events (identified from CPRD or HES) that were within 14 days of one another were excluded as they were likely to be the same event. This is because if a patient is hospitalised with an AECOPD their records can be relayed back to primary care where the event is recorded using read codes in CPRD. The strength of using CPRD and HES together in identifying AECOPD events is that a wide range of AECOPD severities can be captured, which allows a more complete definition of AECOPD events. GP recorded events were considered “moderate” AECOPD events and hospitalised events were considered “severe” AECOPD events. AECOPD events were consequently grouped into categories summarising the frequency of AECOPD events in the first year of follow-up. Categories included:

i) no events;
ii) 1 moderate event and no severe events;
iii) 2 moderate events and no severe events;
iv) ≥3 moderate events and no severe events;
v) 1 severe event and any moderate events;
vi) ≥2 severe events and any moderate events.

COPD related symptoms in CPRD

Breathlessness, chronic cough, and sputum production were COPD related symptoms identified in CPRD through clinical diagnosis codes. These variables were all identified within 3 years prior to the index date.

Modified Medical Research Council (mMRC) dyspnoea in CPRD

mMRC dyspnoea was identified using clinical codes (see **appendix 3**). mMRC codes were identified over a 5-year period close to study index date. Specifically, mMRC was identified within 3 years prior to index date to 2 years after index date. A 5-year period was used to identify mMRC because it is commonly missing in the data and is unlikely to change drastically over a maximum of 3 years. The closest recorded mMRC to the index date was used.

FEV_1 percent predicted in CPRD

FEV_1 percent predicted was identified in CPRD from spirometry test codes (see **appendix 3**). The closest FEV_1 percent predicted to the index date was identified and was often based off the first FEV_1 after the index date that was used to calculate rate of FEV_1 decline. FEV_1 predicted was calculated using height, age, and gender following standard equations [148]:

FEV_1 predicted for men: $\{(4.3 \times height\ in\ meters) - (0.029 \times age)\} - 2.49$

FEV_1 predicted for women: $\{(3.95 \times height\ in\ meters) - (0.025 \times age)\} - 2.60$

FEV_1 percent predicted was calculated using the following calculation: $\frac{\boldsymbol{FEV1}}{\boldsymbol{FEV1\ predicted}} \times \mathbf{100}$

FEV_1 percent predicted was used to define the severity of airflow obstruction based on the GOLD 2011 classification of COPD using post-bronchodilator spirometry alone. The following airflow obstruction categories were defined:

i) Mild airflow obstruction (FEV_1 ≥80% predicted)

ii) Moderate airflow obstruction (FEV_1 80-50% predicted)

iii) Severe airflow obstruction (FEV_1 50-30% predicted)

iv) Very severe airflow obstruction (FEV_1 <30% predicted).

COPD medications in CPRD

COPD medications were identified using prescription codes (see **appendix 3**) and categorized as ICS and non-ICS containing medications. This meant that ICS monotherapy, ICS/LABA, and ICS/LABA/LAMA (in either fixed or combination forms) were classed as ICS-containing medications. Any other COPD medication (i.e. LABA, LAMA, SABA, SAMA) without evidence of ICS was classed as non-ICS-containing medication.

Comorbidities in CPRD

The following comorbidities were identified in CPRD using clinical diagnosis codes (see **appendix 3**): anxiety, depression, gastro-oesophageal reflux disease (GORD), bronchiectasis, lung cancer, heart failure, stroke, and MI. Hypertension was identified using a combination of clinical diagnosis codes and hypertension related prescriptions (Angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics, and vasodilators). Statin use was used as a proxy for high cholesterol and was identified using prescription codes only. It is important to note that the CVD related comorbidities listed here were identified in different ways to the main CVD outcome used in chapter 8. The comorbidities listed here were used to adjust for confounding in models. All comorbidities were categorised as binary variables, where patients either had the comorbidity or did not.

Body mass index (BMI) in CPRD

BMI was identified in two ways:

1) using test result data to identify BMI in kg/m^2

2) using test result data to identify weight and height in order to calculate BMI in kg/m^2.

BMI that was calculated using weight and height was prioritized over BMI that was directly recorded in CPRD in order to minimize measurement error. Calculated BMI that was $<14kg/m^2$ and $>100kg/m^2$ was excluded. If the calculated BMI was missing (due to missing weight or missing height measurements), then BMI that was recorded in CPRD directly was used. It is important to note that BMI and weight are poorly recorded in CPRD and are commonly missing. For this reason, most chapters that include BMI as a covariate define BMI over a 5-year period with the assumption that BMI would not change drastically over 5 years in COPD patients. BMI was categorized into the following categories:

i) underweight ($<18.5kg/m^2$)
ii) normal ($18.5\text{-}25kg/m^2$)
iii) overweight ($25\text{-}30kg/m^2$)
iv) obese ($\geq 30kg/m^2$)

History of asthma in CPRD

Asthma was identified using clinical codes (see **appendix 3**) and defined following previous work on the distinction between current and historic asthma in CPRD [149, 150]. A history of asthma was defined as having an asthma code any time before 2 years prior to index date. Current asthma was defined as having an asthma code within 2 years prior to index date. Both current and historic asthma were defined as "having asthma" and "not having asthma". Both current and historic asthma were used depending on the research question.

Blood counts (other than EOS counts) in CPRD

WBC counts and neutrophil counts were identified using test data from blood test results. These were identified in cells/µl.

3.4 Statistical models

All data management and statistical models were run in STATA v16. The following statistical models were used in the following chapters.

3.4.1 Logistic regression

Logistic regression was used to model a binary outcome. Specifically, this model was used to analyse the outcome, accelerated lung function decline (1=yes, 0=no). This model gives an odds ratio (OR) which is the odds (i.e., probability) of an outcome occurring given the exposure divided by the odds of an outcome occurring in the absence of that exposure. For example, an OR of 1.5 means that the odds of an outcome occurring is 50% more likely in those exposed compared to those not exposed. Logistic regression models do not require a linear relationship between exposure and outcome and residuals (error terms) do not need to be normally distributed. However, key assumptions exist and should be met by the logistic model: i) the dependent variable (i.e., the outcome) must be binary; ii) observations must be independent from each other which means that the outcome cannot include repeated observations; iii) there should be little to no multicollinearity between the independent variables (i.e., exposure variables). This means that variables should not be highly correlated with each other; and iv) there should be a linear relationship between the independent variables and the log odds.

3.4.2 Mixed linear regression

Mixed linear regression models are used for hierarchical data (i.e., repeated observations within an individual) whereby the outcome is linear. Specifically, this was used for analysing the outcome (or exposure for chapter 8), rate of FEV_1 decline. Mixed linear regression models are commonly used for nested data when one sample is nested within another sample and for longitudinal data that has repeated observations over a period of time. This model was used to analyse rate of FEV_1 decline because the data was structured hierarchically with repeated FEV_1 measurements recorded within individual patient's data. The term level 1 is given to the lowest level of the hierarchy, in this case it represents repeated FEV_1 measurements recorded within a single patient. Level 2 is given to the next level up, in this case the highest level, which was the patient identifier (see **figure 3.11** for further detail).

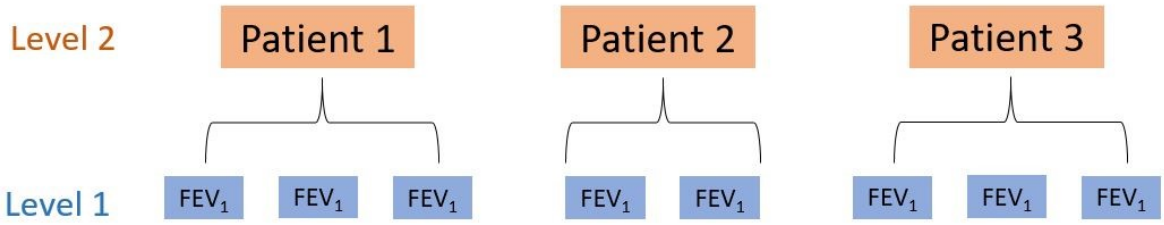


***Figure 3.11**: Hierarchical structure of the data.*

Mixed models have both fixed and random effects. The fixed effects part of the model, like standard linear models, includes terms that are constant across all individuals. For this part of the model, I included FEV_1 measurements and a time variable for time since first FEV_1 measurement. The random effects part of the model allows terms (i.e., variables) to vary across individuals. The random effects part of the model can include terms for random intercepts and random slopes. I included terms for both random intercepts and random slopes because it is likely that the first FEV_1 measurement and the rate at which FEV_1 changes would vary between patients. For this reason, I included the patient identifier as the random intercepts term and time since first FEV_1 measurement as the random slopes part of the model. **Figure 3.12** illustrates the difference between a mixed model with random intercepts only and a mixed model with random intercepts and random slopes. Overall, the mixed linear model reported an estimate that represents the change in FEV_1 in ml per 1 unit increase in time (year) giving an estimate for change in ml/year.

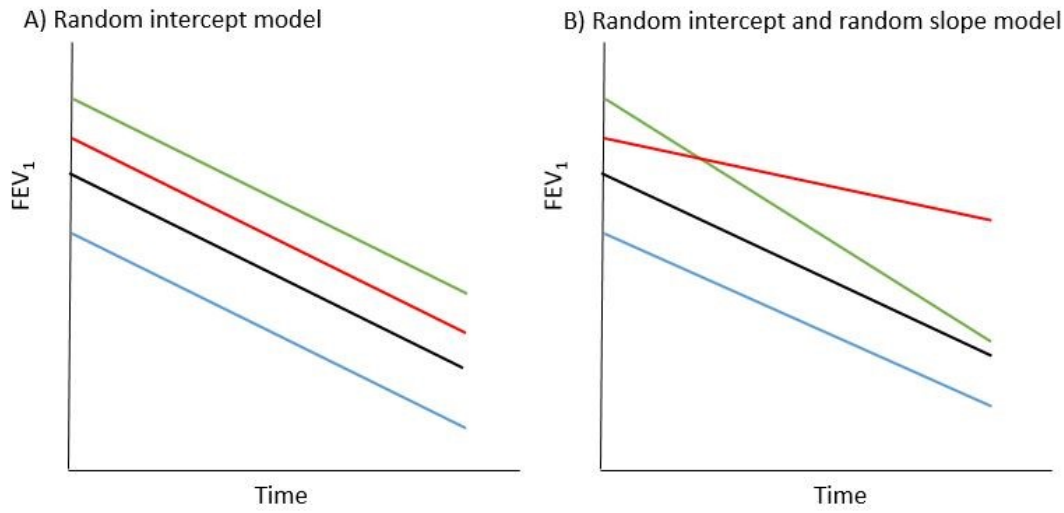


***Figure 3.12**: Difference between a mixed linear model with a) random intercepts only, and b) random intercepts and random slopes.*
Notes: Green line represents example patient 1, red line represents example patient 2, blue line represents example patient 3, black line representation the mean sample population

The random intercept and random slopes model were chosen a priori because in a real-world setting patients' lung function decline would naturally vary. Individuals would have different baseline lung function and varying rates of decline. Despite this, the model was tested to see if it was the model of best fit to estimate rate of FEV_1 decline given the data using the likelihood ratio (LR) test. Firstly, a mixed model with random intercepts only was compared to a mixed model with both random intercepts and random slopes. In all settings, mixed linear regression with random intercepts and random slopes best fit the data. In addition, the two-level model (level 1-repeated FEV_1 measurements, level 2-patient identifier) was compared to a three-level model (level 1-repeated FEV_1 measurements, level 2-patient identifier, level 3-general practice). This was tested because it was possible that quality of spirometry varied across GP practices in the UK. Across all settings the three-level model did not outperform the two-level model and therefore, a two-level mixed linear regression model with random intercepts and random models was used throughout this thesis where appropriate. In terms of the model assumptions, first, the outcome data should be linear. Second, the variance of residuals should be equal across individuals (i.e., the level 2 level). Third, the residuals must be normally distributed.

The linear mixed regression model also reported parameters of the variance of FEV_1 between patients and the variance of FEV_1 within patients. This was used to describe the within patient variation in FEV_1 to understand how variable FEV_1 was over time. Mixed linear regression models were also used to estimate individual patient rates of lung function decline. This was performed in chapters where patients were classed as patients with accelerated FEV_1 decline and patients without accelerated FEV_1 decline. To do this, the following steps were taken: i) a crude mixed linear regression model was run; ii) the fitted linear value

of the outcome variable was predicted; iii) random effects residuals (i.e. the residuals for the random intercept and the random slope) were predicted; and iv) coefficients for the rate of decline per patient was generated by multiplying the mixed linear regression estimate by time and adding patients' predicted random slopes residual [151]. This generated a mean rate of FEV_1 decline per patient which was used to categorise patients into those with accelerated FEV_1 decline and those without accelerated FEV_1 decline using specific thresholds.

It is important to note that rate of FEV_1 decline is not linear in the short term as various factors can change lung function. For example, AECOPD events can lead to a decline in FEV_1 in the short term which can increase again with treatment [33]. Whilst events can influence lung function over the short term, the aim of this thesis was to investigate the change in FEV_1 decline over the long term (i.e. over 10 years) and how factors may be associated with the accelerated decline in lung function over long periods of time. In addition, previous studies have used linear mixed models to estimate lung function decline over long periods of time [17, 72, 152-154]. Therefore, a linear model was used to estimate lung function decline in this thesis.

3.4.3 Cox and Poisson regression

Cox regression models were used to measure time to event outcomes. Specifically, this was used to analyse CVD events as the outcome. Cox regression estimates a hazard ratio (HR) which is the hazard (instantaneous risk) of an event occurring in the exposed group divided by the hazard of an event occurring in the unexposed group. The main assumption of the Cox regression model is the proportional hazard assumption. This assumes that the hazard function of the outcome is constant over time. Other model assumptions include non-informative censoring of patients and independence of events. These assumptions were tested in STATA for all Cox models. Poisson regression was used to investigate repeated events over follow-up.

Chapter 4
Exploring FEV_1 decline in CPRD

EHR are increasingly used for epidemiological research including cohort studies and pragmatic trials however, they are often viewed as lacking quality compared to randomized control trials and prospective cohorts. Rate of FEV_1 decline is the main outcome of this thesis however, it is not yet known how robust this is within EHR, specifically CPRD GOLD, the main data source used in this thesis. This exploratory work was undertaken to understand the how variation in spirometry and rate of lung function decline differs by the criteria used to define rate of lung function decline in COPD patients within CPRD.

4.1 Introduction

EHR databases consist of data routinely collected as part of clinical care and are often used for healthcare research. Whilst EHR databases have many strengths, one concern is that data are not collected for the purpose of research and that when tests are undertaken, they are not done so at routine intervals as they would be in a RCT, nor is the reason for a test being undertaken at that specific point in time always known [75]. EHR databases differ from randomized control trials (RCTs) or prospective cohort studies which have structured data collection where researchers attempt to collect data are collected at specific times for research purposes, by specific healthcare technicians, with specific equipment following specific protocols. EHRs are becoming increasingly used for epidemiological research however, they are often viewed as lacking quality.

In studies of people with COPD, longitudinal spirometry measurements (e.g., FEV_1) are often to estimate lung function decline, a common marker of disease progression [155]. Unlike RCT and cohort studies, the sporadic nature of lung function measurements recorded in EHR can lead to greater apparent variation in lung function in COPD patients. This could be due to measurement error, the number of measurements over follow-up, time intervals between measurements, follow-up time, and the reason or time at which lung function measures are recorded by healthcare practitioners.

In CPRD spirometry measurements in COPD patients are performed during visits to the GP. The quality and outcomes framework for COPD incentivizes GPs to perform spirometry every 15 months in COPD patients [133]. A previous validation study of spirometry recordings in CPRD found that more than 96% of recordings had adequate quality whereby a valid interpretation could be made by a respiratory physician [156]. Despite this, it is possible that other factors such as timings of measurements, time intervals, and follow-up time could lead to differences in longitudinal changes in lung function decline.

I aimed to investigate how variation in FEV_1 and rate of FEV_1 decline differs by the criteria used to define rate of FEV_1 decline. Specifically, how criteria around measurement error, the number of FEV_1 measurements, time intervals between measurements, timing of measurements, follow-up time, and use of linked data sets may lead to differences between COPD populations using CPRD. With the ever-growing use of EHR data for cohort studies and pragmatic trials it is important to understand how robust EHR derived lung function decline is as an outcome.

4.2 Methods

4.2.1 Patient eligibility criteria

Patients were identified in CPRD-GOLD if they were over 35 years of age, were smokers or ex-smokers, with linked HES data, and with a validated diagnosis of COPD [140]. Start of follow-up (index date) was the date of the first FEV_1 measurement after the following criteria were met: i) COPD diagnosis; ii) current registration date; iii) up-to-standard date; iv) date at age 35; and v) from 2004. End of follow-up was the first date of the following: i) death date; ii) date at which the patient transferred to a non-CPRD GP; or iii) the 31st December 2017. **Figure 4.1** describes the study design used to create the base population.

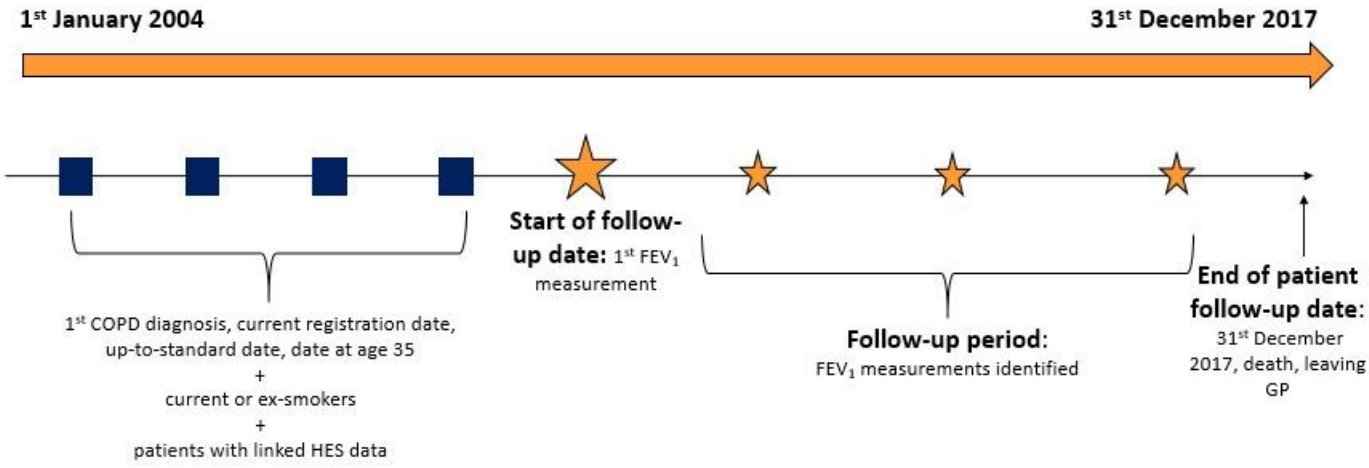


Figure 4.1: *Study design.*

4.2.2 FEV_1 measurements

All FEV_1 measurements recorded between the index date and end of follow-up were identified. FEV_1 measurements were recorded in milliliters. Measurements recorded in liters were transformed to ml and measurements that were higher than 7 liters were excluded (94.8% of all FEV_1 measurements over follow-up were below 7 liters).

4.2.3 Patient populations

In order to understand how the variation in FEV_1 and rate of FEV_1 decline differs based on the criteria used to define longitudinal FEV_1 decline, the following patient populations were created using specific criteria:

1) patients with at least two FEV_1 measurements at least six months apart (base population). A minimum period of 6 months was chosen in order to estimate medium-term lung function decline;

2) patients in the base population excluding those who had an FEV_1 greater than 10%, 20%, and 30% of their previous and subsequent FEV_1 measurement. These measurements were regarded as potential measurement error and patients were hence excluded;

3) patients in the base population excluding individual FEV_1 measurements that were greater than 10%, 20%, and 30% of the previous and subsequent FEV_1 measurement. These measurements were regarded as potential measurement error and were hence excluded;

4) patients in the base population excluding measurements that were within one week of an AECOPD because AECOPD events are associated with decreased FEV_1 both before and after an AECOPD [157];

5) patients with at least three or four FEV_1 measurements, rather than two, of which at least two were at least six months apart (with no other time constraint on the other measurements). At least three and four measurements were chosen following RCT and cohort study measurements that often require a certain number of measurements during follow-up at specific times;

6) patients with at least two FEV_1 measurements with at least six months or 1-year time intervals between all measurements. This was chosen following the nature of RCTs and cohort studies whereby spirometry measurements are recorded at regular intervals;

7) patients in the base population with at least 3 years of follow-up following the maximum length of previous RCTs on lung function decline in COPD patients as seen in chapter 2 [115];

8) patients in the base population without linked HES data because only approximately 60% of CPRD patients are eligible for HES linkage.

Figure 4.2 illustrates how each patient population was identified using spirometry measurements.

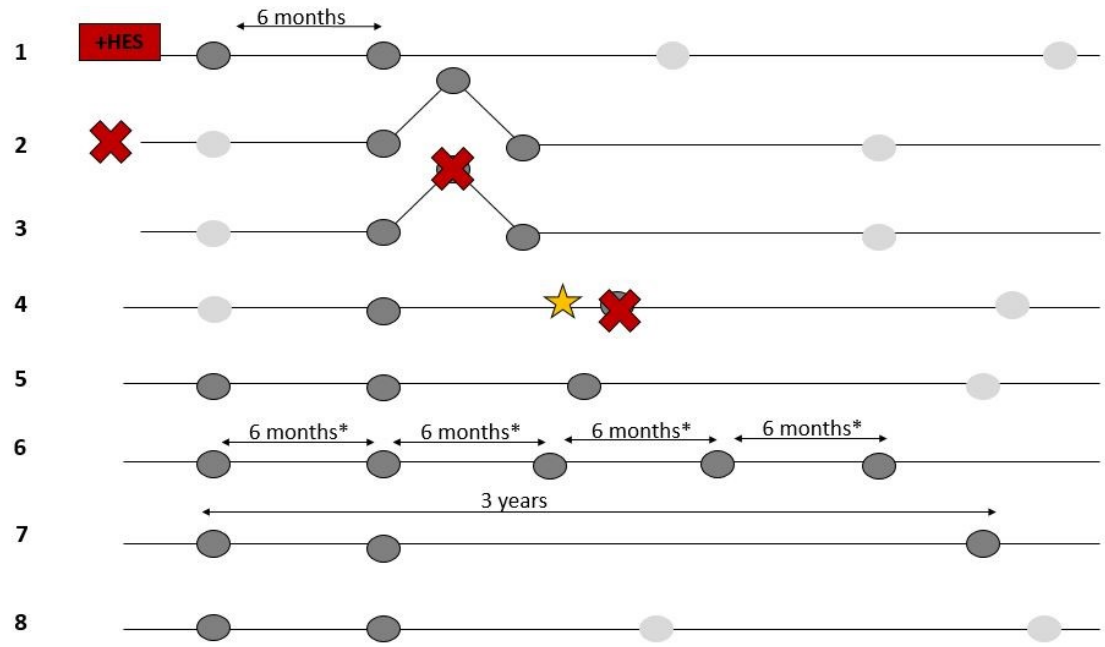


***Figure 4.2**: Summary of criteria used to define each population.*
***Notes**: 1: Patients with at least 2 FEV_1 measurements at least 6 months apart with linked HES data; 2: Excluding patients with an FEV_1 greater than 10, 20, or 30% of the previous FEV_1; 3) Excluding measurements that are greater than 10, 20, 0r 30% of the previous FEV_1 and subsequent FEV_1; 4) Excluding measurements that are within 1 week of an AECOPD; 5) At least 3 (or 4) FEV_1 measurements with at least 2 at least 6 months apart; 6) FEV_1 measurements that are all at least 6 months (*or 1 year) apart; 7) At least 3 years of follow-up with at least 2 FEV_1 measurements at least 6 months apart; 8) At least 2 FEV_1 measurements at least 6 months apart (regardless of linked HES data).*

4.2.4 Statistical analysis

Baseline patient characteristics were described for all patient populations using means (standard deviation [SD]), medians (interquartile range [IQR]), and proportions (%). Baseline characteristics included age, gender, smoking status (smokers or ex-smokers), BMI (underweight, normal, overweight, obese using standard categories), modified MRC dyspnoea (0-4), severity of obstruction using FEV_1 percent predicted (FEV1≥80% predicted, FEV_1 50-80% predicted, FEV_1 30-50% predicted, and FEV_1<30% predicted calculated using patient's first FEV_1 measurement, height, and gender), and AECOPD frequency and severity (none, 1 moderate and 0 severe, 2 moderate and 0 severe, ≥3 moderate and 0 severe, 1 severe and any moderate, and ≥2 severe and any moderate). Moderate AECOPD were defined as GP treated AECOPD and severe AECOPD were defined as hospitalized AECOPD. In addition, the median number of FEV_1 measurements (IQR and minimum/maximum number) and follow-up-up time were described in each population.

Mixed linear regression was used to estimated rate of FEV_1 decline in ml/year. Random effects included both random intercepts and random slopes allowing the intercept and rate of decline to vary by patients. Models included an unadjusted model, a minimally adjusted model adjusted for age and gender, an unadjusted model for patients with complete baseline covariates, and a fully adjusted

model adjusted for age, gender, smoking status, BMI, mMRC, FEV_1 percent predicted, and AECOPD frequency (complete case analysis). Within patient variation in FEV_1 (ml) was estimated from mixed linear models.

In addition, a ninth population was used to describe the rate of FEV_1 decline using linear regression rather than mixed linear regression to understand how clustering at the patient level influences rate of FEV_1 decline. Linear regression models included an unadjusted model, a minimally adjusted model, an unadjusted model for patients with complete baseline covariates, and a fully adjusted model adjusted for the same covariates as those used in the mixed linear regression model. Similarly, RCTs commonly use a baseline FEV_1 measurement and a follow-up measurement to describe the change in FEV_1 over time. This method was used to compare the rates of decline against those estimated using linear regression and mixed linear regression methods. This was calculated using patient's first and last FEV_1 over follow-up divided by the time between these two measurements (in years) to estimate rate of FEV_1 decline in ml/year.

4.3 Results

The numbers of patients included in each population varied because of the different criteria for repeated FEV_1 measurements. Population eight included the greatest number of patients (N=125,682) as it did not require linked HES data and population two included the fewest number of patients because patients were excluded if they had an FEV_1 that was greater than 10% of their previous and subsequent FEV_1 (N=29,058). **Table 4.1** summarises baseline characteristics for all populations. All populations were similar in terms of age, gender, smoking status, BMI, mMRC, and AECOPD frequency. However, population two included fewer severely obstructed patients and more mild COPD patients (i.e., FEV1≥80% predicted).

Table 4.2 summarises the minimum and maximum number of FEV_1 measurements in each population and in patients with and without complete baseline data. **Figure 4.3** illustrates the median number of FEV_1 measurements in each population in patients (regardless of complete baseline data). Most populations had a median of 4 FEV_1 measurements during follow-up however, patients in population two (that excluded patients with an FEV_1 greater than 10% or 20% of previous and subsequent FEV_1 measurements) had fewer FEV_1 measurements over follow-up with a median of 3. On the other hand, population five that included patients with at least 4 FEV_1 measurements had a median of 6 measurements over follow-up.

***Table 4.1**: Baseline characteristics for all populations defined using different criteria for FEV_1 decline.*

Baseline characteristics	Population 1[$]	Population 2			Population 3			Population 4
	N=72,683	10% N=29,058	20% N=41,879	30% N=50,308	10% N=72,683	20% N=72,683	30% N=72,683	N=70,887
Age	66.7 (10.7)	67.3 (11.1)	67.2 (10.9)	67.1 (10.9)	66.7 (10.7)	66.7 (10.7)	66.7 (10.7)	66.7 (10.7)
Females	33,417 (46.0)	13,639 (46.9)	19,504 (46.6)	23,364 (46.4)	33,417 (46.0)	39,266 (54.0)	39,266 (54.0)	32,537 (45.9)
Current smokers	43,902 (60.4)	15,419 (53.1)	25,179 (60.1)	30,267 (60.2)	43,902 (60.4)	43,902 (60.4)	43,902 (60.4)	42,822(60.4)
BMI								
Underweight	2,353 (3.2)	1,004 (3.5)	1,378 (3.3)	1,617 (3.2)	2,353 (3.2)	2,353 (3.2)	2,353 (3.2)	2,258 (3.2)
Normal	20,445 (28.1)	8,431 (29.0)	1,861 (28.3)	14,203 (28.2)	20,445 (28.1)	20,445 (28.1)	20,445 (28.1)	19,895 (28.1)
Overweight	20,017 (27.5)	7,907 (27.2)	11,575 (27.6)	13,953 (27.7)	20,017 (27.5)	20,017 (27.5)	20,017 (27.5)	19,573 (27.6)
Obese	14,749 (20.3)	5,683 (19.6)	8,384 (20.0)	10,146 (20.2)	14,749 (20.3)	14,749 (20.3)	14,749 (20.3)	14,405 (20.3)
missing	15,119 (20.8)	6,033 (20.8)	8,681 (20.7)	10,389 (20.7)	15,119 (20.8)	15,119 (20.8)	15,119 (20.8)	14,756 (20.8)
mMRC								
0	8,098 (11.1)	3,813 (13.1)	5,181 (12.4)	6,040 (12.1)	8,098 (11.1)	8,098 (11.1)	8,098 (11.1)	7,990 (11.3)
1	15,887 (21.9)	6,704 (23.1)	9,505 (22.7)	11,281 (22.4)	15,887 (21.9)	15,887 (21.9)	15,887 (21.9)	15,579 (22.0)
2	9,550 (13.1)	3,756 (12.9)	5,417 (12.9)	6,478 (12.9)	9,550 (13.1)	9,550 (13.1)	9,550 (13.1)	9,335 (13.2)
3	4,533 (6.2)	1,853 (6.4)	2,580 (6.2)	3,301 (6.2)	4,533 (6.2)	4,533 (6.2)	4,533 (6.2)	4,350 (6.1)
4	787 (1.0)	367 (1.3)	483 (1.2)	564 (1.1)	787 (1.1)	787 (1.1)	787 (1.1)	739 (1.0)
missing	33,828 (46.5)	12,565 (43.2)	18,713 (44.7)	22,844 (45.4)	33,828 (46.5)	33,828 (46.5)	33,828 (46.5)	32,894 (46.4)
Airflow obstruction								
Mild	18,267 (25.1)	11,164 (38.4)	13,960 (33.3)	15,356 (30.5)	18,267 (25.1)	18,267 (25.1)	18,267 (25.1)	17,855 (25.2)
Moderate	33,452(46.0)	12,468 (42.9)	19,146 (45.7)	23,465 (46.6)	33,452 (46.0)	33,452 (46.0)	33,452 (46.0)	32,794 (46.3)
Severe	16,522 (22.7)	4,329 (14.9)	7,157 (17.1)	9,363 (18,6)	16,522 (22.7)	16,522 (22.7)	16,522 (22.7)	16,009 (22.6)
Very severe	3,777 (5.2)	765 (2,6)	1,214 (2.9)	1,657 (3.3)	3,777 (5.2)	3,777 (5.2)	3,777 (5.2)	3,601 (5.1)
missing	665 (0.9)	332 (1.1)	402 (1.0)	467 (0.9)	665 (0.9)	665 (0.9	665 (0.9	628 (0.9)
AECOPD								
None	30,178 (41.5)	12,923 (44.5)	18,251 (43.6)	21,583 (42.9)	30,178 (41.5)	30,178 (41.5)	30,178 (41.5)	29,990 (42.3)
1 mod, 0 sev	17,665 (24.3)	6,948 (23.9)	10,140 (24.2)	12,232 (24,3)	17,665 (24.3)	17,665 (24.3)	17,665 (24.3)	17,268 (24.4)
2 mod, 0 sev	9,618 (13.2)	3,655 (12.6)	5.350 (12.8)	6,482 (12.9)	9,618 (13.2)	9,618 (13.2)	9,618 (13.2)	9,324 (13.2)
3+ mod, -0 sev	11,339 (15.6)	4,103 (14.1)	6,090 (14.5)	7,509 (14.9)	11,339 (15.6)	11,339 (15.6)	11,339 (15.6)	10,705 (15.1)
1 sev, any mod	3,126 (4.3)	1,122 (3.9)	1,642 (3.9)	2,011 (4.0)	3,126 (4.3)	3,126 (4.3)	3,126 (4.3)	2,945 (4.2)
2+ sev, any mod	757 (1.0)	307 (1.1)	406 (1.0)	491 (1.0)	757 (1.0)	757 (1.0)	757 (1.0)	655 (0.9)

***Table 4.1**: Baseline characteristics for all populations defined using different criteria for FEV_1 decline (cont.)*

Baseline characteristics	Population 5		Population 6		Population 7	Population 8
	≤3 FEV_1 N=58,121	≤4 FEV_1 N=44,673	≤6 months N=72,683	≤1 year N=65,875	N=59,185	N=125,682
Age	66.5 (10.5)	66.2 (10.2)	66.7 (10.7)	66.6 (10.7)	66.4 (10.6)	66.4 (10.7)
Females	26,540 (45.7)	20,225 (45.3)	33,417 (46.0)	30,494 (46.3)	27,541 (46.5)	58,504 (46.6)
Current smokers	34,791 (59.9)	26,383 (59.1)	43,902 (60.4)	39,813 (60.4)	35,496 (60.0)	77,716 (61.8)
BMI						
Underweight	1,780 (3.1)	1,323 (3.0)	2,353 (3.2)	2,070 (3.1)	1,800 (3.0)	5,056 (4.0)
Normal	16,291 (28.0)	12,417 (27.8)	20,445 (28.1)	18,321 (27.8)	16,399 (27.7)	38,939 (31.0)
Overweight	16,138 (27.8)	12,602 (28.2)	20,017 (27.5)	18,225 (27.7)	16,451 (27.8)	39,091 (31.1)
Obese	11,894 (20.5)	9,130 (20.4)	14,749 (20.3)	13,410 (20.4)	12,133 (20.5)	32,322 (25.7)
missing	12,018 (20.7)	9,201 (20.6)	15,119 (20.8)	13,849 (21.0)	12,402 (21.0)	10,274 (8.2)
mMRC						
0	6,227 (10.7)	4,632 (10.4)	8,098 (11.1)	7,237 (11.0)	6,133 (10.4)	13,958 (11.1)
1	12,582 (21.7)	9,345 (20.9)	15,887 (21.9)	13,900 (21.1)	11,924 (20.2)	28,856 (23.0)
2	7,442 (12.8)	5,447 (12.2)	9,550 (13.1)	8,251 (12.5)	7,026 (11.9)	17,264 (13.7)
3	3,387 (5.8)	2,404 (5.4)	4,533 (6.2)	3,811 (5.8)	3,237 (5.5)	7,943 (6.3)
4	508 (0.9)	310 (0.7)	787 (1.0)	654 (1.0)	517 (0.9)	1,290 (1.0)
missing	27,975 (48.1)	22,535 (50.4)	33,828 (46.5)	32,022 (48.6)	30,348 (51.3)	56,371 (44.9)
Airflow obstruction						
Mild	13,822 (23,8)	10,035 (22.5)	18,267 (25.1)	16,479 (25.0)	14,661 (24.8)	30,695 (24.4)
Moderate	27,268 (46.9)	21,365 (47.8)	33,452(46.0)	30,646 (46.5)	27,671 (46.8)	57,780 (46.0)
Severe	13,571 (23,4)	10,713 (24.0)	16,522 (22.7)	14,905 (22.6)	13,461 (22.7)	26,437 (21.0)
Very severe	3,022 (5.2)	2,291 (5.1)	3,777 (5.2)	3,284 (5.0)	2,942 (5.0)	5,680 (4.5)
missing	438 (0.8)	269 (0.5)	665 (0.9)	561 (0.9)	450 (0.8)	5,090 (4.1)
AECOPD*						
None	23,594 (40.6)	17,859 (40.0)	30,178 (41.5)	27,529 (41.8)	24,284 (41.0)	53,447 (42.5)
1 mod, 0 sev	14,375 (24.7)	11,181 (25.0)	17,665 (24.3)	16,165 (24.5)	12,631 (24.7)	31,431 (25.0)
2 mod, 0 sev	7,933 (13.7)	6,227 (13.9)	9,618 (13.2)	8,781 (13.3)	8,115 (13.7)	17,685 (14.2)
3+ mod, -0 sev	9,323 (16.0)	7,296 (16.3)	11,339 (15.6)	10,246 (15.6)	9,373 (15.8)	23,119 (18.4)

1 sev, any mod	2,390 (4.1)	1,776 (4.0)	3,126 (4.3)	2,584 (3.9)	2,303 (3.9)	n/a
2+ sev, any mod	506 (0.9)	334 (0.8)	757 (1.0)	570 (0.9)	479 (0.8)	n/a

***Note**: Population 1: Patients with at least 2 FEV_1 measurements at least 6 months apart with linked HES data; Population 2: Excluding patients with an FEV_1 greater than 10, 20, or 30% of the previous FEV_1; Population 3) Excluding measurements that are greater than 10, 20, 0r 30% of the previous FEV_1 and subsequent FEV_1; Population 4) Excluding measurements that are within 1 week of an AECOPD; Population 5) At least 3 (or 4) FEV_1 measurements with at least 2 at least 6 months apart; Population 6) FEV_1 measurements that are all at least 6 months (*or 1 year) apart; Population 7) At least 3 years of follow-up with at least 2 FEV_1 measurements at least 6 months apart; Population 8) At least 2 FEV_1 measurements at least 6 months apart (regardless of linked HES data). *AECOPD groups for cohort without HES linkage: none, 1 moderate any severe, 2 moderate any severe, 3+ moderate any severe. $^{\$}$Same for population 9.*

Table 4.2: *Minimum and maximum number of FEV_1 measurements in each population.*

	Patients with and without complete baseline	Patients with complete data
Population 1 (main population)*	2-55	2-42
Population 2 : Excluding patients with FEV_1 >x% of previous FEV_1		
10%	2-18	2-15
20%	2-24	2-21
30%	2-33	2-30
Population 3: Excluding FEV_1 measurements >x% of previous FEV_1		
10%	2-55	2-42
20%	2-55	2-42
30%	2-55	2-42
Population 4: Excluding measurements within 1 week of an AECOPD	2-40	2-26
Population 5: Patients with ≥x FEV_1 measurements over follow-up		
≥3 FEV_1 measurements	3-55	3-42
≥4 FEV_1 measurements	4-55	4-42
Population 6: Patients with measurements ≥x months apart		
≥6 months between FEV_1 measurements	2-17	2-15
≥1 year between FEV_1 measurements	2-11	2-10
Population 7: Patients with ≥3 years of follow-up	2-55	2-42
Population 8: Patients without HES linkage	2-55	2-42

Note*: Population 1: Patients with at least 2 FEV_1 measurements at least 6 months apart with linked HES data; Population 2: Excluding patients with an FEV_1 greater than 10, 20, or 30% of the previous FEV_1; Population 3) Excluding measurements that are greater than 10, 20, 0r 30% of the previous FEV_1 and subsequent FEV_1; Population 4) Excluding measurements that are within 1 week of an AECOPD; Population 5) At least 3 (or 4) FEV_1 measurements with at least 2 at least 6 months apart; Population 6) FEV_1 measurements that are all at least 6 months (or 1 year) apart; Population 7) At least 3 years of follow-up with at least 2 FEV_1 measurements at least 6 months apart; Population 8) At least 2 FEV_1 measurements at least 6 months apart (regardless of linked HES data). *Population 9 includes the same patients included in population 1.*

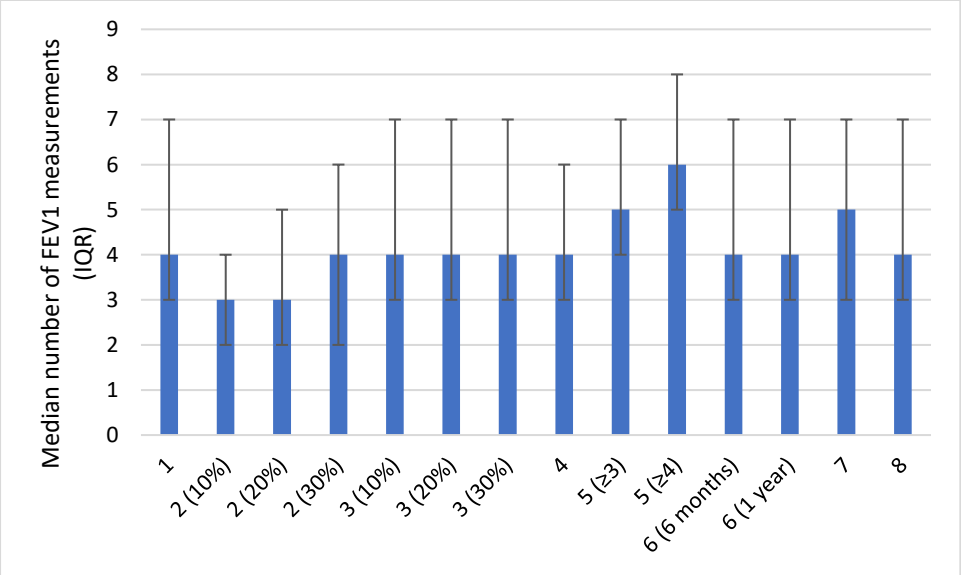


Figure 4.3*: Median number of FEV_1 measurements in each patient population.* ***Note****: Population 1: Patients with at least 2 FEV_1 measurements at least 6 months apart with linked HES data; Population 2: Excluding patients with an FEV_1 greater than 10, 20, or 30% of the previous FEV_1; Population 3) Excluding measurements that are greater than 10, 20, 0r 30% of the*

*previous FEV_1 and subsequent FEV_1; Population 4) Excluding measurements that are within 1 week of an AECOPD; Population 5) At least 3 (or 4) FEV_1 measurements with at least 2 at least 6 months apart; Population 6) FEV_1 measurements that are all at least 6 months (or 1 year) apart; Population 7) At least 3 years of follow-up with at least 2 FEV_1 measurements at least 6 months apart; Population 8) At least 2 FEV_1 measurements at least 6 months apart (regardless of linked HES data). *Population 9 includes the same patients included in population 1.*

Unadjusted, minimally adjusted and fully adjusted mean rates of FEV_1 decline for each population are shown in **figure 4.4**, **figure 4.5, figure 4.6**, and **figure 4.7**. When comparing unadjusted, minimally adjusted, and fully adjusted rates of FEV_1 decline between all patient populations, mean rates of decline were similar across all patient populations except for population two (i.e., exclusion of patients with FEV_1 greater than a) 10%, b) 20%, and c) 30% of previous and subsequent FEV_1 measurements) and population nine, which included the main population but used linear regression rather than mixed linear regression. Minimally adjusted rates of FEV_1 decline in population one, and three-eight ranged from -18.7 ml/year (95% CI -19.2 to -18.2) to -16.5 ml/year (95% CI -17.3 to -15.7). The mean rates of FEV_1 decline for population two was -79.4 ml/year (95% CI -80.7 to -78.2) excluding those with an FEV_1 greater than 10% of their previous FEV_1, -57.1 ml/year (95% CI -58.0 to -56.2) excluding patients with an FEV_1 greater than 20% of their previous FEV_1, and -46.8 ml/year (95% CI -47.6 to -46.0) excluding patients with an FEV_1 greater than 30% of their previous FEV_1. Unadjusted rates of decline were similar to minimally adjusted rates. The unadjusted rate of decline in population nine, which used linear regression, was -12.2 ml/year (95% CI -13.0 to -11.4), whilst the minimally adjusted rate of decline was -18.6 ml/year (95% CI -19.2 to -17.9).

Fully adjusted rates of FEV_1 decline in population one and three-eight ranged from -14.6 ml/year (95% CI -15.7 to -13.6) to -9.8 ml/year (95% CI -11.5 to -8.1). Fully adjusted mean rates of FEV_1 decline for population two was -94.9 ml/year (95% CI -97.5 to -92.3) excluding those with an FEV_1 greater than 10% of their previous FEV_1, -64.3 ml/year (95% CI -66.1 to -62.5) excluding those with an FEV_1 greater than 20% of their previous FEV_1, and -51. 4ml/year (95% CI -53.0 to -49.8) excluding those with an FEV_1 greater than 30% of their previous FEV_1. The fully adjusted mean rate of decline using linear regression was -21.6 ml/year (95% CI -22.6 to -20.5).

Unadjusted rates of decline in patients with complete baseline data were similar to fully adjusted rates in models using mixed linear regression. It is important to note that unadjusted and minimally adjusted models differed by patient numbers compared to fully adjusted models and unadjusted models including only baseline with complete baseline data. This is because complete case analysis was used in fully adjusted models. Fully adjusted complete case analyses included fewer patients due to missing BMI, mMRC, and height (to calculate FEV_1 percent predicted).

Lastly, the rate of FEV_1 decline was assessed in population 1 using patients first and last FEV_1 measurements only. Overall, the mean unadjusted rate of FEV_1 decline using this method was -16.4 ml/year (SD 246.5).

Populations		Patient N	Mean rate of FEV_1 decline (unadjusted) (ml/year with 95% CI)
Main population		72,683	-17.7 (-18.4 to -16.9)
Excluding patients with FEV1 >X% of previous:	>10%	29,058	-79.4 (-80.7 to -78.2)
	>20%	41,879	-56.5 (-57.4 to -55.6)
	>30%	50,308	-46.9 (-47.7 to -46.1)
Excluding FEV1 measurements >X% of previous:	>10%	72,683	-17.8 (-18.6 to -17.1)
	>20%	72,683	-18.0 (-18.8 to -17.2)
	>30%	72,683	-19.0 (-17.2 to -18.2)
Excluding measurements within one week of an AECOPD		70,887	-18.2 (-17.9 to -16.4)
Patients with ≥3 FEV1 measurements over follow-up		58,121	-17.3 (-18.0 to -16.5)
Patients with ≥4 FEV1 measurements over follow-up		44,673	-16.4 (-17.2 to -15.5)
Patients with measurements ≥6 months apart		72,683	-16.8 (-17.6 to -16.1)
Patients with measurements ≥1 year apart		65,875	-16.9 (-17.7 to -16.1)
Patients with ≥3 years of follow-up		59,185	-17.7 (-18.4 to -16.9)
Patients without HES linkage		125,682	-18.6 (-19.2 to -18.0)
Main population using linear regression		72,683	-12.2 (-13.0 - -11.4)

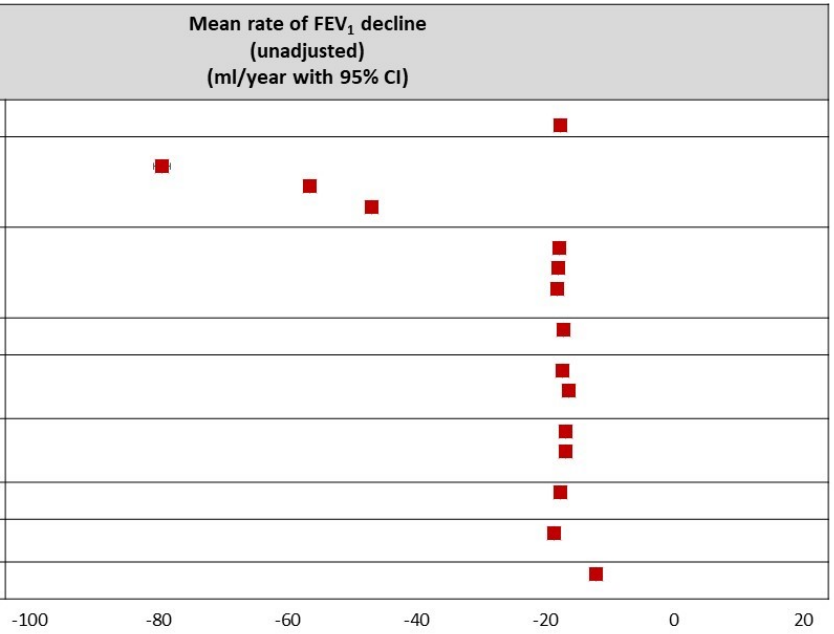


Figure 4.4: *Unadjusted rates of FEV_1 decline.*

Populations		Patient N	Mean rate of FEV_1 decline (age and sex adjusted) (ml/year with 95% CI)
Main population		72,683	-18.0 (-18.7 to -17.2)
Excluding patients with FEV1 >X% of previous:	>10%	29,058	-79.4 (-80.7 to -78.2)
	>20%	41,879	-57.1 (-58.0 to -56.2)
	>30%	50,308	-46.8 (-47.6 to -46.0)
Excluding FEV1 measurements >X% of previous:	>10%	72,683	-17.9 (-18.6 to -17.1)
	>20%	72,683	-18.1 (-18.9 to -17.4)
	>30%	72,683	-18.3 (-19.0 to -17.5)
Excluding measurements within one week of an AECOPD		70,887	-17.5 (-18.2 to -16.8)
Patients with ≥3 FEV1 measurements over follow-up		58,121	-17.2 (-18.0 to -16.5)
Patients with ≥4 FEV1 measurements over follow-up		44,673	-16.5 (-17.3 to -15.7)
Patients with measurements ≥6 months apart		72,683	-17.1 (-17.9 to -16.4)
Patients with measurements ≥1 year apart		65,875	-17.2 (-18.0 to -16.4)
Patients with ≥3 years of follow-up		59,185	-17.7 (-18.4 to -16.9)
Patients without HES linkage		125,682	-18.7 (-19.3 to -18.2)
Main population using linear regression		72,683	-18.6 (-19.2 to -17.9)

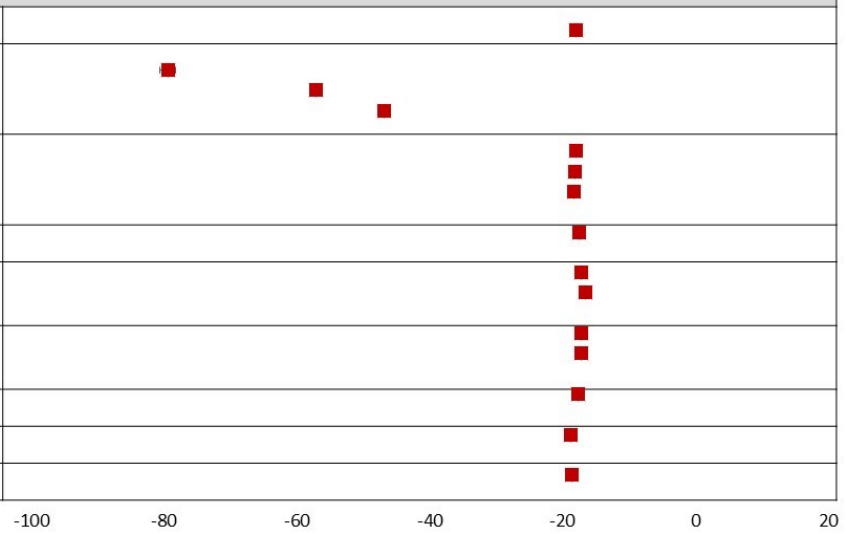


***Figure 4.5**: Minimally adjusted rates of FEV_1 decline.*
***Note**: Adjusted for age and sex.*

Populations		Patient N	Mean rate of FEV_1 decline (unadjusted with complete baseline data) (ml/year with 95% CI)
Main population		30,621	-12.5 (-13.9 to -11.1)
Excluding patients with FEV1 >X% of previous:	>10%	13,066	-92.4 (-94.8 to -90.1)
	>20%	18,348	-63.6 (-65.3 to -61.9)
	>30%	21,755	-50.3 (-51.7 to -48.8)
Excluding FEV1 measurements >X% of previous:	>10%	30,621	-11.7 (-13.2 to -10.2)
	>20%	30,621	-12.1 (-13.5 to -10.9)
	>30%	30,621	-12.3 (-13.8 to -10.9)
Excluding measurements within one week of an AECOPD		29,924	-12.0 (-13.5 to -10.6)
Patients with ≥3 FEV1 measurements over follow-up		23,696	-11.8 (-13.2 to -10.3)
Patients with ≥4 FEV1 measurements over follow-up		17,350	-11.5 (-13.0 to -10.0)
Patients with measurements ≥6 months apart		30,621	-11.4 (-12.9 to -10.0)
Patients with measurements ≥1 year apart		26,556	-11.2 (-12.7 to -9.6)
Patients with ≥3 years of follow-up		22,627	-12.2 (-13.6 to -10.7)
Patients without HES linkage		67,391	-14.0 (-15.0 to -13.1)
Main population using linear regression		30,621	-17.7 (-19.3 to -16.2)

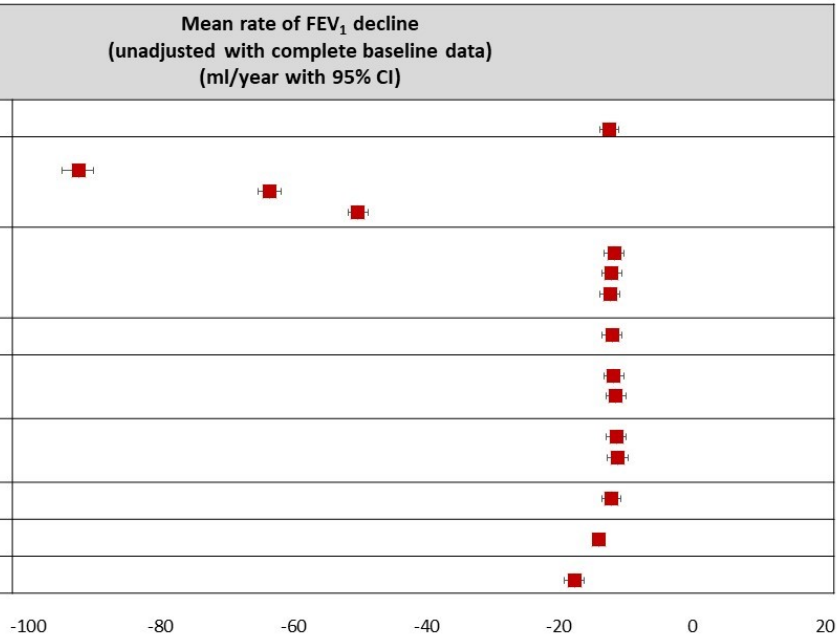


Figure 4.6: *Unadjusted rates of FEV_1 decline in patients with complete baseline data.*

Populations		Patient N	Mean rate of FEV_1 decline (fully adjusted) (ml/year with 95% CI)
Main population		30,621	-11.6 (-13.1 to -10.1)
Excluding patients with FEV1 >X% of previous:	>10%	13,066	-94.9 (-97.5 to -92.3)
	>20%	18,348	-64.3 (-66.1 to -62.5)
	>30%	21,755	-51.4 (-53.0 to -49.8)
Excluding FEV1 measurements >X% of previous:	>10%	30,621	-11.6 (-13.2 to -10.0)
	>20%	30,621	-10.9 (-12.4 to -9.3)
	>30%	30,621	-12.3 (-13.9 to -10.7)
Excluding measurements within one week of an AECOPD		29,924	-11.2 (-12.7 to -9.7)
Patients with ≥3 FEV1 measurements over follow-up		23,696	-11.8 (-13.4 to -10.2)
Patients with ≥4 FEV1 measurements over follow-up		17,350	-11.1 (-12.7 to -9.5)
Patients with measurements ≥6 months apart		30,621	-10.1 (-11.7 to -8.6)
Patients with measurements ≥1 year apart		26,556	-9.8 (-11.5 to -8.1)
Patients with ≥3 years of follow-up		22,627	-12.1 (-13.7 to -10.5)
Patients without HES linkage		67,391	-14.6 (-15.7 to -13.6)
Main population using linear regression		30,621	-21.6 (-22.6 to -20.5)

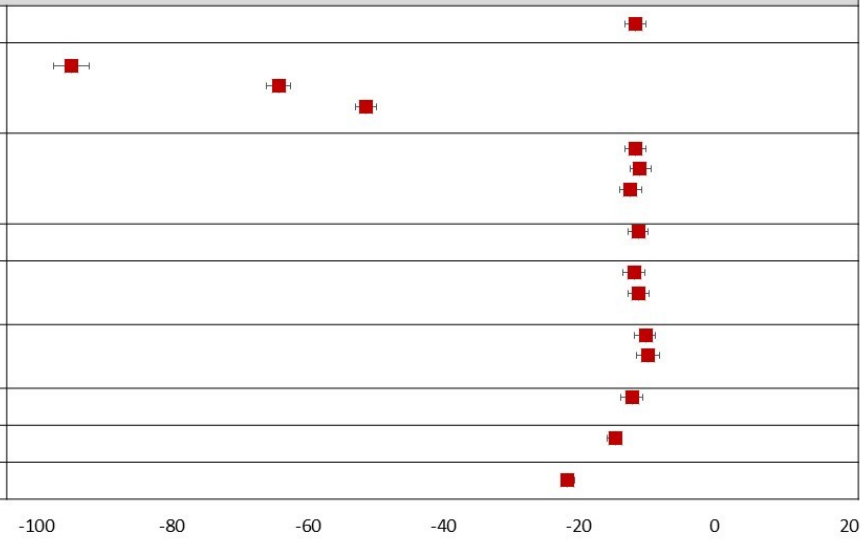


Figure 4.7: *Fully adjusted rates of FEV_1 decline.*
Notes: *Adjusted for all baseline covariates.*

Table 4.3 describes the mean within patient variation in FEV_1 for each population and each model (unadjusted, minimally adjusted, unadjusted in patients with complete baseline data, and fully adjusted models). All models within each population showed similar within patient variation estimates and ranged from 328.5ml to 345.8ml in all populations other than population two and three. Population two had the lowest mean within patient variation and ranged between 184.6ml to 201.2ml. Population three had the second lowest mean within patient variation and ranged between 292.4ml to 299.2ml depending on the adjustment of the model.

Table 4.3: *Mean within patient variation in ml (and 95% CI) for each population and each model.*

	Mean within patient variation in FEV_1 (ml) (95% CI)			
	Unadjusted	Minimally adjusted (age, gender)	Unadjusted with complete baseline data	Fully adjusted*
Population 1	337.5 (336.6-338.5)	337.6 (336.7-338.6)	337.5 (335.9-339.1)	335.7 (334.1-337.2)
Population 2 (10%)	193.7 (192.4-195.1)	193.6 (192.2-194.9)	185.2 (183.2-187.3)	184.6 (182.6-186.7)
(20%)	189.8 (188.9-190.7)	189.7 (188.7-190.6)	185.4 (183.9-186.8)	184.8 (183.3-186.2)
(30%)	201.2 (200.3-202.0)	201.1 (200.3-201.9)	197.1 (195.8-198.4)	196.5 (195.2-197.8)
Population 3 (10%)	292.4 (291.6-293.3)	292.6 (291.7-293.5)	295.3 (293.8-296.8)	293.3 (291.8-294.8)
(20%)	292.5 (291.6-293.4)	292.6 (291.8-293.5)	295.4 (193.9-296.8)	293.5 (292.1-295.0)
(30%)	296.7 (295.8-297.5)	296.8 (295.9-297.7)	299.2 (297.7-300.6)	297.4 (296.0-298.8)
Population 4	334.3 (333.3-335.3)	334.4 (333.4-335.4)	334.0 (332.4-335.7)	332.2 (330.6-333.9)
Population 5 (≥3)	337.0 (336-338)	337.1 (336.1-338.1)	336.7 (335.0-338.3)	335.2 (333.6-336.9)
(≥4)	335.7 (334.7-335.8)	335.8 (334.8-336.8)	334.8 (333.1-336.5)	333.9 (332.2-335.5)
Population 6 (≥6 months)	339.7 (338.6-340.8)	339.8 (338.7-340.9)	339.7 (337.9-341.5)	337.1 (335.3-338.8)
(≥1 year)	345.5 (344.1-346.9)	345.8 (344.4-347.2)	343.3 (340.9-345.8)	338.6 (336.2-341.0)
Population 7	335.5 (334.5-336.5)	335.6 (334.6-336.6)	334.7 (333.0-336.3)	333.3 (331.6-335.0)
Population 8	328.5 (327.8-329.2)	328.5 (327.8-329.6)	329.4 (328.3-330.4)	332.5 (331.1-333.9)

Note: *Population 1: Patients with at least 2 FEV_1 measurements at least 6 months apart with linked HES data; Population 2: Excluding patients with an FEV_1 greater than 10, 20, or 30% of the previous FEV_1; Population 3) Excluding measurements that are greater than 10, 20, 0r 30% of the previous FEV_1 and subsequent FEV_1; Population 4) Excluding measurements that are within 1 week of an AECOPD; Population 5) At least 3 (or 4) FEV_1 measurements with at least 2 at least 6 months apart; Population 6) FEV_1 measurements that are all at least 6 months (or 1 year) apart; Population 7) At least 3 years of follow-up with at least 2 FEV_1*

*measurements at least 6 months apart; Population 8) At least 2 FEV_1 measurements at least 6 months apart (regardless of linked HES data). *Adjusted for all baseline covariates.*

4.4 Discussion

This piece of work set out to describe potential differences in patient characteristics, FEV_1 variability and rates of FEV_1 decline between COPD populations defined using different requirements around FEV_1 measurements in routinely collected data using CPRD. Specifically, how different definitions around measurement error, number of measurements, time intervals between measurements, follow-up time, and secondary care data linkage can lead to the selection of potentially different study populations. Overall, regardless of the number of FEV_1 measurements, time intervals between measurements, follow-up time, and secondary care data linkage, patient demographics, within patient FEV_1 variability, and rates of FEV_1 decline remained consistent. Similarly, results were consistent in populations that excluded individual FEV_1 measurements that were likely due to measurement error. However, excluding patients (rather than individual measurements) with likely measurement error led to the exclusion of a specific group of COPD patients; severely obstructed patients (low FEV_1 percent predicted). In addition, using mixed linear regression provided estimates that were different to those using linear regression, suggesting that clustering at the patient level is important when investigating rate of FEV_1 decline in routinely collected data.

Population two (those who were excluded due to potential measurement error) had faster rates of FEV_1 decline. More patients with low FEV_1 percent predicted were excluded in this population which meant that there were more patients with milder COPD (higher FEV_1 percent predicted) than all other populations. Previous studies have suggested that rates of FEV_1 decline are faster in COPD patients with milder disease because they have more absolute lung function to lose at baseline than those with severe disease [34]. This is also consistent with the hypothesis that patients with lower FEV_1 percent predicted are more likely to have poorly recorded spirometry (potential measurement error). It is possible that patients with more severe disease, and lower FEV_1 percent predicted, were more likely to perform poor spirometry which might have contributed to the high variation seen in this group of patients. Whilst the best of three spirometry recordings should be recorded by healthcare practitioners, it is possible that only one spirometry is performed and recorded if patients are too severe to perform three in a row.

It is also important to note that fewer patients were included in models including patients who had complete baseline covariate data. In CPRD-GOLD this is due to the lack of consistent recording of BMI and mMRC. Fully adjusted analyses produced slower mean rates of FEV_1 decline compared to crude or minimally adjusted rates of decline. However, in the population that excluded patients due to potential measurement error (population two) fully adjusted mean rates of FEV_1 decline were faster than crude and minimally adjusted models. Patient populations that excluded patients with potential measurement error

and who had complete baseline data included slightly milder patients than the same population regardless of complete baseline data. On the other hand, all other patient populations that had complete baseline data included slightly more severe patients than the same populations regardless of complete baseline data. This is consistent with the theory that milder COPD patients might have faster rates of FEV_1 decline due to initial lung function [34]. Therefore, it is possible that missing baseline variables could influence the type of patients included in a study, and the rate of FEV_1 decline.

In terms of within patient variation, most populations were similar except for population two, where patients were excluded if they had potential measurement error, and population three, where individual measurements were excluded if they were thought to be biased by measurement error. Interestingly, whilst excluding individual measurements at higher risk of error decreased within patient variation, it did not change the mean rate of FEV_1 decline. With this in mind, rates of FEV_1 decline in all subsequent chapters were estimated using all FEV_1 measurements that were no greater than 7 liters in order to use as much data as possible.

Lastly, simple linear regression provided estimates that were slightly faster than those using mixed linear regression. Previous studies have used linear regression to describe the rate of FEV_1 decline [17, 158, 159]. The limitation to this model is that within and between patient variation is not taken into consideration by the model. If similar types of patients are included and FEV_1 is not highly variable within or between patients, then linear regression can be sufficient. However, due to the nature of CPRD, a routinely collected EHR, a wide variety of phenotypes can exist, and measurement error is possible therefore, mixed linear regression should be used to take into account FEV_1 variation.

Previous studies (notably RCTs) have also estimated change in FEV_1 using two FEV_1 measurements, one at baseline and one at follow-up [160, 161]. The nature of RCTs ensure that patients are similar in all arms of the trial, other than the intervention of interest, and confounding is adjusted for by the study design. However, in CPRD, and other EHRs, this method could be easily biased by measurement error, change in maintenance therapies during follow-up, AECOPD events during follow-up, and other everyday primary care factors. This method in estimating change in FEV_1 would require the two measurements to be accurate and not be recorded close to AECOPDs, changes in medication, etc. Overall, in order to use as much data as possible over follow-up, and to consider varying changes in individual patient decline and initial lung function, mixed linear regression should be used when studying FEV_1 using EHR.

4.5 Conclusion

Overall, the quality of FEV_1 in CPRD is adequate for the purpose of studying FEV_1 decline. Regardless of potential measurement error, number of FEV_1 measurements, time intervals between measurements, follow-up period, exclusion of specific FEV_1 measurements, and linkage to secondary care data, FEV_1 variability and rate of FEV_1 decline remained similar in a COPD population using mixed linear regression.

This suggests that CPRD is a good resource for investigating rate of FEV_1 decline in epidemiological studies. However, attention should be made around the difference in rate of FEV_1 decline and patient characteristics when excluding individuals with questionable data.

Chapter 5
Rate of FEV_1 and factors associated with accelerated decline

The rate of FEV_1 decline in a general population of COPD patients who are routinely seen in clinical practice has not been investigated in detail. This chapter aims to describe the rate of decline in this population and investigate baseline patient characteristics associated with the rate of FEV_1 decline, specifically accelerated rate of FEV_1 decline, to identify COPD patients more likely to have faster lung function decline. The work described in this chapter has been published in the International Journal of COPD [162].

5.1 Introduction

Rate of FEV_1 decline has been investigated in various settings in people with COPD. However, previous literature shows inconsistent evidence depending on the setting. Previous RCTs have shown that the mean rate of FEV_1 decline in COPD patients is approximately -40 ml/year but most RCTs have strict inclusion and exclusion criteria, leading to inclusion of selected populations of COPD patients whose rates of decline may not be generalisable to the wider population of COPD patients [27, 32, 38, 72]. Recently, a study found that between 2.3% to 46.7% of COPD patients from a French COPD cohort, using Initiative-BPCO data, would have met the eligibility criteria for 16 RCTs that aimed to investigate effects of treatment on AECOPDs (mean eligibility rate 16.5% [95% CI 9.2 – 23.7]) [44]. Observational studies report a lower mean rate of FEV_1 decline compared to those seen in RCTs. For example, the ECLIPSE study reported a mean FEV_1 decline of -33.2 ml/year in COPD patients aged 40 to 75 with a history of smoking [17]. Authors also found that the change in rate of FEV_1 in COPD patients was heterogeneous and varied from as much as -100 ml/year to +50 ml/year. As with the ECLIPSE study, the BODE study found that the change in rate of FEV_1 in COPD patients was heterogeneous and approximately 82% of patients had a non-significant decline in FEV_1 with a mean decline of -28 ml/year [28]. Further observational studies have found declines ranging from -12.6 ml/year to -27 ml/year in COPD patients [29, 30].

In terms of factors that are associated with rate of FEV_1 decline, frequent or severe AECOPD have been identified as a main risk factor for accelerated decline, notably in RCTs [32, 33, 73]. In addition, several RCTs have identified ICS as a type of COPD medication that reduces the rate of FEV_1 decline [89, 104, 112]. Other characteristics associated with lung function decline include higher age, lower baseline FEV_1, current smoking status, and lower BMI and these have been observed to be important not only in COPD populations but in general populations also [32, 33, 163].

Although previous studies have described the rate of FEV_1 decline in COPD populations and have investigated associations between patient characteristics and rate of decline, no studies have investigated this in a generalisable population of primary care COPD patients. In addition, few studies have investigated the association between comorbidities in COPD patients and the rate of FEV_1 decline and other clinical characteristics such as medications (other than RCTs), COPD related symptoms, and patient demographics. This chapter aimed to describe the rate of FEV_1 decline in a primary care population of COPD patients and investigate the relationship between baseline patient characteristics and rate of FEV_1 decline, specifically accelerated FEV_1 decline.

5.2 Methods

5.2.1 Study population & study design

CPRD-GOLD and HES were used. Patients were included if they had been diagnosed with COPD, were current or ex-smokers, were aged 35 or older, had at least two FEV_1 measurements at least 6 months apart, and had linked HES data (leading to the inclusion of only patients in England). Start of follow-up was from the first FEV_1 measurement after: i) COPD diagnosis; ii) current GP registration date, ii) date at which data were deemed to be of research standard (up-to-standard); iii) data up-to-standard which is date, date at which they turned 35, or the 1st January 2004. End of follow-up was the 31st December 2017 or earlier if they died or left the GP. **Figure 5.1** illustrates the study design in more detail.

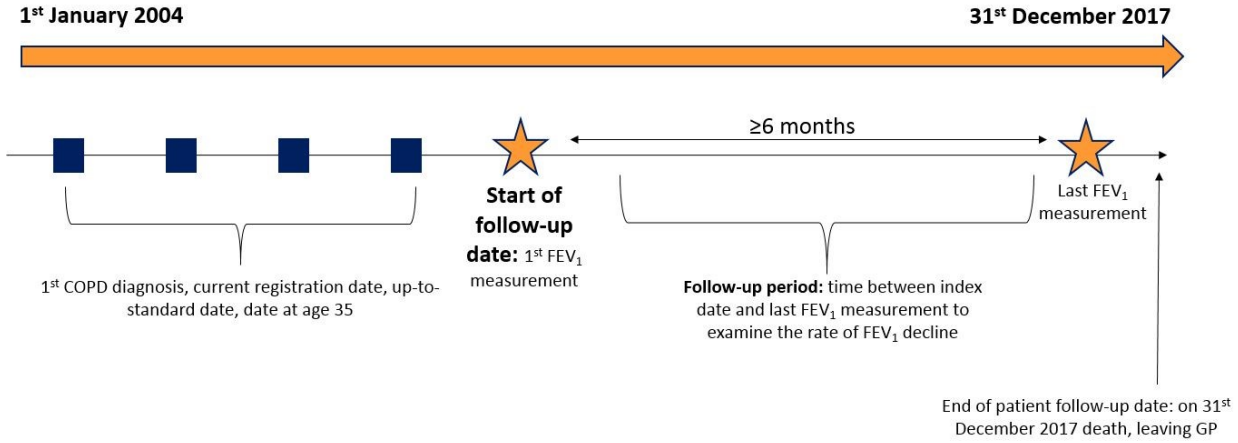


***Figure 5.1**: Study design.*

5.2.2 Exposure variables

Exposure variables were chosen a priori and were based on patient demographics, COPD related symptoms, common comorbidities of COPD, COPD severity, and type of COPD medication which are all recorded in primary or secondary care and could influence patent's rate of lung function decline. See **chapter 3** for more detailed information on definitions of baseline characteristics. Baseline patient demographics included age, gender, smoking status, and socioeconomic status measured using IMD. Symptoms included self-reported breathlessness, chronic cough, and sputum production 3 years prior to index date. Baseline history of comorbidities included MI, ischaemic stroke, lung cancer, and bronchiectasis all identified any time prior to index date. HF, GORD, anxiety, and depression were identified within three years prior to index date and history of asthma was identified as asthma recorded earlier than two years prior to index date. Finally, BMI was defined as the closest BMI recorded to index date from three years prior to two years after. COPD severity included mMRC dyspnoea score (defied as the closest measurement three years prior

to two years after index date), airflow obstruction (using baseline FEV_1 % predicted), and AECOPD frequency and severity in the year prior to the index date. COPD medications included any ICS-containing medications and any non-ICS containing medications in the year prior to index date.

5.2.3 FEV_1 decline

The outcome was accelerated decline in FEV_1 over time. This was identified through spirometry recorded at the GP. Spirometry measurements were identified between the index date and the end of follow-up. Previous work suggests that regardless of the number of FEV_1 measurements, time intervals between measurements, follow-up period, exclusion of specific FEV_1 measurements, and linkage to secondary care data, rate of lung function decline remains similar in a COPD population defined by recorded primary care diagnosis of disease (see **chapter 4**). Rates of FEV_1 decline were estimated using mixed linear regression models. Patients were dichotomised into those with accelerated decline (those in the fastest quartile) and patients without accelerated decline [34, 164, 165]. A dichotomous rate of FEV_1 decline was used as this may be a more meaningful outcome for decision making in primary care and these definitions had been used in previous studies.

5.2.4 Statistical analyses

Main analysis

Baseline characteristics were described for the total population and those with accelerated and non-accelerated FEV_1 decline using proportions (%) and mean (SD). Univariate logistic regression was used to investigate the association between baseline characteristics that were chosen a priori and accelerated rate of FEV_1 decline. Univariate logistic regression was performed in patients with complete baseline data only. Multivariate logistic regression was used to investigate the associations between all baseline characteristics and were adjusted for all other characteristics and FEV_1 at index date. Baseline characteristics included the demographics age, gender, smoking status (current or ex-smoking), and socioeconomic deprivation (IMD). Symptoms included breathlessness, chronic cough, and sputum production. Comorbidities included a history of anxiety, depression, GORD, bronchiectasis, lung cancer, heart failure, stroke, myocardial infarction, asthma, and most recent BMI (underweight, normal, overweight, obese). COPD severity characteristics included mMRC dyspnoea score, FEV_1 percent predicted at baseline (mild: >80% predicted; moderate: 50-79% predicted; severe: 30-49% predicted; and very severe: <30% predicted), frequency and severity of AECOPD and ICS use in the year prior to index date.

Sensitivity analyses

Sensitivity analyses were conducted included different thresholds for accelerated FEV_1 decline. These included:

1) The median rate of decline

2) -40ml/year, previously indicated by RCTs [17, 28]

3) Linear rate of FEV_1 decline using mixed linear regression adjusted for all baseline characteristics.

Bonferroni correction was used because multiple hypotheses were tested (i.e., whether each baseline characteristic was associated with rate of FEV_1 decline or odds of accelerated FEV_1 decline) in separate models. The Bonferroni correction test applies a more stringent p value to protect tests from type 1 errors (i.e. the probability of detecting a false positive due to multiple testing). In this case the threshold for significance was alpha (α=0.05) divided by the number of hypotheses tested (n=21), resulting in a threshold for significance of p=0.002. Test for linear trends were performed for categorical variables. I will refer to baseline characteristics that were associated with FEV_1 decline in at least two of the four analyses (both the main analysis and three sensitivity analyses) as "consistently" associated with FEV_1 decline.

Sample size considerations

Sample size calculations were based on the rate of change in FEV_1. Calculations by Schlesselman (1973) were used which considered repeated measures of FEV_1 over time:

$$N = [2(Z_{\alpha/2} + Z_{\beta})^2 \{\hat{\sigma}_{\beta}^2 + 12(P-1)\hat{\sigma}^2 / [D^2 P(P+1)]\} / \Delta^2$$

Overall, $Z_{\alpha/2}$ and Z_{β} (the unit normal deviates for errors type I and type II) for an alpha value of 0.05 and a power beta value of 0.8 were 1.96 and 0.84 respectively. The variance associated with the rate of FEV_1 decline (σ^2_{β}) was assumed to be 313ml. The within subject variance (σ2) was assumed to be 313ml. The median number of measurements in the study (*P)* was estimated as 3, and the median duration of the study (*D*) was estimated at 4.8 years.

The number of patients required, according to the formulae above, using these estimates, with enough power to detect a unit difference of Δ is shown in **table 5.1.** For example, to evaluate a change in 2 mL/year a sample of 55,293 was needed.

***Table 5.1**: Sample size considerations.*

Δ (ml/year)	Total sample (N)
2	55,293
3	24,575
4	13,824
5	8,847
7	4,514
10	2,212

5.3 Results

In this study 72,683 COPD patients had at least 2 FEV_1 measurements at least 6 months apart. **Figure 5.2** illustrates the proportion of patients included. The median follow-up time was 5.8 years (IQR 3.6-8.5) and median number of FEV_1 measurements over the study period was 4 (IQR 3-7). **Table 5.2** illustrates baseline characteristics for study population. Men, current smokers, patients with a history of asthma and patients with low baseline FEV_1 percent predicted were more likely to be in the accelerated decline group. In this primary care COPD population, the unadjusted mean rate of FEV_1 decline was -17.7 ml/year (95% CI: -18.4 to -16.9). The median rate of FEV_1 was − 18.1 ml/year (IQR: − 31.6 to − 6.0).

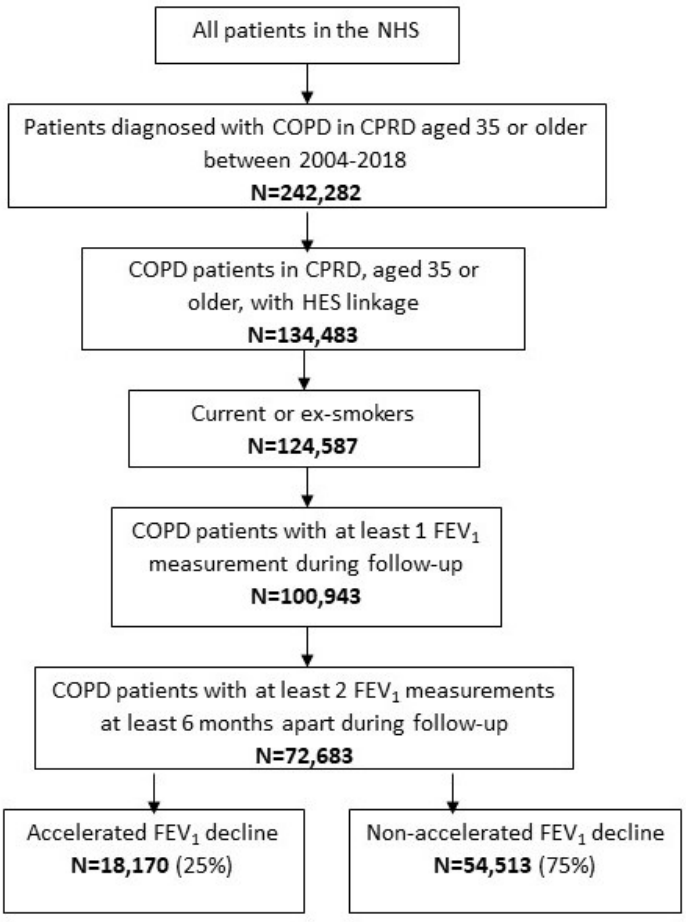


***Figure 5.2**: Patient population using 25th percentile decline (-31.6ml/year) as threshold for accelerated decline.*

Table 5.2: *Baseline characteristics for total population, patients with accelerated decline (≤-31.6ml/year), and patients with non-accelerated decline (>-31.6ml/year). Numbers are n (%) or mean (SD).*

Baseline characteristics	Total population N=72,673	Accelerated decline N=18,170	Non-accelerated decline N=54,513
Patient demographics			
Age	66.7 (10.7)	64.5 (10.6)	67.5 (10.7)
Gender (male)	39,266 (54.0)	11,503 (63.3)	27,763 (50.9)
Smoking status			
Smoker	43,902 (60.4)	11,627 (64.0)	32,275 (59.2)
Ex-smokers	26,781 (39.6)	6,543 (36.0)	22,238 (40.8)
IMD			
1 (most deprived)	10,897 (15.0)	2,728 (15.0)	8,169 (15.0)
2	13,700 (18.9)	3,333 (18.3)	10,367 (19.0)
3	14,455 (19.9)	3,486 (19.2)	10,969 (20.1)
4	16,085 (22.1)	4,040 (22.2)	12,045 (22.1)
5 (least deprived)	17,502 (24.1)	4,569 (25.2)	12,933 (23.7)
Missing	44 (0.1)	14 (0.1)	30 (0.1)
Symptoms			
Breathlessness	11,997 (16.5)	2,951 (16.2)	9,046 (16.6)
Chronic cough	25,129 (34.6)	6,297 (34.7)	18,832 (34.6)
Sputum production	5,104 (7.0)	1,317 (7.3)	3,787 (7.0)
Comorbidities			
Anxiety	5,181 (7.1)	1,317 (7.3)	3,864 (7.1)
Depression	5,818 (8.0)	1,656 (9.1)	4,162 (7.6)
GORD	3,744 (5.2)	967 (5.3)	2,777 (5.1)
BMI			
Underweight	2,353 (3.2)	5,162 (28.4)	15,283 (28.0)
Normal	20,445 (28.1)	539 (3.0)	1,814 (3.33)
Overweight	20,017 (27.5)	4,944 (27.2)	15,073 (29.7)
Obese	14,49 (20.3)	3,57 (19.7)	11,176 (20.5)
Missing	15,119 (20.8)	3,952 (21.8)	11,167 (20.5)
Bronchiectasis	1,869 (2.6)	1,869 (2.6)	1,439 (2.6)
Lung cancer	348 (0.5)	79 (0.4)	269 (0.5)
Heart failure	4,532 (6.2)	984 (5.4)	3,548 (6.5)
Stroke	2,757 (3.8)	628 (3.5)	2,129 (3.9)
MI	5,030 (6.9)	1,225 (6.7)	3,805 (7.0)
Asthma	21,855 (30.1)	5,169 (28.5)	16,686 (20.6)
COPD severity			
mMRC dyspnoea			
0	8,098 (11.1)	2,186 (12.0)	5,912 (10.9)
1	15,887 (21.9)	3,635 (20.0)	12,252 (22.5)
2	9,550 (13.1)	2,002 (11.0)	7,548 (13.9)
3	4,533 (6.2)	858 (4.7)	3,675 (6.7)
4	787 (1.1)	121 (0.7)	666 (1.2)
Missing	33,818 (46.5)	9,368 (51.6)	24,460 (44.9)
FEV_1 percent predicted			
Mild	18,267 (25.4)	8,562 (47.1)	9,705 (17.8)

Moderate	33,452 (46.5)	7,165 (39.4)	26,287 (48.2)
Severe	16,522 (22.9)	2,091 (11.5)	14,431 (26.5)
Very severe	3,777 (5.2)	198 (1.1)	3,579 (6.6)
Missing	665 (0.9)	154 (0.9)	511 (0.9)
AECOPD frequency			
None	30,178 (41.5)	7,945 (43.7)	22,233 (40.8)
1 moderate	17,665 (24.3)	4,437 (24.4)	13,228 (24.3)
2 moderate	9,618 (13.2)	2,353 (13.0)	7,265 (13.3)
≥3 moderate	11,339 (15.6)	2,692 (14.8)	8,647 (15.9)
1 severe, any moderate	3,126 (4.3)	631 (3.5)	2,495 (4.6)
≥2 severe, any moderate	757 (1.0)	112 (0.6)	645 (1.2)
ICS combination use	38,615 (53.1)	9,085 (50.0)	29,530 (54.2)

Figure 5.3 illustrates the frequency of the total number of FEV_1 measurements over follow-up and **figure 5.4** illustrates the distribution of the change in FEV_1 in ml/year. After categorising patients into accelerated and non-accelerated FEV_1 decline using the 25th percentile of the populations declines (threshold of -31.6ml/year), a total of 18,170 (25%) patients were classed as having accelerated decline and 54,513 (75%) patients were classed as having non-accelerated decline. In addition, only 11,862 (16.3%) of patients had an FEV_1 decline faster than -40ml/year.

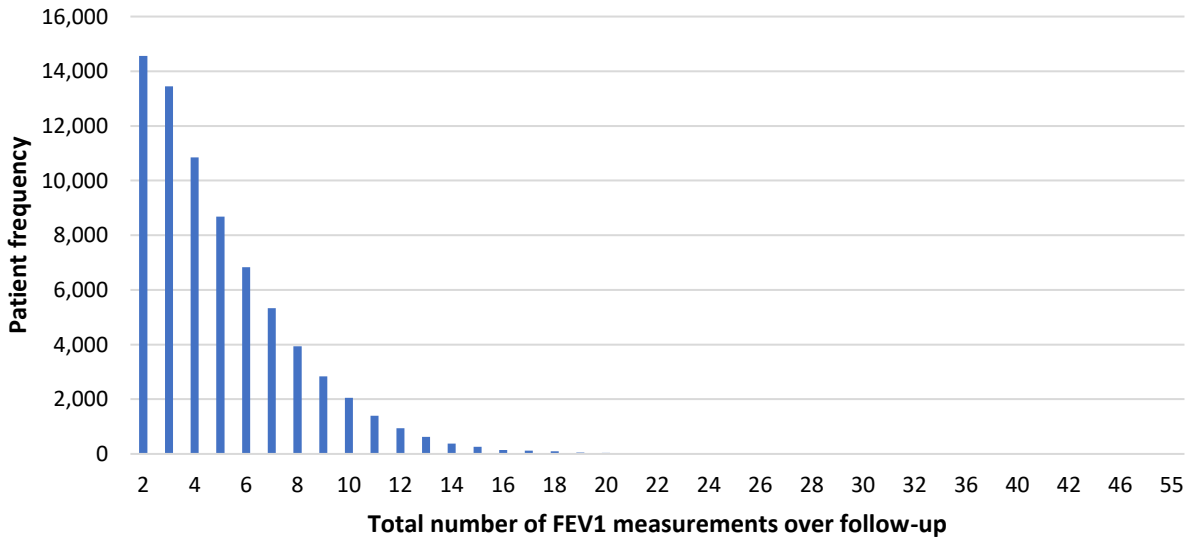


***Figure 5.3**: Frequency of the total number of FEV_1 measurements over follow-up.*

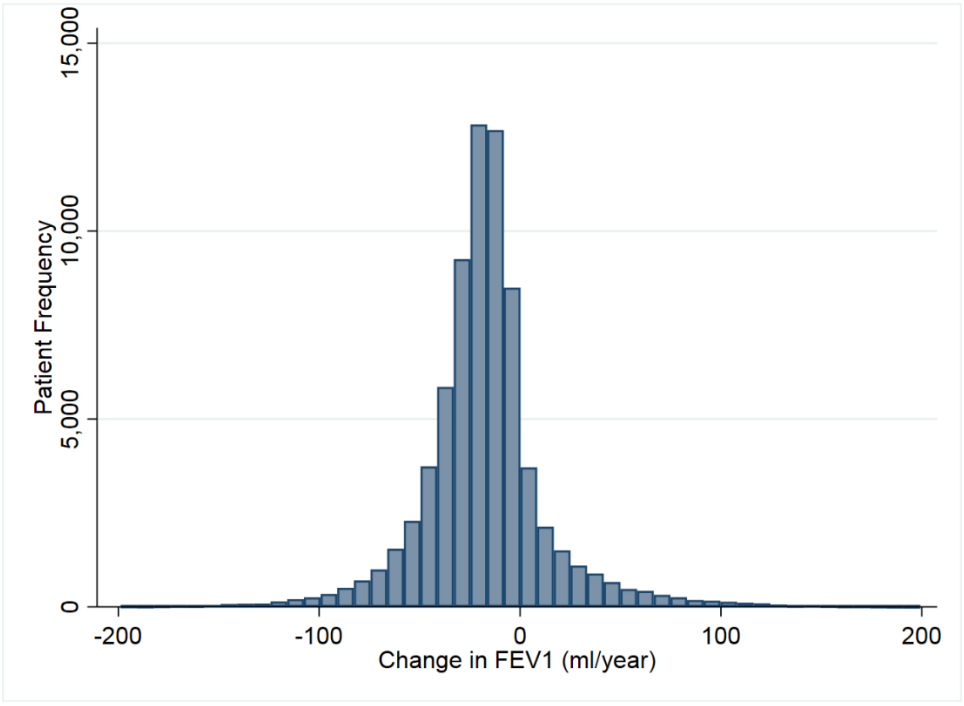


Figure 5.4: *Distribution of the change in FEV_1 over follow-up.*

5.3.1 Baseline characteristics associated with accelerated FEV_1 decline

With regards to the adjusted multivariate analysis, compared to their reference categories, baseline characteristics significantly associated with accelerated FEV_1 decline (defined by upper quartile) included older age (OR_{adj} 1.01 (5% CI 1.00-1.01), current smoking status (OR_{adj} 1.15 95%CI 1.07-1.23), high socioeconomic status (OR_{adj} 1.15 95% CI 1.04-1.27), breathlessness (OR_{adj}1.27 95% CI 1.15-1.39), high mMRC dyspnoea (mMRC 2:OR_{adj} 1.15 95% CI 1.05-1.27; mMRC 3: OR_{adj} 1.20 95% CI 1.07-1.35), mild airflow obstruction (reference group compared to moderate (OR_{adj} 0.74 95% CI 0.67-0.81) and very severe (OR_{adj} 0.65 95% CI 0.47-0.90), frequent AECOPD (more than three AECOPD OR_{adj} 1.18 95% CI 1.07-1.29), and being treated with inhaled corticosteroids (OR_{adj} 1.11 95% CI 1.04-1.19) (**table 5.3**).

***Table 5.3**: Baseline characteristics associated with accelerated FEV_1 decline (defined using upper quartile).*

	Unadjusted analysis (OR 95% CI) N=30,609	P value	Test for trend	Adjusted analysis (OR 95% CI) N=30,609	P value	Test for trend
Age	1.00 (1.00-1.00)	<0.001*		1.01 (1.00 – 1.01)	0.001	
Gender (Males)	0.81 (0.75-0.86)	<0.001*		0.91 (0.83 – 1.00)	0.050	
Current smoking	1.15 (1.08-1.23)	<0.001*		1.15 (1.07 – 1.23)	<0.001*	
IMD						
1 (most deprived)	Ref	Ref	<0.001	Ref	Ref	0.015
2	1.01 (0.91-1.13)	0.791		1.00 (0.90 – 1.11)	0.976	
3	1.06 (0.96-1.18)	0.249		1.04 (0.93 – 1.16)	0.482	
4	1.05 (0.94-1.17)	0.328		1.01 (0.91 – 1.12)	0.878	
5 (least deprived)	1.22 (1.10-1.35)	<0.001*		1.15 (1.04 – 1.27)	0.009	
Breathlessness	1.31 (1.19-1.43)	<0.001*		1.27 (1.15 – 1.39)	<0.001*	
Cough	1.13 (1.06-1.21)	<0.001*		1.07 (0.99 – 1.16)	0.079	
Sputum	1.20 (1.06-1.35)	0.004		1.06 (0.92 – 1.21)	0.424	
Asthma	1.00 (0.93-1.07)	0.972		0.93 (0.86 – 1.01)	0.079	
MI	0.94 (0.84-1.06)	0.317		0.94 (0.84 – 1.06)	0.311	
Stroke	1.13 (0.97-1.31)	0.111		1.10 (0.95 – 1.28)	0.206	
HF	0.93 (0.81-1.05)	0.237		0.88 (0.77 – 1.00)	0.057	
Lung cancer	1.22 (0.80-1.87)	0.361		1.19 (0.78 – 1.12)	0.419	
Bronchiectasis	0.97 (0.80-1.19)	0.792		0.91 (0.74 – 1.12)	0.364	
GORD	0.98 (0.86-1.11)	0.715		0.96 (0.84 – 1.10)	0.552	
Anxiety	1.00 (0.89-1.13)	0.979		0.93 (0.82 – 1.05)	0.231	
Depression	1.10 (0.99-1.23)	0.077		1.09 (0.97 – 1.22)	0.150	
BMI						
Normal	Ref	Ref	<0.001	Ref	Ref	<0.001
Underweight	1.19 (1.01-1.40)	0.043		1.16 (0.98 – 1.37)	0.084	
Overweight	0.84 (0.78-0.90)	<0.001*		0.85 (0.79 – 0.91)	<0.001*	
Obese	0.85 (0.78-0.91)	<0.001*		0.84 (0.78 – 0.91)	<0.001*	

mMRC						
0	Ref	Ref	0.009	Ref	Ref	0.947
1	1.04 (0.96-1.12)	0.374		1.02 (0.94 – 1.11)	0.676	
2	1.21 (1.11-1.32)	<0.001*		1.15 (1.05 – 1.27)	0.003	
3	1.28 (1.14-1.43)	<0.001*		1.20 (1.07 – 1.35)	0.003	
4	1.26 (0.98-1.61)	0.067		1.15 (0.90 – 1.48)	0.272	
Airflow obstruction						
Mild	Ref	Ref	0.121	Ref	Ref	<0.001
Moderate	0.72 (0.66-0.80)	<0.001*		0.74 (0.67 – 0.81)	<0.001*	
Severe	0.93 (0.79-1.10)	0.396		0.91 (0.77 – 1.07)	0.232	
Very severe	0.70 (0.51-0.97)	0.034		0.65 (0.47 – 0.90)	0.010	
AECOPD frequency						
0	Ref	Ref	0.140	Ref	Ref	0.001
1 moderate, 0 severe	1.05 (0.97-1.13)	0.227		1.04 (0.96 – 1.12)	0.322	
2 moderate, 0 severe	1.11 (1.01-1.21)	0.034		1.09 (0.99 – 1.20)	0.079	
≥3 moderate, 0 severe	1.23 (1.13-1.35)	<0.001*		1.18 (1.07 – 1.29)	0.001*	
1 severe, any moderate	1.19 (1.01-1.41)	0.033		1.10 (0.93 – 1.29)	0.277	
≥2 severe, any moderate	1.20 (0.84-1.74)	0.317		1.11 (0.77 – 1.60)	0.576	
ICS-combination therapy	1.13 (1.07-1.21)	<0.001*		1.11 (1.04 – 1.19)	0.002	

Note: *For variables breathless, cough, sputum, asthma, MI, stroke, HF, lung cancer, bronchiectasis, GORD, anxiety, depression, and ICS use, the reference groups are not having the symptom/comorbidity/medication. For smoking status, the reference group is ex-smoking patients. *significant after correcting for multiple testing (p<0.002).*

5.3.2 Sensitivity analyses

Using the median rate of FEV_1 decline as the cut off for accelerated decline, baseline characteristics significantly associated with accelerated FEV_1 decline (in fully adjusted analyses) included increasing age (OR_{adj} 1.01 95% CI 1.01-1.01), women (reference group compared to men OR_{adj} 0.88 95% CI 0.82-0.95), current smokers(OR_{adj} 1.17 95% CI 1.10-1.23), high socioeconomic deprivation (OR_{adj} 1.15 95% CI 1.06-1.26), breathlessness(OR_{adj} 1.10 95% CI 1.02-1.19), chronic cough (OR_{adj} 1.10 95% CI 1.02-1.17), patients without a history of asthma (reference group compared to those with a history of asthma OR_{adj} 0.93 95% CI 0.87-0.99), being underweight (OR_{adj} 1.20 95% CI 1.05-1.38), mild airflow obstruction (compared to moderate (OR_{adj} 0.55 95% CI 0.51-0.61), severe (OR_{adj} 0.51 95% CI 0.44-0.58), and very severe (OR_{adj} 0.41 95% CI 0.32-0.51)), and ICS use (OR_{adj} 1.07 95% CI 1.01-1.13) compared to reference categories (**table 5.4**).

Using -40 ml/year as the cut off for accelerated FEV_1 decline, baseline characteristics significantly associated with accelerated FEV_1 decline (in fully adjusted analyses) included age (OR_{adj} 1.01 95% CI 1.00-1.01), current smokers (OR_{adj} 1.18 95 % CI 1.09-1.28), high socioeconomic deprivation (OR_{adj} 1.17 95% CI 1.03-1.32), breathlessness (OR_{adj} 1.39 95% CI 1.25-1.55), being underweight (OR_{adj} 1.31 95% CI 1.08-1.58), high mMRC dyspnoea (mMRC2: OR_{adj} 1.25 95% CI 1.12-1.48; mMRC3: OR_{adj} 1.29 95% CI 1.12-1.48), mild airflow obstruction (as compared to moderate (OR_{adj} 0.71 95% CI 0.64-0.80), severe (OR_{adj} 0.82 95% CI 0.67-0.99), and very severe (OR_{adj} 0.57 95% CI 0.38-0.86)), frequent moderate AECOPD or one severe AECOPD (≥3 moderate AECOPD: OR_{adj} 1.26 95% CI 1.13-1.40; 1 severe AECOPD: OR_{adj} 1.22 95% CI 1.01-1.48), and ICS use (OR_{adj} 1.17 95% CI 1.08-1.26) compared to reference categories (**table 5.5**).

Table 5.6 reports the associations between baseline characteristics and rate of FEV_1 decline as a continuous outcome. Overall, the following baseline characteristics were associated with FEV_1 decline (in fully adjusted analyses) : breathlessness (-7.66 ml/year (95% CI -12.20 to -3.11) compared to no breathlessness), stroke (-15.66 ml/year (95% CI -24.14 to -7.18) compared to no stroke), anxiety (-10.81 ml/year (95% CI -17.20 to -4.41) compared to no anxiety), being obese (5.05 ml/year (95% CI 1.28 to 8.82) compared to normal BMI), and increasing airflow obstruction (i.e. higher airflow obstruction associated with a slower rate of FEV_1 decline compared to mild airflow obstruction). To put this into context, the mean change in FEV_1 in patients who were breathless was 7.66 ml/year faster than patients who were not breathless. Similarly, the mean change in FEV_1 in patients who were obese was 5.05 ml/year slower than in patients who had normal BMI.

Table 5.4: *Baseline characters associated with accelerated FEV_1 decline (defined using median rate of decline i.e., -18.1ml/year).*

	Unadjusted analysis (OR 95% CI) N=30,609	P value	Test for trend P value	Adjusted analysis OR (95% CI) N=30,609	P value	Test for trend P value
Age (per increasing year)	1.01 (1.01-1.02)	<0.001*		1.01 (1.01 – 1.01)	<0.001*	
Gender (Males)	0.67 (0.64-0.71)	<0.001*		0.88 (0.82 – 0.95)	0.001*	
Current smoking	1.18 (1.12-1.25)	<0.001*		1.17 (1.10 – 1.23)	<0.001*	
IMD						
1 (most deprived)	Ref	Ref	0.161	Ref	Ref	0.015
2	1.01 (0.93 – 1.09)	0.789		1.05 (0.95 – 1.15)	0.334	
3	0.99 (0.92 – 1.07)	0.829		1.03 (0.94 – 1.13)	0.534	
4	1.02 (0.94 – 1.10)	0.613		1.00 (0.91 – 1.09)	0.975	
5 (least deprived)	1.06 (0.98 – 1.14)	0.152		1.15 (1.06 – 1.26)	0.001*	
Breathlessness	1.12 (1.04-1.21)	0.004		1.10 (1.02 – 1.19)	0.019	
Cough	1.11 (1.05-1.17)	<0.001*		1.10 (1.03 – 1.17)	0.006	
Sputum	1.12 (1.01-1.25)	0.031		1.01 (0.90 – 1.13)	0.892	
Asthma	0.97 (0.92-1.03)	0.353		0.93 (0.87 – 0.99)	0.037	
MI	1.03 (0.94-1.14)	0.493		1.03 (0.93 – 1.13)	0.566	
Stroke	1.08 (0.95-1.22)	0.223		1.07 (0.94 – 1.21)	0.313	
HF	1.00 (0.90-1.11)	0.963		1.00 (0.89 – 1.11)	0.926	
Lung cancer	1.03 (0.72-1.47)	0.858		1.05 (0.74 – 1.50)	0.785	
Bronchiectasis	1.04 (0.88-1.23)	0.614		1.01 (0.85 – 1.19)	0.928	
GORD	0.99 (0.88-1.11)	0.808		0.98 (0.87 – 1.10)	0.669	
Anxiety	1.08(0.97-1.19)	0.145		1.04 (0.93 – 1.15)	0.524	
Depression	1.05 (0.96-1.16)	0.306		1.02 (0.92 – 1.23)	0.705	
BMI						
Normal	Ref	Ref	<0.001	Ref	Ref	<0.001
Underweight	1.22 (1.06-1.40)	0.004		1.20 (1.05 – 1.38)	0.009	
Overweight	0.86 (0.81-0.91)	<0.001*		0.87 (0.82 – 0.93)	<0.001*	
Obese	0.84(0.78-0.90)	<0.001*		0.84 (0.78 – 0.90)	<0.001*	

mMRC						
0	Ref	Ref	0.568	Ref	Ref	0.947
1	1.04 (0.97-1.11)	0.310		1.03 (1.05 – 1.38)	0.412	
2	1.10 (1.01-1.18)	0.021		1.07 (0.99 – 1.16)	0.077	
3	1.13 (1.03-1.25)	0.011		1.10 (0.99 – 1.21)	0.056	
4	1.01 (0.84-1.23)	0.890		0.97 (0.80 – 1.18)	0.791	
Airflow obstruction						
Mild	Ref	Ref	<0.001	Ref	Ref	<0.001
Moderate	0.55 (0.50-0.60)	<0.001*		0.55 (0.51 – 0.61)	<0.001*	
Severe	0.51 (0.45-0.59)	<0.001*		0.51 (0.44 – 0.58)	<0.001*	
Very severe	0.42 (0.34-0.53)	<0.001*		0.41 (0.32 – 0.51)	<0.001*	
AECOPD frequency						
0	Ref	Ref	0.400	Ref	Ref	0.782
1 moderate, no severe	1.03 (0.96-1.10)	0.415		1.02 (0.96 – 1.09)	0.483	
2 moderate, no severe	1.03 (0.95-1.11)	0.504		1.02 (0.94 – 1.11)	0.622	
≥3 moderate, no severe	1.11 (1.03-1.19)	0.009		1.08 (1.00 – 1.17)	0.057	
1 severe, any moderate	1.00(0.88-1.14)	0.995		0.94 (0.83 – 1.08)	0.405	
≥2 severe, any moderate	1.13 (0.86-1.49)	0.373		1.08 (0.82 – 1.00)	0.580	
ICS-containing therapy	1.07 (1.01-1.12)	0.016		1.07 (1.01 – 1.13)	0.019	

Note: *For variables breathless, cough, sputum, asthma, MI, stroke, HF, lung cancer, bronchiectasis, GORD, anxiety, depression, and ICS use, the reference groups are not having the symptom/comorbidity/medication. For smoking status, the reference group is ex-smoking patients. *significant after correcting for multiple testing (p<0.002).*

***Table 5.5**: Baseline characteristics associated with accelerated FEV_1 decline (defined using -40 ml/year).*

	Unadjusted analysis (OR 95% CI) N=30,609	P value	Test for trend P value	Adjusted analysis OR (95%) N=30,609	P value	Test for trend P value
Age (per increasing year)	1.01 (1.00-1.01)	<0.001*		1.01 (1.00 – 1.01)	0.010	
Gender (Males)	0.76 (0.69-0.82)	<0.001*		0.90 (0.80 – 1.00)	0.052	
Current smoking	1.18 (1.10-1.28)	<0.001*		1.18 (1.09 – 1.28)	<0.001*	
IMD						
1 (most deprived)	Ref	Ref	0.017	Ref	Ref	0.055
2	1.03 (0.95 – 1.12)	0.466		1.02 (0.89 – 1.15)	0.812	
3	0.99 (0.91 – 1.07)	0.814		1.04 (0.92 – 1.19)	0.494	
4	1.03 (0.95 – 1.11)	0.478		0.97 (0.86 – 1.10)	0.677	
5 (least deprived)	1.11 (1.03 – 1.20)	0.008		1.17 (1.03 – 1.32)	0.013	
Breathlessness	1.45 (1.31-1.60)	<0.001*		1.39 (1.25 – 1.55)	<0.001*	
Cough	1.16 (1.07-1.25)	<0.001*		1.08 (0.99 – 1.18)	0.101	
Sputum	1.21 (1.05-1.40)	0.008		1.03 (0.88 – 1.21)	0.674	
Asthma	1.02 (0.94-1.11)	0.562		0.93 (0.85 – 1.02)	0.105	
MI	0.89 (0.78-1.02)	0.098		0.87 (0.76 – 1.00)	0.058	
Stroke	1.20 (1.00-1.43)	0.044		1.16 (0.97 – 1.38)	0.103	
HF	0.93 (0.80-1.08)	0.352		0.87 (0.74 – 1.02)	0.088	
Lung cancer	1.41 (0.87-2.28)	0.164		1.36 (0.84 – 2.21)	0.212	
Bronchiectasis	0.97 (0.76-1.23)	0.797		0.87 (0.69 – 1.11)	0.263	
GORD	1.06 (0.91-1.23)	0.449		1.04 (0.89 – 1.21)	0.612	
Anxiety	1.00 (0.87-1.15)	0.995		0.91 (0.79 – 1.05)	0.211	
Depression	1.08 (0.96-1.23)	0.204		1.05 (0.92 – 1.20)	0.446	
BMI						
Normal	Ref	Ref	<0.001	Ref	Ref	<0.001
Underweight	1.34 (1.11-1.62)	0.003		1.31(1.08 – 1.58)	0.006	
Overweight	0.85 (0.78-0.93)	<0.001*		0.87 (0.80 – 0.94)	0.001*	
Obese	0.81 (0.74-0.89)	<0.001*		0.79 (0.72 – 0.87)	<0.001*	

mMRC						
0	Ref	Ref	0.008	Ref	Ref	0.097
1	1.09 (0.99-1.19)	0.083		1.06 (0.96 – 1.16)	0.235	
2	1.33 (1.20-1.48)	<0.001*		1.25 (1.12 – 1.39)	<0.001*	
3	1.40 (1.23-1.60)	<0.001*		1.29 (1.12 – 1.48)	<0.001*	
4	1.33 (0.99-1.79)	0.059		1.18 (0.87 – 1.60)	0.282	
Airflow obstruction						
Mild	Ref	Ref	0.108	Ref	Ref	0.018
Moderate	0.70 (0.62-0.78)	<0.001*		0.71 (0.64 – 0.80)	<0.001*	
Severe	0.87 (0.72-1.05)	0.152		0.82 (0.67 – 0.99)	0.043	
Very severe	0.66 (0.43-0.99)	0.043		0.57 (0.38 – 0.86)	0.008	
AECOPD frequency						
0	Ref	Ref	0.052	Ref	Ref	0.213
1 moderate, no severe	1.08 (0.99-1.18)	0.100		1.06 (0.97 – 1.17)	0.178	
2 moderate, no severe	1.16 (1.03-1.29)	0.011		1.13 (1.01 – 1.26)	0.038	
≥3 moderate, no severe	1.34(1.21-1.49)	<0.001*		1.26 (1.13 – 1.40)	<0.001*	
1 severe, any moderate	1.36 (1.13-1.64)	0.001*		1.22 (1.01 – 1.48)	0.043	
≥2 severe, any moderate	1.32(0.85-2.03)	0.212		1.20 (0.78 – 1.86)	0.407	
ICS-combination therapy	1.21 (1.13-1.30)	<0.001*		1.17 (1.08 – 1.26)	<0.001*	

Note: *For variables breathless, cough, sputum, asthma, MI, stroke, HF, lung cancer, bronchiectasis, GORD, anxiety, depression, and ICS use, the reference groups are not having the symptom/comorbidity/medication. For smoking status, the reference group is ex-smoking patients. *significant after correcting for multiple testing (p<0.002).*

***Table 5.6**: Baseline characteristics associated with continuous FEV_1 decline.*

	Unadjusted analysis (difference in mean change in FEV_1 (ml/year) and 95% CI N=30,609	P value	Test for trend P value	Adjusted analysis (difference in mean change in FEV_1 (ml/year) and 95% CI N=30,609	P value	Test for trend P value
Age (per increasing year)	-0.25 (-0.41 to -0.09)	0.002		-0.24 (-0.39 to-0.08)	0.003	
Gender (Males)	3.44 (0.24 to 6.65)	0.035		3.33 (0.13 to 6.52)	0.041	
Current smoking	-5.77 (-9.02 to -2.51)	0.001*		0.65 (-5.52 to 6.80)	0.837	
IMD						
1 (most deprived)	Ref	Ref	0.237	Ref	Ref	0.455
2	-2.71 (-8.39 to 2.96)	0.349		-2.8 (-8.41 to 2.91)	0.341	
3	2.67 (-2.91 to 8.25)	0.349		2.56 (-3.00 to 8.12)	0.367	
4	4.62 (-0.82 to 10.07)	0.096		4.65 (-0.78 to 10.08)	0.093	
5 (least deprived)	-4.43 (-9.72 to 0.87)	0.102		-4.51 (-9.79 to 0.77)	0.094	
Breathlessness	-7.76 (-12.32 to -3.20)	0.001*		-7.66 (-12.20 to -3.11)	0.001*	
Cough	-1.06 (-4.50 to 2.37)	0.544		-1.02 (-4.44 to 2.41)	0.561	
Sputum	-5.30 (-11.74 to 1.17)	0.109		-5.32 (-11.77 to 1.13)	0.106	
Asthma	5.52 (1/97 to 9.07)	0.002		5.52(1.99 to 9.06)	0.002	
MI	-0.36 (-6.48 to 5.77)	0.090		-0.17 (-6.28 to 5.94)	0.956	
Stroke	-15.78 (-24.29 to -7.27)	<0.001*		-15.66 (-24.14 to -7.18)	<0.001*	
HF	-9.88 (-16.88 to -2.88)	0.006		-9.86 (-16.84 to -2.89)	0.006	
Lung cancer	-6.06 (-29.97 to 17.85)	0.620		-5.57 (-29.42 to 18.28)	0.647	
Bronchiectasis	-11.63 (-22.21 to -1.05)	0.031		-11.78 (-22.33 to -1.23)	0.029	
GORD	-9.62 (-16.73 to -2.51)	0.008		-9.38 (-16.47 to -2.29)	0.010	
Anxiety	-10.81 (-17.22 to -4.40)	0.001*		-10.81 (-17.20 to -4.41)	0.001*	
Depression	-5.01 (-10.90 to 0.88)	0.096		-4.99 (-10.86 to 0.88)	0.096	
BMI						
Normal	Ref	Ref	0.001	Ref	Ref	0.004
Underweight	0.17 (-8.80 to 9.12)	0.971		0.38 (-8.56 to 9.31)	0.934	
Overweight						

Obese	5.02 (1.25 to 8.81) 7.52 (3.38 to 11.67)	0.005 0.001		5.05 (1.28 to 8.82) 7.50 (3.37 to 11.63)	0.009 <0.001*	
mMRC						
0	Ref	Ref	0.069	Ref	Ref	0.275
1	6.44(2.63 to 10.23)	0.001*		5.98 (1.73 to 10.23)	0.006	
2	6.15 (1.92 to 10.38)	0.004		4.33 (-0.39 to 9.05)	0.072	
3	4.88 (-.44 to 10.20)	0.072		2.41 (-3.50 to 8.31)	0.424	
4	12.11 (0.13 to 24.08)	0.048		7.49 (-5.60 to 20.57)	0.262	
Airflow obstruction						
Mild	Ref	Ref	<0.001	Ref	Ref	<0.001
Moderate	78.36 (75.85 to 81.87)	<0.001*		77.70 (73.90 to 81.49)	<0.001*	
Severe	109.13 (105.05 to 113.21)	<0.001*		108 (104.14 to 112.96)	<0.001*	
Very severe	141.66 (134.39 to 148.92)	<0.001*		141.66 (133.85 to 149.48)	<0.001*	
AECOPD frequency						
0	Ref	Ref	0.522	Ref	Ref	0.289
1 moderate, no severe	0.64 (-3.00 to 4.29)	0.729		0.20 (-3.85 to 4.23)	0.926	
2 moderate, no severe	4.71 (0.25 to 9.17)	0.039		4.97 (0.02 to 9.91)	0.049	
≥3 moderate, no severe	-2.92 (-7.18 to 1.33)	0.178		-2.41 (-7.11 to 2.29)	0.315	
1 severe, any moderate	6.06 (-1.80 to 13.91)	0.131		2.39 (-6.22 to 10.99)	0.587	
≥2 severe, any moderate	-8.18 (-27.30 to 10.95)	0.402		-12.93 (-33.40 to 7.55)	0.216	
ICS-containing therapy	4.50 (1.62 to 7.39)	0.002		4.10 (0.91 to 7.29)	0.012	

Note: *For variables breathless, cough, sputum, asthma, MI, stroke, HF, lung cancer, bronchiectasis, GORD, anxiety, depression, and ICS use, the reference groups are not having the symptom/comorbidity/medication. For smoking status, the reference group is ex-smoking patients. *significant after correcting for multiple testing (p<0.002).*

5.4 Discussion

This was the first study to describe the annual rate of FEV_1 decline and to explore clinical and demographic patient characteristics associated with accelerated decline in a large primary care population of COPD patients over 13 years in England. Baseline characteristics that were consistently associated with accelerated FEV_1 included older age, current smoking, high socioeconomic status, being breathless and having a high mMRC dyspnoea, being underweight, milder airflow obstruction, frequent AECOPD, and being treated with ICS. This study was important to understand the rate of FEV_1 decline in more detail in more generalisable COPD patients seen in primary care in the UK and understand which patients may be more likely to decline faster than others.

5.4.1 Rates of decline in previous studies

Previous studies have shown that rate of FEV_1 decline is heterogeneous in COPD. The ECLIPSE study showed that change in FEV_1 varied from declines faster than -100ml/year to increases greater than 100ml/year [17]. The ECLIPSE study, a non-interventional, multicentre observational study, collected lung function measurements at regular intervals. Using electronic healthcare records (EHR) the distribution in the change in FEV_1 in a primary care population in England was similar yet slightly wider in distribution. This is expected because the patients seen in primary care would have a wider distribution of disease severity and comorbidities than those specifically identified in RCTs or pragmatic trials.

To date, RCTs are the gold standard in scientific research and are used to direct clinical guidelines. Rates of FEV_1 decline in COPD RCTs are generally faster than the rates described in this study and other observational studies [154, 159, 166]. The SUMMIT trial reported mean FEV_1 declines between -37 ml/year to -47 ml/year depending on the treatment arm [86]. Similarly, mean rates of FEV_1 decline from the UPLIFT study were -43.9 ml/year (SE:1.41) in COPD patients on tiotropium and -45.1 ml/year (SE1:45) in patients on placebo [72]. Patients included in RCTs are not always generalisable to the wider population due to strict inclusion and exclusion criteria such as requiring patients to have moderate or severe COPD, heightened risk of CVD, and specific number of pack years smoking [72, 89]. Therefore, it is likely that differences in FEV_1 decline will exist between RCTs and observational populations. This highlights the need for incorporating real-word and observational studies in clinical guidelines.

Previous observational studies have reported a range of estimates for the mean rate of FEV_1 decline in COPD patients from -28 ml/year to -12.6 ml/year, similar to the mean rate of -17.7 ml/year observed

in this study [28-30]. Some of these estimates are slower than those reported in general populations, reinforcing the fact that the rate of FEV_1 decline is more complex than initially thought and high heterogeneity exists. A previous general population study of the rate of FEV_1 decline by Luoto and colleagues found that the mean absolute decline in FEV_1 in a general population of people age 60 to 100 years old was -51.7 ml/year (95% CI -63.7 to -39.9) [160]. A possible explanation for this is that healthy patients have a higher baseline FEV_1 and therefore, can lose more lung function than those who have lower lung function to start with [34]. For example, the mean baseline FEV_1 in health participants in the general population study was 2.37L (SD 0.86) compared to 1.7L (SD 0.7) in this COPD cohort.

Interestingly, the mean rate of FEV_1 decline seen in this study is slower than the mean decline in healthy non-smokers as estimated by reference equations [167]. It is important to note that rates of change in FEV_1 will depend on the prevalence of risk factors within specific COPD populations and criteria used to define populations. This population included current or ex-smoking COPD patients who were required to have spirometry performed at least twice at least six months apart. Patients were required to be registered at a general practice in England, be fit enough to be able to attend their general practice and have their lung function measured and have been alive for at least six months in order to have at least two measurements taken. Despite this, other studies such as ECLIPSE also found a mean rate of decline similar to the estimated rate of decline in healthy adults. The ECLIPSE study also found that rate of FEV_1 decline varies widely, which might explain why different rates of FEV_1 decline are seen in different COPD populations and settings. One other possible explanation is that most COPD patients would be on maintenance COPD therapy to reduce symptoms and potentially improve lung function. This might explain why the mean rate of FEV_1 decline in a population of primary care COPD patients is slower than that seen in the general population.

5.4.2 Characteristics associated with accelerated lung function decline

Age and smoking status

Age and smoking status are well-known risk factors of lung function decline and have been described in many previous studies of COPD populations and general populations [23, 168, 169]. It is important to highlight that never smokers were excluded in case of misdiagnosis of asthma with COPD. In addition, it is not common for GPs to diagnose non-smokers with COPD and only 7.4% of patients with a diagnosis of COPD were non-smokers in this study.

ICS

Interestingly, patients on ICS-containing medications were more likely to have accelerated FEV_1 decline. Many RCTs have investigated the relationship between ICS and lung function in COPD and results have shown that patients on ICS have attenuated rate of FEV_1 decline compared to non-ICS treatments [27, 38]. SUMMIT, a large RCT, found that over approximately 2 years, patients on combined fluticasone furoate/vilanterol declined 10 ml/year slower than patients on vilanterol alone or placebo [89]. This study found the opposite effect whereby patients on ICS were more likely to have accelerated FEV_1 decline compared to those on non-ICS-containing medication. It is highly likely that this is due to confounding by indication whereby patients with faster disease progression who are more symptomatic are more likely to be prescribed ICS.

Sex

The literature on FEV_1 decline and sex is inconsistent [160, 170]. Only when using the median rate of FEV_1 decline as the cut off for accelerated decline were men less likely to have accelerated decline. It is important to note that baseline FEV_1 was adjusted for in order to account for biological differences in airway size [171]. Previous studies suggest that women have faster relative lung function decline compared to men [34, 160]. It is thought that women may be more responsive to tobacco smoke however, no significant interaction between gender and smoking status was observed (results not shown) [172]. Other studies suggest that sex differences may exist due to differences in hormones and the presentation and progression of COPD [171, 173]. Despite this, no conclusive evidence for the association between sex and accelerated FEV_1 decline was seen in this study.

mMRC dyspnoea and breathlessness

Interestingly, higher mMRC dyspnoea score and being breathless were associated with accelerated FEV_1 decline. Previous cross-sectional studies have shown that FEV_1 and MRC score are not associated however, longitudinally mMRC dyspnoea score may be a good predictor of accelerated FEV_1 decline [174]. Currently, NICE guidelines recommend various clinical characteristics such as spirometry, AECOPD frequency, and smoking status to be used to assess COPD progression [21]. Whilst these are all important in assessing lung function progression, breathlessness should also be considered in assessing this progression. This may be a more important marker of lung function progression compared to baseline spirometry given the association with airflow obstruction seen in this study.

Baseline FEV_1 percent predicted

Patients with a lower baseline FEV_1 percent predicted were more likely to have accelerated FEV_1 decline compared to those with higher baseline lung function, which is in keeping with previous literature [34, 175]. This is because patients with higher lung function at baseline are able to lose more

lung function than those with less lung function to start with [34]. It is important to note that the use of absolute lung function in accessing change in lung function has been criticized because it does not take into consideration baseline lung function. Rather, it is thought that percentage change from baseline better describes the rate of change in lung function. For example, a decline of 40 ml/year for a patient with 2 liters of baseline FEV_1 is different to a decline of 40 ml/year in a patient with 1 liter of baseline FEV_1. Whilst it may seem that both these patients have the same rate of FEV_1 decline the percentage change from baseline would be 2% and 4% per year, respectively. Interestingly, results found that the mean rate of change in FEV_1 increased in patients with lower baseline FEV_1 % predicted (i.e., more severe disease). As described in chapter 4, this group of COPD patients are more likely to have higher variation in FEV_1 and show increases in FEV_1 greater than 20% of previous and subsequent measurements. This phenomenon is likely driving the mean increase in FEV_1 seen in patients with low baseline FEV_1 % predicted. These patients may not have the ability to perform adequate spirometry and there's a higher chance than healthcare practitioners input a measurement that does not truly reflect the patient's lung function at that given time. Another possible explanation for the increase in FEV_1 in severe COPD patients could be survival bias as patients with very severe COPD and low FEV_1 % predicted are more likely to die. Patients needed at least 2 lung function measurements at least 6 months apart so severe COPD patients would have had to survived at least six months to be included in this study and lung function decline in these patients may not be representative of all severe COPD patients.

AECOPD frequency

Frequent AECOPD, notably frequent moderate AECOPD, were associated with accelerated FEV_1 decline which is in line with previous studies [29, 32, 33, 73, 176]. It is thought that patients experiencing AECOPD do not fully recover from these events and therefore lung function worsens with the increased number of AECOPD a patient experiences [12]. Whilst AECOPD frequency was only defined at baseline, studies show that the increased number of AECOPD a patient experiences, the higher the likelihood that the patient will experience future moderate or severe AECOPD [12]. This may explain the increased decline in FEV_1 seen with more than 3 moderate AECOPD. Interestingly, whilst effect estimates suggested an increased odd of accelerated decline in patients with severe AECOPD (notably 2 or more), this was not statistically significant. This might be due to lack of power because only approximately 5% of the whole population had at least one severe AECOPD event at baseline.

BMI

Patients with low BMI were more likely to decline faster whilst patients with higher BMI were more likely to have slower FEV_1 decline [160, 170]. This is consistent with a previous meta-analysis of RCTs investigating BMI and rate of FEV_1 decline [35]. It has been suggested that reverse causation could explain the association between low BMI and accelerated FEV_1 decline. Severe COPD, including faster lung function decline or increased AECOPD, could lead to increased weight loss. Therefore, patients with low BMI seem to be more likely to have accelerated decline and patients with high BMI have the slowest decline, which is consistent with the "obesity paradox" [177, 178]. It is also possible that low BMI causes lung function decline as seen in animal models whereby starvation led to signs of emphysema [179, 180].

High socioeconomic status

Previous studies have shown that patients with low socioeconomic status are more likely to decline faster that those with higher socioeconomic status [181-183]. Reasons for this association are not quite understood however, it is possible that environmental, parental, and occupational exposures play a role. However, this study found that patients with high socioeconomic status were more likely to have accelerated FEV_1 decline. Previous studies have largely consisted of cross-sectional studies and inconsistencies exist between definitions of socioeconomic deprivation [184]. This study used the IMD which is a composite weighted score based on deprivation measures for small areas across England and includes income, employment, education, disability, crime, housing services, and environmental deprivation. It is possible that IMD may be imprecise as this is an area level marker of deprivation not an individual marker of deprivation.

5.4.3 Strengths and Limitations

This is the first study to describe the rate of FEV_1 decline in a primary care COPD population and investigate baseline characteristics associated with accelerated decline. Overall, this study has not only highlighted well-known characteristics but has shed light on other characteristics that were associated with accelerated FEV_1 decline and may be useful in assessing COPD progression in clinical practice. EHR are not always seen as reliable sources of data compared to RCTs or prospective cohort studies because of the way in which the data were collected. Despite this, this study found similar patterns of lung function decline to that of the ECLIPSE study, a 3-year prospective cohort study which would have had more standardized data collection, emphasizing the strengths of using EHR to investigate lung function decline. A further strength of routinely collected data is that it allows large

sample sizes and provides information on the prognosis of people diagnosed with COPD by UK primary care physicians rather than a highly select groups of people with COPD who are enlisted for RCTs.

A limitation of this work is that baseline characteristics such as smoking status, BMI, mMRC score, and AECOPD could have varied over follow-up. In clinical practice patients would be seen during a consultation and decision could be made based on observations presented at that time. Therefore, only baseline characteristics were investigated in relation to rate of FEV_1 decline. Further work should aim to investigate how the rate of FEV_1 decline is associated with time varying covariates. In addition, smoking status may not be reliable because the closest smoking status record was used to define ex-smokers and current smokers. Lifestyle variables in routinely collected data are not always updated. Therefore, it was assumed that the most recent smoking status was still true for patients prior to follow-up. Finally, airflow obstruction was defined using FEV_1 percent predicted. This definition did not require patients to have an FEV_1/FVC less than 70% because not all patients have an eligible FVC measurement that can be used to calculate obstruction. Rather, a diagnosis of COPD was used as a proxy for FEV1/FVC<70%. Despite this, a validated definition of COPD was used that used clinical codes and only included smokers and ex-smokers [140].

In addition, with regards to the linear rate of FEV_1 decline used as the outcome, it is important to be aware of when differences in rates of decline might be clinically significant. Due to the large sample size, it is common to get significant results when clinically there may not be large differences between groups and caution should be made when interpreting such results. It has previously been suggested by the ATS and the ERS that a minimal important difference in FEV_1 between two intervention arms ranges from 100ml to 140ml [130]. However, this is with regards to pharmacological trials which generally have a maximum follow-up of three years. If one were to assume that a difference of 120ml over three years between two groups was clinically meaningful the difference in the rate of decline would be ~40 ml/year. For example, patients who were breathless were more likely to decline faster, by 7.6 ml/year, compared to those who did not report being breathless. Over the average study follow-up of 5.8 years this equates to a difference of 44.4ml/year between patients who reported being breathless and those who did not. As a second example, patients with sputum (whilst not statistically significant after correction for multiple testing) declined faster than those without sputum by 5.3 ml/year. Over the average study follow-up of 5.8 years this equates to a difference of 30.7 ml/year between the two rates of decline, which following this definition of clinically significant would not be clinically meaningful. Interpreting what is clinically significant and what is not is complicated and might also depend on other patient characteristics and degree of disease severity.

Lastly, there was a high proportion of missing data for some baseline characteristics, specifically BMI and mMRC. Whilst a relatively large baseline period (5 years) was used to identify these measurements, 20.8% of BMI measurements and 46.5% of mMRC measurements were missing. If these measurements are not missing at random it is possible that using complete case analysis could have biased my results. For example, it is possible that mMRC is not missing at random as patients were unable to come into the general practice due to extreme breathlessness. Descriptive baseline characteristics suggest that more men were defined as accelerated FEV_1 decline however, in complete case analyses men were less likely to have accelerated FEV_1 decline. This phenomenon is likely to occur due to the use of complete case analysis where a high proportion of baseline data were missing not at random and if the probability of being missing is dependent on the outcome. Findings should therefore be interpreted with caution and further work into understanding the missingness of BMI and mRMC should be investigated.

5.5 Conclusion

This study aimed to describe the rate of FEV_1 decline in a primary care population of COPD patients in England who were more generalisable to COPD patients commonly seen in clinical practice compared to previous COPD populations studied. Older age, current smoking status, high socioeconomic status, being underweight, high mMRC dyspnoea and breathlessness, mild airflow obstruction (higher FEV_1 percent predicted), frequent moderate AECOPD, and ICS use were associated with an accelerated rate of FEV_1 decline. It was important to understand the rate of FEV_1 decline in COPD patients in more detail and identify COPD patients who are more likely to have accelerated FEV_1 decline in the future. This could help inform general practitioners and healthcare professionals in early identification and better management of these COPD patients routinely seen in clinical practice.

Chapter 6
Inhaled corticosteroids, blood eosinophil level, and rate of FEV_1 decline

Results from chapter 5 found that patient characteristics are associated with varying changes in the rate of FEV_1. As highlighted in chapter 2 (systematic review), ICS use is commonly used in patients with COPD and many RCTs have investigated its relationship with change in FEV_1 over time. However, many of these RCTs have very short follow-up and have strict inclusion and exclusion criteria which lead to the inclusion of very specific COPD populations. As RCTs largely inform clinical guidelines around the use of ICS, the aim of this chapter was to investigate the relationship between ICS and rate of change in FEV_1 in a generalisable COPD population seen in primary care. In addition, blood eosinophils have been shown to modify the relationship between ICS and change in FEV_1 however, this has not been investigated in a generalisable COPD population. Therefore, this chapter also investigates the relationship between ICS use and rate of change in FEV_1 by blood eosinophil level in COPD patients seen in English general practices. The work described in this chapter has been published in the International Journal of COPD [158].

6.1 Introduction

Initial treatment of COPD usually comprises of long-acting bronchodilators, i.e. LABA and LAMAs, to increase and maintain lung function, improve health-related quality of life and reduce the risk of AECOPD [185]. ICS are additionally recommended by NICE and GOLD guidelines in combination with LABA or LAMA/LABA for people with frequent AECOPD, who remain breathless, or who have high blood eosinophils [82] [1]. Studies to date have shown that ICS reduce the rate of moderate and severe AECOPD, reduce the rate of hospitalisation, and decrease the rate of decline of FEV_1 over time [86, 186]. However, studies also suggest that ICS increase the risk of pneumonia and increase the risk of URTIs, suggesting that more careful phenotyping of patients most likely to benefit from ICS is required [41, 187].

Blood EOS have been considered a potential biomarker in COPD in relation to ICS. Studies have shown that ICS are more effective in COPD patients with higher blood EOS counts rather than lower in terms of reducing AECOPD risk [40, 188, 189]. Recently, clinical guidelines state that ICS combination treatment should be considered in patients with blood EOS greater than 300cells/µl [1, 82]. A few studies have explored the relationship between ICS and blood EOS count in terms of FEV_1 decline but the majority have consisted of randomised control trials with strict inclusion criteria, and short term follow-up of roughly less than 3 years limiting their external validity to the wider COPD population [40, 188, 190].

Results from the previous chapter showed that patient characteristics and other factors such as ICS use were associated with accelerated FEV_1 decline. Whilst it is possible that this could be due to confounding by indication, it could also be that the relationship is modified by blood EOS level. Therefore, in order to better understand the relationship between ICS and FEV_1 decline, the association between ICS, blood EOS, and FEV_1 decline in a generalisable primary care setting was investigated.

6.2 Methods

6.2.1 Study population and design

Patients with data recorded in CPRD-GOLD and HES were included. CPRD-GOLD data that was recorded from the 1st January 2004 onwards to the 29th February 2016 was used. Patients were included at the date at which all of the following were satisfied: i) date at which the general practice was up-to-standard (UTS); ii) date at which patients were 35 years old; iii) date of first COPD diagnosis; and iv) date at which patients were registered at their current GP. The date of the first FEV_1 measurement after all these criteria were satisfied was the date from which patients were followed up from.

6.2.2 Baseline ICS use

Prevalent ICS use (prevalent cohort)

Baseline ICS use was determined prior to patient's start of follow-up. Prevalent baseline ICS use was defined as the presence of at least one ICS-containing medication in the year prior to patient follow-up. This was determined through recorded ICS prescriptions. Patients were categorised into those prescribed an ICS-containing medication and those who were not prescribed an ICS-containing medication at baseline. In addition, patients who were grouped into those who were not on ICS at baseline were censored at the first ICS prescription date during patient follow-up. This ensured that patients who were not on ICS at baseline remained were also not on ICS during follow-up. 98% of patients who were on ICS at baseline remained on ICS during follow-up. For ease, this study population that identified ICS use at baseline was called the "prevalent" cohort.

Incident ICS use (incident cohort)

A secondary population aimed to investigate incident ICS use rather than prevalent ICS use. The aim of this was to investigate newly initiating ICS patients compared to patients not on ICS, similar to RCT study designs. This incident population included patients who were not on ICS-containing medications prior to patient follow-up (as described above). Incident ICS use was defined as the prescription of at least one ICS-containing medication in the first year after the date at which patients were followed up from. Unlike the prevalent cohort patients not on ICS in the first year of follow-up were not censored at first ICS-containing medication prescription date. For ease, this study population that identified ICS use in the first year of follow-up in ICS naive patients was called the "incident" cohort.

6.2.3 Baseline blood eosinophil level

Baseline absolute blood EOS counts were identified prior to patient start of follow-up. Specifically, patients were required to have at least one blood EOS measurement within two years prior of the patient's start of follow-up. Blood EOS measurements that were within four weeks of an AECOPD or prescribed oral corticosteroid were excluded in order to identify stable EOS measurements following previous literature [144]. The closest viable baseline measurement to the start of follow-up the start of follow-up was used and patients were grouped into those with high or low blood EOS counts using a cut off of 150 cells/µl [144]. This cut off was chosen based on EOS thresholds used in the WISDOM trial, KRONOS trial, IMPACT trial and in other previous RCTs that stratified by blood EOS [143, 188, 191-193]. This threshold was considered the lowest possible threshold for stratification of high and low blood EOS from the literature.

6.2.4 Baseline ICS and blood eosinophil groups combined

After the identification of ICS or no ICS use (in both prevalent and incident cohorts) and the identification of baseline blood EOS level, patients were grouped into the following exposure categories:

i) high blood eosinophils on ICS-containing medications;

ii) high blood eosinophils not on ICS-containing medications;

iii) low blood eosinophils on ICS-containing medications;

iv) low blood eosinophils not on ICS-containing medications.

6.2.5 FEV_1 decline

The outcome of this aim was rate of change in FEV_1. Patients were required to have at least two FEV_1 measurements (measured in milliliters) recorded at least 6 months apart between the start of follow-up and the end of follow-up in order to estimate the rate of change of FEV_1. Since 2004 as part of the QOF FEV_1 should be measured every 15 months in COPD patients at their GP and quality of spirometry in primary care is of good quality [78, 156].

All FEV_1 measurements recorded between the start of follow-up and the end of follow-up were identified. Specifically, end of follow-up was the 29th February 2016 or beforehand if the patient died or transferred to a non-CPRD general practice. In addition, as mentioned in section 6.2.2, patients not on an ICS at baseline were censored at first ICS prescription date. FEV_1 measurements that were recorded between the start of follow-up and end of follow-up were used to calculate rate of FEV_1

decline. It is important to note that with the incident cohort, only FEV_1 measurements after the first year of follow-up were used to estimate rate of FEV_1 decline. **Figure 6.1** illustrates the main study design elements for both prevalent and incident cohorts. Specifically, it highlights definitions of patient start and end of follow-up, when prevalent ICS use, incident ICS use, and blood EOS measurements were identified, and the follow-up period for identification of FEV_1 measurements.

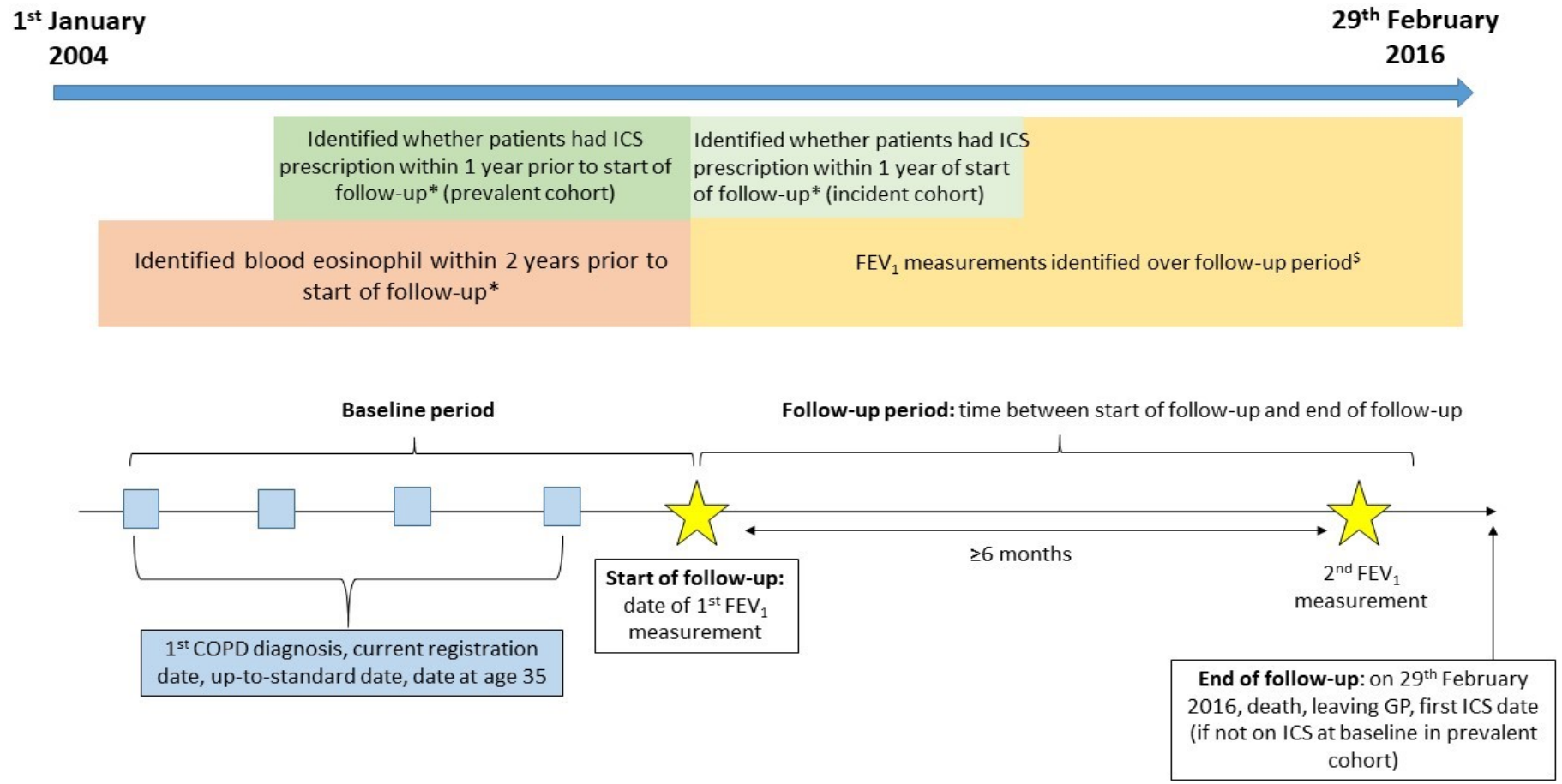


Figure 6.1*: Study design for prevalent and incident cohorts.*
Note: **Patients were then categorised into four groups: high blood eosinophil level & ICS use, high blood eosinophil & no ICS use, low blood eosinophil & ICS use, low blood eosinophil & no ICS use.* $^{\$}$ *For the incident cohort, FEV_1 measurements that over one year after start of follow-up and before end of follow-up were identified.*

6.2.6 Statistical analysis

Baseline characteristics were described using medians (IQR), means (SD), and proportions (%). Mixed effects linear regression was used due to the repeated measures of FEV_1 within patients. The model used two reference categories to evaluate the relationship between ICS and blood eosinophil level (see **table 6.1**). Analyses were adjusted for baseline characteristics including smoking status, gender, age, BMI, mMRC dyspnoea score, history of GORD, anxiety, depression MI, stroke, heart failure, lung cancer, bronchiectasis, heart failure, closest WBC and neutrophil count prior to index date, COPD severity, AECOPD frequency, and history of asthma (see chapter 5 for time periods in which baseline covariates were identified).

***Table 6.1**: Important reference and comparison patient groups.*

Reference group	Comparison group
High blood eosinophils and ICS	High blood eosinophils and no ICS
	Low blood eosinophils and ICS*
Low blood eosinophils and ICS	Low blood eosinophils and no ICS
	High blood eosinophils and ICS*

***Note:** *Same comparisons.*

Sensitivity analyses included using blood eosinophil cut-offs of 300 and 500 cells/µl, continuous blood EOS count, and excluding patients with a history of asthma [194]. Exploratory analyses included stratification by airflow obstruction, AECOPD frequency, smoking status, ICS-duration, and type of ICS. Specifically, continuous duration on ICS-containing medication at baseline was split into four categories: those on an ICS-containing medication for one to three months, four to six months, seven to nine months, and ten to twelve months before start of follow-up. This was determined through prescription dates and patients had to have an ICS-containing medication in the quartile prior to follow-up to be included in this exploratory analysis. In addition, type of ICS-containing medication included beclomethasone dipropionate, budesonide, or fluticasone-based medications. Methodology for sensitivity and exploratory analyses were similar to those used in the main analysis.

Sample size calculations were based on rate of FEV_1 change as described in chapter 5 and the following formulae by Schlesselman [195]:

$$N_1 = Z^2_{\alpha/2}\hat{\sigma}^2_p(r+1)/r\Delta^2$$

whereby,

$$\hat{\sigma}^2_p = \hat{\sigma}^2_\beta + 12(P\text{-}1)\hat{\sigma}^2/[D^2P(P+1)]$$

R was the ratio of the estimated sample sizes associated with each two exposure groups (ICS and non-ICS r=1.7). **Table 6.2** illustrates sample sizes needed to detect a change in FEV_1 in the total sample and the number of patients needed on ICS to compare the rates of FEV_1 decline in patients on ICS compared to those not on ICS. Bonferonni correction was used to account for multiple testing. Significance threshold after Bonferonni correction was considered as p<0.0125 (where α=0.05 and the number of tests=4).

Table 6.2: *Sample size needed to detect a difference in rates of change in FEV_1 between ICS and non-ICS groups of patients.*

Δ (ml/year)	Number of patients on ICS
2	13,016
3	5,785
4	3,254
5	2,082
7	1,063
10	521

6.3 Results

A total of 26,675 patients met all inclusion criteria and were included in this study. **Figure 6.2** illustrates the distribution of patients in each EOS/ICS group. Of those meeting the inclusion criteria, 16,601 (62%) patients were on ICS at baseline and 10,074 (28%) were not. Of those on ICS at baseline, 69% of patients had high blood eosinophils (≥150cells/µl) and of those not on ICS at baseline, 66% had high blood eosinophils. **Table 6.3** provides additional information on the type of ICS-containing medications and non-ICS containing medications prescribed at baseline. Of those on ICS-containing medications at baseline, 11,850 (71%) patients were prescribed ICS/LABA combinations, and 4,684 (28%) patients were prescribed ICS/LABA/LAMA combinations. The median length of follow-up in this study was 4.2 years (IQR:2.5-6.5), the median number of FEV_1 measurements during follow-up was 3 (IQR: 2-5), and the time between FEV_1 measurements did not differ between blood eosinophil and ICS group.

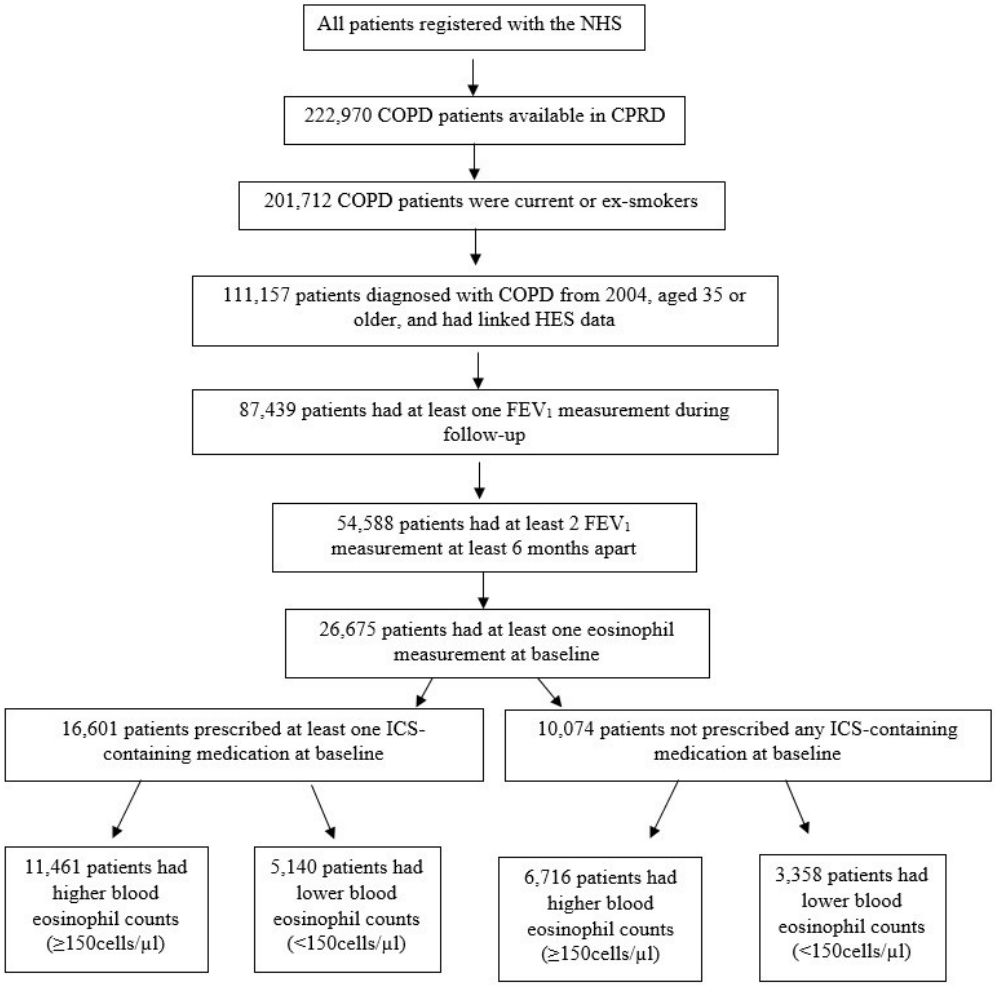


Figure 6.2: *Patients included in the study.*

***Table 6.3**: Medication prescribed in the year prior to the start of follow-up by baseline ICS use.*

COPD medications	ICS combinations at baseline (n=16,601)		No ICS at baseline (n=10,074)
	ICS (n=6,515 (40%))	ICS/LABA (n=10,086 (60%))	
LABA	1,764 (27)	n/a	658 (7)
LAMA	1,061 (16)	4,110 (41)	1,728 (17)
LABA and LAMA	288 (4)	286 (3)	154 (2)

Table 6.4 describes the study population and each EOS/ICS group in terms of baseline characteristics. Patients in the four subgroups were similar in terms of all baseline characteristics however, fewer women and fewer patients with a history of MI were in the low eosinophil groups and ex-smokers, patients with a history of asthma, severe patients (FEV_1<30% predicted), patients experiencing frequent AECOPD, and patients with higher mMRC dyspnoea were more likely to be on ICS at baseline.

Table 6.4: *Baseline characteristics for all included patients and by eos/ics group.*

Variables	All patients (N=26,675)	Blood eosinophil and ICS group			
		Higher blood eosinophils & ICS (N=11,461)	Higher blood eosinophils & no ICS (N=6,716)	Lower blood eosinophils & ICS (N=5,140)	Lower blood eosinophils & no ICS (N=3,358)
Female gender	12,379 (46.4)	5,206 (45.4)	2,574 (38.3)	2,920 (56.8)	1,679 (50.0)
Age (years)	69 (62-89)	69 (62-76)	69 (62-76)	70 (62-77)	69 (62-77)
Current smoking status	12,825 (48.1)	5,195 (45.3)	3,564 (53.1)	2,361 (45.9)	1,705 (50.8)
History of MI	2,415 (9.1)	1,105 (9.6)	687 (10.2)	380 (7.4)	243 (7.2)
History of stroke	401 (1.5)	165 (1.4)	104 (1.6)	76 (1.5)	56 (1.7)
History of heart failure	1,802 (6.8)	786 (6.9)	428 (6.4)	380 (7.4)	208 (6.2)
History of lung cancer	171 (0.6)	56 (0.5)	42 (0.6)	43 (0.8)	30 (0.9)
History of bronchiectasis	616 (2.3)	317 (2.8)	91 (1.4)	154 (3.0)	54 (1.6)
History of GORD	1,761 (6.6)	780 (6.8)	371 (5.5)	378 (7.4)	232 (6.9)
History of anxiety	2,133 (8.0)	919 (8.0)	453 (6.8)	466 (9.1)	295 (8.8)
History of depression	2,343 (8.8)	1,028 (9.0)	545 (8.1)	488 (9.5)	282 (8.4)
History of asthma	9,623 (36.1)	5,839 (51.0)	574 (8.6)	2,540 (49.4)	279 (8.3)
BMI (N=25,528)					
Underweight (BMI<18.5kg/m^2)	1,053 (4.1)	366 (3.3)	243 (3.8)	249 (5.1)	105 (6.1)
Normal (BMI 18.5-25kg/m^2)	8,130 (31.9)	3,248 (29.6)	2,023 (31.4)	1,649 (33.8)	1,210 (27.7)
Overweight (BMI 25-30kg/m^2)	8,718 (34.2)	3,814 (34.7)	2,293 (35.5)	1,585 (32.5)	1,026 (32.0)
Obese (BMI<305kg/m^2)	7,627 (29.9)	3,552 (32.4)	1,894 (29.4)	1,401 (28.7)	780 (24.3)
White blood cell count (cells/µl)	7.6 (6.4 – 9.1)	7.9 (6.6 – 9.3)	7.8 (6.6 – 9.2)	7.2 (6.0 – 8.7)	7.1 (5.9 – 8.5)
Neutrophil count (cells/µl) (N=26,585)	4.5 (3.6 – 5.7)	4.7 (3.7- 5.8)	4.5 (3.6 – 5.6)	4.5 (3.5 – 5.8)	4.3 (3.4 – 5.5)
Airflow obstruction (N=26,518)					
Mild *(≥80%* FEV_1 *predicted)*	5,550 (20.9)	2,185 (19.2)	1,556 (23.3)	957 (18.8)	852 (25.5)
Moderate *(50-80%* FEV_1 *predicted*)	13,834 (52.2)	5,640 (49.5)	3,879 (58.1)	2,469 (48.4)	1,846 (55.3)
Severe *(30-50%* FEV_1 *predicted)*	5,988 (22.6)	2,935 (25.8)	1,092 (16.3)	1,407 (27.6)	554 (16.6)
Very severe *(≤30%* FEV_1 *predicted)*	1,146 (4.3)	633 (5.6)	154 (2.3)	270 (5.3)	89 (2.7)
AECOPD frequency					
None	11,132(41.7)	4,009 (35.0)	3,508 (52.2)	1,835 (35.7)	1,780 (53.0)
1 moderate, 0 severe	6,462 (24.2)	2,733 (23.9)	1,663 (24.8)	1,178 (22.9)	887 (26.4)
2 moderate, 0 severe	3,530 (13.2)	1,680 (14.7)	754 (11.2)	765 (14.9)	331 (9.9)
≥3 moderate, 0 severe	4,226 (15.8)	2,317 (20.2)	635 (9.5)	999 (19.4)	275 (8.2)
1 severe, any moderate	1,084 (4.1)	583 (5.1)	135 (2.0)	292 (5.7)	74 (2.2)
≥2 severe, any moderate	242 (0.9)	139 (1.2)	21 (0.3)	71 (1.4)	11 (0.3)
mMRC dyspnoea score (N=18,090)					
0	3,749 (20.7)	1,313 (17.6)	1,287 (26.2)	531 (15.8)	618 (26.2)
1	7,457 (41.2)	2,911 (39.0)	2,177 (44.3)	1,315 (39.2)	1,054 (44.7)
2	4,435 (24.5)	2,030 (27.2)	986 (20.1)	945 (28.2)	474 (20.1)
3	2,066 (11.4)	998 (13.4)	396 (8.1)	493 (14.7)	179 (7.6)
4	383 (2.1)	215 (2.9)	66 (1.3)	68 (2.0)	34 1.4)

6.3.1 Rate of change in FEV_1 with prevalent ICS use

The mean adjusted rate of change of FEV_1 in those on ICS-containing medication was -13.3 ml/year (95% CI -22.3 to -4.4) and -21.4 ml/year (95% CI -25.4 to -17.3) in patients not on an ICS-containing medication (p=0.001). Reference classes include women, ex-smokers, no comorbidities, mild airflow obstruction, no AECOPD in first year of follow-up, mMRC score of 0, and normal BMI, mean wbc (7,700 cells/µl), and mean neutrophil count (4,600 cells/µl).

Table 6.5 illustrates the rates of change in FEV_1 for each EOS/ICS group. Irrespective of blood eosinophil level, patients on an ICS-containing medication have slower rates of change in FEV_1 compared to those not on an ICS-containing medication (adjusted mean rates -14.4 ml/year and -11.0 ml/year in ICS groups compared to -21.1 ml/year and -22.0 ml/year in non-ICS groups).

***Table 6.5**: Rate of change in FEV_1 by EOS/ICS group in prevalent ICS cohort.*

	Crude rate of FEV_1 change ml/year (95% CI) (N=26,675)	P value for significant differences between rates		Adjusted* rate of FEV_1 change ml/year (95% CI) (N=17,557)	P value for differences between rates	
Higher blood eosinophil level & ICS (crude n=11,461, adjusted n=7,255)	-16.8 (-18.9 to -14.8)	1 (ref)		-14.4 (-17.6 to -11.1)	1 (ref)	
Higher blood eosinophil level & no ICS (crude n=6,716, adjusted n=4,783)	-24.3 (-30.5 to -18.2)	<0.0001		-21.1 (-30.2 to -11.9)	0.026	
Lower blood eosinophil level & ICS (crude n=5,140, adjusted n=3,238)	-15.5 (-21.2 to -9.7)	0.479	1 (ref)	-11.0 (-20.1 to -1.9)	0.261	1 (ref)
Lower blood eosinophil level & no ICS (crude n=3,358, adjusted n=2,281)	-28.4 (-35.8 to -21.0)	<0.0001	<0.0001	-22.0 (-33.1 to -10.9)	0.058	0.013

***Note**: *adjusted for: gender, age, smoking status, MI, stroke, HF, lung cancer, bronchiectasis, GORD, anxiety, depression, BMI, WBC count, neutrophil count, airflow obstruction, AECOPD frequency, and mMRC dyspnoea.*

6.3.2 Rate of change in FEV_1 with incident ICS use

The incident cohort included patients who were not on an ICS-containing medication at baseline. A total of 12,469 patients who were included in this study population of which 3,417 patients newly initiated ICS-containing medication (LABA/ICS 2,604 (76%); ICS 813 (24%)). It is important to note that whilst 10,074 patients were classed as non-ICS users in the prevalent cohort, a total of 12,469 were included in the incident cohort. This is because the prevalent cohort included non-ICS users censored at their first ICS prescription during follow-up and patients were still required to have at least two FEV_1 measurements at least 6 months apart. This meant that patients who were censored at time of first prescription without 2 FEV_1 measurements 6 months apart within this follow-up were not included in the prevalent cohort. However, these patients could have been included in the incident cohort if their first ICS prescription was in the first year of follow-up. Similar to the prevalent patients not on ICS-containing medications at baseline in the incident cohort were censored at their first ICS prescription during follow-up. In addition, patients prescribed ICS only were on other maintenance therapy including LAMA, SABA, and SAMA. In this cohort, the median number of FEV_1 measurements during follow-up was 4 (IQR:3-6).

The mean adjusted rate of change in FEV_1 in patients on newly initiating ICS-containing medication was +3.7 ml/year and -21.6 ml/year in patients not on an ICS-containing medication ($p<0.0001$). Reference classes include women, ex-smokers, no comorbidities, mild airflow obstruction, no AECOPD in first year of follow-up, mMRC score of 0, normal BMI, mean wbc (8,300 cells/µl), and mean neutrophil count (4,800 cells/µl).

A significant difference was seen between patients with higher blood eosinophils on ICS-containing medication and all other groups (**table 6.6**). Whilst FEV_1 declined slower in patients with lower eosinophils on an ICS-containing medication, there was no significant difference between patients with ICS and lower blood eosinophils and those with no ICS-containing medication.

***Table 6.6**: Rates of change in FEV_1 by EOS/ICS group in incident ICS cohort.*

	Crude rate of FEV_1 change ml/year (95% CI) (N=12,469)	P value for significant differences between rates		Adjusted* rate of FEV_1 change ml/year (95% CI) (N=6,402)	P value for differences between rates	
High blood eosinophil level & ICS (crude n=2,336, adjusted n=315)	-10.7 (-15.5 to -5.9)	1 (ref)		12.1 (-3.5 to 27.0)	1 (ref)	
High blood eosinophil level & no ICS (crude n=5,984, adjusted n=4,006)	-25.9 (-36.9 to -15.0)	<0.0001		-21.7 (-53.6 to 10.3)	<0.0001	
Low blood eosinophil level & ICS (crude n=1,081, adjusted n=148)	-15.5 (-29.0 to -1.9)	0.284	1 (ref)	-16.2 (-59.6 to 27.1)	0.046	1 (ref)
Low blood eosinophil level & no ICS (crude n=3,068, adjusted n=1,933)	-29.7 (-41.6 to -17.9)	<0.0001	0.002	-21.5 (-54.4 to 11.3)	<0.0001	0.668

***Note:** *adjusted for: gender, age, smoking status, history of MI, history of stroke, history of HF, history of lung cancer, history of bronchiectasis, history of GORD, history of anxiety, history of depression, BMI, WBC count, neutrophil count, airflow obstruction, AECOPD frequency, and MRC dyspnoea.*

6.3.3 Exploratory analyses results

Rate of change of FEV_1 between each EOS/ICS group did not differ by baseline airflow obstruction (FEV_1 percent predicted) (**table 6.7**). When stratified by AEOCPD frequency, rate of change of FEV_1 was slower in ICS-containing groups compared to non-ICS-containing medication groups however, no significant difference was seen **(table 6.8).** In terms of smoking status, rate of change of FEV_1 was significantly slower in ex-smokers with high blood eosinophils regardless of ICS use. Whilst a similar trend was seen in lower blood eosinophil groups, no significant difference was seen between smokers and ex-smokers (**table 6.9**).

Table 6.7: *Rates of change of FEV_1 by EOS/ICS group, stratified by COPD severity.*

Airflow obstruction (percent FEV_1)	EOS/ICS	Adjusted* rate of FEV_1 change ml/year (95% CI)	P value for differences between rates	
Mild (≥80% FEV_1 predicted)	Higher blood eosinophil level & ICS (n=1,505)	-76.2 (-85.4 to -71.0)	1 (ref)	
	Higher blood eosinophil level & no ICS (n=1,165)	-77.9 (-97.3 to -58.5)	0.956	
	Lower blood eosinophil level & ICS (n=682)	-75.2 (-95.5 to -55.0)	0.659	1 (ref)
	Lower blood eosinophil level & no ICS (n=604)	-73.5 (-96.1 to -50.8)	0.549	0.842
Moderate (50-80% FEV_1 predicted)	Higher blood eosinophil level & ICS (n=3,672)	-9.8 (-13.7 to -5.9)	1 (ref)	
	Higher blood eosinophil level & no ICS (n=2,803)	-12.6 (-23.3 to -2.0)	0.409	
	Lower blood eosinophil level & ICS (n=1,607)	-7.5 (-18.5 to 3.5)	0.522	1 (ref)
	Lower blood eosinophil level & no ICS (n=1,264)	-12.5 (-25.2 to 0.4)	0.550	0.323
Severe (30-50% FEV_1 predicted)	Higher blood eosinophil level & ICS (n=1,752)	13.5 (6.2 to 20.9)	1 (ref)	
	Higher blood eosinophil level & no ICS (n=721)	30.8 (6.6 to 55.0)	0.044	
	Lower blood eosinophil level & ICS (n=813)	21.1 (0.5 to 41.7)	0.263	1 (ref)
	Lower blood eosinophil level & no ICS (n=366)	27.9 (-3.0 to 58.8)	0.233	0.594
Very Severe (<30% FEV_1 predicted)	Higher blood eosinophil level & ICS (n=326)	43.3 (23.0 to 63.58)	1 (ref)	
	Higher blood eosinophil level & no ICS (n=94)	76.3 (-4.2 to 156.8)	0.283	
	Lower blood eosinophil level & ICS (n=136)	46.7 (-12.9 to 106.3)	0.865	1 (ref)
	Lower blood eosinophil level & no ICS (n=47)	104.8 (-2.1 to 211.7)	0.164	0.209

Note*: *adjusted for: gender, age, smoking status, history of MI, history of stroke, history of HF, history of lung cancer, history of bronchiectasis, history of GORD, history of anxiety, history of depression, BMI, WBC count, neutrophil count, airflow obstruction, and mMRC dyspnoea.*

***Table 6.8**: Rates of change of FEV_1 by EOS/ICS group, stratified by AECOPD frequency.*

AECOPD frequency	EOS/ICS group	Adjusted* rate of FEV_1 change ml/year (95% CI)	P value for differences between rates	
0	Higher blood eosinophil level & ICS (n=2,609)	-12.8 (-18.3 to -7.4)	1 (ref)	
	Higher blood eosinophil level & no ICS (n=2,502)	-19.7 (-33.9 to -5.6)	0.120	
	Lower blood eosinophil level & ICS (n=1,176)	-9.2 (-24.5 to 6.2)	0.467	1 (ref)
	Lower blood eosinophil level & no ICS (n=1,221)	-20.3 (-36.8 to -3.8)	0.184	0.084
1 moderate, 0 severe	Higher blood eosinophil level & ICS (n=1,702)	-15.0 (-21.6 to -8.5)	1 (ref)	
	Higher blood eosinophil level & no ICS (n=1,195)	-20.8 (-39.1 to -2.6)	0.334	
	Lower blood eosinophil level & ICS (n=740)	-3.9 (-21.9 to 14.6)	0.069	1 (ref)
	Lower blood eosinophil level & no ICS (n=597)	-21.5 (-43.5 to 0.5)	0.411	0.045
2 moderate, 0 severe	Higher blood eosinophil level & ICS (n=1,049)	-16.4 (-24.0 to -8.7)	1 (ref)	
	Higher blood eosinophil level & no ICS (n=534)	-24.9 (-48.5 to -81.4)	0.288	
	Lower blood eosinophil level & ICS (n=492)	-19.8 (-41.2 to -1.7)	0.627	1 (ref)
	Lower blood eosinophil level & no ICS (n=237)	-25.3 (-55.3 to 4.7)	0.431	0.648
3+ moderate, 0 severe	Higher blood eosinophil level & ICS (n=1,460)	-14.9 (-22.1 to -7.7)	Ref	
	Higher blood eosinophil level & no ICS (n=452)	-25.0 (-51.0 to 1.1)	0.295	
	Lower blood eosinophil level & ICS (n=621)	-14.5 (-35.0 to 5.9)	0.954	Ref

	Lower blood eosinophil level & no ICS (n=177)	-29.5 (-68.3 to 9.3)	0.364	0.368
1 severe, any moderate	Higher blood eosinophil level & ICS (n=355)	-8.0 (-25.2 to 9.1)	Ref	
	Higher blood eosinophil level & no ICS (n=87)	-12.0 (-85.4 to 61.3)	0.888	
	Lower blood eosinophil level & ICS (n=167)	-15.0 (-62.9 to 33.0)	0.658	ref
	Lower blood eosinophil level & no ICS (n=43)	-43.5 (-131.8 to 44.8)	0.328	0.488
2+ severe, any moderate	Higher blood eosinophil level & ICS (n=80)	-67.7 (-113.8 to -21.7)	Ref	
	Higher blood eosinophil level & no ICS (n=13)	62.0 (-259 to 383.9)	0.356	
	Lower blood eosinophil level & ICS (n=42)	-17.1 (-135.9 to 101.7)	0.172	Ref
	Lower blood eosinophil level & no ICS (n=6)	-53.0 (-434.1 to 328.0)	0.931	0.834

Note: **adjusted for: gender, age, smoking status, history of MI, history of stroke, history of HF, history of lung cancer, history of bronchiectasis, history of GORD, history of anxiety, history of depression, BMI, WBC count, neutrophil count, airflow obstruction, and mMRC dyspnoea.*

***Table 6.9**: Rates of change of FEV_1 by EOS/ICS group, stratified by smoking status.*

EOS/ICS group	Smoking status	Adjusted* rate of FEV_1 change ml/year (95% CI)	P value for difference between rates
Higher blood eosinophils & ICS	Smokers (n=3,344)	-19.4 (-30.4 to -8.4)	1 (ref)
	Ex-smokers (n=3,911)	-10.3 (-14.7 to -5.8)	0.007
Higher blood eosinophils & no ICS	Smokers (n=2,537)	-27.9 (-44.5 to -11.2)	1 (ref)
	Ex-smokers (n=2,246)	-13.9 (-20.8 to -6.9)	0.004
Lower blood eosinophils & ICS	Smokers (n=1,502)	-15.1 (-31.6 to 1.3)	1 (ref)
	Ex-smokers (n=1,736)	-8.5 (-15.1 to -1.8)	0.183
Lower blood eosinophils & no ICS	Smokers (n=1,155)	-24.7 (-48.1 to -1.3)	1 (ref)
	Ex-smokers (n=1,126)	-19.1 (-28.8 to -9.4)	0.425

***Note:** *adjusted for: gender, age, history of MI, history of stroke, history of HF, history of lung cancer, history of bronchiectasis, history of GORD, history of anxiety, history of depression, BMI, WBC count, neutrophil count, airflow obstruction, AECOPD frequency, and mMRC dyspnoea.*

Those on ICS-containing medication continuously for 1-3 months prior to start of follow-up had a slower rate of change of FEV_1 (-5.6 ml/year) compared to those on ICS continuously for 4-6 months (-15.8 ml/year) and a significantly slower rate compared to 10-12 months (-18.2 ml/year) in the complete study population (test for trend p=0.012). Whilst there was a similar pattern in patients with low and high eosinophils separately, the trend was non-significant (**Table 6.10**). In terms of drug type, no significant difference in rate of change of FEV_1 was seen between patients on any ICS-containing medication (**table 6.11**).

***Table 6.10**: Rates of change of FEV_1, stratified by ICS duration and EOS level.*

Blood eosinophil level	Duration on ICS-containing medication at baseline	Adjusted* rate of FEV_1 change ml/year (95% CI)	P value	P value for test for trend
Higher & lower blood eosinophils (all)	1-3 months (n=3,312)	-5.6 (-10.6 to -0.6)	1 (ref)	0.012
	4-6 months (n=1,077)	-15.8 (-30.7 to -0.9	0.044	
	7-9 months (n=736)	-8.7 (-25.4 to 8.0)	0.597	
	10-12 months (n=4,456)	-18.2 (-29.7 to -6.6)	<0.0001	
Lower blood eosinophils	1-3 months (n=965)	-0.3 (-9.2 to 8.87	1 (ref)	0.074
	4-6 months (n=332)	-20.6 (-47.5 to 6.3)	0.027	
	7-9 months (n=232)	-10.6 (-39.8 to 18.6)	0.318	
	10-12 months (n=1,373)	-16.6 (-37.3 to 4.1)	0.007	
Higher blood eosinophils	1-3 months (n=2,167)	-8.0 (-14.0 to -2.0)	1 (ref)	0.062
	4-6 months (n=745)	-13.8 (-31.7 to 4.1)	0.340	
	7-9 months (n=504)	-8.0 (-28.3 to 12.3)	0.998	
	10-12 months (n=3,083)	-19.1 (-33.0 to -5.2)	0.006	

***Note:** *adjusted for: gender, age, smoking history, history of MI, history of stroke, history of HF, history of lung cancer, history of bronchiectasis, history of GORD, history of anxiety, history of depression, BMI, WBC count, neutrophil count, AECOPD frequency, airflow obstruction, mMRC dyspnoea, and blood eosinophil level (only in analysis including both blood eosinophil levels).*

Table 6.11: *Rates of change of FEV_1, stratified by type of ICS-containing medication and EOS level.*

Blood eosinophil level	Type of ICS-containing medication	Adjusted* rate of FEV_1 change ml/year (95% CI)	P value for differences between rates	
Higher & lower blood eosinophils (all)	Beclometasone diproprionate (n=3,161)	-16.2 (-20.9 to -11.4)	1 (ref)	
	Budesonide (n=2,017)	-13.7 (-26.5 to -1.0)	0.546	0.574
	Fluticasone (n=5,314)	-11.6 (-22.5 to -0.7)	0.148	1 (ref)
Lower blood eosinophils	Beclometasone diproprionate (n=989)	-16.4 (-24.8 to -8.0)	1 (ref)	
	Budesonide (n=665)	-5.3 (-27.7 to 17.0)	0.119	0.430
	Fluticasone (n=1,584)	-10.6 (-30.1 to 8.8)	0.306	1 (ref)
Higher blood eosinophils	Beclometasone diproprionate (n=2,172)	-16.3 (-22.1 to -10.6)	1 (ref)	
	Budesonide (n=1,352)	-17.6 (-33.0 to -2.1)	0.807	0.236
	Fluticasone (n=3,730)	-12.1 (-25.2 to 1.1)	0.257	1 (ref)

Note: **adjusted for: gender, age, smoking history, history of MI, history of stroke, history of HF, history of lung cancer, history of bronchiectasis, history of GORD, history of anxiety, history of depression, BMI, WBC count, neutrophil count, AECOPD frequency, airflow obstruction, mMRC dyspnoea and blood eosinophil level (only in analysis including both blood eosinophil levels).*

6.3.4 Sensitivity analyses results

When using blood eosinophil cut offs of 300 and 500cells/µl, patients with low blood eosinophils on an ICS-containing medication had significantly slower rates of change of FEV_1 compared to those not on an ICS-containing medication (**table 6.12**). However, patient numbers were low in these sub-groups and there was inadequate statistical power for a reliable analysis. Furthermore, when continuous eosinophil count was modelled, there was no association with change in FEV_1 in patients on or not on ICS-containing medications at baseline (**table 6.13**).

When patients with a history of asthma were excluded, 17,052 patients remained. The decline in FEV_1 across eosinophil/ICS groups varied from -12.3 ml/year to -21.6 ml/year. The pattern in differences between eosinophil/ICS groups was similar to that in the main analysis, but no significant differences were seen (**table 6.14**).

Table 6.12: *Rates of change of FEV_1 by EOS/ICS group using EOS cut-offs of 300cells/ul and 500 cells/ul.*

Eosinophil cut-off	EOS/ICS	Adjusted* rate of FEV_1 ml/year (95% CI) (N=17,557)	P value for differences between rates	
300cells/µl	Higher blood eosinophil level & ICS (n=3,465)	-12.8 (-17.5 to -8.1)	1 (ref)	
	Higher blood eosinophil level & no ICS (n= 2,106)	-20.3 (-33.9 to -6.7)	0.097	
	Lower blood eosinophil level & ICS (n=7,028)	-13.6 (-24.1 to -3.2)	0.763	1 (ref)
	Lower blood eosinophil level & no ICS (n=4,958)	-21.8 (-33.3 to -10.4)	0.008	0.006
500cells/µl	Higher blood eosinophil level & ICS (n=916)	-12.0 (-21.3 to -2.8)	1 (ref)	
	Higher blood eosinophil level & no ICS (n=498)	-17.8 (-45.2 to 9.6)	0.531	
	Lower blood eosinophil level & ICS (n=9,577)	-13.4 (-32.4 to 5.4)	0.767	1 (ref)
	Lower blood eosinophil level & no ICS (n=6,566)	-21.6 (-41.6 to -2.2)	0.064	0.002

Note: **adjusted for: gender, age, smoking status, history of MI, history of stroke, history of HF, history of lung cancer, history of bronchiectasis, history of GORD, history of anxiety, history of depression, BMI, WBC count, neutrophil count, airflow obstruction, AECOPD frequency, and mMRC dyspnoea.*

Table 6.13*: Rates of change of FEV_1 per unit increase in EOS count.*

ICS use at baseline	Change in crude rate of FEV_1 ml/year (95% CI) per 1 unit increase in eosinophil count	P value	Change in adjusted* rate of FEV_1 ml/year (95% CI) per 1 unit increase in eosinophil count	P value
ICS (Crude n=16,601, adjusted n=10,493)	0.0008 (-0.008 to 0.01)	0.857	-0.01 (-0.03 to 0.003)	0.124
No ICS (Crude n=10,074, adjusted n=7,064)	-0.004 (-0.02 to 0.01)	0.684	-0.001 (-0.03 to 0.02)	0.932

Note: **adjusted for: gender, age, smoking status, history of MI, history of stroke, history of HF, history of lung cancer, history of bronchiectasis, history of GORD, history of anxiety, history of depression, BMI, WBC count, neutrophil count, airflow obstruction, AECOPD frequency, and mMRC dyspnoea.*

Table 6.14: *Rates of change of FEV_1 by EOS/ICS group excluding patients with a history of asthma.*

	Crude rate of FEV_1 change ml/year (95% CI) (N=17,052)	P value for significant differences between rates		Adjusted* rate of FEV_1 change ml/year (95% CI) (N=11,708)	P value for significant differences between rates	
Higher blood eosinophil level & ICS (crude n=5,535, adjusted n=3,667)	-20.1 (-23.2 to -17.0)	1 (ref)		-20.6 (-25.4 to -15.8)	1 (ref)	
Higher blood eosinophil level & no ICS (crude n=5,940, adjusted n=4,279)	-24.0 (-31.9 to -16.0)	0.121		-21.6 (-33.5 to -15.8)	0.773	
Lower blood eosinophil level & ICS (crude n=2,605, adjusted n=1,704)	-16.8 (-25.4 to -8.1)	0.237	1 (ref)	-13.9 (-27.3 to -0.5)	0.128	1 (ref)
Lower blood eosinophil level & no ICS (crude n=2,972, adjusted n=2,058)	-28.6 (-37.9 to -19.4)	0.007	0.001	-21.9 (-35.8 to -8.1)	0.766	0.132

Note: **adjusted for: gender, age, smoking status, history of MI, history of stroke, history of HF, history of lung cancer, history of bronchiectasis, history of GORD, history of anxiety, history of depression, BMI, WBC count, neutrophil count, airflow obstruction, AECOPD frequency, and mMRC dyspnoea.*

6.4 Discussion

6.4.1 Main findings

This was the first observational study to investigate the relationship between ICS-containing medication and blood eosinophils on the rate of change of FEV_1 over an extended period. COPD patients of different degrees of airflow limitation were included, who may not have met inclusion criteria for some of the randomised clinical trials, in which FEV_1 decline has been previously investigated. Overall, the rate of FEV_1 decline was slower in patients on prevalent ICS-containing medication compared to patients not on ICS, regardless of blood eosinophil level. However, the difference in the decline was not statistically significant after Bonferroni correction. In addition, patients with higher blood eosinophils who initiated ICS-containing treatment had an increase in change in FEV_1 compared to a decline in the change in FEV_1 seen in patients in the other three groups. These results suggest that whilst receiving an ICS-containing medication slows down the rate of FEV_1 decline in COPD patients (by approximately 6-10ml/year), new ICS-users with higher blood eosinophils may benefit more when first started on ICS than those with lower blood eosinophils. Overall, however, these results suggest prevalent ICS-containing medication use in COPD patients is associated with slower rate of FEV_1 decline irrespective of eosinophil level.

Interestingly, the exploratory analysis that investigated the effect of time on baseline ICS also highlighted that patients who had not been on ICS containing medications for long prior to start of follow-up had a slower rate of FEV_1 decline compared to patients on ICS containing medication for more than three months to up to one year or more. Whilst the trend in time on ICS was not statistically significant (only border line not significant) it is possible that if groups of patients were broken down further to include a category for being on ICS for more than one year, a clearer difference could have been seen. This analysis echoes the finding that incident ICS users had a slower mean rate of FEV_1 decline compared to that of prevalent ICS users.

6.4.2 Previous literature

Few observational studies have investigated the relationship between rate of change of FEV_1, ICS-containing medication, and blood eosinophils. In contrast to the main finding, a study in non-asthma COPD patients from the Korean COPD Subtype Study (KOCOSS) cohort found no difference in rate of decline in FEV_1 between those with higher or lower blood eosinophils (using 200cells/µl and 600cells/µl cut-off), whether on ICS/LABA, or not. Findings from KOCOSS showed that FEV_1 increased in patients with higher eosinophils, regardless of being on an ICS or not and in those with lower eosinophils (≤200cells/µl) FEV_1 declined faster in ICS users [190]. Furthermore, in contrast to our main finding, a further study on blood eosinophils and FEV_1 over time found that higher blood eosinophils >400cells/µl were associated with greater decline in FEV_1 in a relatively small general population of people living in New Zealand (the Dunedin Multidisciplinary Health and Development Study) [196]. The differences between previous studies and this

study could be explained by differences in study populations and definitions of study exposures. For example, the KOCOSS study included fewer COPD patients and identified patients from hospital whereas this study included more patients primarily identified at the GP and the Dunedin Multidisciplinary Health and Development Study included people from the general population rather than a COPD population.

In addition, in terms of the incident ICS-containing cohort, a post-hoc analysis of the ISOLDE trial found that COPD patients with higher blood eosinophil levels greater than 2% of their total WBC count who were on an ICS had lower rates of FEV_1 decline compared to those on a placebo. No difference was seen between patients with lower blood eosinophil counts on an ICS or a placebo [40]. However, a post-hoc analysis of two RCTs found that there was a numerically lower mean improvement in trough FEV_1 over one year in patients treated with ICS/LABA with lower eosinophils, compared to those with higher eosinophils, but the confidence intervals between the two groups overlapped widely [188]. Those studies, like the majority of RCTs, included a wash-out period before initiating patients on randomised medication and are therefore similar to our incident cohort design. This explains why the findings from the incident ICS cohort were similar to previous RCT findings as they had a similar study design.

One explanation as to why changes in FEV_1 were much slower in patients initiating ICS than those on prevalent ICS might be that their adherence to their new treatment was better. It is possible that patients were more compliant with newly prescribed medications or more aware of their inhaler technique. A recent study found that in only 33.6 % of COPD patients showed complete adherence to their treatments (defined as ≥ 80% of prescribed inhalers dispensed) and adherence was higher in more severe patients [197]. Other studies have also found that in COPD patients, adherence to ICS is low at 20-33% [198, 199]. On the other hand, Mueller and colleagues found that adherence to ICS in a population of German COPD patients was higher at 78% [200]. This might explain differences seen between the incident and prevalent ICS cohorts in this study as patients in the incident cohort might be adhering to their ICS treatments more as they start their treatments. In addition, one study found that risk of discontinuation of LABA was higher in COPD patients also taking ICS and it is possible that the anti-inflammatory effect of ICS is greater in the presence of beta agonists by increasing the number of beta-receptors to improve bronchodilation from LABA [120, 121, 201]. Therefore, the discontinuation of LABA may also have influenced the effectiveness of ICS and consequently rate of FEV_1 decline.

6.4.3 Limitations

Despite using a highly sensitive algorithm to identify patients with COPD, misdiagnosis of asthma as COPD and vice versa could not be excluded, notably in patients over the age of forty [196, 202]. Based on findings from previous work on misclassification of asthma and COPD, patients with a history of asthma were excluded in a sensitivity analysis. Specifically, those with an asthma diagnosis more than 2 years prior to study start were excluded following previous work on COPD and asthma diagnosis [194]. After excluding

patients with a history of asthma no significant differences were seen between groups in the rate of decline in FEV_1. This is probably due to a smaller sample size and thus underpowered analysis rather than asthma driving the association between ICS-containing medication and rate of change of FEV_1, given we adjusted for history of asthma in all other analyses.

Only COPD patients whose general practices contribute to CPRD were included in my cohort and patients may not be representative of the true UK population of people with COPD. In addition, included patients had to have at least one blood eosinophil measurement at baseline, which introduces selection bias. Blood tests for COPD patients may have been performed due to reasons other than COPD, such as infections. To obtain a patient's stable blood eosinophil measurement blood eosinophil counts that were within four weeks of an AECOPD, or prescribed oral corticosteroid were not included and research suggests blood eosinophils are stable over relatively short periods of time [144].

In addition, missing data were present for the BMI, mMRC, neutrophil count, and airflow obstruction. Whilst complete case analysis was performed in adjusted models, previous work suggests that patients with complete data on specific variables could have a different rate of lung function decline compared to those without complete data (see chapter 4) and should be noted. This is likely to occur is baseline data are not missing completely at random and if the probability of being missing is dependent on the outcome. Specifically, BMI and mMRC had high proportions of missing data. Findings from the incident cohort found that the unadjusted estimate for patients with high blood eosinophils on ICS different drastically from the adjusted estimate for the same group. This might be due to a difference in the type of patients included in the fully adjusted complete case analysis population compared to the total population used in the unadjusted analysis. Future work should investigate the use of complete case analysis and methodology to overcome biases that might occur due to missing baseline data.

Similarly, patients with low baseline FEV_1 % predicted had mean rates of change in FEV_1 that increased compared to patients with higher FEV_1 % predicted, which was also seen in chapter 5. This might be due to poorly recorded spirometry or survival bias in patients with severe disease. Lastly, this study is an observational study so we cannot infer causation. It is also important to note that residual confounding may still exist due to the observational nature such as ICS dosage.

6.5 Conclusion

In conclusion, in a large primary care cohort of COPD patients, FEV_1 decline was slower in prevalent ICS-containing medication patients, regardless of blood eosinophil level. Incident ICS-containing medication in patients with higher blood eosinophil levels showed more benefit more compared to patients with lower blood eosinophils however, over time this difference was lost. Further long-term observational studies on the use of ICS-containing medications stratified by eosinophil levels are needed and research into further

possible biomarkers and patient characteristics may help define a subgroup of COPD patients who benefit from ICS-containing medications more than others in terms of FEV_1 decline.

Chapter 7
ICS withdrawal from triple therapy and rate of FEV_1 decline

Findings from previous chapters have found that the rate of FEV_1 decline in ICS and non-ICS users is similar over the long-term. Recent ERS guidelines state that ICS withdrawal should be considered in specific COPD patients on triple therapy however, the relationship between ICS withdrawal and rate of FEV_1 decline has not been investigated in a population of generalisable COPD patients seen in everyday clinical practice.

7.1 Introduction

ICS are commonly prescribed in patients with COPD along with LABA to reduce future risk of AECOPD and to improve lung function. Following NICE and GOLD guidelines, triple therapy (ICS/LABA/LAMA) should be prescribed to COPD patients who have a history of frequent or severe AECOPDs requiring hospitalisation, who have blood eosinophils ≥300cells/µl, or who have a history of asthma [21, 203]. Despite this, ICS has been associated with an increased risk of pneumonia and it is important to identify subpopulations of COPD patients who benefit from continued use [26, 204]. Recent guidelines state that ICS withdrawal should be considered in patients on triple therapy who do not have a history of frequent AECOPD in the previous 12 months and have blood eosinophils less than 300cells/µl [203]. This guideline is largely backed up by results from the WISDOM trial.

The WISDOM trial is multicentered, double blind RCT that compared outcomes between COPD patients on triple therapy (18µg tiotropium, 50µg salmeterol, 500µg fluticasone propionate) and COPD patients who started on triple therapy but withdrew from the ICS component (fluticasone propionate) in a stepwise fashion over 18 weeks. All patients were on triple therapy for 6 weeks prior to randomisation of the intervention, ICS withdrawal. Patients were followed up for a year and outcomes including first AECOPD event and lung function were assessed [161]. Overall, the trial found that regardless of ICS withdrawal, COPD patients were at a similar risk of AECOPD (hazard ratio (HR) for first moderate or severe AECOPD: 1.06 (95% CI 0.94 – 1.19). On the other hand, the trial found that patients with withdrew from ICS had a larger decline in pre-bronchodilator FEV_1 compared to patients who remained on triple therapy with a 43ml difference in FEV_1 after one year of follow-up (approximate adjusted mean rates were -20ml/year in patients who remained on triple therapy and -60ml/year in patients who withdrew from ICS).

One main criticism of the trial was that a select group of COPD patients were included in the trial. The WISDOM trial inclusion criteria required patients to be over the age of 40, be current smokers (≥10 pack years) or ex-smokers, have a diagnosis of severe or very severe COPD based on an FEV_1<50% predicted and FEV_1/FVC<70%, and have at least one AECOPD in the year prior to randomisation. In addition to that, the trial exclusion criteria required patients to not have a current diagnosis of asthma, to not have a history of bronchiectasis, to not have a record of an MI or cardiac arrythmia 3 months prior to randomisation, to not have had heart failure one year prior to randomisation, and to not have had an AECOPD 6 weeks prior to randomization [161]. While randomised controlled trials (RCT) will continue to be the gold standard for assessing the efficacy of medical interventions, they do not typically represent patients seen day to day in clinical practice. Specifically, the WISDOM trial excluded patients with mild COPD and patients with specific comorbidities. This means that a large proportion

of patients seen in everyday clinical practice would not have been included in this trial. Findings from RCTs, such as the WISDOM trial, should therefore be investigated in more generalisable populations to fully understand the relationship between ICS withdrawal and rate of FEV_1 decline.

This study aimed to determine if ICS withdrawal led to faster rates of decline, as observed in the WISDOM trial, in three different types of COPD populations using routinely collected healthcare record data. Firstly, the relationship between ICS withdrawal and rate of FEV_1 decline was investigated in a population of COPD patients who would have met the inclusion and exclusion criteria for the WISDOM trial and who should be similar to those included in the WISDOM trial. Secondly, in a general population of COPD patients who are more generalisable to the wider population of COPD patients seen in clinical practice and thirdly, in COPD patients who have comorbidities that would have meant they were excluded from WISDOM. These patients are important as they are often excluded from trials despite being a common population seen in clinical practice [205, 206].

7.2 Methods

7.2.1 Data sources and study populations

CPRD-Aurum and HES were both used in this study. All patients were included if they had been diagnosed with COPD, were current or ex-smokers, had at least two FEV_1 measurements at least 6 months apart, and had been on triple therapy (ICS/LABA/LAMA) for at least 4 months. A four-month period was chosen to better identify patients on triple therapy in clinical practice compared to a six-week run in that the WISDOM trial used. A clinical diagnosis of COPD was used following a validated algorithm in CPRD [140]. Following this basic inclusion criteria, three different populations were identified:

1) A population of COPD patients who would have met inclusion and exclusion criteria for the WISDOM trial.

2) A general primary care COPD population.

3) A specific population of COPD patients who would have been excluded from the WISDOM trial due to the presence of comorbidities.

Figure 7.1 illustrates how these populations are related in more detail. Specifically:

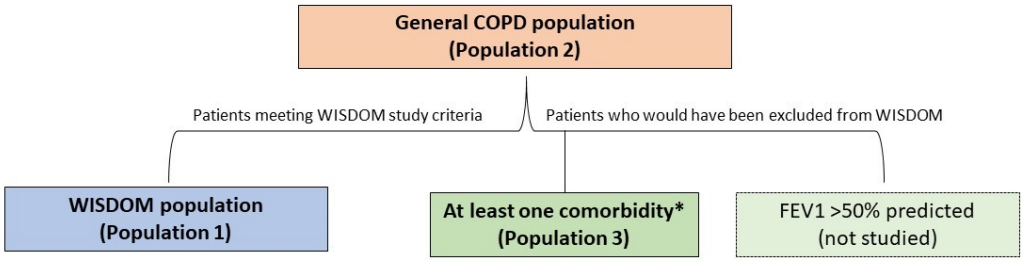
Cohort 1 included COPD patients who would have met the WISDOM inclusion and exclusion criteria. Specifically, patients were included if they were aged 40 or older, had severe or very severe airflow obstruction (FEV_1 percent predicted <50%), had no AECOPD events 6 weeks prior to start of follow-up but did have an AECOPD event within one year of start of follow-up (excluding the 6 week period), no current asthma diagnosis (defined as an asthma diagnosis in the 2 years prior to the start of follow-up), no history of arrhythmia (3 months prior to start of follow-up) and bronchiectasis, no history of MI (3 months prior to the start of follow-up), and no history of hospitalised heart failure (in the 1 year prior to start of follow-up).

Cohort 2 included all COPD patients who met the basic study inclusion criteria and were aged over 35 years old following the validated definition of COPD.

Cohort 3 included a specific population of COPD patients with comorbidities who would have met part of the exclusion criteria for WISDOM and would have been excluded. Comorbidities are common in people with COPD and it is important to understand the relationship between ICS withdrawal and lung function decline in these patients who are commonly seen clinical practice. It is also important to investigate these relationships in people not captured by RCTs that have specific inclusion and exclusion and are not generalisable to the wider population of COPD patients. Specifically, cohort 3

included patients aged 35 or older with at least of the following comorbidities: a history of arrythmia, bronchiectasis, MI, hospitalised heart failure, an AECOPD 6 weeks prior to start of follow-up and current asthma. It is important to note that other than COPD patients with comorbidities (i.e., cohort *3*), patients with FEV_1 >50% predicted would have also been excluded from WISDOM however, these patients were not studied on their own.

***Figure 7.1**: Definition of study populations.*



***Note:** *at least one of the following comorbidities: a history of arrythmia, bronchiectasis, MI, hospitalised heart failure, an AECOPD 6 weeks prior to start of follow-up and current asthma.*

7.2.2 Triple therapy and ICS withdrawal exposure

All patients were required to be on triple therapy (ICS/LABA/LAMA) for at least 4 months prior to the start of follow-up. A triple therapy prescription was defined as an ICS/LABA/LAMA prescription or a fixed dose combination prescription of an ICS/LABA and LAMA or LABA/LAMA and ICS, or an ICS, LABA, and LAMA separately within one month of each other. Four months of triple therapy was defined as having two triple therapy prescriptions at least 60 days apart within a four-month period. Patients were classed as withdrawing from ICS if they had a LABA/LAMA prescription without evidence of a prescription of ICS within one month of LABA/LAMA after having been on triple therapy for at least 4 months. All patients were required to be registered at their GP, have an up-to-standard date, be over the age of 35 or 40 (depending on the cohort), have a validated COPD diagnosis and have data from the 1st of January 2004 prior to baseline triple therapy.

Start of follow-up for patients who withdrew from ICS was the date of first LABA/LAMA after being on triple therapy for at least four months. Start of follow-up for patients who remained on triple therapy was the date of the first ICS/LABA/LAMA prescription after being on triple therapy for four months (**figure 7.2**). End of follow-up for all patients was the 30th September 2019, or beforehand if they died, transferred out of the practice, or at the patient's last collection date.

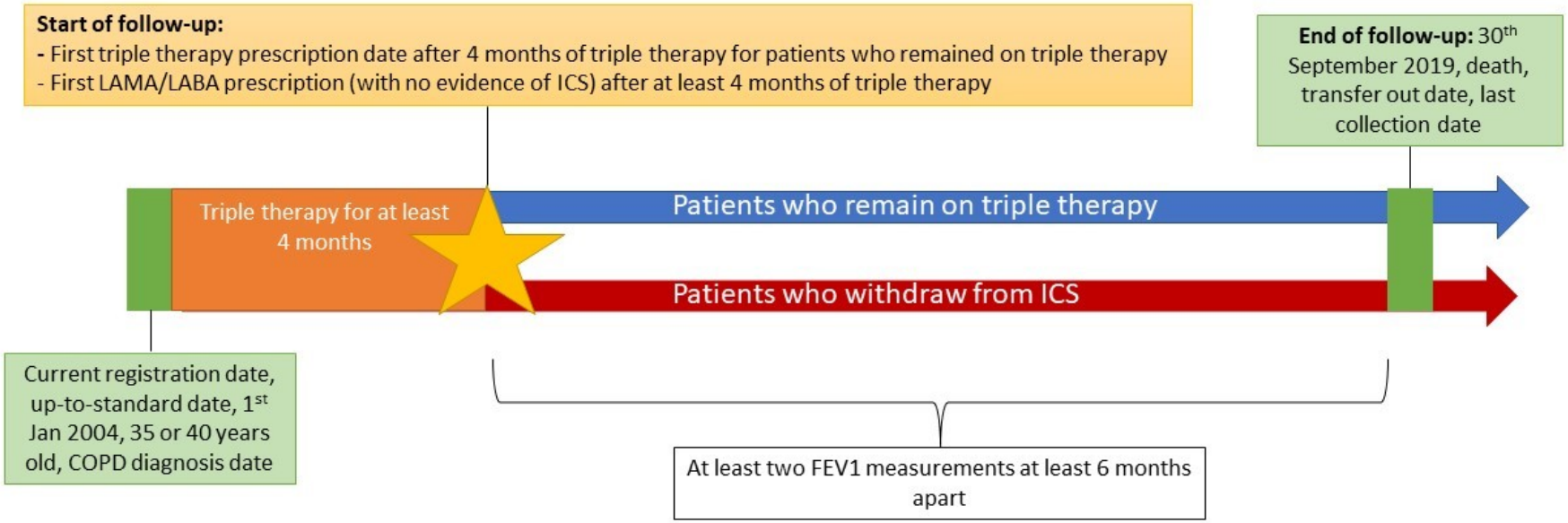


***Figure 7.2**: Study design.*

7.2.3 FEV_1 measurements

FEV_1 measurements were identified from the start of follow-up to the end of follow-up. Patients were required to have at least two FEV_1 measurements at least 6 months apart within this period. In addition, a baseline FEV_1 measurement was included in order to capture the change in FEV_1 prior to ICS withdrawal, similar to baseline FEV_1 used in RCTs. Therefore, the nearest FEV_1 measurement within 15 months to the start of follow-up was identified and used in the analysis for rate of FEV_1 decline. A 15-month period was used following QOF guidelines that state that spirometry should be recorded every 15 months at a GP in COPD patients [78].

7.2.4 Statistical analysis

Main analysis

Baseline characteristics within patients who remained on triple therapy and patients who withdraw from ICS were described using proportions (%) and means (SD). Rate of FEV_1 decline between the two groups of patients was estimated using a mixed linear regression model with an interaction between exposure group and time from first FEV_1 measurement. Rates of FEV_1 decline were reported using ml/year. Adjusted rates of decline were additionally adjusted for the following baseline characteristics: age, gender, smoking status (current or ex-smoking), index of multiple deprivation (IMD), airflow obstruction (mild: $FEV_1 \geq 80\%$ predicted, moderate: 50-70% predicted, severe: 30-49% predicted, and very severe: ≤30% predicted), AECOPD frequency in the year prior to the start of follow-up (none, 1, 2, or ≥3), BMI (underweight:<18.5kg/m^2, normal:18.5-24.9kg/^{2}, overweight: 25-29.9kg/m^2, and obese:≥30kg/m^2), and time on triple therapy (from the first date of triple therapy to the last date of triple therapy). This was the end of follow-up for patients who remained on triple therapy and the last triple therapy prescription prior to ICS withdrawal in the ICS withdrawal group). Cohorts 2 and 3 additionally adjusted for current asthma, hospitalised heart failure, and a history of arrythmia, bronchiectasis, and MI. Cohort 1 did not adjust for these baseline characteristics because they were part of the exclusion criteria used to define cohort 1.

Sensitivity analyses

Sensitivity analyses were performed to better understand the relationship between ICS withdrawal and rate of FEV_1 decline. Firstly, analyses were stratified by smoking status, degree of airflow obstruction, and AECOPD frequency. These characteristics were chosen as they are common effect modifiers within COPD patients and are closely associated with lung function decline.

Second, analyses were repeated in all three cohorts where patients who withdrew from ICS were censored at their first triple therapy prescription date during follow-up. This differed from the main analysis which used an intention to treat methodology.

Third, cohorts were created using a different definition for identifying triple therapy prescription. Unlike the main analysis that defined triple therapy as ICS/LABA and LAMA or LABA/LAMA and ICS or LABA and LAMA and ICS prescriptions recorded within one month of each other, the sensitivity analysis used a definition of triple therapy that required each prescription component to be recorded on the same day. This definition was also used for LABA and LAMA prescriptions to identify ICS withdrawers.

Sample size considerations

Sample size calculations were based on rate of FEV_1 change as described in chapter 5. **Table 7.1** illustrates sample sizes needed to detect a change in FEV_1 in the total sample and the number of patients needed to compared rates of decline between patients who withdrew from ICS and patients who remained on triple therapy. The estimated ratio of patients withdrawing compared to remaining on was 10%/90%=0.1).

***Table 7.1**: Sample size considerations for the number of patients withdrawing from ICS.*

Δ (ml/year)	Patients withdrawing from ICS
2	95,585
3	41,593
4	23,396
5	14,973
7	7,639
10	3,743

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7.3 Results

Overall, a total of 6,008 COPD patients were included in population 1 which represented patients who would have met the WISDOM inclusion and exclusion criteria. All these patients were on triple therapy for at least 4 months. Of those patients, 5,470 (91.0%) remained on triple therapy and 538 (9.0%) withdrew from ICS. The mean follow-up for this population was 5.9 years (SD 3.0).

A total of 60,645 COPD patients were included in population 2 which represented a general population of COPD patients. Of these patients, 53,671 (88.5%) remained on triple therapy and 6,974 (11.3%) withdrew from ICS. Th mean follow-up for this population was 5.9 years (SD 3.1).

Lastly, 32,882 COPD patients were included in population 3 which represented COPD patients who would have been excluded from the WISDOM trial due to comorbidities. Of these patients, 29,301 (89.1%) remained on triple therapy and 3,581 (10.9%) withdrew from ICS. The mean follow-up for this population was 6.1 years (SD 3.3). **Figure 7.3 and Figure 7.4** illustrate the inclusion and exclusion criteria used to create all three cohorts.

Table 7.2 reports baseline characteristics for all three populations in those who withdrew from ICS and those who remained on triple therapy as well as mean follow-up and number of FEV_1 measurements over follow-up for each subgroup. Population 1 included more males than population 2 and 3. In all populations the ICS withdrawal groups included slightly older patients, more ex-smokers, and less socioeconomically deprived patients. In addition, population 1 had more patients with normal or underweight BMI than patients in population 2 and 3. In terms of baseline GOLD grade more very severe patients in population 1 withdrew from ICS however, the proportion of patients in GOLD groups in populations 2 and 3 were similar. In terms of AECOPD frequency, patients with no AECOPD events at baseline were more likely to be ICS withdrawers in population 2. Lastly, in terms of comorbidities, a greater number of patients in population 3 had current asthma, heart failure, bronchiectasis, arrythmia, and myocardial infarction.

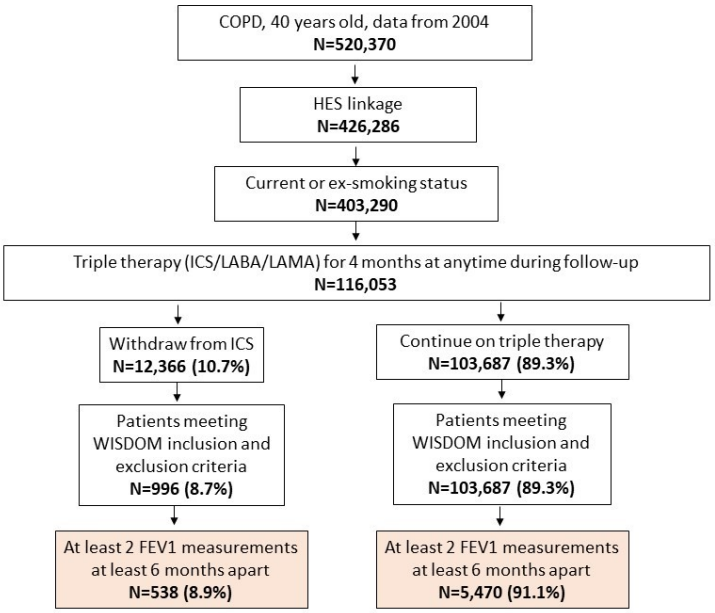


***Figure 7.31**: COPD patients meeting WISDOM inclusion and exclusion criteria (population 1)*

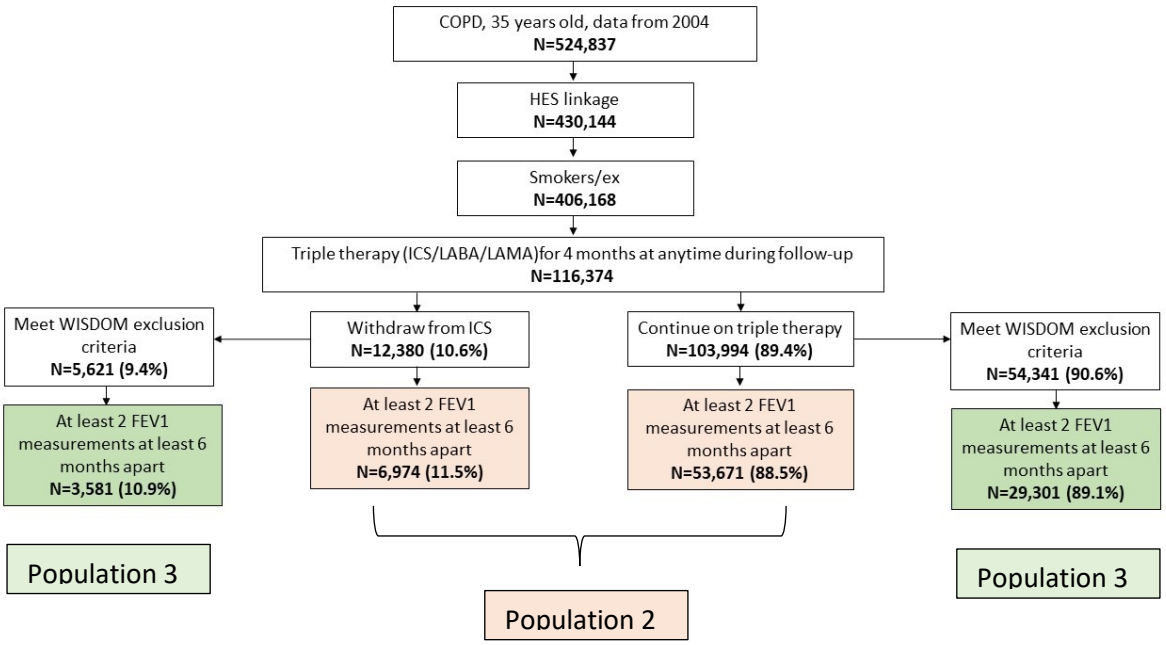


***Figure 7.4:** COPD patients included in population 2 and population 3.*

***Table 7.2**: Baseline characteristics in patients who withdrew from ICS and patients who continued triple therapy in populations 1, 2, and 3.*

	Population 1		Population 2		Population 3	
Baseline characteristics	**Continue triple (n=5,470)**	**Withdraw ICS (n=538)**	**Continue triple (n=53,671)**	**Withdraw ICS (n=6,974)**	**Continue triple (n=29,301)**	**Withdraw ICS (n=3,581)**
Follow-up years (SD)	6.0 (2.9)	5.3 (3.2)	6.0 (3.0)	5.3 (3.4)	6.2 (3.2)	5.6 (3.7)
Median number of FEV_1 measurement (IQR)	5 (4-7)	5 (4-8)	5 (3-7)	4 (3-7)	6 (5-9)	6 (5-9)
Mean age (SD)	67.8 (9.1)	68.8 (8.6)	67.8 (10.2)	69.5 (9.5)	67.3 (10.7)	69.3 (9.7)
Gender (male)	3,360 (61.4)	316 (58.7)	28,848 (53.8)	3,713 (53.2)	14,946 (51.0)	1,855 (51.8)
Airflow obstruction						
Mild	-	-	9,120 (18.4)	1,260 (19.0)	5,306 (19.7)	655 (19.5)
Moderate	-	-	22,404 (45.3)	3,150 (47.6)	12,443 (46.2)	1,535 (45.7)
Severe	4,469 (81.70)	426 (79.2)	14,763 (29.8)	1,799 (27.2)	7,528 (27.9)	939 (28.0)
Very severe	1,001 (18.3)	112 (20.8)	3,199 (6.5)	408 (6.2)	1,679 (6.2)	229 (6.8)
Smoking status						
Ex-smokers	2,691 (49.2)	284 (52.8)	26,792 (49.9)	3,699 (53.0)	15,519 (53.0)	2,003 (55.9)
Smokers	2,779 (50.8)	254 (47.2)	26,879 (50.1)	3,275 (47.0)	13,782 (47.0)	1,578 (44.1)
IMD						
1 (least deprived)	741 (13.6)	87 (16.2)	7,739 (14.4)	1,092 (15.7)	4,319 (14.7)	583 (16.3)
2	990 (18.1)	104 (19.4)	9,280 (17.3)	1,303 (18.7)	5,088 (17.4)	673 (18.8)
3	1,076 (19.7)	81 (15.1)	10,084 (18.8)	1,333 (19.1)	5,506 (18.8)	683 (19.1)
4	1,191 (21.8)	120 (22.4)	11,755 (21.9)	1,507 (21.6)	6,322 (21.6)	774 (21.6)
5 (most deprived)	1,470 (26.9)	145 (27.0)	14,773 (27.5)	1,736 (24.9)	8,040 (27.4)	867 (24.2)
Missing	<5 (0.0)	<5 (0.0)	40 (0.1)	<5 (0.0)	26 (0.1)	<5 (0.0)
BMI						
Underweight	423 (7.7)	32 (6.0)	2,314 (4.3)	252 (3.6)	1,074 (3.7)	140 (3.9)
Normal	2,186 (40.0)	224 (41.6)	16,751 (31.2)	2,161 (31.0)	8,461 (28.9)	1,080 (30.2)

Overweight Obese Missing	1,525 (27.9) 1,151 (21.0) 185 (3.4)	162 (30.1) 102 (19.0) 18 (3.4)	16,824 (31.5) 16,017 (29.8) 1,765 (3.3)	2,339 (33.5) 1,993 (28.6) 229 (3.3)	9,205 (31.4) 9,222 (31.5) 1,339 (4.6)	1,165 (32.5) 1,068 (29.8) 128 (3.6)
AECOPD frequency 0 1 2 3+	 - 2,355 (43.1) 1,441 (26.3) 1,674 (30.6)	 - 246 (45.7) 130 (24.2) 162 (30.1)	 17,495 (32.6) 13,409 (25.0) 8,898 (16.6) 13,869 (25.8)	 2,768 (39.7) 1,609 (23.1) 942 (13.5) 1,655 (23.7)	 7,537 (25.7) 6,620 (22.6) 4,978 (17.0) 10,166 (34.7)	 920 (25.7) 809 (22.6) 542 (15.1) 1,310 (36.6)
Current asthma	-	-	20,369 (38.0)	2,196 (31.5)	20,897 (71.3)	2,368 (66.1)
Hospitalised HF	-	-	346 (0.6)	27 (0.5)	373 (1.3)	36 (1.0)
MI	-	-	186 (0.4)	24 (0.3)	198 (0.7)	29 (0.8)
Bronchiectasis	-	-	1,677 (3.1)	204 (2.9)	1,788 (6.1)	222 (6.2)
Arrythmia	-	-	3,570 (6.7)	385 (5.5)	3,846 (13.1)	445 (12.4)

7.3.1 Withdrawal of ICS and FEV_1 decline

Figure 7.5 illustrates the unadjusted and adjusted rates of FEV_1 decline in all three populations. In population 1 (patients who met WISDOM inclusion and exclusion criteria), patients who withdrew from ICS did not have a significantly different rate of FEV_1 decline compared to patients who remained on triple therapy (adjusted mean rates -7.8 ml/year (95% CI -19.7 to +4.1) and -15.2 ml/year (95% CI -18.7 to -11.8), respectively. P value for difference between rate p=0.264).

In population 2, patients who remained on triple therapy had a mean adjusted rate of FEV_1 decline of -32.6 ml/year (95% CI -33.6 to -31.5) and patients who withdrew from ICS had a mean adjusted rate of -36.4 ml/year (95% CI -33.6 to -31.5). Whilst the difference between rates was statistically significant (p=0.014) the rates were not clinically different.

Lastly, in population 3 there was no significant difference between patients who remained triple therapy and patients who withdrew from ICS (adjusted mean rates -29.4 ml/year (95% CI -30.8 to -28.1 and -31.3 ml/year (95% CI -35.0 to -27.5); difference between rates p=0.371.

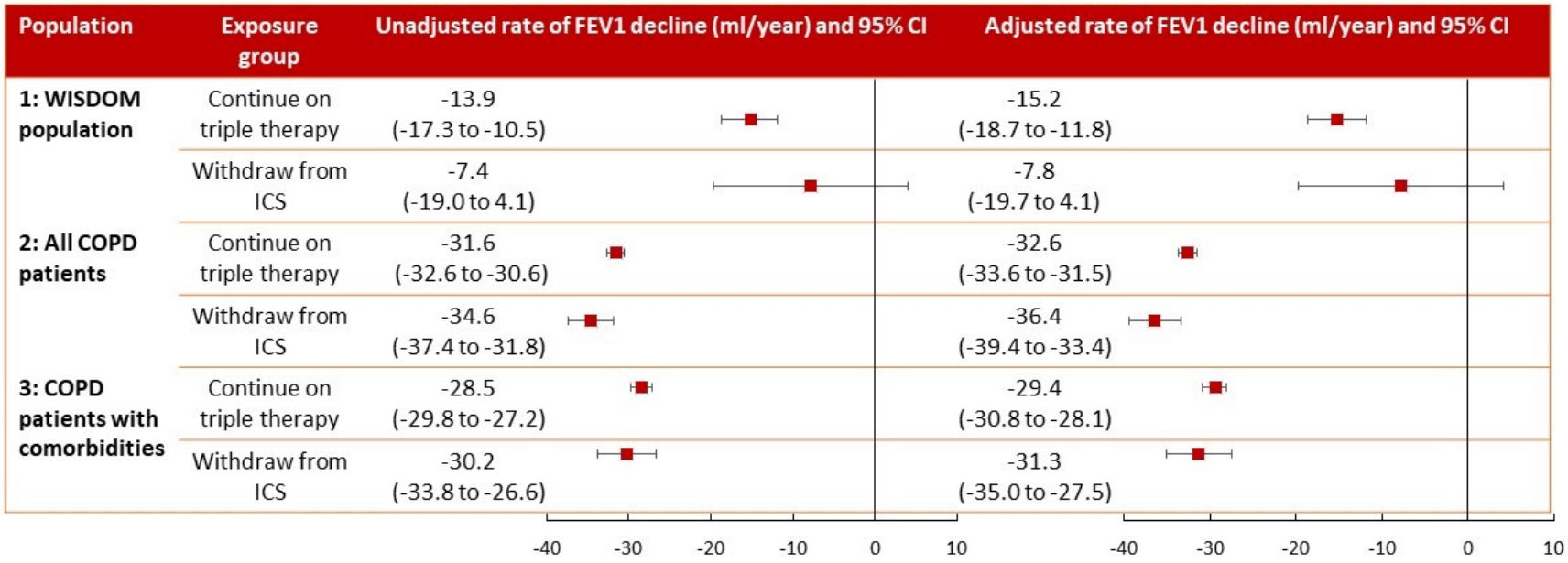


Figure 7.5: *Unadjusted and adjusted rates of FEV_1 decline in patients who continued triple and patients who withdrew from ICS.*
Note: *Cohort 1 unadjusted N=6,008, adjusted N=5,862, cohort 2 unadjusted N=60,645, adjusted N=54,473, cohort 3 unadjusted N=32,882, adjusted N=29,142.*

7.3.2 Stratification by smoking status, airflow obstruction, and AECOPD frequency

Analyses were additionally performed stratified by smoking status, airflow obstruction, and AECOPD frequency to understand whether the association between withdrawal of ICS and lung function decline is modified by specific patient characteristics. **Table 7.3** reports mean rates of FEV_1 decline in patients who remained on triple therapy compared to patients who withdrew from ICS in ex-smokers and current smokers. No significant difference in the rate of FEV_1 decline was seen between patients who remained on triple therapy and patients who withdrew from ICS in either current or ex-smokers.

Table 7.4 reports rates of FEV_1 decline in patients who remained on triple therapy compared to patients who withdrew from ICS with mild, moderate, severe, and very severe airflow obstruction. No significant difference in rate of FEV_1 decline was seen in patients with mild airflow obstruction in population 2 however, patients who withdrew from ICS in population 3 had a significantly slower rate of FEV_1 decline compared to patients who remained on triple therapy (adjusted mean rates of FEV_1 decline (adjusted mean rates of FEV_1 decline: -58.9 ml/year (95% CI -67.8 to -50.0) and -72.0 ml/year (95% CI -75.1 to -69.0), respectively). In addition, no significant difference in rates of FEV_1 decline was seen in patients with moderate airflow obstruction in population 3 however, patients who withdrew from ICS in population 2 had a significantly faster rate of FEV_1 decline compared to those who remained on triple therapy (adjusted mean rates of FEV_1 decline: -37.3 ml/year (95% CI -41.0 to -33.8) and -31.3 ml/year (95% CI -32.7 to -30.0), respectively).

No significant difference in rate of FEV_1 decline between patients who remained on triple therapy and patients who withdrew from ICS with severe and very severe airflow obstruction in population 2 and 3 however, in population 1 patients who continued triple therapy had a faster mean decline or a slower mean increase in FEV_1 compared to patients who withdrew from ICS. In is important to note that statistical power was reduced in these stratified analyses because sample sizes were lower and results from these analyses should be interpreted with caution.

Table 7.5 reports mean rates of FEV_1 decline in patients who remained on triple therapy compared to patients who withdrew from ICS with no AECOPD in the year prior, 1 AECOPD in the year prior, 2 AECOPD in the year prior, and 3 or more AECOPD in the year prior. No significant difference in mean adjusted rates of decline was seen between patients who continued triple therapy compared to those who withdrew from ICS in all three populations in each AECOPD frequency category.

***Table 7.3**: Rates of FEV_1 decline in ex-smokers and current smokers.*

	Model	Withdrawal group	Cohort 1	P for difference	Cohort 2	P for difference	Cohort 3	P for difference
Ex-smokers	Unadjusted	Continue triple	-9.4 (-13.8 to -4.9)	0.547	-25.3 (-26.6 to -24.0)	0.305	-22.4 (-24.1 to -20.7)	0.244
		Withdraw ICS	-4.3 (-17.6 to 8.0)		-27.0 (-30.4 to -23.6)		-25.1 (-29.4 to -20.7)	
	Fully adjusted*	Continue triple	-10.3 (-14.8 to -5.7)	0.624	-26.2 (-27.5 to -24.8)	0.141	-23.2 (-25.1 to -21.4)	0.208
		Withdraw ICS	-6.5 (-20.4 to 4.4)		-28.6 (-32.3 to -24.9)		-26.2 (-30.8 to -21.6)	
Smokers	Unadjusted	Continue triple	-18.5 (-23.6 to -13.4)	0.419	-38.0 (-39.5 to -36.5)	0.028	-35.4 (-37.4 to -33.3)	0.747
		Withdraw ICS	-11.6 (-33.3 to 10.1)		-44.1 (-48.7 to -39.4)		-36.9 (-42.9 to -30.8)	
	Fully adjusted*	Continue triple	-20.3 (-25.6 to -15.1)	0.308	-39.1 (-40.7 to -37.5)	0.014	-36.4 (-38.6 to -34.3)	0.751
		Withdraw ICS	-10.7 (-32.8 to 11.4)		-46.1 (-51.1 to -41.1)		-38.0 (-44.2 to -31.7)	

***Note:** cohort 1 unadjusted ex-smokers n=2,975, adjusted ex-smokers n=2,870, unadjusted smokers n=3,033, adjusted smokers n=2,932. Cohort 2 unadjusted ex-smokers n=30,491, adjusted ex-smokers n=27,254, unadjusted smokers n=30,154, adjusted smokers n=27,219. Cohort 3 unadjusted ex-smokers n=17,522, adjusted ex-smokers n=15,420, unadjusted smokers n=15,360, adjusted smokers n=13,722. *Adjusted for baseline characteristics.*

Table 7.4: *Rates of FEV_1 decline in patients with mild, moderate, severe, and very severe airflow obstruction.*

Airflow obstruction	Model	Withdrawal group	Cohort 1		Cohort 2		Cohort 3	
Mild	Unadjusted	Continue triple	-		-73.4 (-75.7 to -71.1)	0.660	-70.6 (-73.6 to -67.7)	0.005
		Withdraw ICS	-		-73.1 (-80.0 to -66.1)		-58.6 (-67.3 to -50.0)	
	Fully adjusted *	Continue triple	-		-74.2 (-76.5 to -71.8)	0.623	-72.0 (-75.1 to -69.0)	0.003
		Withdraw ICS	-		-73.3 (-80.5 to -66.1)		-58.9 (-67.8 to -50.0)	
Moderate	Unadjusted	Continue triple	-		-31.4 (-32.7 to -30.1)	0.013	-28.3 (-30.1 to -26.6)	0.301
		Withdraw ICS	-		-36.3 (-39.9 to -32.8)		-30.7 (-35.3 to -26.2)	
	Fully adjusted *	Continue triple	-		-31.3 (-32.7 to -30.0)	0.002	-28.2 (-30.0 to -26.4)	0.194
		Withdraw ICS	-		-37.3 (-41.0 to -33.8)		-31.4 (-36.1 to -26.8)	
Severe	Unadjusted	Continue triple	-17.2 (-20.9 to -13.6)	0.823	-16.3 (-18.3 to -14.2)	0.927	-10.1 (-12.8 to -7.4)	0.076
		Withdraw ICS	-18.9 (-31.6 to -6.2)		-16.6 (-22.6 to -10.6)		-17.5 (-24.8 to -10.2)	
	Fully adjusted *	Continue triple	-18.3 (-22.0 to -14.6)	0.852	-17.3 (-19.4 to -15.3)	0.879	-11.0 (-13.8 to -8.2)	0.118
		Withdraw ICS	-19.9 (-32.7 to -7.0)		-17.8 (-24.0 to -11.6)		-17.7 (-25.2 to -10.2)	
Very severe	Unadjusted	Continue triple	1.1 (-7.9 to 10.0)	0.028	4.6 (-0.6 to 9.7)	0.083	9.6 (2.6 to 16.6)	0.136
		Withdraw ICS	34.2 (5.4 to 63.1)		1.9 (-13.5 to 17.4)		-5.1 (-25.8 to 15.6)	

	Fully adjusted *	Continue triple	-0.7 (-10.0 to 8.5)	0.017	3.5 (-1.9 to 8.9)	0.715	9.1 (1.9 to 16.4)	0.077
		Withdraw ICS	34.3 (4.3 to 64.3)		-1.3 (-18.0 to 15.4)		-10.9 (-32.3 to 10.4)	

***Note**: cohort 1 unadjusted severe n=4,895, adjusted severe n=4,724, unadjusted very severe n=1,113, adjusted very severe n=1,078. Cohort 2 unadjusted mild n=10,380, adjusted mild n=10,152, unadjusted moderate n=25,554, adjusted moderate n=24,881, unadjusted severe n=16,562, adjusted severe n=15,999, unadjusted very severe n=3,607, adjusted very severe n=3,441. Cohort 3 unadjusted mild n=5,961, adjusted mild n=5,767, unadjusted moderate n=13,978, adjusted moderate n=13,478, unadjusted severe n=8,467, adjusted severe n=8,106, unadjusted very severe n=1,908, adjusted very severe n=1,791. *Adjusted for baseline characteristics.*

***Table 7.5**: Rates of FEV_1 decline by baseline AECOPD frequency.*

Baseline AECOPD frequency	Model	Withdrawal group	Population 1		Population 2		Population 3	
0 AECOPD	Unadjusted	Continue triple	-		-33.7 (-35.6 to -31.8)	0.187	-29.5 (-32.3 to -26.7)	0.679
		Withdraw ICS	-		-37.6 (-42.6 to -32.5)		-27.5 (-35.1 to -19.9)	
	Fully adjusted *	Continue triple	-		-34.7 (-36.7 to -32.6)	0.117	-30.2 (-33.2 to -27.2)	0.786
		Withdraw ICS	-		-38.8 (-44.2 to -33.4)		-28.4 (-36.2 to -20.5)	
1 AECOPD	Unadjusted	Continue triple	-16.9 (-22.2 to -11.5)	0.477	-33.1 (-35.1 to -31.1)	0.515	-29.7 (-32.6 to -26.9)	0.850
		Withdraw ICS	-10.2 (-27.6 to 7.3)		-35.1 (-40.8 to -29.4)		-31.3 (-39.9 to -22.7)	
	Fully adjusted *	Continue triple	-17.1 (-22.6 to -11.7)	0.390	-33.6 (-35.7 to -31.4)	0.130	-30.4 (-33.5 to -27.4)	0.570
		Withdraw ICS	-7.4 (-24.4 to 9.6)		-38.5 (-44.7 to -32.3)		-33.8 (-43.2 to -24.4)	
2 AECOPD	Unadjusted	Continue triple	-9.9 (-16.6 to -3.3)	0.731	-30.5 (-32.8 to-28.1)	0.305	-27.0 (-30.1 to -23.9)	0.020
		Withdraw ICS	-4.4 (-34.2 to 14.3)		-34.6 (-42.5 to -26.7)		-38.1 (-47.6 to -28.7)	
	Fully adjusted *	Continue triple	-13.0 (-19.8 to -6.1)	0.706	-32.3 (-34.8 to -29.8)	0.537	-28.7 (-32.0 to -25.5)	0.096
		Withdraw ICS	-16.3 (-45.6 to 12.9)		-34.9 (-43.2 to -26.6)		-36.5 (-46.1 to -26.7)	
3+ AECOPD	Unadjusted	Continue triple	-13.1 (-18.8 to -7.3)	0.149	-27.9 (-29.7 to -26.2)	0.648	-26.8 (-28.9 to -24.7)	0.897

		Withdraw ICS	3.2 (-14.8 to 21.1)		-28.4 (-33.3 to -23.5)		-26.9 (-32.2 to -21.6)	
	Fully adjusted *	Continue triple	-14.6 (-20.5 to -8.7)	0.164	-29.6 (-31.4 to -27.7)	0.374	-28.4 (-30.6 to -26.2)	0.808
		Withdraw ICS	1.9 (-16.9 to 20.6)		-32.2 (-37.5 to -26.9)		-28.8 (-34.3 to -23.3)	

Note: *Cohort 1 unadjusted AECOPD 1 n=2,601, adjusted AECOPD 1 n=2,499, adjusted AECOPD 2 n=1,571, adjusted AECOPD 2 n=1,522, unadjusted AECOPD 3 n=1,836, adjusted AECOPD 3 n=1,781. Cohort 2 unadjusted AECOPD 0 n=20,263, adjusted AECOPD 0 n=18,217, unadjusted AECOPD 1 n=15,018, adjusted AECOPD 1 n=13,457, unadjusted AECOPD 2 n=9,840, adjusted AECOPD 2 n=8,844, unadjusted AECOPD 3 n=15,524, adjusted AECOPD 3 n=13,955. Cohort 3 unadjusted AECOPD 0 n=8,457, adjusted AECOPD 0 n=7,564, unadjusted AECOPD 1 n=7,429, adjusted AECOPD 1 n=6,604, unadjusted AECOPD 2 n=5,520, adjusted AECOPD 2 n=4,869, unadjusted AECOPD 3 n=11,476, adjusted AECOPD 3 n=10,105. *Adjusted for baseline characteristics.*

7.3.3 Censoring patients who withdraw from ICS at first triple therapy prescription

This sensitivity analysis censored patients who withdrew from ICS at their first triple therapy prescription date during follow-up in case patients withdrew from ICS but later during their follow-up they went back onto triple therapy. Overall, 5,972 patients were included in censored population 1, of which 514 (8.6%) patients were categorised as ICS withdrawers. A total of 60,236 patients were included in censored population 2, of which 6,565 (10.9%) patients were categorised as ICS withdrawers. Finally, 32,686 patients were included in censored population 3, of which 3,385 (10.4%) patients were categorised as ICS withdrawers. Patients numbers for this sensitivity analysis were lower than the patient numbers in the main analysis because patients were still required to have at least 2 FEV_1 measurements at least 6 months apart from the time of ICS withdrawal to the first ICS censor date.

Figure 7.6 illustrates unadjusted and adjusted mean rates of FEV_1 decline in patients who remained on triple therapy and patients who withdrew from ICS in all three populations. There was no significant difference in rate of FEV_1 decline between patients who remained on triple therapy and patients who withdrew from ICS in populations 1 and 3. However, in population 2 patients who withdrew from ICS had a significantly faster mean rate of FEV_1 decline than those who remained on triple therapy (mean adjusted rates of FEV_1 decline: -35.6 ml/year (95% CI -38.8 to -32.4) and -32.6 ml/year (95% CI -33.6 to -31.5), respectively and p=0.047).

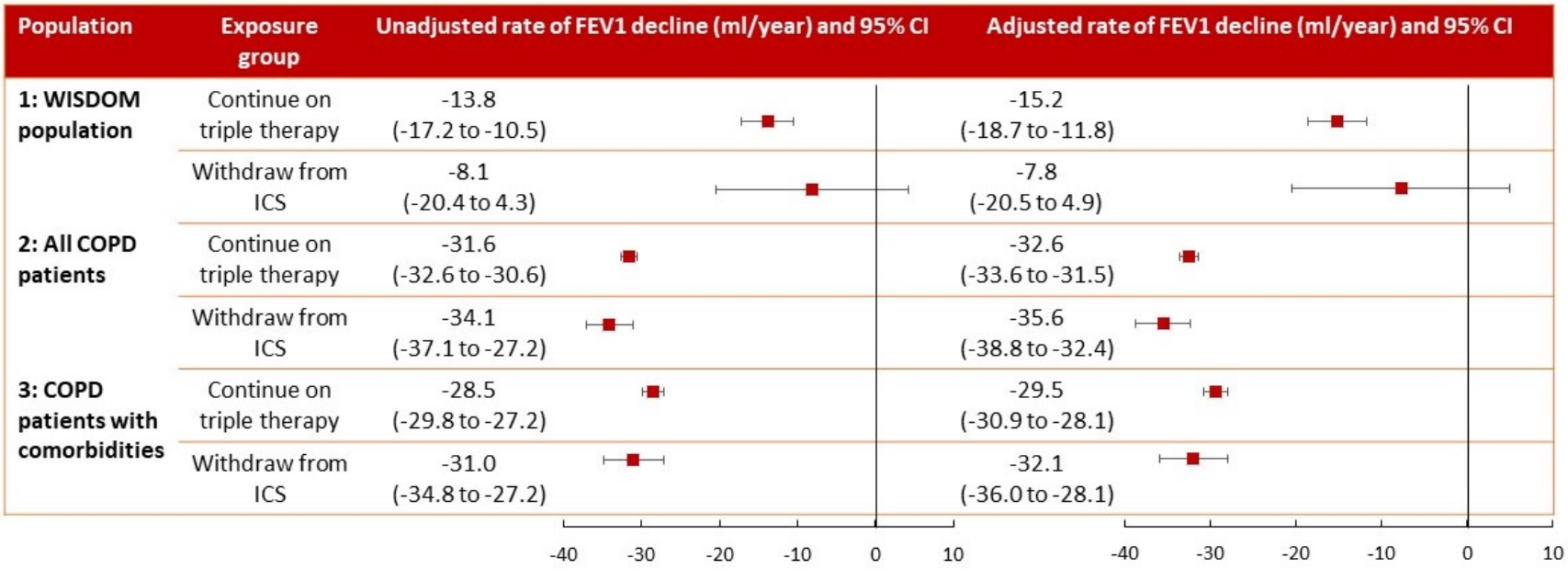


Figure 7.6: *Rates of FEV1 decline in censored populations.*
Note: *Cohort 1 unadjusted N=5,972, adjusted N=5,766, cohort 2 unadjusted N=60,236, adjusted N=54,118, cohort 3 unadjusted N=32,686, adjusted N=28,917.*

7.3.4 Using an alternative definition of triple therapy

In this sensitivity analysis triple therapy components such as LABA/ICS and LAMA or LABA/LAMA and ICS that were prescribed on the same day, rather than within one month, were defined as a triple therapy prescription. Following this definition, a total of 5,201 patients were included in population 1 of which 4,856 (93.4%) remained on triple therapy and 345 (6.6%) withdrew from ICS. A total of 52,951 patients were included in population 2 of which 48,529 (91.7%) remained on triple therapy and 4,422 (8.4%) withdrew from ICS. Finally, a total of 26,419 patients were included in population 3 of which 24,624 (93.2%) remained on triple therapy and 1,795 (6.8%) withdrew from ICS.

Figure 7.7 illustrates the unadjusted and adjusted mean rates of FEV_1 decline in patients who remained on triple therapy and patients who withdrew from ICS in all three populations. There was no significant difference in rate of FEV_1 decline between patients who remained on triple therapy and patients who withdrew from ICS in populations 1 and 3. However, in population 2 patients who withdrew from ICS had a significantly faster mean rate of FEV_1 decline than those who remained on triple therapy (mean adjusted rates of FEV_1 decline: -39.0 ml/year (95% CI -43.3 to -34.7) and -33.2 ml/year (95% CI -34.3 to -32.1), respectively and p=0.010).

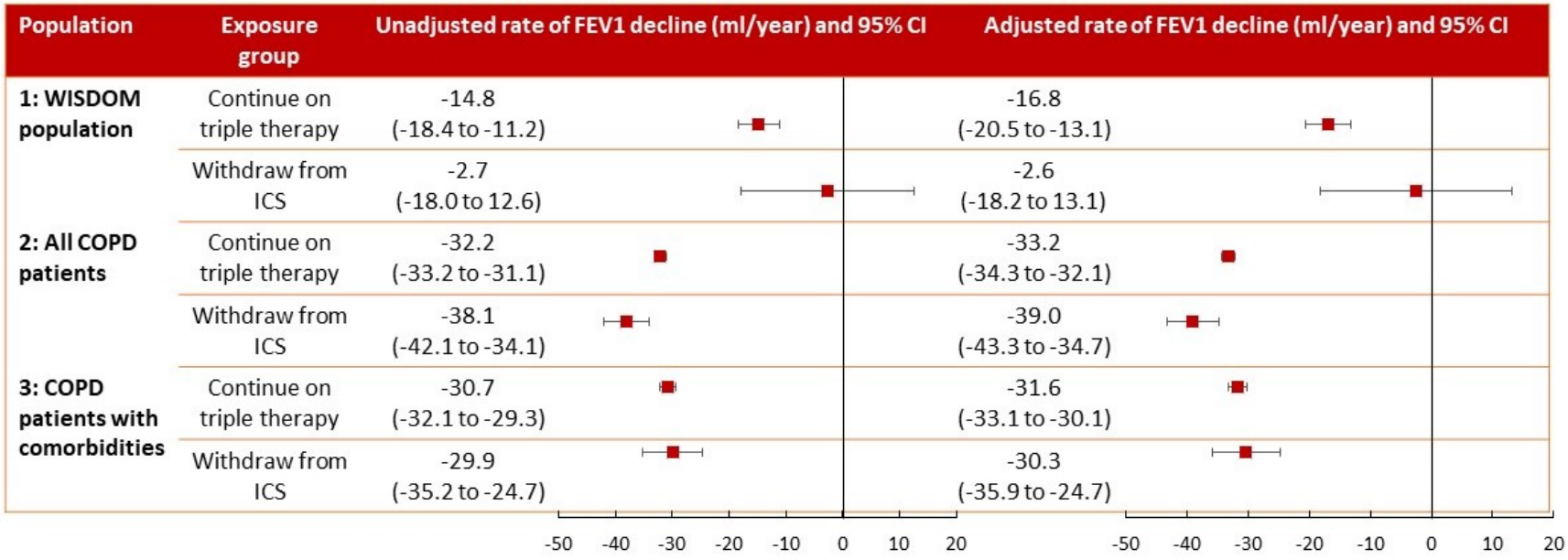


Figure 7.7*: Rates of FEV1 decline in populations who were prescribed components of triple therapy on the same day.*
Note*: Cohort 1 unadjusted N=5,201, adjusted N=5,199, cohort 2 unadjusted N=52,951, adjusted N=47,777, cohort 3 unadjusted N=26,419, adjusted N=23,722.*

7.4 Discussion

This piece of work aimed to understand the relationship between ICS withdrawal in patients on triple therapy and rate of FEV_1 decline in COPD patients who would have been included in the WISDOM trial and in more generalisable COPD populations.

Overall, when only patients who would have met WISDOM inclusion and exclusion criteria were included, there was no difference in FEV_1 decline between patients who remained on triple therapy and patients who withdrew from the ICS. Similarly, there was no difference in the rate of FEV_1 decline between patients who remained on triple therapy and patients who withdrew from ICS in patients who would have been specifically excluded from the WISDOM trial because of their comorbidities. However, in a general population of COPD patients, those who withdrew from ICS had a faster mean rate of FEV_1 decline compared to patients who remained on triple therapy. These patients were the most generalisable population of all three populations studied. Despite the significant difference in the rate of FEV_1 decline in this population, the difference of 3.8 ml/year between the two exposure groups is not clinically meaningful. For example, even if the estimated trajectories continued over 10 years the difference in lung function between the two groups would be 38ml.

It is likely that the significant results were due to large sample size, residual confounding, or by chance from multiple testing. Further sensitivity analyses showed consistent results whereby there was no difference in rate of FEV_1 decline between patients who remained on triple therapy and patients who withdrew from ICS and where a significant difference was seen, the difference was not clinically meaningful. In addition, stratified analyses should be interpreted with caution because sample sizes were not large enough to have enough power to detect small differences in rates of FEV_1 decline between the two exposure groups.

Interestingly, patients in the general COPD population (and in population 3) were more likely to have no or few AECOPD in the year prior and be ex-smokers compared to patients who remained on triple therapy. This is in line with ERS guidelines that state that COPD patients should be considered for ICS withdrawal if they do not have a history of AECOPD [37]. Additional ERS guidelines state that ICS should be withdrawn if patients have an EOS count less than 300cell/µl. This was not investigated in this study; however, it would be interesting to investigate whether clinical practices adhere to these guidelines.

7.4.1 Previous literature

A recent study investigated changes in ICS regimens between 2014 and 2018 in a population of COPD patients using CPRD data. The authors found that approximately 2-3% of COPD patients withdrew from triple therapy each year between 2014 and 2018 [207]. This is consistent with the overall proportion of patients who withdrew from ICS in this study (approximately 10-11% between 2014 and the start of 2019). This suggests that in general practice a relatively small proportion of COPD patients are being withdrawn from ICS, regardless of whether they are eligible for ICS withdrawal following guidelines.

The landmark study that guided ICS withdrawal guidelines in the UK was the WISDOM trial. This study found that patients who withdrew from ICS (after having been on triple therapy) had a significantly faster decline in FEV_1 than those who remained on triple therapy by 43ml at week 52 [161]. Patients in this study were given tiotropium (18ug once daily), salmeterol (50ug twice daily), and fluticasone propionate (500ug twice daily). These patients would have all been monitored regularly, along with their inhaler technique, and would have adhered properly to their assigned treatment. Patients who are seen in clinical practice who are given triple therapy in a fixed combination dose form may not truly take each component properly. It is highly likely that in routine clinical practice, patients could miss doses if they are required to take more than one medication per day [208]. The possible lack of adherence to medications in this population of COPD patients may explain why patients who withdrew from ICS in this study did not have a clinically faster rate of FEV_1 decline compared to those who remained on triple therapy. In addition, in clinical practice, GPs would have considered whether it was safe to withdraw patients from ICS. Therefore, these patients are likely to be very different to patients in the withdrawal group seen in WISDOM. For example, I found that patients who withdrew from ICS were more likely to be ex-smokers and have fewer AECOPDs prior to ICS withdrawal whereas baseline characteristics were similar between the two groups in the WISDOM trial, given the nature of RCTs.

A recent study also aimed to investigate outcomes between COPD patients who withdrew from ICS and those who remained on triple therapy in a population of primary care patients using data from the Optimum Patient Care Research Database (OPCRD) [209]. Authors aimed to use this EHR database to investigate primarily risk of AECOPD in a more general population of COPD patients, similar to population 2 in this chapter, between triple therapy users and those who withdrew from ICS with a follow-up of one year. Secondary analyses investigated change in FEV_1 and authors found that in a total population of 5,230 patients, those who withdrew from ICS had a mean decline in FEV_1 of 48 ml (SD 226) compared to a mean decline of 18.8 ml (SD 253) in those who remained on triple therapy over a year however, this difference was not statistically significant. This study differed in terms of study design whereby patients who withdrew from ICS and patients who remained on triple therapy were matched 4:1 based on time on triple therapy. This population also excluded patients with a current diagnosis of asthma, who were not excluded in population 2 of this chapter.

The study to understand the safety and efficacy of ICS withdrawal from triple therapy (SUNSET) trial was an additional RCT, similar to the WISDOM trial, that investigated the effects of ICS withdrawal from patients on triple therapy. Patients were included if they were over 40 years old, had spirometry confirmed COPD, FEV_1 percent predicted 40-80%, had a history of smoking and had a maximum of one AECOPD in the previous year. Patients were excluded from the SUNSET trial if they had a history of asthma and blood eosinophil levels greater than 600 cell/ul. Findings from the SUNSET trial showed a non-significant difference in change in post dose FEV_1 between the two groups of -26 ml (95% CI -53 to 1) after 26 weeks

of follow-up [210]. Interestingly, patients included in SUNSET were more similar to patients included in population 2 and 3 in this study than those recruited in the WISDOM trial. This was because SUNSET COPD patients had a wider range of comorbidities, airflow obstruction, and fewer AECOPDs at baseline. Therefore, it possible that ICS withdrawal is associated with increased loss of FEV_1 in specific COPD populations however, not in all COPD patients as demonstrated by SUNSET and this observational study.

A systematic review of ICS withdrawal additionally found that only three of five RCTs showed a significant difference in change in FEV_1 from baseline between COPD patients who withdrew from ICS and COPD patients who did not withdraw and WISDOM was one of those [211]. The COSMIC (COPD and Seretide: a Multi-centre Intervention and Characterisation) study additionally found that patients who withdrew from ICS after being on ICS/LAMA had a significantly faster decline in FEV_1 than those who stayed ICS/LAMA (mean change from baseline after one year 24% compared to 20.1%, respectively) [212]. Furthermore, a study by O'Brien and colleagues found that patients with severe irreversible airway obstruction had a significantly larger decrease in FEV_1 after switching from ICS monotherapy to placebo [213]. It is important to note that these studies did not directly compare patients on triple therapy (ICS/LAMA/LABA) to those who withdrew from ICS and were on LAMA/LABA during follow-up. As shown in chapter 2 (systematic review of change in FEV_1 in patients on ICS and not on ICS), there can be high between study variation in rates of FEV_1 decline due to differences in specific combinations of medications. In addition, withdrawing from ICS monotherapy or from the ICS component of ICS/LAMA is likely to have different outcomes than withdrawing from triple therapy due to the synergistic effect of LABA and LAMA combined [122, 123]. Overall, previous literature and results from this study show inconsistencies in the relationship between ICS withdrawal and rate of FEV_1 decline due to difference in populations, medications and study design and further work is needed.

7.4.2 Strengths and limitations

The main strengths of this study were the large sample size the inclusion of populations that were more generalisable to the wider population of diagnosed COPD patients in UK primary care however, limitations exist. Firstly, medication use was defined by GP prescriptions which only indicates that a medication was prescribed but not whether the medication was taken by the patient. Triple therapy is often prescribed as a fixed dose combination therapy and patients will have two or three components to take every day. In COPD patients seen in routine clinical practice, it is possible that adherence is lower than in populations used in RCTs and therefore the difference in lung function between patients on LAMA/LABA/ICS and LAMA/LABA may not be as pronounced as that seen in RCTs like WISDOM.

In addition, the definition used to identify ICS withdrawers picked up patients who were prescribed a LAMA and LABA but not an ICS within one month of each other. However, it is possible that medications were prescribed just over one month from each other and whilst patients may have been on triple therapy, they

were categorised as ICS withdrawers. It is therefore possible that patients were misclassified. Further work should investigate more accurate algorithms for identification of patients who remained or withdrew from ICS by using duration and number of units prescribed to better understand how long the prescriptions were for. For example, if ICS was prescribed for a duration of 2 months but LABA/LAMA was prescribed twice with a duration of one month the algorithm in this study would have potentially identified these patients as ICS withdrawers when in reality they remained on triple therapy. Despite this, one sensitivity analysis censored patients who withdrew from ICS at their first prescription date during follow-up in case these patients did go back onto triple therapy. These patients were still required to have at least 2 FEV_1 measurements at least 6 months apart therefore patients who were misclassified as ICS withdrawers and had an ICS prescription less than 6 months after their index date would have been excluded. This analysis found similar results to the main analysis suggesting that despite the possible misclassification in the main analysis, findings remain.

One main limitation of this study is that confounding by indication is likely to exist. Epidemiological studies using routinely collected data are increasing used to investigate safety and effectiveness of treatments in populations not necessarily included in RCTs. However, one main limitation of this is that confounding can arise when factors influence the decision to treat or not treat a patient. In this case the GP's decision to withdraw ICS from patients on triple therapy is likely to have been influenced by their own judgement on how well the COPD patient was doing on their current treatment, how stable they were, or whether they met ERS guidelines for ICS withdrawal [214]. In this study patients who withdrew from ICS were more likely to be ex-smokers and have fewer AECOPD compared to those who remained on triple therapy. These factors could have therefore influenced the physician's decision to withdraw ICS from the patient. One way in which to reduce or eliminate confounding by indication is to use propensity score matching. This method estimates each patient's probability of being assigned to the treatment (i.e., continue triple therapy vs ICS withdrawal) based on various factors that may have influenced this decision such as disease severity and AECOPD frequency. These weighted probability scores can then be used in the final model to adjust for confounding from treatment assignment [215]. Further work should explore this further to understand whether residual confounding by indication existed in analyses performed in this study.

Similarly, patient characteristics that were used as the inclusion and exclusion criteria for WISDOM were adjusted for (where relevant) in this study however, future work could adjust for further confounders to reduce residual confounding. Lastly, patients were required to have at least two FEV_1 measurements at least 6 months apart which meant that minimum follow-up time was six months. This would have introduced survival bias and should be recognised.

7.5 Conclusion

Overall, this study found that the rate of FEV_1 decline was similar between patients on triple therapy and patients who withdrew from ICS regardless of the specific COPD population studied (i.e., patients meeting strict WISDOM criteria, general primary care COPD patients, and COPD patients with comorbidities). Whilst residual confounding and confounding by indication may have influenced these findings, COPD patients who are seen in clinical practice may not adhere to their treatments and are often different in terms of comorbidities and disease severity to those included in RCTs such as WISDOM. Further observational studies using propensity scores, or pragmatic trials should be performed in order to better understand the relationship between ICS withdrawal and rate of FEV_1 decline in more generalisable COPD patients.

Chapter 8
Accelerated FEV_1 decline and risk of cardiovascular disease and cardiovascular disease mortality

Previous chapters have investigated characteristics associated with future rate of FEV_1 decline. Little is understood about the rate of FEV_1 decline and the risk of future clinical events in a COPD population. CVD is one of the main comorbidities in COPD due to their shared risk factors. This chapter aimed to investigate the association between accelerated FEV_1 decline and the risk of developing or death from CVD in a COPD population. This work presented in this chapter has been published in the European Respiratory Journal [216].

8.1 Introduction

One of the most prevalent comorbidities in COPD patients is CVD [56]. Both COPD and CVD share common risk factors such as smoking and aging [60, 61]. Specifically, exposure to toxic particles in cigarette smoke or air pollutants can cause the increased systemic inflammation that characterizes both COPD and CVD [62]. It is not fully understood how COPD and CVD are linked beyond their shared risk factors, but researchers have identified a number of possible mechanisms such as hypoxia and oxidative stress that might be involved [56, 60]. Furthermore, numerous studies have reported the existence of associations between various measures of impaired lung function and an increased likelihood of developing CVD, as well as an increased risk of hospitalisation and death secondary to CVD [64-70].

More recently, it has been suggested that the rate at which lung function is lost may be associated with increased risk of CVD. This has been demonstrated in the general population; for instance, among the participants of the ARIC study, accelerated decline in FEV_1, over a baseline period of three years, was associated with an increased risk of hospitalisation and death from heart failure and stroke [74]. To date, no studies have investigated the association between rate of FEV_1 decline and risk of CVD outcomes and mortality in patients with COPD, who are already at greater risk of CVD than the general population [56]. Therefore, I aimed to investigate whether COPD patients with accelerated FEV_1 decline were more likely to develop CVD, or die from a CVD cause, in a primary care population of COPD patients in England.

8.2 Methods

8.2.1 Study population

CPRD GOLD was linked to HES and the Office of National Statistics (ONS). Patients were included if they met the following minimum inclusion criteria: (i) patients were eligible for HES linkage; ii) diagnosed with COPD; iii) aged 35 or older; iv) current or ex-smokers; and v) had data recorded from 2004 onwards. Specifically, the inclusion date was the date of patients' first FEV_1 measurement after the date at which they were diagnosed with COPD, registered with their current GP, aged 35 years, and the date at which the practice was deemed of research quality [133] (**figure 8.1**).

Following the inclusion date, patients were required to have 3 years of baseline follow-up with at least 2 FEV_1 measurements at least 6 months apart in order to estimate the patient's rate of FEV_1 decline as changes in lung function should be estimated over longer periods of time in order to draw conclusions about long term lung function decline and to reduce possible measurement error [217]. The index date was the date at the end of the baseline period and indicated the start of follow-up (**figure 8.1).** Patients were consequently followed up from their index date until the 31st December 2017 or the first date of any of the following events: transferred to a non-CPRD general practice, the last date of data collection, died from non-CVD causes, or had a CVD event. In addition, patients were required to have no history of stroke, heart failure, myocardial infarction, atrial fibrillation, and coronary artery disease ever recorded prior to the index date. This allowed for the identification of incident CVD outcomes in CVD-naïve COPD patients.

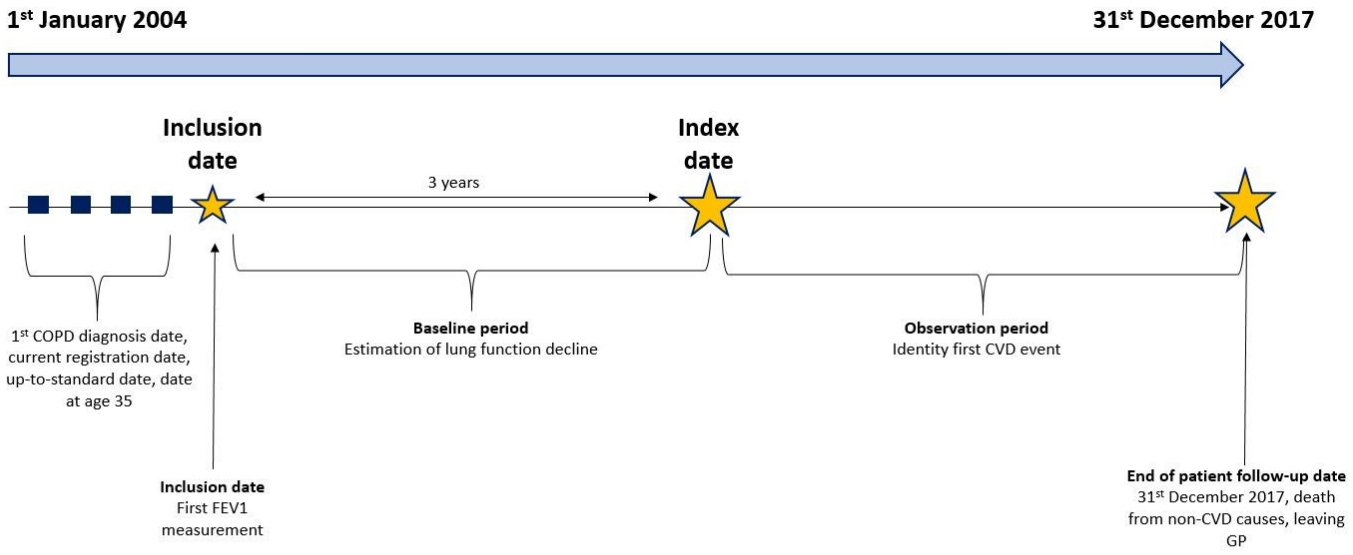


***Figure 8.1**: Study design.*

8.2.2 FEV_1 decline

The exposure of interest was accelerated FEV_1 decline. For each study eligible patient, all absolute FEV_1 measurements recorded in CPRD-GOLD between the inclusion date and the index date were identified and the rate of FEV_1 decline estimated using mixed linear regression modelling with random intercepts and random slopes. Patients with rate of decline in the fastest quartile of decline were classed as having accelerated FEV_1 decline, with the remainder classified as being "without accelerated FEV_1 decline". This cut off was chosen as it is in line with that used in chapter 6.

8.2.3 Cardiovascular disease outcomes

The primary outcome was a composite measure defined as the time to first CVD event (both fatal and non-fatal) during follow-up and compromised myocardial infarction, heart failure, ischaemic stroke, atrial fibrillation, and coronary artery disease excluding myocardial infarction. These events were identified through primary care records (CPRD-GOLD), hospital admissions data (HES), and mortality statistics (ONS). ICD-10 codes were used to identify hospitalisations (primary diagnosis) and CVD deaths (see **appendix 4** for CPRD, HES, and ONS CVD codes). CVD events that were recorded on the same day in CPRD-GOLD, HES, and/or ONS were further explored to avoid duplication of events. In these cases, mortality events were prioritised, followed by hospitalisations, and then GP-recorded events. Secondary outcomes included time to first myocardial infarction, heart failure, stroke, atrial fibrillation, and coronary artery disease excluding myocardial infarction alone.

8.2.4 Statistical analyses

Main analysis

Baseline characteristics were described using proportions, medians, and interquartile ranges (IQR). Cox regression was used to investigate time to the first CVD event, comparing patients with and without accelerated FEV_1 decline, adjusted for gender, age (continuous), smoking status (current or ex-smoker), and level of airflow obstruction (mild: FEV_1 ≥80% predicted; moderate: FEV_1 50–80% predicted; severe: FEV_1 30—50% predicted; very severe: FEV_1 <30%), modified MRC dyspnoea (0–4), BMI (underweight, normal, overweight, obese), history of hypertension, diabetes and asthma, statin use, and AECOPD frequency and severity (none; 1 moderate (GP-recorded AECOPD) and 0 severe (hospitalisation for AECOPD); 2 moderate and 0 severe; 3 or more moderate and 0 severe; 1 severe and any number of moderate; and 2 or more severe and any number of moderate AECOPD. Secondary analyses investigated the association between accelerated FEV_1 decline and each separate CVD; myocardial infarction, heart failure, stroke, atrial fibrillation, and coronary artery disease excluding myocardial infarction.

Sensitivity analyses

In addition, sensitivity analyses were performed to better understand the potential association between lung function decline and risk of CVD outcomes. Firstly, additional analyses around other measures of lung function were used including the relative change in FEV_1 and the change in FEV_1 percent predicted as these are also common measures of lung function [160, 218]. Secondly, sensitivity analyses around how rate of FEV_1 decline was categorised were performed. Other categorisations included all four quartiles of FEV_1 decline (and the fastest quartile of decline was compared to the other three quartiles separately), clinically important cut offs based on previous literature (>-20ml/year (reference group), -20 to -40ml/year, -40 to -60ml/year, and <-60ml/year) [17], and the relationship between the linear rate of FEV_1 decline and risk of CVD was analysed. Third, severity of CVD outcomes was assessed by modelling the relationship between accelerated FEV_1 decline and risk of GP recorded CVD outcomes, hospitalised outcomes, and deaths from CVD alone. Fourth, the main model was stratified by gender, age, smoking status, AECOPD frequency, and airflow obstruction (i.e. baseline FEV_1 percent predicted) to investigate whether the relationship between accelerated FEV_1 decline and risk of CVD outcomes was more prominent in specific individuals.

Sample size considerations

In this study accelerated FEV_1 decline was categorised using a 25^{th} percentile threshold. This meant that one quarter of patients included in the study were categorised as accelerated FEV_1 decliners and

three quarters were categorised as not having accelerated FEV_1 decline. A previous observational study using ARIC data reported a hazard ratio of 1.15 for the association between accelerated FEV_1 decline and risk of future CVD [74]. Following sample size calculations by Schonfeld, a total of 2,511 CVD events were needed to estimate a hazard ratio of 1.15 with 80% power and alpha of 0.05 [219].

8.3 Results

8.3.1 Patient characteristics

A total of 132,923 patients in CPRD-GOLD met the minimum eligibility criteria. After applying further inclusion criteria, a total of 36,382 patients were included in the final study population (see **figure 8.2).** The median follow-up time was 3.6 years (IQR, 1.7–6.1). The median rate of FEV_1 decline was –19. 4ml/year (IQR, –40.5 to 1.9) and thus patients were categorised as having accelerated FEV_1 decline if they had an FEV_1 decline faster than –40.5 ml/year. This meant that 9,095 (25%) of patients were classed as having accelerated decline and 27,287 (75%) were classed as non-accelerated decliners. Patients had a median of 3 (IQR, 2-4) FEV_1 measurements over the three-year baseline period and **Figure 8.3** illustrates the number of FEV_1 measurements recorded within patients during the baseline period.

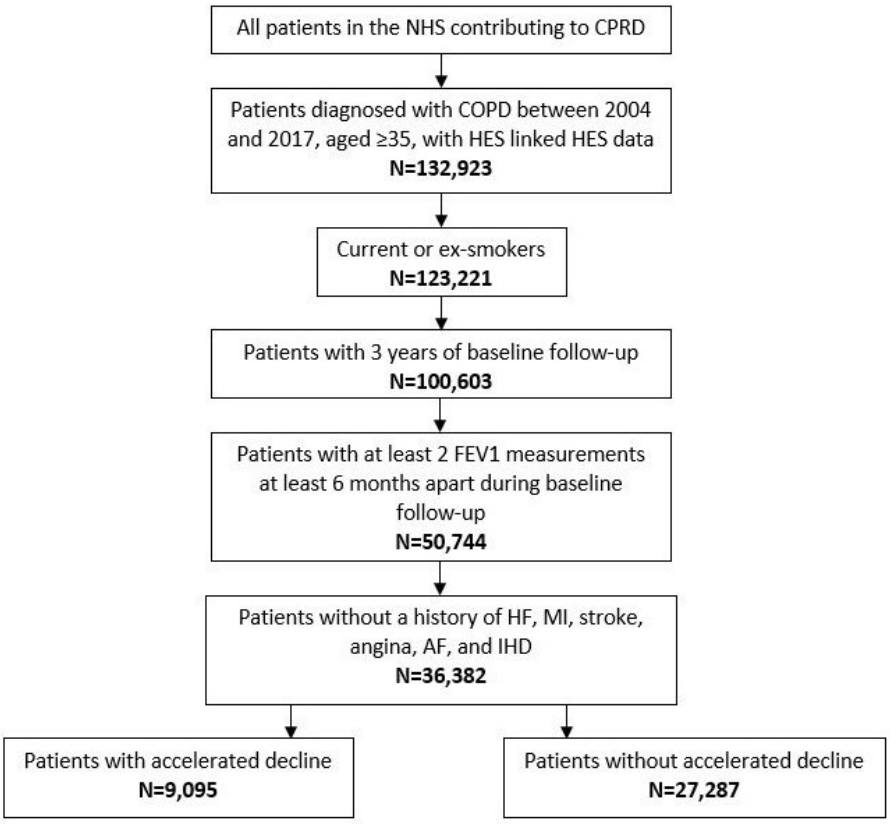


***Figure 8.2**: Patients meeting inclusion criteria.*

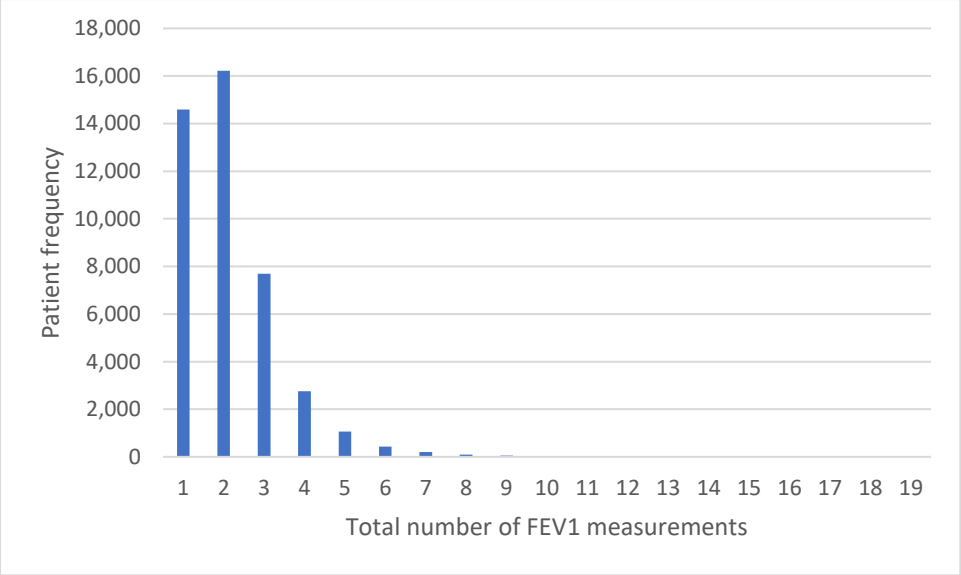


Figure 8.3: *Number of FEV_1 measurements recorded within patients during baseline period.*

Table 8.1 reports baseline characteristics for patients with and without accelerated FEV_1 decline. Patients with accelerated decline were more likely to be male, have severe airflow obstruction (lower FEV_1 percent predicted), be current smokers, but less likely to have hypertension. Patients were similar in terms of all other CVD characteristics (diabetes and statin use).

***Table 8.1**: Baseline characteristics of patients with and without accelerated FEV_1 decline. Numbers are n (%) or median (IQR).*

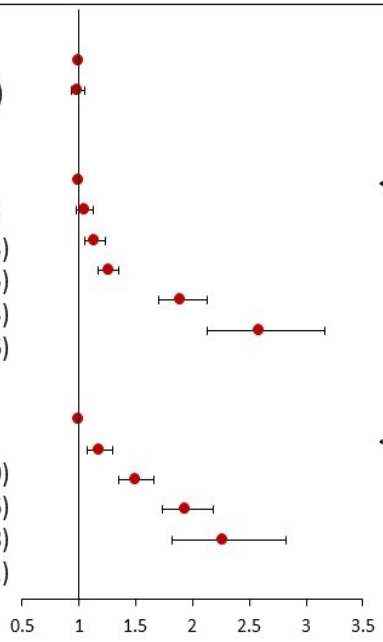
Baseline characteristics	Non-accelerated FEV_1 decline n=27,287	Accelerated FEV_1 decline n=9,095
Males	12,942 (47.4)	5,381 (59.2)
Age	68.9 (61.7 – 76.1)	66.8 (59.6 – 74.0)
Smoking status		
Current smokers	16,912 (62.0)	6,013 (66.1)
Ex-smokers	10,375 (38.0)	3,082 (33.9)
Airflow obstruction*		
Mild	7,566 (27.9)	1,567 (17.4)
Moderate	11,771 (43.5)	3,851 (42.7)
Severe	6,321 (23.3)	2,801 (31.0)
Very severe	1,424 (5.3)	804 (8.9)
AECOPD		
None	10,954 (40.1)	3,496 (38.4)
1 moderate, 0 severe	6,478 (23.7)	2,031 (22.3)
2 moderate, 0 severe	3,730 (13.7)	1,278 (14.1)
≥3 moderate, 0 severe	4,703 (17.2)	1,697 (18.7)
1 severe, any moderate	1,116 (4.1)	466 (5.1)
≥2 severe, any moderate	306 (1.1)	127 (1.4)
mMRC*		
0	3,797 (20.9)	1,206 (20.2)
1	7,396 (40.6)	2,289 (38.4)
2	4,448 (24.4)	1,526 (25.6)
3	2,196 (12.1)	784 (13.1)
4	365 (2.0)	160 (2.7)
BMI*		
Underweight	1.181 (4.9)	390 (4.9)
Normal	8,089 (33.6)	2.750 (34.6)
Overweight	8,060 (33.5)	2,628 (33.1)
Obese	6,727 (28.0)	2,180 (27.4)
Hypertension	11,770 (43.1)	3,660 (40.2)
Diabetes	3,040 (11.1)	974 (10.7)
Asthma	11,238 (41.2)	3,566 (39.2)
Statin use	8,350 (30.6)	2,774 (30.5)

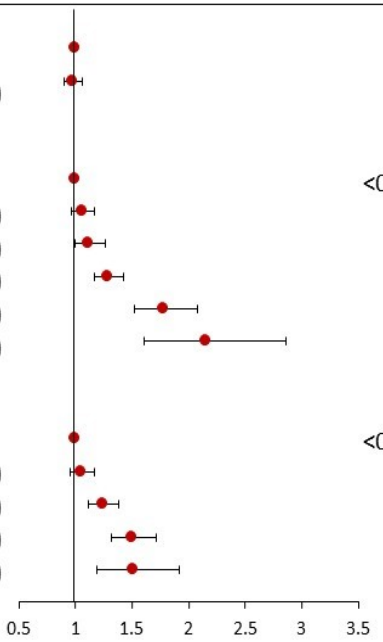
***Note:** *Airflow obstruction N=36,105; mMRC N=24,167; BMI N=32,005.*

8.3.2 Risk of Cardiovascular Disease

During follow-up 6,110 patients had a CVD event, which equates to a rate of 4.6 events per 100 person-years (95% CI, 4.5 – 4.7). No evidence of an association between risk of composite CVD events and accelerated FEV_1 decline was found, in either unadjusted analysis (HR_{unadj}=0.99 (95% CI, 0.93–1.05) or fully adjusted analyses (HR_{adj}=0.98 (95% CI, 0.90–1.06); see **figure 8.4**). However, there was evidence of an association between increased frequency and severity of AECOPD and CVD outcomes. Likewise, increased breathlessness was found to be associated with an increased likelihood of cardiovascular disease as did increasing age, male gender, current smokers, patients with hypertension and patients using statins relative to their reference groups (see **table 8.2**).

Baseline variables	Patients N=36,382	CVD events n=6,110	Risk of composite CVD (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	CVD events n=3,128	Risk of composite CVD (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	4,594	1 (reference)		16,567	2,388	1 (reference)	
Accelerated decline	9,095	1,516	0.99 (0.93 -1.05)		5,392	740	0.98 (0.90 – 1.06)	
AECOPD frequency								
None	14,450	2,175	1 (reference)	<0.001	8,957	1,134	1 (reference)	<0.001
1 moderate, 0 severe	8,509	1,375	1.05 (0.98-1.13)		5,188	715	1.06 (0.97 – 1.17)	
2 moderate, 0 severe	5,008	871	1.14 (1.05 – 1.23)		2.977	426	1.12 (1.00 – 1.26)	
3+ moderate, 0 severe	6,400	1,233	1.26 (1.17 – 1.35)		3,680	607	1.29 (1.17 – 1.43)	
1 severe, any moderate	1,582	353	1.90 (1.70 – 2.13)		926	195	1.78 (1.52 – 2.08)	
2+ severe, any moderate	433	103	2.59 (2.13 – 3.16)		231	231	2.15 (1.61 – 2.86)	
mMRC*								
0	5,003	577	1 (reference)	<0.001	4,468	525	1 (reference)	<0.001
1	9,685	1,261	1.18 (1.07 – 1.30)		8,813	1,134	1.05 (0.95 – 1.17)	
2	5,974	945	1.50 (1.35 – 1.66)		5,478	865	1.24 (1.11 – 1.38)	
3	2,980	568	1.94 (1.73 – 2.18)		2,734	519	1.50 (1.32 – 1.71)	
4	525	94	2.27 (1.82 – 2.82)		466	85	1.51 (1.19 – 1.92)	





*mMRC missing in 12,215 patients

***Figure 8.4**: Hazard ratios (95% CI) illustrating the association between accelerated FEV_1 decline, AECOPD frequency, mMRC, and risk of CVD outcomes and mortality.*

***Table 8.21**: Association between accelerated FEV_1 decline and risk of CVD and mortality.*

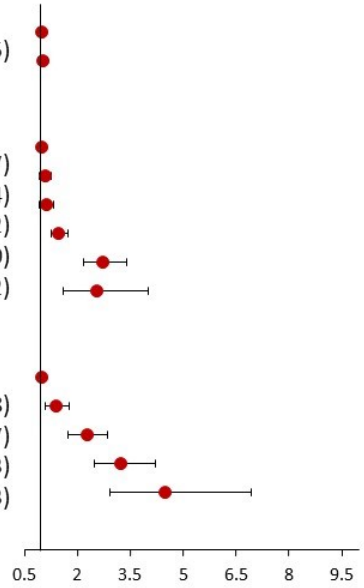
Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR (95% CI)
Accelerated FEV_1 decline	0.99 (0.93 – 1.05)	0.98 (0.90 – 1.06)
AECOPD frequency		
None	Ref	Ref
1 moderate, 0 severe	1.05 (0.98 – 1.13)	1.06 (0.97 – 1.17)
2 moderate, 0 severe	1.14 (1.05 – 1.23)*	1.12 (1.00 – 1.26)*
≥3 moderate, 0 severe	1.26 (1.17 – 1.35)**	1.29 (1.17 – 1.43)**
1 severe, any moderate	1.90 (1.70 – 2.13)**	1.78 (1.52 – 2.08)**
≥2 severe, any moderate	2.59 (2.13 – 3.16)**	2.15 (1.61 – 2.86)**
Airflow obstruction		
Mild	Ref	Ref
Moderate	1.05 (0.98 – 1.12)	1.06 (0.96 – 1.16)
Severe	1.15 (1.07 – 1.24)**	1.02 (0.92 – 1.14)
Very Severe	1.23 (1.10 – 1.38)**	1.10 (0.93 – 1.30)
Age	1.05 (1.04 – 1.05)**	1.04 (1.04 – 1.05)**
Men	1.33 (1.27 – 1.40)**	1.40 (1.29 – 1.51)**
Current smokers	0.83 (0.78 – 0.87)**	1.13 (1.05 – 1.22)*
BMI		
Normal	Ref	Ref
Underweight	1.04 (0.91 – 1.20)	1.08 (0.89 – 1.30)
Overweight	1.10 (1.03 – 1.18)*	1.01 (0.93 – 1.10)
Obese	1.11 (1.04 – 1.19)**	1.09 (0.99 – 1.19)
mMRC		
0	Ref	Ref
1	1.18 (1.07 – 1.30)*	1.05 (0.95 – 1.17)
2	1.50 (1.35 – 1.66)**	1.24 (1.11 – 1.38)**
3	1.94 (1.73 – 2.18)**	1.50 (1.32 – 1.71)**
4	2.27 (1.82 – 2.82)**	1.51 (1.19 – 1.92)*
Asthma	0.91 (0.87 – 0.96)**	1.02 (0.95 – 1.10)
Hypertension	1.66 (1.58 – 1.74)**	1.31 (1.21 – 1.41)**
Diabetes	1.39 (1.30 – 1.50)**	1.09 (0.99 – 1.21)
Statin use	1.40 (1.33 – 1.47)**	1.14 (1.05 – 1.23)*

***Note**: *p<0.05; **p<0.0001. Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

Of 6,110 patients who had a CVD event during follow up, 1,220 were recorded as having had heart failure, 788 a myocardial infarction, 1,039 a stroke, while 1,427 were diagnosed with atrial fibrillation, and 1,636 with coronary artery disease excluding myocardial infarction. Effect estimates for the association between accelerated FEV_1 decline, and AECOPD frequency and mMRC, and the risk of individual CVD outcomes are shown in **figure 8.5-figure 8.10**. Whilst no association was seen between accelerated FEV_1 decline and risk of individual CVD outcomes, increased frequency and severity of AECOPD, and increased mMRC were both associated with all CVD outcomes individually. **Appendix 4**

provides hazard ratios for all covariates in each model for heart failure, myocardial infarction, stroke, atrial fibrillation, coronary artery disease excluding myocardial infarction, and CVD mortality respectively.

Baseline variables	Patients N=36,382	HF Events N=1,220	Risk of heart failure (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	HF Events n=617	Risk of heart failure (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	913	1 (reference)		16,567	464	1 (reference)	
Accelerated decline	9,095	307	1.01 (0.89 – 1.15)		5,392	153	0.99 (0.83 – 1.20)	
AECOPD frequency								
None	14,450	407	1 (reference)	<0.001	8,957	208	1 (reference)	0.006
1 moderate, 0 severe	8,509	268	1.09 (0.93 – 1.27)		5,188	125	0.97 (0.78 – 1.22)	
2 moderate, 0 severe	5,008	161	1.12 (0.93 – 1.34)		2.977	88	1.22 (0.95 – 1.57)	
3+ moderate, 0 severe	6,400	270	1.47 (1.26 – 1.72)		3,680	134	1.46 (1.17 – 1.82)	
1 severe, any moderate	1,582	95	2.72 (2.18 – 3.40)		926	53	2.22 (1.62 – 3.02)	
2+ severe, any moderate	433	19	2.54 (1.60 – 4.02)		231	9	1.60 (0.81 – 3.16)	
mMRC*								
0	5,003	84	1 (reference)	<0.001	4,468	74	1 (reference)	<0.001
1	9,685	218	1.39 (1.08 – 1.78)		8,813	199	1.19 (0.91 – 1.55)	
2	5,974	206	2.27 (1.73 – 2.87)		5,478	194	1.60 (1.22 – 2.11)	
3	2,980	138	3.23 (2.47 – 4.23)		2,734	126	1.94 (1.44 – 2.63)	
4	525	27	4.49 (2.91 – 6.93)		466	24	2.10 (1.30 – 3.40)	



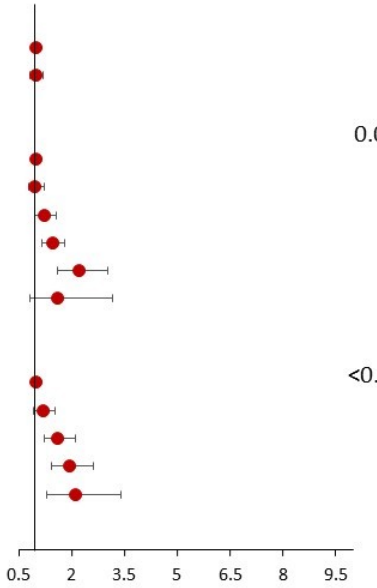


Figure 8.5: *Hazard ratios (95% CI) illustrating the association between accelerated FEV_1 decline, AECOPD frequency, mMRC and risk of heart failure.*
Note: *Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

Baseline variables	Patients N=36,382	MI Events n=788	Risk of myocardial infarction (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	MI Events n=398	Risk of myocardial infarction (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	588	1 (reference)		16,567	308	1 (reference)	
Accelerated decline	9,095	200	1.02 (0.87 – 1.19)		5,392	90	0.89 (0.70 – 1.12)	
AECOPD frequency								
None	14,450	258	1 (reference)	<0.001	8,957	132	1 (reference)	0.003
1 moderate, 0 severe	8,509	173	1.07 (0.89 – 1.29)		5,188	99	1.21 (0.94 – 1.56)	
2 moderate, 0 severe	5,008	105	1.10 (0.88 – 1.37)		2.977	53	1.13 (0.83 – 1.55)	
3+ moderate, 0 severe	6,400	177	1.44 (1.20- 1.74)		3,680	81	1.38 (1.04 – 1.81)	
1 severe, any moderate	1,582	52	2.19 (1.63 – 2.94)		926	24	1.57 (1.01 – 2.45)	
2+ severe, any moderate	433	18	3.49 (2.16 – 5.62)		231	9	2.58 (1.29 – 5.16)	
mMRC*								
0	5,003	66	1 (reference)	<0.001	4,468	59	1 (reference)	0.001
1	9,685	146	1.23 (0.92- 1.63)		8,813	134	1.14 (0.85 – 1.54)	
2	5,974	120	1.65 (1.23-2.21)		5,478	111	1.45 (1.06 – 1.99)	
3	2,980	86	2.50 (1.82 – 3.44)		2,734	81	2.11(1.48 – 2.99)	
4	525	14	2.85 (1.60 -5.06)		466	13	2.07 (1.11 – 3.7)	

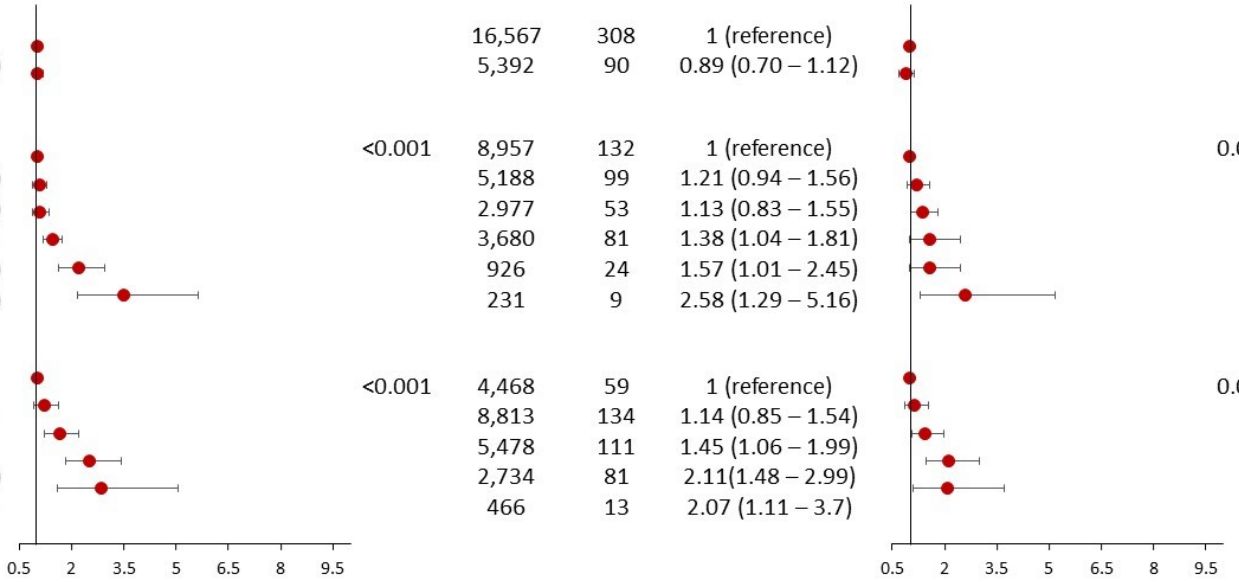


Figure 8.62: *Hazard ratios (95% CI) illustrating the association between accelerated FEV_1 decline, AECOPD frequency, mMRC and risk of myocardial infarction.*
Note: *Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

Baseline variables	Patients N=36,382	Stroke Events N=1,039	Risk of stroke (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	Stroke Events N=523	Risk of stroke (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	781	Ref		16,567	396	Ref	
Accelerated decline	9,095	258	0.99 (0.86- 1.14)		5,392	127	1.01(0.82- 1.23)	
AECOPD frequency								
None	14,450	392	Ref	<0.001	8,957	204	Ref	0.330
1 moderate, 0 severe	8,509	228	0.97 (0.82 – 1.14)		5,188	121	1.01 (0.81- 1.27)	
2 moderate, 0 severe	5,008	170	1.23 (1.03 – 1.47)		2.977	71	1.06 (0.81- 1.39)	
3+ moderate, 0 severe	6,400	178	1.00 (0.84 – 1.20)		3,680	92	1.14 (0.88 – 1.46)	
1 severe, any moderate	1,582	53	1.58 (1.19 -2.11)		926	30	1.54 (1.04 – 2.29)	
2+ severe, any moderate	433	18	2.50 (1.56 – 4.01)		231	<5	1.22 (0.50 – 3.01)	
mMRC*								
0	5,003	111	Ref	<0.001	4,468	104	Ref	0.046
1	9,685	224	1.09 (0.87 – 1.36)		8,813	200	0.96 (0.76 – 1.22)	
2	5,974	141	1.17 (0.91 – 1.49)		5,478	123	0.94 (0.72 – 1.24)	
3	2,980	91	1.62 (1.23 -2.14)		2,734	81	1.31 (0.96 – 1.78)	
4	525	18	2.27 (1.38 – 3.74)		466	15	1.56 (0.89 – 2.75)	

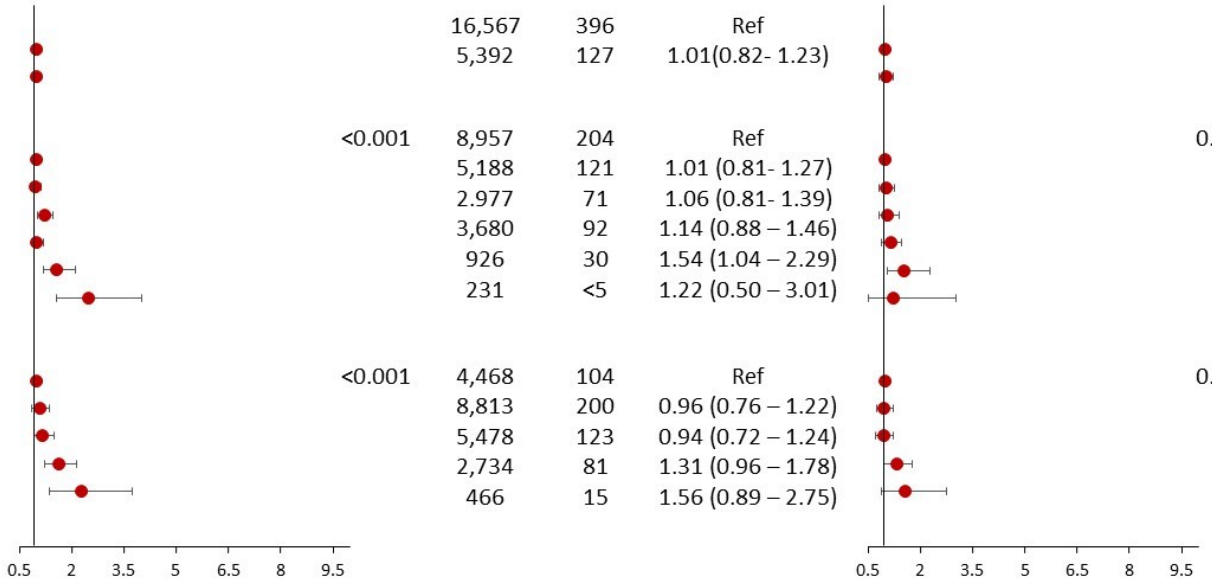
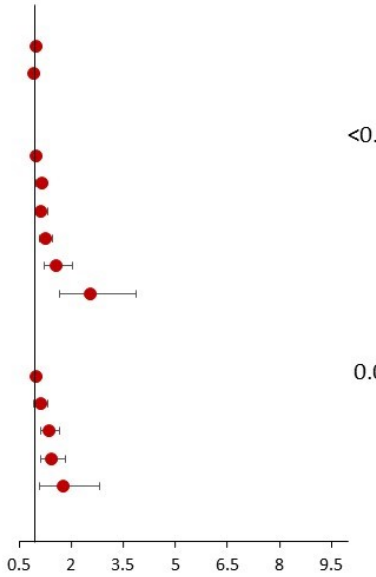


Figure 8.7*: Hazard ratios (95% CI) illustrating the association between accelerated FEV_1 decline, AECOPD frequency, mMRC and risk of stroke.*
Note*: Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

Baseline variables	Patients N=36,382	AF Events n=1,427	Risk of atrial fibrillation (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	AF Events n=727	Risk of atrial fibrillation (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	1,092	1 (reference)		16,567	564	1 (reference)	
Accelerated decline	9,095	335	0.92(0.82-1.04)		5,392	163	0.97 (0.81 -1.15)	
AECOPD frequency								
None	14,450	508	1 (reference)	<0.001	8,957	273	1 (reference)	<0.001
1 moderate, 0 severe	8,509	346	1.14 (0.99 – 1.30)		5,188	170	1.06 (0.87 – 1.28)	
2 moderate, 0 severe	5,008	199	1.12 (0.95 – 1.32)		2.977	94	1.06 (0.83- 1.34)	
3+ moderate, 0 severe	6,400	288	1.27 (1.10-1.47)		3,680	140	1.31 (1.07 – 1.61)	
1 severe, any moderate	1,582	67	1.57 (1.22 – 2.03)		926	37	1.53 (1.07 – 2.17)	
2+ severe, any moderate	433	23	2.56 (1.68- 3.88)		231	13	2.64 (1.49 – 4.66)	
mMRC*								
0	5,003	154	1 (reference)	0.006	4,468	132	1 (reference)	0.524
1	9,685	317	1.11 (0.91 -1.34)		8,813	278	0.98 (0.79 – 1.20)	
2	5,974	227	1.36 (1.11 – 1.66)		5,478	202	1.06(0.85 – 1.33)	
3	2,980	110	1.43 (1.12 – 1.82)		2,734	97	1.03 (0.78 – 1.37)	
4	525	19	1.75 (1.09 – 2.82)		466	18	1.16 (0.69 – 1.93)	



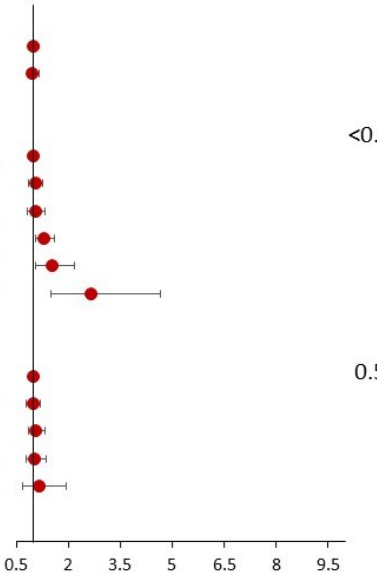


Figure 8.83: *Hazard ratios (95% CI) illustrating the association between accelerated FEV_1 decline, AECOPD frequency, mMRC and risk of atrial fibrillation.*
Note: *Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

Baseline variables	Patients N=36,382	CAD Events N=1,636	Risk of coronary artery disease (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	CAD Events n=863	Risk of coronary artery disease (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	1,220	Ref		16,567	656	Ref	
Accelerated decline	9,095	416	1.03(0.93-1.15)		5,392	207	1.02(0.87 – 1.19)	
AECOPD frequency								
None	14,450	610	Ref	<0.001	8,957	317	Ref	<0.001
1 moderate, 0 severe	8,509	355	0.98 (0.87 – 1.12)		5,188	200	1.11 (0.93 – 1.32)	
2 moderate, 0 severe	5,008	236	1.09 (0.94- 1.26)		2.977	120	1.18 (0.96 – 1.44)	
3+ moderate, 0 severe	6,400	324	1.14 (1.00 – 1.31)		3,680	160	1.20 (0.99 – 1.45)	
1 severe, any moderate	1,582	86	1.64 (1.32 -2.04)		926	51	1.86 (1.39 – 2.50)	
2+ severe, any moderate	433	25	2.17 (1.46 - 3.21)		231	15	2.69 (1.61 – 4.49)	
mMRC*								
0	5,003	162	Ref	0.082	4,468	156	Ref	0.317
1	9,685	356	1.14 (0.95 – 1.37)		8,813	323	1.05 (0.87 – 1.27)	
2	5,974	251	1.43 (1.18 – 1.73)		5,478	235	1.30 (1.06 -1.60)	
3	2,980	143	1.77 (1.43 – 2.20)		2,734	134	1.59 (1.26 – 2.01)	
4	525	16	1.26 (0.75 – 2.10)		466	15	1.04 (0.60 – 1.79)	

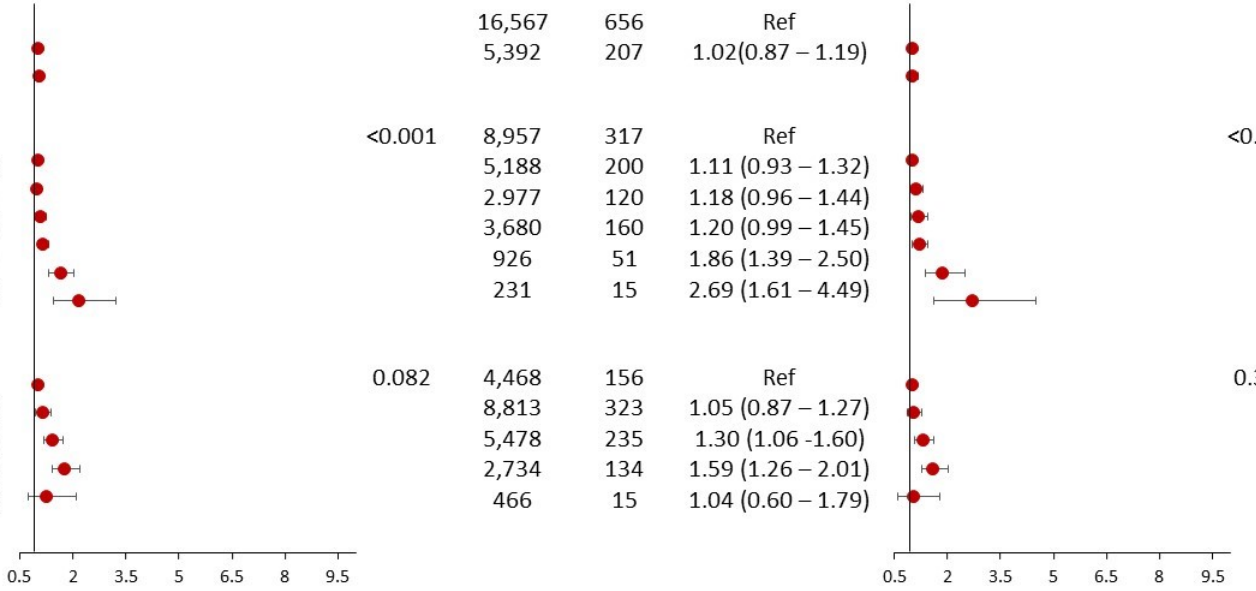
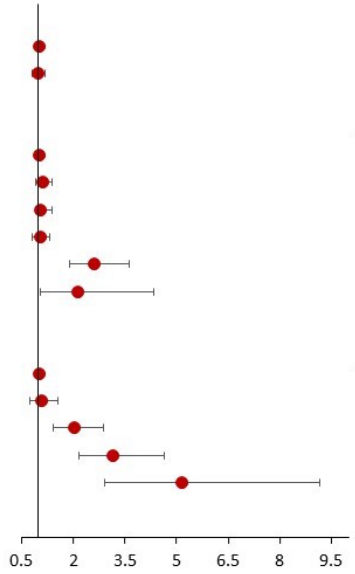


***Figure 8.9**: Hazard ratios (95% CI) illustrating the association between accelerated FEV_1 decline, AECOPD frequency, mMRC and risk of coronary artery disease excluding MI.*
***Note:** Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

Baseline variables	Patients N=36,382	Events N=556	Risk of CVD mortality (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	Events n=282	Risk of CVD mortality (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	421	Ref		16,567	215	Ref	
Accelerated decline	9,095	125	0.96 (0.79-1.17)		5,392	67	0.94 (0.71-1.25)	
AECOPD frequency								
None	14,450	200	Ref	<0.001	8,957	105	Ref	0.854
1 moderate, 0 severe	8,509	135	1.12 (0.90-1.39)		5,188	75	1.19 (0.89-1.61)	
2 moderate, 0 severe	5,008	75	1.06 (0.90-1.38)		2.977	40	1.13 (0.78-1.63)	
3+ moderate, 0 severe	6,400	93	1.03 (0.81-1.31)		3,680	34	0.73 (0.5-1.09)	
1 severe, any moderate	1,582	45	2.61 (1.90-3.61)		926	25	1.94 (1.24-3.05)	
2+ severe, any moderate	433	8	2.13 (1.05-4.34)		231	<3	0.91 (0.29-2.92)	
mMRC*								
0	5,003	43	Ref	<0.001	4,468	39	Ref	<0.001
1	9,685	86	1.08 (0.75-1.55)		8,813	77	0.94 (0.64-1.39)	
2	5,974	95	2.02 (1.41-2.89)		5,478	85	1.57 (1.06-2.32)	
3	2,980	69	3.16 (2.16-4.63)		2,734	68	2.52 (1.66-3.83)	
4	525	16	5.15 (2.90-9.16)		466	13	2.94 (1.52-2.94)	



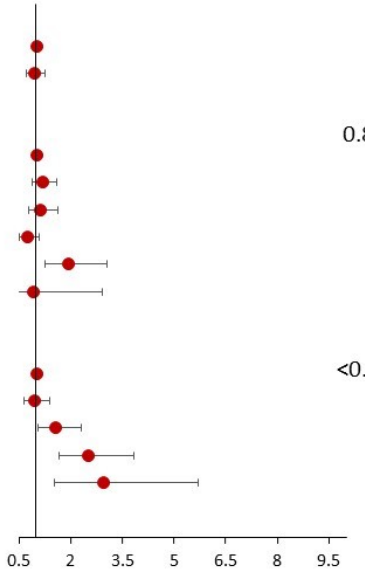


***Figure 8.10**: Hazard ratios (95% CI) illustrating the association between accelerated FEV_1 decline, AECOPD frequency, mMRC and risk of CVD mortality.*
***Note:** Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

8.3.3 Sensitivity analyses

Risk of CVD was similar between patients with and without accelerated decline irrespective of the definitions and cut-offs used to categorise patients according to their rate of loss of lung function (FEV_1). The "no association" finding remained unchanged when accelerated decline was quantified in terms of FEV_1 percent predicted or relative change in FEV_1 from baseline, and there was no association between linear rate of FEV_1 decline and risk of CVD (**table 8.3).** In addition, there was no difference in risk of CVD between patients with FEV_1 decline > –20 ml/year and patients with FEV_1 decline in the range –20 to –40 ml/year, –40 to –60 ml/year, and < –60 ml/year (**Table 8.4).**

Table 8.3: *Relationship between accelerated FEV_1 decline (all four quartiles, relative FEV_1, FEV_1 percent predicted, linear) and risk of CVD.*

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Quartile 1 (slowest decline)	Ref	Ref
Quartile 2	1.05 (0.98 – 1.13)	0.96 (0.87 – 1.06)
Quartile 3	1.06 (0.98 – 1.14)	0.96 (0.87 – 1.06)
Quartile 4 (accelerated decline)	1.02 (0.95– 1.10)	0.95 (0.85 – 1.05)
Accelerated decline in relative FEV_1	1.06 (1.00 – 1.13)	1.00 (0.91 – 1.09)
Accelerated decline in FEV_1 % predicted	1.05 (0.98 – 1.13)	1.00 (0.90 – 1.11)
Linear FEV_1 decline	1.00 (0.99 – 1.01)	1.05 (0.99 – 1.02)

Note: **p value <0.05; **p value<0.0001. Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

Table 8.4: *Relationship between rate of FEV_1 decline (defined by categories used in previous studies) and risk of CVD.*

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR (95% CI)
FEV_1 Decline		
>-20 ml/year	Ref	Ref
-20 to -40 ml/year	1.05 (0.99 – 1.12)	1.00 (0.91 - 1.09)
-40 to -60 ml/year	0.98(0.91 – 1.07)	0.91 (0.81-1.02)
<-60 ml	1.01 (0.93 – 1.09)	1.02 (0.91 – 1.14)

Note: **p value <0.05; **p value<0.0001. Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

Similarly, restricting the analysis to events recorded in primary care (GP-diagnosed CVD), to hospitalisations for CVD or to CVD deaths only did not materially affect the effect estimates (**table 8.5** The finding of "no association" between accelerated FEV_1 decline and risk of cardiovascular disease and death also persisted after stratification by gender, age, smoking status, AECOPD frequency, and airflow obstruction (baseline FEV_1 percent predicted) (**table 8.6).**

Table 8.5: *Relationship between accelerated FEV_1 decline and risk of GP diagnosed CVD, hospitalised CVD, and death from CVD.*

Model	Crude HR (95% CI)	Adjusted HR (95% CI)
GP diagnosed CVD	0.96 (0.89 – 1.04)	0.93 (0.83 – 1.05)
Hospitalised CVD	1.02 (0.90 – 1.16)	0.96 (0.79 – 1.16)
Death from CVD	0.94 (0.75 – 1.16)	0.83 (0.60– 1.15)

Note: **p value <0.05; **p value<0.0001. Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

Table 8.62: *Relationship between accelerated FEV_1 decline and risk of CVD stratified by gender, age, smoking status, AECOPD frequency, mMRC, and airflow obstruction.*

Stratified by	Model	Crude HR (95% CI)	Adjusted HR (95% CI)
Gender	Males	0.93 (0.85 – 1.03)	0.98 (0.85 – 1.12)
	Females	0.97 (0.90 – 1.04)	0.98 (0.88– 1.09)
Age groups	35-50	0.92 (0.62 – 1.38)	0.58 (0.30 – 1.12)
	50-65	1.07 (0.95 – 1.20)	1.02 (0.86 – 1.21)
	65-80	1.04 (0.96 – 1.13)	0.91 (0.81 – 1.02)
	≥80	1.15 (1.00 – 1.32)	1.11 (0.92 – 1.35)
Smoking status	Ex-smoker	0.94 (0.86 – 1.03)	0.93 (0.81 – 1.07)
	Current smoker	1.03 (0.96 – 1.11)	1.00 (0.89 – 1.11)
AECOPD frequency	0, 1, or 2 moderate & no severe	0.98 (0.92 – 1.05)	0.98 (0.89 – 1.09)
	3 mod & no severe or any severe	0.98 (0.88 – 1.09)	0.99 (0.84 – 1.16)
mMRC	0	1.05 (0.86 – 1.27)	1.02 (0.82 – 1.26)
	1	1.00 (0.88 – 1.14)	0.98 (0.85 – 1.12)
	2	0.94 (0.81 – 1.09)	0.99 (0.84 – 1.16
	3	0.89 (0.73 – 1.08)	0.95 (0.77 – 1.17)
	4	0.73 (0.46 – 1.16)	0.73 (0.44 – 1.21)
Airflow obstruction	≥80% FEV_1 predicted	1.01 (0.88 - 1.16)	0.97 (0.83 – 1.12)
	50-80% FEV_1 predicted	0.99 (0.90 – 1.08)	1.02 (0.93 – 1.13)
	30-50% FEV_1 predicted	0.92 (0.83 – 1.02)	0.99 (0.88 – 1.11)
	≤30% FEV_1 predicted	1.02 (0.83– 1.26)	1.08 (0.86 – 1.36)

Note: **p value <0.05; **p value<0.0001. Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

No association was seen between accelerated FEV_1 decline and risk of heart failure, myocardial infarction, stroke, atrial fibrillation, and coronary artery disease excluding myocardial infarction either as separate outcomes or a composite in the first year of follow-up (**figure 8.11).**

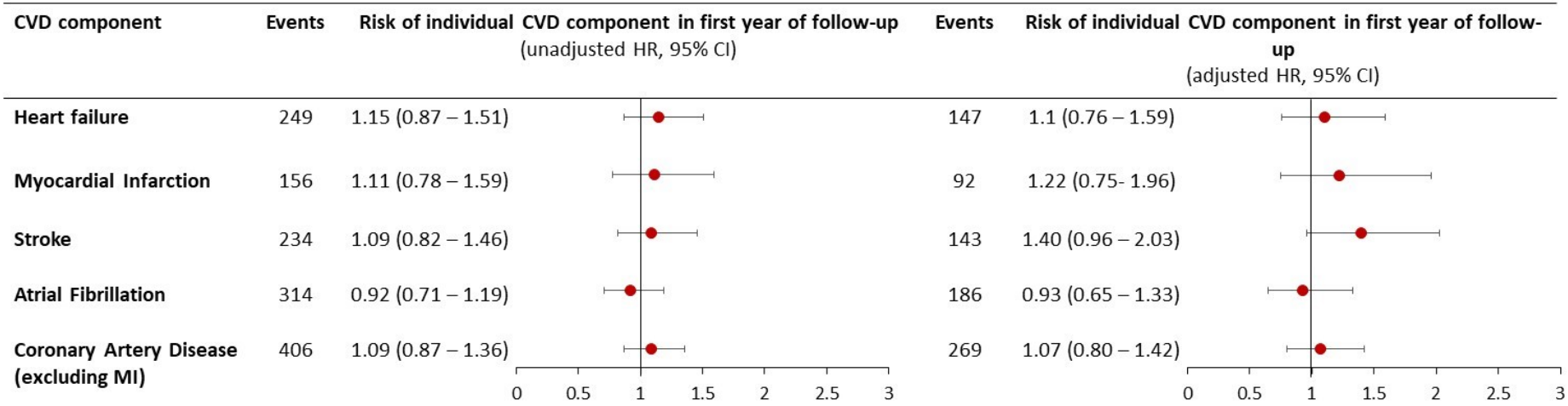


Figure 8.114*: Relationship between accelerated FEV_1 decline and risk of composite CVD, MI,HF, stroke, AF, and CAD excluding MI in the first year of follow-up.*
Note*: Fully adjusted model adjusted for: gender, age, smoking status, airflow obstruction, mMRC dyspnoea (0–4), BMI, hypertension, diabetes, asthma, statin use, and AECOPD frequency and severity.*

8.4 Discussion

This is the first large observational study to investigate the association between accelerated FEV_1 decline and risk of CVD outcomes and mortality in COPD. In patients with no history of CVD, those with accelerated FEV_1 decline had a similar risk of CVD outcomes and mortality compared to patients without accelerated decline, regardless of type of CVD or COPD severity. Rather, other disease characteristics were more closely related to CVD outcomes and mortality, including history of frequent and/or severe AECOPD and increased breathlessness.

8.4.1 Comparison with previous studies

No previous studies have investigated the possible association between lung function decline and CVD risk in a COPD population. This relationship has however been explored in a general population (the ARIC cohort) by Silvestre and colleagues [74]. The authors of this study, which drew on data gathered over a 17-year period, found that people with accelerated FEV_1 decline had a greater risk of a CVD compared to those without accelerated decline. CVD was defined as a composite endpoint that included hospitalisation or death from heart failure, stroke, and coronary heart disease, including myocardial infarction. Separate analyses revealed this increase in CVD risk to be driven by an increased risk for heart failure and stroke events but not coronary heart disease events. This differs to the findings in this study where no association was found between accelerated FEV_1 decline and risk of myocardial infarction, heart failure, stroke, atrial fibrillation, and coronary artery disease excluding myocardial infarction separately.

Inherent differences in the data sources and study design may account for some of the apparent discrepancy in findings between this study and that of Silvestre and colleagues. The latter is a cohort study that followed participants from 1987 in order to understand the causes of atherosclerosis and other clinical outcomes (including CVD risk factors) and data were collected systematically at four phases during follow-up by trained healthcare staff. This study, however, uses routinely collected primary care healthcare records collected from general practices across the UK. Whilst both types of data collection have their own merits, results could differ due to excess variability in spirometry in routinely collected data due to non-standardised collection of data leading to random error. Whilst there are merits to both types of databases, study results are likely to differ [220, 221].

Furthermore, Silvestre et al. used relative change in FEV_1 percent predicted from baseline to categorise study participants in term of rate of FEV_1 decline. This study used absolute change in FEV_1 adjusting for baseline FEV_1. However, sensitivity analyses (in which change in FEV_1 was defined using percent predicted and relative change in absolute FEV_1) demonstrated the robustness of the main findings and definition of the exposure. Lastly, whilst Silvestre et al adjusted for baseline FEV_1, they did not account for other diagnoses such as COPD or airflow obstruction, and it therefore possible that patients with COPD were confounding the relationship between rate of FEV_1 decline and CVD outcomes. It is also important to note

that the magnitude of association with CVD outcomes between people with and without accelerated FEV_1, was small in the Silvestre et al study, suggesting only a marginal increase in their risk (HR_{adj}=1.15 (95% CI 1.04–1.26)). It is possible that the association found in the ARIC study could be lost if other clinically important diagnoses such as COPD were adjusted for and would be consistent with the findings from this study in a COPD population.

Other studies have found that low lung function (both FEV_1 and FVC) in early adulthood is associated with risk of CVD in later life in general populations [64-67]. For example, participants enrolled in the ARIC study in the lowest quartile for FEV_1 had an increased risk of incident hospitalisation or death from heart failure compared with those in the highest quartile. This risk of CVD was also higher in participants with airflow obstruction (FEV_1/FVC<70%) compared to those without, in both men and women [64]. Again, this is likely driven by COPD patients who generally have a lower FEV_1 compared to healthy individuals of the same age. Similarly, the Health, Aging and Body Composition (ABC) study and the Coronary Artery Risk Development in Young Adults (CARDIA) study, two US community- based studies, found linear associations between FEV_1 percent predicted and incident heart failure and stroke hospitalisations over a 10 year period [68, 69]. Overall, however, there is little evidence to suggest that low lung function, compared to high lung function, in patients with COPD is associated with CVD outcomes and mortality. Recently, a post-hoc analysis of the SUMMIT trial data found that FEV_1 percent predicted was not associated with CVD events in a COPD population who were at an increased risk of CVD over a three year period [51]. This is in line with my findings where baseline FEV_1 percent predicted was not associated with risk of CVD and mortality. The association between FEV_1, FEV_1 decline and CVD differs between non-COPD general populations and COPD populations.

8.4.2 Exacerbations of COPD, mMRC, and CVD

Interestingly, increasing frequency and severity of AECOPD and increased breathlessness (mMRC) were associated with increased risk of CVD outcomes and mortality in this COPD patient cohort. This suggests that other markers of disease severity, rather than rate of lung function decline, might be more closely related to CVD outcomes and mortality [1]. This observation is in keeping with previous observational studies which have demonstrated that the period immediately following an AECOPD, especially severe AECOPD, are extremely high risk for CVD events such as MI and stroke relative to periods of more stable disease. For example, Rothnie et al. used linked UK primary care data (CPRD-GOLD and HES) to investigate the relationship between AECOPD (both moderate and severe) and myocardial infraction and stroke (up to 91 days after an AECOPD) [222]. The risk of myocardial infarction and stroke increased after an AECOPD and was higher in patients with more severe AECOPD. Another observational UK study of primary care patients (THIN database) also found that people with COPD had a higher risk of myocardial infarction for up to 5 days after an AECOPD [223]. Likewise, a post-hoc analysis of data from the SUMMIT study reported an association between AECOPD and increased risk of CVD outcomes (including death, myocardial

infarction, stroke, angina, transient ischemic attack) for up to 1 year after an AECOPD, which was heightened after severe AECOPDs [224]. It is possible that the higher risk of CVD associated with AECOPD and breathlessness is because patients who are breathless and experience AECOPD are more likely to go to their GP for further evaluation and there is a higher chance of identifying further comorbidities such as CVD.

Few studies have investigated the long-term association between AECOPD frequency and CVD outcomes. One study by Windsor et al. used UK primary care GP data (CPRD-GOLD) to perform a case–control study that compared the odds of having a stroke in frequent (≥2 AECOPD in the year prior to index date) and infrequent exacerbators. They found no relationship between AECOPD frequency and stroke over a maximum of 9 years [225]. However, this study relied exclusively on primary care data to identify both AECOPD and stroke events, a strategy which in light of findings of later validation studies that highlight the importance of using linked secondary care data with CPRD for identifying events [146], may have resulted in potentially significant event misclassification. In particular, the Windsor et al study may well have missed a substantial proportion more severe AECOPD or strokes. In contrast, our study, which employed a cohort design in HES–CPRD linked data, found that both frequency and severity of AECOPD were strongly associated with risk of CVD outcomes over a maximum follow-up of 13 years.

The relationship between AECOPD and acute CVD events could be driven by increased systematic inflammation during an AECOPD event. Previous studies found that C-reactive protein, IL-6, and fibrinogen increased during an AECOPD event [226]. The increase in inflammatory markers both before and after and AECOPD event are consequently associated with CVD events [223]. In addition, increased inflammation might decrease CD34+ cells which could lead to arterial stiffness and CVD events [227]. Low lung function has also been associated with increased inflammatory markers including CRP and fibrinogen [228, 229] however, increased inflammatory markers have not been associated with the rate at which lung function declines [230]. This could explain why AECOPDs were associated with increased risk of CVD events via increased systematic inflammation whilst rate of FEV_1 decline was not.

Overall, this work suggests that while lung function and rate of lung function decline are associated with an increased risk of CVD outcomes in general population, this association is not seen in a COPD population. It is interesting that no association was seen in a COPD population and this suggests that the accelerated FEV_1 decline phenotype may not be clinically important with regards to risk of developing or dying from CVD. Rather, it is possible that AECOPD are driving the association with COPD and CVD. Patients who experience frequent or more severe AECOPD are more likely to have lower lung function or accelerated lung function decline (as seen in chapter 5), but the AECOPD themselves seem to be contributing to the risk of CVD in COPD patients. Patients who experience multiple AECOPD in close succession may not be managing their COPD properly which could also add to their risk of CVD outcomes.

8.4.3 Strengths and limitations

This is the first study to investigate the relationship between rate of lung function decline and risk of CVD outcomes in a COPD population. By using electronic healthcare records, I identified a large population of COPD patients with varying degree of disease severity, thereby creating a broadly representative COPD population. A wide range of CVD end points were included which allowed me to capture both acute CVD events which required hospitalisation and more chronic forms of disease which are treated in primary care.

In common with previous studies on lung function decline, change in absolute FEV_1 was used as the main exposure. However, baseline FEV_1 percent predicted was included as a confounder in the model and a sensitivity analysis using relative change in FEV_1 was also performed [17, 28, 89]. Similarly, because research suggests that FEV_1 percent predicted is better at estimating change in lung function in studies with follow-up less than 5 years (due to high within-patient variation in absolute FEV_1), a sensitivity analysis using change in FEV_1 percent predicted was also performed [90]. In both cases, results were consistent with those of the main analysis. In order to determine rate of lung function decline at baseline, minimise the effect of measurement error, and accurately summarise a patient's lung function decline, patients were required to have at least three years of baseline follow-up prior to the start of follow-up following previous research [74]. Whilst an adequate baseline period was needed to estimate lung function decline it is important to acknowledge that this could lead to immortal time bias.

In addition, it is possible that patients with COPD could have been misdiagnosed with asthma and vice versa. This is more common in patients over the age of 40 [202]. This is a limitation of the data as we depend on diagnoses and symptoms recorded by the GP however, previous chapters that have excluded patients with a history of asthma showed little difference in effect estimates to those of main analyses. Furthermore, not all patient characteristics or lifestyle factors are recorded within primary and secondary care, such as physical exercise. Therefore, residual confounding is likely to exist. Lastly, statin use was used as a proxy for cholesterol level and pack years smoking was not used due to its poor reliability. Despite this, robust sensitivity analyses were consistent with the main findings.

8.5 Conclusion

This is the first observational study to investigate the relationship between accelerated FEV_1 decline and risk of CVD outcomes and mortality in COPD patients. This study found no association between rate of FEV_1 decline and composite CVD outcomes or heart failure, myocardial infarction, stroke, atrial fibrillation, coronary artery disease (excluding MI), and CVD mortality as separate outcomes. Interestingly, frequent and severe AECOPD and increased breathlessness were closely associated with risk of CVD outcomes and mortality. These findings suggest that accelerated FEV_1 decline may not be a clinically important biomarker for risk of developing CVD or dying from CVD causes, but rather frequent and severe AECOPD are closely associated with risk of CVD and mortality.

Chapter 9
Discussion

This final discussion chapter will summarise the findings from each chapter in a single cohesive discussion that addresses the aims in context of the overarching thesis. Detailed discussions around each specific results chapter can be found at the end of the relevant chapter. Within those discussions, findings have been contextualised with existing literature and strengths and limitations within each individual chapter have been discussed. This format is designed to help fully discuss the rate of FEV_1 decline in a primary care COPD population, factors associated with the decline, and the implications for clinical practice and guidelines in its entirety. This chapter also highlights future research that would contribute to the understanding of the rate of FEV_1 decline in primary care COPD that was outside the scope of this thesis.

Overall, this thesis aimed to: i) investigate the rate of FEV_1 decline in a generalisable primary care population of COPD patients and understand baseline patient and disease related factors that influence the rate of decline; ii) investigate the rate of FEV_1 decline in a generalisable population of COPD patients in relation to ICS use specifically, because clinical guidelines on ICS use have changed and all evidence regarding ICS use and FEV_1 decline originates from RCTs; and iii) investigate whether the rate of FEV_1 decline in a generalisable population of COPD patients is associated with future comorbidity, specifically CVD, a common comorbidity in COPD patients seen in clinical practice. Summaries of these three aims are outlined below.

9.1.1 Aim 1: Understand the rate of FEV_1 decline in a primary care population of COPD patients

Aim 1 was the focus of chapters 4 and 5, which investigated ways in which to define the longitudinal rate of FEV_1 decline available in CPRD, describe the rate of FEV_1 decline in a primary care population of COPD patients, and investigate baseline factors associated with rate of FEV_1 decline, specifically in relation to accelerated FEV_1 decline.

Aim 1.1: Investigate the recording of FEV_1 in CPRD and ways to define longitudinal change in FEV_1 (chapter 4)

This chapter set out to investigate ways to define and estimate longitudinal change in FEV_1 using criterion based on FEV_1 variability, length of follow up time, number of FEV_1 measurements taken during follow-up, time between recorded spirometry measurements, AECOPD recorded close to spirometry, and the inclusion of patients with linked data (HES). The rationale behind this was that due to the nature of routinely collected data, COPD patients may have spirometry recorded at the GP, not only for their annual review, but also on other occasions (possibly due to AECOPDs), which may have led to variation in the frequency and number of FEV_1 measurements within COPD patients in primary care.

First, I found that excluding patients for reasons such as high within patient variation – which could represent measurement error - led to the inclusion of a specific group of patients who do not necessarily represent the wider population of patients seen in everyday practice. In this case, excluding patients with high within patient variation in FEV_1 led to the exclusion of severely obstructed COPD patients. It is possible that these patients had very poor lung function and were unable to perform adequate spirometry. It is common for three spirometry measurements to be performed and for the best measurement to be recorded by the healthcare practitioner. Patients with severe disease may not be able to perform multiple spirometry measurements and therefore only one was performed and recorded, which might not have represented the patient's true FEV_1. However, the use of all other FEV_1 measurements, regardless of follow-up time, number of FEV_1 measurements, time between measurements, the proximity to recorded AECOPD, and the use of HES data, did not affect estimated rates of FEV_1 decline in a primary care COPD population.

Second, the use of mixed linear regression may be a better method to use when estimating FEV_1 decline in routinely collected data, such as CPRD, compared to multiple linear regression and calculating the rate using the difference between first and last FEV_1 measurements divided by duration of follow-up. This is because the model accounts for both within and between patient variation in the model. Many RCTs and other observational studies have used techniques that only include a baseline FEV_1 and one other FEV_1 measurement to estimate FEV_1 decline over a specific period. Whilst this is an appropriate method to use in RCTs or prospective cohort studies, which have regular monitoring of spirometry over follow-up, it may not be the best option when using routinely collected data because reasons for the recording of spirometry measurements is not always known and measurement techniques may vary by GP and healthcare professionals. Due to potential measurement error in routinely collected data, relying on two measurements alone may introduce bias if those two measurements were not recorded correctly, which is more likely in routinely collected data than RCTs and prospective cohort studies. Using as many appropriate FEV_1 measurements over follow-up as possible from routinely collected data may help reduce any biases from measurement error and poorly recorded measurements. Therefore, more robust regression models such as mixed linear regression may be a more appropriate model for estimating FEV_1 decline in routinely collected data.

It would be interesting to investigate the definitions of rate of FEV_1 decline described in chapter 4 in other EHRs or claims databases to understand whether similar methods should be used in similar healthcare databases or whether different definitions of longitudinal change in FEV_1 should be used even between routinely collected databases. In addition, if reasons for why spirometry is recorded is not always known, it would be interesting to investigate whether only using FEV_1 measurements recorded at annual reviews would be a better way of estimating rate of FEV_1 decline. One study of adults with cystic fibrosis found that annual review lung function underestimated lung health in the UK and that approximately 20% of all annual review visits were performed during periods of clinical instability [231]. Further work could investigate this in COPD to explore the quality of spirometry performed on annual review dates. Whilst this method may help to include more reliable FEV_1 measurements, the limitation is that patients would have to have at least one year of follow-up, rather that the required 6 months in this thesis, and this would exclude more patients, specifically those who might have died before a second annual review measurement was identified.

Overall, rate of FEV_1 decline using all interpretable measurements in CPRD is adequate if mixed linear regression is used and researchers should be aware of excluding patients based on within patient variation as it could lead to unrepresentative COPD populations.

Aim 1.2: Describe the rate of FEV_1 decline in a primary care COPD population and investigate patient characteristics that are associated with the decline (chapter 5)

Chapter 5 subsequently described the rate of FEV_1 decline in COPD patients in CPRD using the knowledge obtained in chapter 4. It was important to investigate factors associated with the decline in a primary care setting so that healthcare practitioners can identify early signs of accelerated FEV_1 decline and better manage COPD patients.

Overall, I found that the mean rate of FEV_1 decline in a generalisable COPD population was -17.7 ml/year, which fits with existing literature around FEV_1 decline in COPD [17, 28-30, 38]. The rate of FEV_1 decline in this study population was also heterogenous, which has also been shown in the ECLIPSE study. Interestingly, the ECLIPSE study was an observational study with regular data collection, which suggests that CPRD, a routinely collected database, is a suitable database to estimate FEV_1 decline. The ECLIPSE study also found a mean decline of -33ml/year in COPD patients, similar to the mean rates reported in healthy non-smokers [17, 167]. However, the distribution of rates of decline varied greatly in COPD patients which might explain why mean rates of decline reported in COPD studies are dependent on the type of patients included. Also, most COPD patients (approximately 80% of COPD patients registered in CPRD) are prescribed COPD maintenance therapies aimed to improve symptoms and lung function. This might explain why the rates of FEV_1 decline in primary care COPD populations are slower than what one might expect.

In addition, I found specific patient and disease related characteristics that were associated with accelerated rate of FEV_1 decline. Other than increasing age and current smoking status, which have already been shown to be associated with FEV_1 decline, low BMI, worse COPD disease severity (i.e., high mMRC and frequent moderate AECOPD), high baseline FEV_1 percent predicted, and prevalent ICS use were associated with an increased rate of FEV_1 decline. Whilst factors such as increased frailty (i.e., low BMI) and increased disease severity are likely possible associations, prevalent ICS use may be due to confounding by indication, a common bias seen in routinely collected databases and observational data in general [232]. The association between mild airflow obstruction (i.e., higher baseline FEV_1 percent predicted) and accelerated FEV_1 decline was likely due to higher initial baseline FEV_1. These patients therefore have more absolute lung function to lose compared to more severe patients with lower baseline FEV_1. Interestingly, results suggested that patients with low baseline FEV_1 percent predicted had mean changes of FEV_1 that increased over follow-up. This might be explained by the high within patient variation of FEV_1 seen in these patients, as described in chapter 4. These patients may not be able to perform adequate spirometry measurements, especially as their disease worsens. Further work should set out to explore the recording of FEV_1 in these specific patients to dissect these findings where FEV_1 increases in severe COPD patients.

Future work could also investigate a different measure of change in FEV_1 which incorporates baseline FEV_1. One measure could be the percentage change in FEV_1 from baseline. A previous study investigated both

absolute change and relative change in FEV_1 in a general population and reported baseline characteristics associated with both measures of change [160]. The authors found some inconsistency between baseline characteristics that were significantly associated with both measures of change in FEV_1, notably with gender due to the inclusion of height in FEV_1 percent predicted. Whilst relative change in FEV_1 was used as a sensitivity analysis in chapter 8, future studies should investigate the relationship between a wide range of baseline characteristics, as presented in this chapter, and relative change in FEV_1 to understand whether risk factors associated with change in absolute and relative FEV_1 differ. This would help to understand whether both measures of change in FEV_1 are needed to make clinical decisions. In addition, whilst rate of FEV_1 decline over the long term was estimated using linear models, change in FEV_1 can vary in the short term and future work could investigate the non-linear rate of FEV_1 decline over short periods of time using joint analysis methodology.

9.1.2 Aim 2: Understand the relationship between ICS and rate of FEV_1 decline in a primary care population of COPD patients

Aim 2 relates to the information from chapter 2 (systematic review on ICS and FEV_1 decline), chapter 6 (the relationship between ICS, EOS, and FEV_1 decline), and chapter 7 (the relationship between ICS withdrawal and FEV_1 decline). The previous chapter found that various factors influenced the rate of FEV_1 decline in COPD patients seen in primary care, and ICS use was one of these factors. However, this was likely to be confounded by indication. Many RCTs have shown that ICS use is associated with an attenuated rate of FEV_1 decline however, no studies have investigated this in a more general cohort of COPD patients or over longer periods of time. Similarly, recent ERS guidelines state that ICS should be withdrawn from patients on triple therapy however, the evidence guiding these clinical guidelines includes very specific groups of COPD patient who were not generalisable to the wider population of COPD patients. Guidelines also indicate that blood eosinophils should be used a marker of ICS response. Overall, this chapter described previous literature on ICS use and rate of FEV_1 decline, investigated the relationship between ICS use and the rate of FEV_1 decline in a primary care COPD population and its interaction with blood eosinophils, and investigated the relationship between ICS withdrawal and rate of FEV_1 decline in COPD patients.

Aim 2.1: Conduct a systematic review of the rate of FEV_1 decline associated with use of inhaled corticosteroids in COPD (chapter 2)

This chapter reviewed the existing literature on ICS and rate of FEV_1 decline. Findings from this systematic review showed that RCTs with follow-up of less than one year reported slower rates of decline, or even increases in FEV_1, in ICS trial arms compared to non-ICS trial arms. However, in RCTs with longer follow-up (greater than one year), there was little difference between the rates of FEV_1 decline between in ICS and non-ICS trial arms. This suggested that whilst there seems to be an effect in the short term, long term use of ICS may not help improve lung function in COPD patients by a clinically meaningful amount. It is

important to weigh out the benefits of ICS use compared to risks, specifically the increased risk of pneumonia that is well established in this population.

Aim 2.2: Investigate the relationship between ICS use, eosinophil counts, and rate of FEV_1 decline (chapter 6)

Given the findings from chapter 2 (systematic review), this chapter estimated the rate of FEV_1 decline in a primary care COPD population over a maximum of 12 years and investigate whether blood eosinophil levels modify the relationship between ICS and rate of FEV_1 decline. Interestingly, I found that the rate of FEV_1 decline was not clinically different between patients on ICS and those not on ICS over a maximum of 12-years. In addition, having high blood eosinophils did not modify the relationship between ICS use and rate of FEV_1 decline.

However, when patients first started taking ICS medications there were some differences in the rate of FEV_1 decline compared to those not taking ICS medications and differences related to baseline eosinophil level. Results suggested that FEV_1 increased in patients initiating ICS compared to those not on ICS. Results also suggested that the improvement in FEV_1 when initiating ICS was greater in patients with high baseline blood eosinophils and less so in patients with low blood eosinophils. This suggests a potential short-term effect of ICS, notably in patients with high blood eosinophils, but in the long term, ICS users do not have a clinically different rate of FEV_1 decline compared to those not on ICS. Further sensitivity analyses were consistent with this finding.

These results were in line with what I found in the systematic review of RCTs highlighting little benefit in FEV_1 decline with the long-term use of ICS compared to in the short term [115]. Future work should aim to confirm this and help to understand how long this time frame is. This needs to be confirmed because comparative effectiveness analyses studying prevalent users are likely to have more confounding than those of new users [45]. For example, prevalent users might meet study inclusion criteria after the initiation of the treatment and these patients might have been affected by the treatment prior to study follow-up [45]. More evidence on the time frame in which ICS reduces FEV_1 decline could help guide the length of ICS use to improve lung function in specific patients. Spline analysis may be one method to use to investigate the difference in rate of FEV_1 decline between new ICS users and non-ICS users over specific time intervals.

It is possible that some patients benefit from the long-term use of ICS and this should also be investigated to understand for how long and in which patients ICS should be prescribed for. For example, ICS use is associated with lower C-reactive protein (CRP), which is also associated with lung function and mortality [233, 234]. The relationship between ICS, CRP, and FEV_1 decline could be investigated to investigate whether patients with higher CRP benefit from ICS use in the long term. In addition, other than further biomarkers of inflammation, factors such as genetics could play a role whereby COPD patients with a specific genetic variant could benefit more from long term ICS use compared to other COPD patients with

regards to FEV_1 decline. Recently, Obeidat and colleagues performed a GWAS study and found five loci that showed an interaction with positive response to ICS. Specifically, one genotype was associated with the rate of FEV_1 decline in COPD patients on ICS [235]. Further studies should investigate whether such genetic variants modify the relationship between ICS and FEV_1 decline over longer periods of time.

Aim 2.3: Investigate the relationship between withdrawal of ICS and rate of FEV_1 decline (chapter 7)

Clinical guidelines for COPD now state that ICS should be withdrawn if patients experience few or no AECOPD and have low blood eosinophils [37]. This is largely based on results from the WISDOM trial that found that patients who withdrew from ICS has a similar risk of AECOPD compared to those who remained on ICS. However, the WISDOM study also found those who withdrew from ICS had a faster FEV_1 decline than those who remained. These findings were based on a specific COPD population who had severe COPD and who exacerbated. Therefore, the aim of this chapter was to investigate the association between ICS withdrawal and rate of FEV_1 decline in a generalisable population of COPD patients, as well as a similar population to WISDOM and a further population that included patients specifically with comorbidities as these patients are often excluded from RCTs.

Overall, I found that there was no clinical difference in rate of FEV_1 decline between patients who withdrew from ICS compared to those who did not withdraw in any of the three populations or sensitivity analyses. This suggests that withdrawing patients on triple therapy from ICS may not influence patients' rate of FEV_1 decline. However, a main limitation of this study, was that the classification of patients who did and did not withdraw from ICS was confounded by indication. This meant that patients classed as ICS withdrawers were patients who GPs would have considered would do well after withdrawing ICS.

EHRs are valuable databases to investigate treatment effects because of their rich information on prescriptions, patient characteristics, and a wide variety of outcomes, including rate of FEV_1 decline. Emulating trials using EHR may be beneficial when RCTs are not possible, ethical, or if broader populations are to be investigated. However, there are important design aspects to bear in mind when using these databases to emulate trials including treatment assignments (i.e., defining patients who withdrew from ICS and patients who remained on ICS), defining time zero (i.e., the time at which patients withdraw from ICS), and analysis plan (i.e., intention to treat or censored analysis) [45]. If factors such as these are not properly emulated, then biases can arise such as selection bias and confounding by indication. Confounding by indication was likely to be a main source of confounding in the analysis performed in chapter 7. This is because healthcare practitioners would have decided to whether they should withdraw ICS from patients on triple therapy. This decision would have been influenced by a variety of factors including the healthcare practitioner's perception of how well the patient is, how well they are responding to their current therapy, their own experience withdrawing patients from ICS, whether the patient asked to change treatment, and many more [214, 215]. Understanding why patients withdrew from ICS is important to fully understand the

patient characteristics of those who withdrew from ICS compared to those who remained on triple therapy. Methods exist to overcome confounding by indication and future work should use these to investigate the relationship between ICS withdrawal and rate of FEV_1 decline whilst minimising confounding by indication. One way to do this is using propensity scores to estimate a probability score for every patient based on the odds of the patient withdrawing from ICS. Factors that are likely to influence the decision for withdrawal should be used to estimate this probability score. The score could then be used to match treatment groups so that patients are similar in t of the probability of being withdrawn from ICS [214, 215].

Interestingly, Wing and colleagues recently used CPRD to apply trial emulation methods to replicate the TORCH study [236]. They used patient level TORCH data to match COPD patients in CPRD to COPD patients in the TORCH study using propensity scores. Overall, the authors found similar results to those reported in the TORCH study except for in placebo comparisons. This suggests that these techniques are useful in minimising biases, such as confounding by indication, in non-placebo comparisons when using routinely collected data to emulate a trial. Further work following on from chapter 7 should aim to develop more robust methodology to better emulate the WISDOM trial and extrapolate findings to more generalisable populations. One way to validate findings of the WISDOM trial would be to perform similar methods to those performed by Wing and colleagues and use patient level WISDOM data to match COPD patients in CPRD to those in the WISDOM trial. In addition, it is possible that patients captured in routinely collected data can have multiple eligibility periods. This means that patients could have withdrawn from ICS but have been prescribed ICS again (as triple therapy) later during follow-up, thus switching exposure group. It is therefore possible to include patients multiple times depending on their exposure at a given time and adjust for baseline characteristics associated with each eligibility time point. This could help increase sample size and properly capture all exposure groups during follow-up.

9.1.3 Aim 3: Investigate the relationship between rate of FEV_1 decline and future risk of CVD (chapter 8)

All previous chapters investigated the relationships between patient characteristic, with an emphasis on ICS use, and the rate of FEV_1 decline in primary care COPD patients. I found that various characteristics do influence the rate of FEV_1 decline, which is important for disease management however, little is known about the rate of FEV_1 decline and future risk of comorbidities, specifically CVD, a common comorbidity of COPD patients. This was important to understand because lung function decline has been previously associated with HF and stroke in a general population and it is important to identity early markers of developing comorbidities, which have further detriment to COPD disease progression [74]. Therefore, the aim of chapter 8 was to investigate the relationship between accelerated FEV_1 decline and risk of future CVD in a CVD naive primary care COPD population.

Overall, I found that COPD patients with accelerated FEV_1 decline had the same risk of developing CVD or CVD mortality as COPD patients without accelerated FEV_1 decline in a CVD naive population of COPD patients. I repeated analyses using different thresholds for accelerated FEV_1 decline, investigated each CVD event separately, included repeated events however, all analyses suggested that there was no association between accelerated FEV_1 decline and risk of future CVD. Rather, it seems that other COPD related factors such as AECOPD were more closely associated with future risk of CVD, which is already a well-established association seen in previous studies. It is possible that AECOPD are driving the relationship between FEV_1 decline and risk of CVD as lung function decreases both during and after an AECOPD and in some patients this decline in lung function cannot be restored and therefore patients who exacerbate more often will have lower lung function as well as increased risk of CVD. It would be useful to compare the findings of this study to similar COPD studies using different databases and slightly different COPD populations, not just primary care for example, to validate and contextualize these findings further.

9.1.4 Thesis conclusions

Overall, FEV_1 decline in COPD patients seen in primary care is heterogenous and various factors are associated with the rate of decline which are important in identification of patients at risk of accelerated decline and better disease management. In addition, ICS use was not associated with reduced rate of FEV_1 decline in the long term however, incident ICS use was associated with improved lung function, notably in COPD patients with high blood eosinophils. Further work is needed to fully understand the time that the benefits of ICS use in relation to rate of FEV_1 decline are seen. In addition, rate of FEV_1 decline was similar between patients who withdrew from ICS compared to patients who remained on triple therapy, however further effort is needed to ensure robust methodology. Lastly, the rate of FEV_1 decline was not associated with future risk of developing CVD or CVD mortality.

This thesis has furthered the discipline by studying COPD patients who are not commonly represented in RCTs or observational studies. Whilst limitations exist and further work is needed, healthcare practitioners should be aware of the patient characteristics and the presentation of disease related characteristics to identify patients who are more likely to have faster rates of FEV_1 decline, and who would be more at risk of mortality. In addition, healthcare practitioners should be aware that ICS use may not improve lung function over the long term and could be withdrawn from ICS if appropriate however, further work is needed to fully understand the effects of ICS withdrawal in these patients with more robust methodology.

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Whittaker HR, Jarvis D, Sheikh MR, Kiddle SJ, Quint JK. Inhaled corticosteroids and FEV_1 decline in chronic obstructive pulmonary disease: a systematic review. Respir Res. 2019 Dec 4;20(1):277. doi: 10.1186/s12931-019-1249-x. PMID: 31801539; PMCID: PMC6894275.	The Authors	CC BY
Whittaker HR, Bloom C, Morgan A, Jarvis D, Kiddle SJ, Quint JK. (2020). Accelerated FEV_1 decline and risk of cardiovascular disease and mortality in a primary care population of COPD patients. *ERJ.* DOI: 10.1183/13993003.00918-2020	ERS	See Permissions

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1.2	Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Camblor P, Meek P, Owen CA, Petersen H, Pinto-Plata V, Schnohr P, Sood A, Soriano JB, Tesfaigzi Y, Vestbo J. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. N Engl J Med. 2015 Jul 9;373(2):111-22. doi: 10.1056/NEJMoa1411532. PMID: 26154786.	NEJM	CC BY
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1.5	Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice?. *Ther Adv Respir Dis*. 2018;12:1753465817750524. doi:10.1177/1753465817750524	Therapeutic Advances in Respiratory Disease	See Permissions

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Many thanks in advance,
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To whom it may concern,

I am completing my PhD thesis at Imperial College London entitled '**Factors associated with the rate of FEV1 decline in a primary care COPD population**".

I seek your permission to reprint, in my thesis, the published version of two papers I published in: Whittaker HR, Müllerova H, Jarvis D, et al. Inhaled corticosteroids, blood eosinophils, and FEV_1 decline in patients with COPD in a large UK primary health care setting. *Int J Chron Obstruct Pulmon Dis*. 2019;14:1063-1073. Published 2019 May 23. doi:10.2147/COPD.S200919; and Whittaker HR, Pimenta JM, Jarvis D, Kiddle SJ, Quint JK. Characteristics Associated with Accelerated Lung Function Decline in a Primary Care Population with Chronic Obstructive Pulmonary Disease. Int J Chron Obstruct Pulmon Dis. 2020;15:3079-3091

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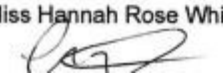
Yours sincerely,

Miss Hannah Rose Whittaker



Approval for use- International Journal of COPD

ACI211087 - COPD/Whittaker - Permission Granted

SA Shannon Ainsworth <shannonainsworth@dovepress.co.uk>
To Whittaker, Hannah R
Cc Claire Wilshaw

Hi Hannah Whittaker

Thank you for your below enquiry.

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Characteristics Associated with Accelerated Lung Function Decline in a Primary Care Population with Chronic Obstructive Pulmonary Disease
Whittaker H et al
International Journal of Chronic Obstructive Pulmonary Disease 2020 15 3079-3091

Inhaled corticosteroids, blood eosinophils, and FEV1 decline in patients with COPD in a large UK primary health care setting
Whittaker H et al
International Journal of Chronic Obstructive Pulmonary Disease 2019 14 1063-1073

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Request for reprint – European Respiratory Journal (ERJ)

Permission to replicate published article for PhD thesis

WH Whittaker, Hannah R
To Sarah.Cleveland@ersnet.org

06/01/2021

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I have attached a form from my Institute (Imperial College London)that needs to be signed by both myself and the journal to prove that permission to use aspects of my published work in my thesis was granted.

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Many thanks in advance,
Hannah Whittaker

06/01/21

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I am completing my PhD thesis at Imperial College London entitled '**Factors associated with the rate of FEV1 decline in a primary care COPD population"**.

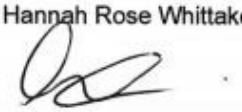
I seek your permission to reprint, in my thesis, the published version of a paper I published in: Hannah R. Whittaker, Chloe Bloom, Ann Morgan, Deborah Jarvis, Steven J. Kiddle, Jennifer K. Quint. European Respiratory Journal Jan 2020, 2000918; DOI: 10.1183/13993003.00918-2020.

I would like to include the paper in my thesis which will be added to Spiral, Imperial's institutional repository http://spiral.imperial.ac.uk/ and made available to the public under a Creative Commons Attribution-Non Commercial-No Derivatives 4.0 International Licence (CC BY-NC-ND).

If you are happy to grant me all the permissions requested, please return a signed copy of this letter. If you wish to grant only some of the permissions requested, please list these and then sign.

Yours sincerely,

Miss Hannah Rose Whittaker



Approval for use- European Respiratory Journal (ERJ)

RE: Permission to replicate published article for PhD thesis

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To Whittaker, Hannah R

Reply | Reply All | Forward | ...
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Accelerated FEV_1 decline and risk of cardiovascular disease and mortality in a primary care population of COPD patients
Hannah R. Whittaker, Chloe Bloom, Ann Morgan, Deborah Jarvis, Steven J. Kiddle, Jennifer K. Quint
European Respiratory Journal 2000918; **DOI:** 10.1183/13993003.00918-2020 Published 24 September 2020
Material: Entire Article

Request for reprint – American Journal of Respiratory and Critical Care Medicine

Permission to replicate figure for PhD thesis

WH Whittaker, Hannah R
To 'dgern@thoracic.org'

12/01/2021

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Approval for use- American Journal of Respiratory and Critical Care Medicine

RE: Permission to replicate figure for PhD thesis

AP

ATS Permission Requests <permissions@thoracic.org>
To Whittaker, Hannah R

13/01/2021

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Best regards,

Megan

Request to reprint- BMJ

Permission to replicate figure in PhD thesis

WH

Whittaker, Hannah R

To bmj.permissions@bmj.com

12/01/2021

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Many thanks in advance,
Hannah Whittaker

Approval for use- BMJ

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N noreply@bmj.com
To Whittaker, Hannah R

12/01/2021

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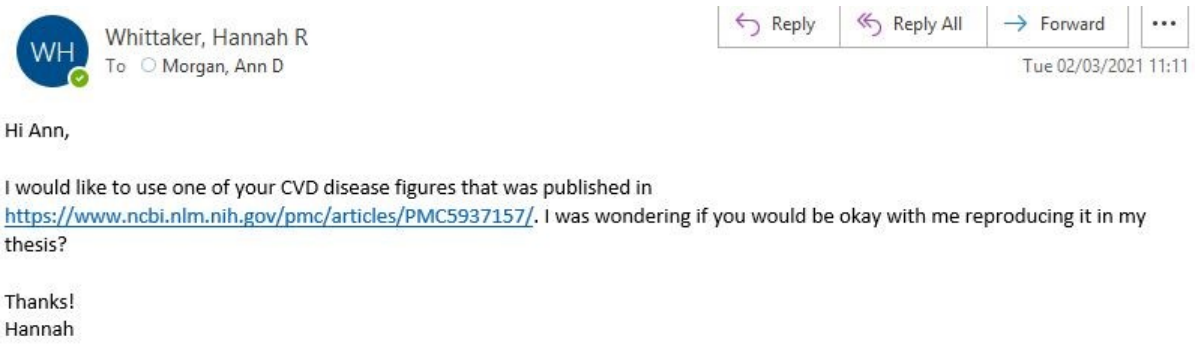
Request to reprint - Therapeutic Advances in Respiratory Disease



Whittaker, Hannah R
To Morgan, Ann D

Reply | Reply All | Forward | ...
Tue 02/03/2021 11:11

Hi Ann,

I would like to use one of your CVD disease figures that was published in https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5937157/. I was wondering if you would be okay with me reproducing it in my thesis?

Thanks!
Hannah

Approval for use – Therapeutic Advances in Respiratory Disease

RE: Reproducing figure in thesis

Morgan, Ann D
To Whittaker, Hannah R

Reply | Reply All | Forward | ...
Tue 02/03/2021 11:31

Yep! Go ahead.

Appendix 2: Supplementary material to chapter 2

Population inclusion and exclusion criteria for studies included in the systematic review.

Author	Inclusion criteria	Exclusion criteria
Calverley 2003	Age 40-74; clinical diagnosis of COPD; history of current/previous smoking; FEV_1 % predicted <85%; FEV_1/FVC <70%; FEV_1 ≥0.8L	Clinical diagnosis asthma; require non-trial anti-inflammatory treatment for lung disease or β-adrenoblockers; <5 years life expectancy due to concomitant disease; unable to meet required standards for spirometry
Auffarth 1991	Smoking ≥1 cigarette/day for at least 5 years; FEV_1 % predicted 30-75; reversibility less than 20% FEV_1 % predicted; provocative concentration of histamine causing a 20% fall in FEV_1 less than 16mg/ml; negative skin test response to 12 allergens/IgE for house dust mite; total serum IgE below 470IU/ml; blood eosinophils below $0.2x10^6$/L; no URTI or ocs 2 months prior to start; ICS stopped 2 weeks prior	
Bourbeau 1998	Age ≥40; smokers or ex-smokers; no asthma history in childhood or adulthood; no AECOPD in last 2 months; pre-bronchodilator FEV_1>65% predicted; FEV_1/FVC>0.65; post-bronchodilator FEV_1 <80% predicted; regular treatment with ≥1 bronchodilator; no ICS or ocs in previous 2 months; no other active lung disease or diabetes, peptic ulcer disease, uncontrolled high blood pressure; hf, any disease other than COPD that would affect qol; non-responders to ocs	
Vestbo 2017	Age ≥40; current or ex-smoker; COPD diagnosis with post bronchodilator FEV_1<50% predicted; FEV_1/FVC<0.7; ≥1	ICS/LAMA/LABA 2 months prior; asthma diagnosis; allergic rhinitis or atrophy; AECOPD 4 weeks prior; clinically significant cardiovascular

	moderate/severe AECOPD in prior year; used ICS +LABA or ICS+LAMA or LAMA monotherapy for≥2 months prior to start	conditions or laboratory abnormalities; unstable concurrent disease that could influence safety and efficacy
Burge 2000	Age 40-75; current or former smokers; non-asthma COPD; FEV_1 post bronchodilator >0.8L and <85% predicted; FEV_1/FVC<70%	FEV_1 response to 400ug salbutamol exceeding 10% predicted; life expectancy <5 years; concurrent diseases; used β-blockers
Pauwels 1999	Age 30-65; current smokers at least 5 cigarettes/day, smoked cigarettes for >10 years, smoking history ≥5 pack years; FEV_1 % predicted 50-100; FEV_1/FVC<70%; increase in FEV_1 after inhalation of 1mg terbutaline <10%; change in FEV_1 between the end of first 3 months of run in and end of second <15%	History of asthma, allergic rhinitis, allergic eczema; oral glucocorticoids for >4 weeks during 6 months follow-up
Vestbo 1999	Age 30-70; FEV1/FVC<0.7; FEV_1 reversibility after inhalation of 1mg terbutaline<15%; FEV_1 reversibility after 10 days treatment with oral prednisolone<15%; informed consent	Long term treatment (>2 episodes of >4 weeks) ocs or ICS within 6 months of study entry; pregnancy or lactation; intention to become pregnant; other serious systemic disease that could influence results; chronic alcohol and drug use; participation in other clinical studies of COPD within 1 month of inclusion
Ohar 2014	Age ≥40; AECOPD within 2 weeks of start and hospitalised for ≤1 days or emergency room observation for ≥24hours with ocs & abx treatment or visit to GP or emergency room for <24 hours with ocs & abx treatment plus 6 months history of AECOPD related hospitalisations	Other significant co-morbid conditions (current or history) including asthma, lung cancer, uncontrolled diabetes and hypertension, angina etc., abnormal ECG or chest x-rays at visit 1, pregnancy, physical disability, hypersensitivity to β-agonists, any adverse reaction, substance abuse or psychiatric disease that might interfere with study
Calverley 2018 & Vestbo 2016	Age 40-80; current or former smokers with ≥10 pack-years; post bronchodilator FEV_1 50%-70% predicted; FEV_1/FVC<0.7; MRC≥2; history or at risk of CVD	Current diagnosis of asthma; significant lung disease other than COPD; lung reduction surgery; receiving long term O_2 therapy or ocs; severe hf; life expectancy less than 2 years; end-stage chronic renal disease
Cazzola 2000	Age ≥50; well controlled COPD; 20≤ smoking pack years; change in FEV_1≤12% predicted following salbutamol 400ug; post-bronchodilator FEV1<85%; good MDI technique; previously been	Asthma as primary diagnosis; unstable respiratory disease requiring oral/parenteral steroids within 4 weeks prior to start; upper or lower RTI within 4 weeks of screening visit; unstable angina or unstable arrythmia; concurrent use of medications that affected COPD or interact with

	individually dose titrated with SR theophylline to serum theophylline level 10-20 ug/mL	methylxanthine products (macrolides or fluoroquinolones, evidence of alcohol abuse)
Vestbo 2005	Age 40-79; COPD by ERS definition; >10 smoking pack years; pre-bronchodilator FEV_1 25-70% predicted; FEV_1/FVC<70%; poor short-term reversibility (<10% predicted FEV1 30 mins post 400ug salbutamol); chronic bronchitis with exacerbations in the last three years	Current diagnosis asthma; eczema; allergic rhinitis; treatment with systemic steroids, antibiotics; change in COPD medication in last 4 weeks; use of SABAs, other ICSs, other LABAs and combination bronchodilators (Combivent, berodual, duovent)
Renkema 1996	Clinical diagnosis of COPD based on history (persistent dyspnoea, on exertion, without sudden attacks of dyspnoea); FEV_1<80% predicted ;RV>100% predicted; specific compliance (Csp%pred)>100% post BD - if air trapping> 1.5L Csp allowed to be <100%pred; no signs of allergy (-ve SPT, <200IU/mL IgE, <250x10^3/mL peripheral blood eosinophils; serum α_1-anti-trypsin level within normal range; clinically stable disease	>70 years old at entry; receiving continuous corticosteroid therapy; severe concomitant disease which may interfere with the study
Lee 2015	Age ≥40 years; clinical diagnosis of COPD with symptoms for >2 years; history of ≥1 AECOPD requiring steroids/abx within 1-12 months; current or prior smoking history of ≥10 pack years; pre-bronchodilator FEV_1 ≤50% predicted; pre-bronchodilator FEV1/FVC <70%	History of asthma; history of seasonal allergic rhinitis before age 40; AECOPD requiring hospitalisation/A&E admission 4 weeks prior to or during run-in period; used systemic/inhaled glucocorticosteroids 4 weeks/2 weeks before run-in period; significant cardiovascular disorder; significant respiratory tract disorder (not COPD); received non-cardio selective oral or ophthalmic β-blocking agents; narrow-angle glaucoma; prostatic hyperplasia; bladder neck obstruction
Shaker 2009	Aged 50-80; current smokers with history of ≥10 cigarettes a day during last 6 months and previous history of ≥20 pack years; clinical diagnosis of COPD for <2 years; FEV1 35-70% predicted; FEV_1/FVC≤60%	Ex-smokers; FEV_1 reversibility ≥12% and 200ml from baseline 15 mins after 1mg terbutaline inhalation or ≥15% and 300ml after 2 weeks on oral prednisolone (25mg); any severe concomitant disease; AECOPD 30 days prior to first visit; ocs for >4 weeks 6 months prior to first visit; long-term O_2 therapy

Wise 2000	Age 40-69; FEV_1/FVC<0.7; FEV1 30-90% predicted; current smokers or ex-smokers who had quit within previous 2 years	Any other medical conditions; recent mi, alcoholism; hf; insulin-dependent diabetes mellitus; neuropsychiatric disorders; bronchodilator use or ics/ocs in previous year
Weir 1999	Clinical diagnosis COPD; adult onset airflow obstruction; FEV_1<70% predicted; FEV_1/FVC<65%	Diagnosis of asthma; clinically significant bronchodilator reversibility; history of acute attacks of breathlessness and recovery between episodes; significant improvement with steroid use in the past; patients who thought that steroid treatment was clinically indicated; prescribed ocs ≥3 months in previous year or anytime in 4 weeks before trial

Quality assessment and support for judgement for each article included in the systematic review.

Author & year: Calverley 2003		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Unclear	Quote: "Treatment was randomized" Comment: Probably done however, more detail is needed
Allocation concealment *Selection bias*	Unclear	Did not mention
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: "Double blind" Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "Double blind" Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	While 156/376 patients withdrew from ICS and 193/375 withdrew from placebo, all patients were included in analyses and patients who withdrew were compared with patients who completed the study in terms of outcomes

Author & year: Auffarth 1991		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Unclear	Quote: "They were then allocated at random to one of two parallel groups in a double blind design" Comment: Probably done but no description of how it was done
Allocation concealment *Selection bias*	Unclear	Not mentioned
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: "double blind design" Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double blind design" Comment: Probably done
Incomplete outcome data *Attrition bias*	High	Quote: "Eleven of the 12 placebo treated and 10 of the 12 budesonide treated patients completed the trial". Comment: ITT patients used for baseline characteristics, FEV% predicted however, complete population used for PC20 ratio, and n=12 (ICS) and n=11 (placebo) for diary card data.

Author & year: Bourbeau 1998		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "Patients were randomly assigned"; "Randomisation was carried out in blocks of four patients to ensure similar numbers of patients in each treatment group" Comment: Probably done
Allocation concealment *Selection bias*	Low	Quote: "Identification of individual treatment assignments was only possible in case of emergency by breaking the sealed envelope kept by the investigator. The envelopes had to be kept with the case record forms and be returned unbroken at the end of the study" Comment: Probably done
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other biases
Blinding of participants and personnel *Performance bias*	Low	Quote: "double blind" Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double blind" Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	Quote: "All the analyses were performed on an intention-to-treat basis, meaning that all patients randomised to treatment were included in the analysis, regardless of protocol violations, and including those who had to be withdrawn up to the point of withdrawal" 3/39 withdrew from ICS, 10/40 withdrew from placebo Comment: Probably done

Author & year: Vestbo 2017		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "Patients were randomised to treatment by investigators contacting an interactive response technology (IRT) system, which used a randomisation list generated by the IRT provider. Randomisation was in the ratio 2:2:1" Comment: Probably done
Allocation concealment *Selection bias*	Low	Quote: "Patients, investigators, site staff, and funder personnel were masked to treatment assignment for the duration of the study" Comment: Probably done
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: "double blind, double dummy" Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double blind, double dummy" Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	Quote: "We analysed primary, key secondary, and other secondary endpoints in the intention-to-treat population" 92/1077 withdrew from fixed triple, 161/1075 withdrew from non-ICS group, 42/538 withdrew from open triple Comment: Probably done

Author & year: Burge 2000		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "We used a computer generated allocation schedule stratified by centre (block size of six). Patients were randomised sequentially from a list comprising treatment numbers only" Comment: Probably done
Allocation concealment *Selection bias*	Low	Quote: "Patients were randomised sequentially from a list comprising treatment numbers only" Comment: Probably done
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: "double blind" Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double blind" Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	Quote: "Analyses for each parameter included all randomised patients with at least one valid measurement" 160/376 withdrew from ICS, 195/375 withdrew from placebo Comment: Complete case analysis

Author & year: Pauwels 1999		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Unclear	Not stated
Allocation concealment *Selection bias*	Unclear	Not stated
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: "double blind" Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double blind" Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	Quote: "Data on the randomized subjects were analyzed on an intention-to-treat basis" 176 withdrew from ICS, 189 withdrew from placebo Comment: complete case analysis

Author & year: Vestbo 1999		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "Randomisation was masked and the randomisation sequence generated by computer at Astra. Study numbers were allocated in a consecutive order" Comment: Probably done
Allocation concealment *Selection bias*	Low	Quote: "The randomisation code was held by Astra and was not available to the researchers until the study had been completed" Comment: Probably done
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: "double blind" Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double blind" Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	Quote: "only intention-to-treat results are shown" Comment: Both ITT and per protocol population were used but only ITT population were shown.

Author & year: Ohar 2014		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "Allocation of double-blinded study treatments was conducted using RAMOS (GlaxoSmithKline, UK), an interactive voice response system" Comment: Probably done
Allocation concealment *Selection bias*	Low	Quote: "Allocation of double-blinded study treatments was conducted using RAMOS (GlaxoSmithKline, UK), an interactive voice response system" Comment: Probably done
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other biases
Blinding of participants and personnel *Performance bias*	Low	Quote: "double-blind" Comment: probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double-blind" Comment: probably done
Incomplete outcome data *Attrition bias*	Low	Quote: "All efficacy and safety analyses were performed in the intent-to-treat (ITT) population" 26/314 withdrew from ICS; 39/325 withdrew from non-ICS Comment: Randomised population used

Author & year: Calverley 2018		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "Participants were randomly assigned through a centralized randomization service in permuted blocks to one of four treatments" Comment: Previous article (Vestbo 2016) has more detail
Allocation concealment *Selection bias*	Low	Quote: "Participants were randomly assigned through a centralized randomization service in permuted blocks to one of four treatments" Comment: Previous article (Vestbo 2016) has more detail
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: "double-blind" Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double-blind" Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	Quote: "were included in the intention-to-treat efficacy population"; "Patients had to have a baseline measurement and at least one on-treatment measurement to be included in this analysis" Comment: ITT population not always performed

Author & year: Vestbo 2016		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "The randomisation schedule was generated using the GSK validated randomisation software RANDALL." Comment: Probably done
Allocation concealment *Selection bias*	Low	Quote: "only the database administrators having knowledge of treatment assignment" Comment: probably done
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: "double blind" Comment: probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double blind" Comment: probably done
Incomplete outcome data *Attrition bias*	Low	Both "on-treatment" and "intention to treat" populations were used.

Author & year: Cazzola 2000		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "All patients who enter the run-in period were randomized to treatment in blocks of four according to a list of randomized codes" Comment: Probably done
Allocation concealment *Selection bias*	Unclear	Quote: "randomized to treatment in blocks of four according to a list of randomized codes" Comment: Unclear allocation concealment
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Unclear	Not mentioned. Only say "randomised.
Blinding of outcome assessment *Detection bias*	Unclear	Not mentioned. Only say "randomised".
Incomplete outcome data *Attrition bias*	High	Quote: "In order to qualify for efficacy analysis, the patient had to complete the 3-month treatment period"; "69 patients completed the 3-month treatment period" Comment: Complete case analysis. No mention of how many people were enrolled to start with.

Author & year: Vestbo 2005		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Not mentioned in article however, refer to paper Calverley 2003: Quote:" We used a randomisation schedule generated by the patient allocation for clinical trials (PACT) program to assign patients to study treatment groups." Comment: Probably done
Allocation concealment *Selection bias*	Low	Not mentioned in article however, refer to paper Calverley 2003: Quote: "Every participating centre was supplied with a list of patient numbers (assigned to patients at their first visit) and a list of treatment numbers." Comment: probably done
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other bias
Blinding of participants and personnel *Performance bias*	Low	Quote: "double blind"; (From Calverley 2003):"Study drugs were labelled in a way to ensure that both the patient and the investigator were unaware of the allocated treatment" Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double blind" Comment: Probably done
Incomplete outcome data *Attrition bias*	High	140/361 withdrew from placebo, 119/372 withdrew from sal, 108/374 withdrew from flut, 89/358 withdrew from combination. Quote: "Drop outs in the first 2 weeks were excluded from analyses". (75 withdrew in first 2 weeks) Comment: Not ITT analysis

Author & year: Renkema 1996		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "patients were allocated blindly (by computerized randomization stratified for smoking)" Comment: Probably done
Allocation concealment *Selection bias*	Low	Quote: "computerized randomisation" Comment: Probably done
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other biases
Blinding of participants and personnel *Performance bias*	Low	Quote: "double-blind" Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: "double-blind" Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	2/21 withdrew from bud, 4/19 withdrew from bud+pred, 5/18 withdrew from placebo Quote: "For the whole group (n=58).." Comment: All randomised patients included

Author & year: Lee 2015		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Unclear	Not mentioned
Allocation concealment *Selection bias*	Unclear	Not mentioned
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other biases
Blinding of participants and personnel *Performance bias*	High	Quote: "Patients were randomised.." Comment: No mention of blinding participants or personnel
Blinding of outcome assessment *Detection bias*	High	Quote: "Patients were randomised.." Comment: No mention of blinding participants or personnel
Incomplete outcome data *Attrition bias*	Low	Quote: "FAS, full analysis set; SAS, safety analysis set" Comment: lung function analysed in full analysis set ie all patients who were randomised

Author & year: Shaker 2009		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "Patients were allocated into either group in a proportion of 1:1 by block randomisation using a random sequence generated by a computer program at AstraZeneca" Comment: probably done
Allocation concealment *Selection bias*	Low	Quote: "Patients were allocated into either group in a proportion of 1:1 by block randomisation using a random sequence generated by a computer program at AstraZeneca" Comment: probably done
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other biases
Blinding of participants and personnel *Performance bias*	Low	Quote: "double blinded"
Blinding of outcome assessment *Detection bias*	Low	Quote: "double blinded"
Incomplete outcome data *Attrition bias*	Unclear	62/127 withdrew from placebo, 55/127 withdrew from ICS Comment: Reported numbers are complete case for baseline characteristics however, random effects linear regression was used, which indicated complete case?

Author & year: Wise 2000		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Low	Quote: "The participants were randomly assigned to one of two treatment groups with stratification according to clinical centre and smoking status (participants were current smokers or had recently quit" Comment: Probably done. Patients at individual test centres probably similar.
Allocation concealment *Selection bias*	Unclear	Not mentioned
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other biases
Blinding of participants and personnel *Performance bias*	Low	Quote: "The participants and clinical center staff were unaware of the study drug assignments"
Blinding of outcome assessment *Detection bias*	Low	Quote: "The participants and clinical center staff were unaware of the study drug assignments"
Incomplete outcome data *Attrition bias*	High	Quote: "The data were fitted to a linear longitudinal random-effects model" 38 withdrew from placebo, 28 withdrew from ICS Comment: Complete case analysis used

Author & year: Weir 1999		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation *Selection bias*	Unclear	Not mentioned
Allocation concealment *Selection bias*	Unclear	Not mentioned
Selective reporting *Reporting bias*	Low	All outcomes measures listed in methods section were reported in results
Other sources of bias *Other bias*	Low	No other biases
Blinding of participants and personnel *Performance bias*	Low	Quote: “double blind”
Blinding of outcome assessment *Detection bias*	Low	Quote: “double blind”
Incomplete outcome data *Attrition bias*	High	Quote: “Only patients with data points for at least 12 months were included in the final analysis” Comment: Not all randomised patients included in analysis

Appendix 3: Supplementary material to chapter 3

Approved Independent Scientific Advisory Committee (ISAC) protocol for chapter 4 and 5 (ISAC protocol 18_249R)

GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY
Study Title (Max. 255 characters) Changes in lung function over time in a primary care COPD cohort and their relationship with patient demographic, clinical and health-care utilization characteristics.
Research Area (place 'X' in all boxes that apply)

Drug Safety		Economics	
Drug Utilisation		Pharmacoeconomics	
Drug Effectiveness		Pharmacoepidemiology	
Disease Epidemiology	x	Methodological	
Health Services Delivery			

Chief Investigator

Title:	Dr
Full name:	Jennifer Quint
Job title:	Reader in Respiratory Epidemiology
Affiliation/organisation:	Imperial College London
Email address:	j.quint@imperial.ac.uk
CV Number (if applicable):	042_15CEPSL

Corresponding Applicant	
Title:	Miss
Full name:	Hannah Whittaker
Job title:	Research Assistant and PhD student
Affiliation/organisation:	Imperial College London
Email address:	h.whittaker@imperial.ac.uk
CV Number (if applicable):	535_17
List of all investigators/collaborators	
Title:	Dr
Full name:	Steven Kiddle
Job title:	Research Fellow
Affiliation/organisation:	Cambridge University
Email address:	steven.kiddle@mrc-bsu.cam.ac.uk
CV Number (if applicable):	650_16S
Will this person be analysing the data? (Y/N)	Y
Title:	Dr
Full name:	Jeanne Pimenta
Job title:	Director Epidemiology
Affiliation/organisation:	GSK
Email address:	Jeanne.m.pimenta@gsk.com
CV Number (if applicable):	023_19

Will this person be analysing the data? (Y/N)	N
Title:	Professor
Full name:	Deborah Jarvis
Job title:	Professor of Public Health
Affiliation/organisation:	Imperial College London
Email address:	d.jarvis@imperial.ac.uk
CV Number (if applicable):	256_18
Will this person be analysing the data? (Y/N)	N
Title:	Professor
Full name:	Peter Burney
Job title:	Professor of Respiratory Epidemiology and Public Health
Affiliation/organisation:	Imperial College London
Email address:	p.burney@imperial.ac.uk
CV Number (if applicable):	
Will this person be analysing the data? (Y/N)	N

Experience/expertise available

List below the member(s) of the research team who have experience with CPRD data.

Name:	Protocol Number/s:
Hannah Whittaker	17_229R, 18_152R
Jennifer Quint	13_116R

13_116RA

12_065A

14_108R

15_052R

15_114R

12_016R

13_030R

12_065

13_086

13_084

14_100R

15_156

15_193R

15_226

15_257

16_014

16_067

16_089

16_095

16_103R2

16_186R

17_013R

17_060

17_083

17_086R

17_082

16_276R

17_068

17_130

17_113R

17_090

17_152

17_248

17_229R

18_006R2

18_025

17_279

18_055R

18_074R

18_057R

18_068R

18_080R

18_058R

18_142

17_276R2

18_152R

	18_133R
	18_120
	18_219
	18_194
	18_193
	18_211
	18_185
Jeanne Pimenta	17_066
	15_059
	16_058
Steven Kiddle	17_229R
	18_152R
	16_186R
	16_276R
	15_106RA2
Deborah Jarvis	18_152R

List below the member(s) of the research team who have statistical expertise.

Name(s):

Quint

Kiddle

Jarvis

Burney

Pimenta

Whittaker

List below the member(s) of the research team who have experience of handling large datasets (greater than 1 million records).

Name(s):

Quint

Kiddle

Whittaker

Pimenta

List below the member(s) of the research team, or supporting the research team, who have experience of practicing in UK primary care.

Name(s):

Quint

ACCESS TO THE DATA

Sponsor of the study

Institution/Organisation:	GSK
Address:	Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, United Kingdom

Funding source for the study	
Same as Sponsor?	Yes X No
Institution/Organisation:	GSK
Address:	Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, United Kingdom
Institution conducting the research	
Same as Sponsor?	Yes No X
Institution/Organisation:	Imperial College London
Address:	Emmanuel Kaye Building, 1b Manresa Road, London, SW3 6LR
Data Access Arrangements	
Indicate with an '**X**' the method that will be used to access the data for this study:	
Study-specific Dataset Agreement	
Institutional Multi-study Licence	X
Institution Name	Imperial College London
Institution Address	Emmanuel Kaye Building, 1b Manresa Road, London, SW3 6LR
Will the dataset be extracted by CPRD?	
Yes No X	
If yes, provide the reference number:	
Data Processor(s):	

Processing	X	
Accessing	X	
Storing	X	

Processing area (UK/EEA/Worldwide)	
Organisation name	NHLI, Imperial College London
Organisation address	Emmanuel Kaye Building, 1b Manresa Road, London, SW3 6LR

INFORMATION ON DATA

Primary care data (place 'X' in all boxes that apply)

CPRD GOLD	X	CPRD Aurum	

X

Please select any linked data or data products being requested

Patient Level Data (place '**X**' in all boxes that apply)

ONS Death Registration Data	X	CPRD Mother Baby Link	
HES Admitted Patient Care	X	Pregnancy Register	
HES Outpatient		NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data	
HES Accident and Emergency		NCRAS Cancer Patient Experience Survey (CPES) data	
HES Diagnostic Imaging Dataset		NCRAS Systemic Anti-Cancer Treatment (SACT) data	

HES PROMS (Patient Reported Outcomes Measure)		NCRAS National Radiotherapy Dataset (RTDS) data	
		Mental Health Services Data Set (MHDS)	

Area Level Data (place '**X**' in all boxes that apply)

Practice level (UK)		Patient level (England only)	
Practice Level Index of Multiple Deprivation (Standard)		Patient Level Index of Multiple Deprivation	X
Practice Level Index of Multiple Deprivation (Non-standard)		Patient Level Townsend Score	
Practice Level Index of Multiple Deprivation Domains (Non-standard)			
Practice Level Carstairs Index for 2011 Census (Excluding Northern Ireland) (Standard)			
2011 Rural-Urban Classification at LSOA level (Non-standard)			

Reference number (where applicable):

Are you requesting linkage to a dataset not listed above?

Yes No X If yes, provide the reference number:
Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index? Yes No X If yes, provide further details:
VALIDATION/VERIFICATION
Does this protocol describe an observational study using purely CPRD data? Yes X No
Does this protocol involve requesting any additional information from GPs, or contact with patients? Yes No X If yes, provide the reference number:

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*' and justification provided**
Study Title (Max. 255 characters) Changes in lung function over time in a primary care COPD cohort and their relationship with patient demographic, clinical and health-care utilization characteristics.
Lay Summary (Max. 250 words) Lung function tests relate to how well our lungs are working and measure such things as how much air our lungs can hold and how easily we can breathe in and out. All individuals have some decline in their lung function over time, particularly in later life. People with chronic obstructive pulmonary disease (COPD) lose lung function faster than the general population, particularly those who continue to smoke. Lower lung function is associated with premature death and may lead to the inability to perform simple physical tasks such as walking short distances unaided. No studies have looked at the decline in the total volume of air in the lungs of people with COPD. Using statistical models, we will describe how lung function changes in people with COPD over a 14 year time period and look at which groups of patients have the biggest decline.
Technical Summary (Max. 300 words) People with COPD have a faster decline in their lung function than people without COPD. However, little is known about how quickly lung function decline in a primary care cohort in an average COPD patient. Additionally, little is known about the decline in forced vital capacity (FVC). Using a mixed effects linear model, we will investigate decline in lung function in people with prevalent COPD over a 14 year period, we will also model patient characteristics associated with fast or slow lung function decline using logistic regression.
Outcomes to be Measured 1) Rate of FEV_1 and FVC decline in COPD patients 2) Risk of being a fast FEV_1 or FVC decliner

Objectives, Specific Aims and Rationale

The aim of this study is to describe the rate of decline in lung function in primary care COPD patients.

Specifically, we will, among COPD patients:

1. Describe baseline characteristics of patients who are eligible and not eligible for the study in terms of demographics, COPD severity, comorbidities, AECOPD frequency, COPD treatment, and FEV_1 or FVC.

2. To describe the rate of FEV_1 decline in COPD patients.

3. To describe the rate of FVC decline in COPD patients.

4. To investigate the association between baseline patient characteristics and rate of FEV_1 and FVC decline.

5. To investigate the association between baseline patient characteristics and the risk of having fast FEV_1 decline or fast FVC decline using a selected cut off.

Using routinely collected lung function data (measured usually every 15 months in people with COPD as part of QoF from 2004), we will describe the pattern of lung function decline in an average COPD patient as mean decline in FEV_1 and FVC per year in mLs and investigate factors that may influence the speed of lung function decline. The main benefit of this work will be information on the average decline in FEV_1 and FVC in a representative population of those with COPD. The additional analysis of factors associated with decline among those with COPD will lead on to future work which may aim to target therapies at particular groups or to identify a 'rapid decliner' phenotype.

Study Background

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation that is not fully reversible, is progressive and is associated with a range of pathological changes in the lung, significant co-morbidities and extra-pulmonary manifestations (1). It is estimated that 3 million individuals in the UK have COPD however, only 1/3 of them are currently diagnosed. Direct UK health care costs secondary to COPD equate to £805 million. COPD is both preventable and treatable and one of the commonest causes of hospital admission. The prevalence of COPD is increasing globally and it is projected to be not only the third leading cause of death, but also the seventh leading cause of disability adjusted life years (DALYs) lost worldwide by 2030.

COPD is an obstructive lung disease, and people with COPD have a faster decline in their lung function (FEV_1) than people without COPD. However, among people with COPD the speed with which lung function is lost varies. Little is known particularly in a primary care cohort about how quickly lung function declines in an average COPD patient (2). As loss of lung function is often used as an outcome in RCTs, our lack of knowledge of average FEV_1 decline makes the interpretation of clinical trials outcomes difficult as it is unclear what would constitute a representative "baseline" rate of loss of lung function. COPD is a very heterogeneous disease, with groups of clinical, pathophysiological and demographic characteristics considered to be important in describing the natural history of disease, and which may be useful in describing distinct phenotypes, targeting therapies or predicting risk. Lung function decline (as measured by FEV_1) is an important characteristic which may be useful for all three of these purposes. Indeed, previous work has indicated that some patients with COPD have more "active" disease; i.e. lose lung function faster (> 40mls/year) (3,4). While lung function decline is faster in frequent exacerbators (5,6), some COPD patients have more rapid decline in FEV_1 irrespective of exacerbations, suggesting that other characteristics seem to be important too. These individuals tend to have mild to moderate disease, be current smokers and have a more emphysematous phenotype. Further work is therefore required to 1) describe the average loss of lung function in a representative population of COPD patients; and 2) identify particular groups of COPD patients who may have faster decline in lung function.

In addition, no previous study has described the rate of FVC decline in a primary care cohort of COPD patients. It is important to describe the rates of both FEV1 and FVC as FEV1 decline may be associated with the size of patients' total lung volume.

In summary, little is known about the rate at which lung function declines in a primary care population. The majority of previous studies have consisted of randomized control trials and it is important to describe lung function decline in "real world" data that is representative of the general patient population. This is because patients identified through "real world" data do not always meet the inclusion criteria for clinical trials and thus results of clinical trials can often only be generalizable to specific patients.

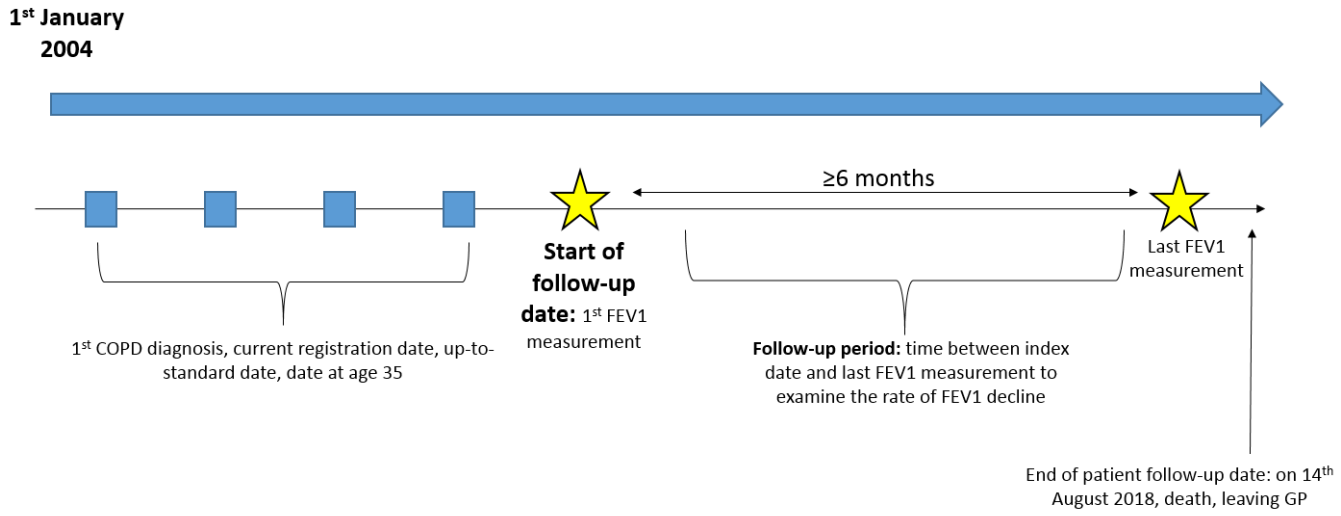
Study Type

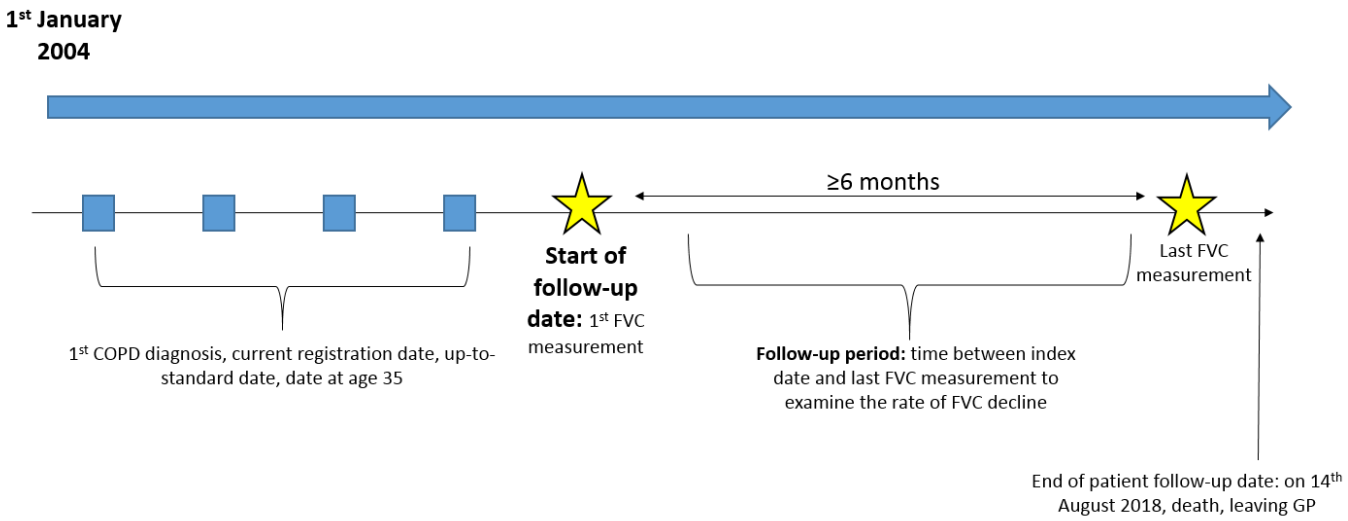
This will be a descriptive longitudinal piece of work. This work is primarily exploratory. We will use two cohorts of COPD patients in order to investigate the rate of FEV_1 decline and FVC decline separately. Two cohorts may be required due to different patient numbers with valid recordings for each measure.

Study Design

This will be a retrospective cohort study using routinely collected primary care electronic health records (EHR) from the Clinical Practice Research Datalink (CPRD) and linked data from HES. The nature of this design will allow us to follow FEV_1 and FVC longitudinally to investigate the rates of FEV_1 and FVC decline in COPD patients. Since 2004 as part of the QOF guidelines lung function should be measured every 15 months in COPD patients, which makes CPRD-GOLD a reliable source of observational data for investigating lung function decline. Whilst spirometric recordings in primary care are high, the use of linked hospital admission data will allow us to obtain a bigger picture of the decline in lung function (7).

People with COPD will be identified based on a validated diagnosis of COPD [8] from the 1st of January 2004 to the 14th August 2018. COPD patients will be included if they are aged 35 or over, have a current registration date, an up to standard GP date, are smokers or ex-smokers, have FEV_1 or FVC measurements recorded twice or more in their data and are at least 6 months apart. The first FEV_1 or FVC measurement after all these requirements are met will be the index date for each respective cohort (FEV_1/FVC). End of follow up will be earliest of the end of database (expected as 14th August 2018), transfer out of GP, last date of data collection, or date of death.





Feasibility counts

Initial feasibility counts have been explored and this study has enough power to be carried out. 61,077 and 41,507 COPD patients are aged 35 or older, are smokers or ex-smokers, have at least 2 FEV_1 or FVC measurements in their data at least 6 months apart, respectively.

Sample size considerations

Sample size calculations from previous work using CPRD and FEV_1 decline have been performed. (No data are available for FVC as of yet).

The following formula by Schlesselman was used to determine sample size in longitudinal study with repeated measures of FEV1: $N = [2(Z_{\alpha/2} + Z_{\beta})^2 \{\hat{\sigma}_{\beta}^2 + 12(P-1)\hat{\sigma}^2 / [D^2 P(P+1)]\} / \Delta^2$

In this formula $Z_{\alpha/2}$ and Z_{β} refer to the unit normal deviates for errors type I and type II, which for an alpha value of 0.05 and a power beta value of 0.8 give a $Z_{\alpha/2}$ and Z_{β} of 1.96 and 1.64 respectively. σ^2_{β} is the estimate of the variance associated with the rate of FEV_1 decline (66.5ml/year), σ^2 is the estimate of the within subject variance (313ml) , *P* is the number of measurements in the study (3), *D* is the duration of the study (median 4.8 years), and Δ is the unit difference between groups.

We expect a total sample of approximately 71,000 COPD patients, which will be sufficient to investigate the study objectives.

Δ (ml/year)	Total sample (N)
2	55,293
3	24,575
4	13,824
5	8,847
7	4,514
10	2,212

Planned use of linked data (if applicable):

IMD- to allow use of SES in the model

HES APC- to identify hospitalised exacerbations to determine exacerbation frequency and severity
ONS- to identify COPD-related deaths

Definition of the Study population

The source population will include all men and women who are registered with a GP in the UK and have data available in the CPRD-GOLD database. Patients will be included in the study if they meet the following eligibility criteria:

- are aged 35 or over
- have been diagnosed with COPD
- have FEV_1 measurements recorded twice or more in their data and at least 6 months apart (for FEV_1 cohort)
- have FVC measurements recorded twice or more in their data and at least 6 months apart (for FVC cohort)
- are ex or current smokers
- have up-to-standard (UTS) data available in CPRD-GOLD and are currently registered at a GP

Patients will also be included irrespective of their country of origin, any comorbidities, or COPD severity.

The study follow-up period for the FEV_1 cohort will start at the first FEV_1 measurement after the patient's first COPD diagnosis, UTS data and current registration date and will end on the 14th August 2018 or before if the patient died or transferred out of the GP.

The study follow-up period for the FVC cohort will start at the first FVC measurement after the patient's first COPD diagnosis, UTS data and current registration date and will end on the 14th August 2018 or before if the patient died or transferred out of the GP.

Selection of comparison group(s) or controls

Following the estimation of the rate of FEV_1 and FVC decline, we will identify "fast" and "slow" lung function decliners using distribution method as well as applying previously reported cut-offs. We will consequently investigate whether there is an association between baseline patient characteristics and the risk of being a "fast" decliner compared to a "slow decliner" using logistic regression.

Exposures, Outcomes and Covariates

Exposure: The primary exposure of interest is a COPD diagnosis. The COPD validated codelist is published (8). GP diagnosed COPD will be used to define COPD. First GP-diagnosed COPD will be used.

In order to investigate the association between baseline covariates and risk of being a "fast" lung function decliner. For these analyses exposures include baseline covariates, listed under the covariates section.

Outcome: Average yearly FEV_1 and FVC change in mL/year as determined by spirometry values. This is obtained from the Additional file. Where more than one record is available on the same day, we will use the highest value.

Covariates

Demographic: Age, sex, socioeconomic status (individual linked data from IMD), ethnicity, BMI (weight in kilograms divided by height in meters squared), and smoking status (current smoker, ex-smoker, never smoker). These are all recorded in the Clinical/Additional files in the CPRD extract and the group have extensive experience in defining them.

Other co-morbid conditions: asthma, heart failure, myocardial infarction, stroke, lung cancer, bronchiectasis, gastro-oesophageal reflux disease (GORD, anxiety, and depression.

COPD medications: These will include inhaled corticosteroids, combination inhaled corticosteroids and long acting beta agonists, long and short acting beta agonists, oral prednisolone, short and long acting anti-cholinergics, theophyllines, combination short acting beta agonists and short acting anti-cholinergics, nebulised therapy.
COPD severity: MRC dyspnoea, white blood cell count, neutrophil count, eosinophil count, airflow obstruction, history of AECOPD, time varying AECOPD during follow-up, and hospitalised AECOPD.

Data/ Statistical Analysis

Baseline characteristics will be explored. Examined baseline characteristics include gender, age, ethnicity, SES, smoking status (current/ex), comorbidities, BMI, airflow obstruction at start of follow up and other markers of COPD severity, COPD medications, AECOPD, and mean follow up times. Appropriate statistical testing will be used to highlight any statistically significant differences between these groups. Missing data will be imputed if data are missing at random.

The main outcome of this study is annual rate of FEV_1 and FVC decline in our eligible population.

To do this a mixed linear regression model will be used due to the nature of the study using repeated measures of FEV_1/FVC within patients. This model will be fitted for repeated measures of FEV_1FVC within patients. The fixed part of the model will include FEV_1 or FVC, depending on the cohort, as the dependent variable and time from 1st FEV_1/FVC as the independent variable. The random effects part of the model will include patient ID as the level 2 variable and time from first FEV_1/FVC. This will allow patients to have different intercepts and difference rates of FEV_1/FVC decline. Models will adjusted for baseline covariates.

Rates of FEV_1FVC decline in ml/year will be derived from the coefficient for time. This coefficient illustrates the mean rate of FEV_1/FVC decline.

If necessary, non-linear regression modelling with additionally be used as this method will allow for variability in FEV_1 decline over time. This model will be used if rate of FEV_1 decline is not found to be linear and varies over time.

We will additionally investigate the association between baseline characteristics and rate of FEV_1 and FVC decline.

Furthermore, after exploring the data we will define fast and slow FEV_1 and FVC decliners using a specified cut-off. Logistic regression will be performed to investigate the association between baseline covariates and the risk of being a fast FEV_1 and FVC decliner, respectively using variable selection. Statistical significance will be defined as $p<0.05$. Patient baseline characteristics that will be investigated include:

- Age
- Gender
- SES
- Smoking status (current/ex)
- Comorbidities (including heart failure, MI, stroke, lung cancer, bronchiectasis, GORD, anxiety, depression, asthma)
- BMI
- Dyspnoea score (MRC breathlessness scale)
- Blood Neutrophils
- Blood Eosinophils
- White blood cells

- AECOPD including hospitalisations
- COPD medications

Sensitivity and exploratory analyses will include:

1) Exploring rate of FEV_1 and FVC stratified by GOLD classes, AECOPD frequency, smoking status and MRC dyspnoea score.
2) Assessing the sensitivity and robustness of our logistic regression model. We will explore different thresholds of "fast" and "slow" lung function decliners. We will explore thresholds based on previous literature, the fit of the data, medians, and means.
3) Excluding patients with a history of asthma in the analysis on lung function decline. In the main analysis only patients without a history of asthma are used due to the possibility of misclassification of asthma and COPD. This limits the generalizability of results due to a more specific cohort inclusion criteria. Therefore, an additional analysis will be performed to observe lung function decline in the population of patients with and without a history of asthma to see if results differ.
4) If suitable, time varying covariates will be used in order to appropriately investigate the associations between patient characteristics and rate of FEV_1 and FVC decline over time.

Plan for addressing confounding

This is a descriptive study. While we will adjusted and explore patient characteristics in our models, we will not make causal statements.

Plans for addressing missing data

We will explore the pattern of missingness and consider the use of multiple imputation when using the mixed effects linear model if we are able to assume data are missing at random.

Patient or user group involvement (if applicable)

n/a

Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The study findings will be submitted for publication in peer-reviewed scientific journals, and will be presented at appropriate conferences and other meetings; the latter will include scientific meetings externally, for example the American and European Respiratory Society Meetings and internally within Imperial College London.

Conflict of interest statement: Dr Quint's research group has received funding from The Health Foundation, MRC, Welcome Trust, BLF, Insmed, AZ, Bayer and BI for other projects, none of which relate to this work and from GSK for this work. Dr Quint has received funds from AZ, GSK, Chiesi, Teva and BI for Advisory board participation or travel. Professor Jarvis and Professor Burney's research group has received funding from MRC, European Union and Cystic Fibrosis Trust for other projects, none of which relate to this work. Her contribution to this work is not funded by GSK. Dr Kiddle has previously received research funding from EPSRC, BBSRC, MRC, NIHR, Alzheimer's Society, Eli Lily and Janssen for other projects, and funding from Roche Diagnostics for advisory board participation and travel. None of this relates to this work. Dr Pimenta is employed by and hold stocks in GSK.

Limitations of the study design, data sources, and analytic methods

Observational studies allow understanding of disease progression and associations using real world data sources, in this case electronic health data. However, strengths and limitations are associated with this study design.

Firstly, it is important to note that although CRPD is broadly representative of the UK population in terms of age, sex, and socio-economic status, it may not be representative of all GPs across the UK [9]. Selection of patients into the study will be based on prospectively recorded diagnoses of COPD, FEV_1 /FVC measurement and will be representative of COPD patients in the UK. However, it is important to note that studies using CPRD cannot prove causality, and merely find results that are consistent with casual hypotheses backed up by trials. Even when accounting for many confounders, there can always be residual confounding.

Algorithms used to identify patients with COPD have high sensitivity and PPV [8]: however, it could be possible that GPs misdiagnose asthma as COPD or COPD as asthma, particularly in patients aged over forty years [10]. To avoid misclassification of these diseases we did not include COPD patients with asthma in the study cohort. Nevertheless, it may also be possible that not all COPD patients were included in the study. In addition, CPRD only contains diagnosed COPD and symptomatic patients without a diagnosis of COPD would thus not be included. Furthermore, AECOPD frequency may be misclassified as those who have worse disease severity may meet with their GP more often and there would be more opportunity to report milder or self-managed exacerbations. To avoid this, the algorithm does not include patients who have self-managed an exacerbation using a rescue pack.

“Fast” and “slow” lung function decliners will be defined using a specified cut-off. Exploratory analyses will use explore other specified cut-offs as well as continuous variables in the model.

In addition, data quality between GPs may vary. Despite the implementation of the Quality and Outcomes Framework (QOF) in 2004, which encouraged GPs to record key data at a high level and lung function in COPD patients every 15 months, there is still some variation between GPs in terms of coding variables and recording data as free text, which researchers may miss. This therefore means not all available data is or can be used.

References

1. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A,et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013; 187:347–65. doi: 10.1164/rccm.201204-0596PP PMID: 22878278

2. Kim SJ, Lee J, Park YS et al. Age related annual decline of lung function in patients with COPD. International Journal of COPD 2016:11 51–60

3. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011 Sep 29; 365(13):1184–92. doi: 10.1056/NEJMoa1105482 PMID: 21991892

4. Casanova C, de Torres JP, Aguirre-Jaíme A, Pinto-Plata V, Marin JM, Cordoba E et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. Am J Respir Crit Care Med. 2011; 184:1015–21. doi: 10.1164/rccm.201105-0831OC PMID: 21836135

5. Donaldson, G. C., et al. (2002). "Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease." Thorax **57**(10): 847-852.

6. Kanner, R. E., et al. (2001). "Lower Respiratory Illnesses Promote FEV 1 Decline in Current Smokers But Not Ex-Smokers with MildChronic Obstructive Pulmonary Disease." American Journal of Respiratory and Critical Care Medicine **164**(3): 358-364.

7. Rothnie, K. J., et al. (2017). "Validity and interpretation of spirometric recordings to diagnose COPD in UK primary care." Int J Chron Obstruct Pulmon Dis **12**: 1663-1668

8. Quint JK, Müllerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR, & Smeeth L (2014). Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD).*BMJ open*, *4*(7), e005540.

9. Herrett, E., et al. (2015). "Data Resource Profile: Clinical Practice Research Datalink (CPRD)." Int J Epidemiol **44**(3): 827-836.

10. Tinkelman, D. G., et al. (2006). "Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over." J Asthma **43**(1): 75-80.

List of Appendices

Approved Independent Scientific Advisory Committee (ISAC) protocol for chapter 6 (ISAC protocol 17_229R).

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title[§] (*Please state the study title below)*
Inhaled corticosteroids, blood eosinophils and lung function (FEV_1) decline over time in a primary care COPD cohort

[§]Please note: This information will be published on the CPRD's website as part of its transparency policy.

2. Has any part of this research proposal or a related proposal been previously submitted to ISAC?
Yes[*] ☒ No ☐

**If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.*

16_186R

3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)
Yes[*] ☐ No ☒

**If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :*

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☒
Drug Utilisation	☐	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐
Health care resource utilisation	☐	Methodological Research	☐
Health/Public Health Services Research	☐	Other[*]	☐

[*]If Other, please specify the type of study here and in the lay summary below:

5. Health Outcomes to be Measured[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy.*

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

- Lung function decline using FEV1
-
-
-
-
-
-
-
-

[Please add more bullet points as necessary]

6. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☒	Regulatory purposes	☐
Other*	☐		

**If Other, please provide further information:*

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

7. Chief Investigator[§]

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Jennifer Quint, Clinical Senior lecturer in Respiratory epidemiology, Imperial College London, j.quint@imperial.ac.uk

[§]*Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy*

CV has been previously submitted to ISAC	☒ **CV number:**	042_15CEPSL
A new CV is being submitted with this protocol	☐	
An updated CV is being submitted with this protocol	☐	

8. Affiliation of Chief Investigator (full address)

Respiratory Epidemiology, Occupational Medicine and Public Health

G48, Emmanuel Kaye Building

Manresa Road

National Heart and Lung Institute

Imperial College

London, SW3 6LR

9. Corresponding Applicant[§]

Please state the full name, affiliation(s) and e-mail address below:

Hannah Whittaker, h.whittaker@imperial.ac.uk

[§]*Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy*

Same as chief investigator	☐	
CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	☒	
An updated CV is being submitted with this protocol	☐	

10. List of all investigators/collaborators[§]

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

[§]*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator: Dr Hana Müllerova, GSK, hana.x.muellerova@gsk.com

CV has been previously submitted to ISAC	☒	**CV number:**	365_15E
A new CV is being submitted with this protocol	☐		
An updated CV is being submitted with this protocol	☐		

Other investigator: Hannah Whittaker, Imperial College London, h.whittaker@imperial.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 Steven Kiddle, Cambridge University, steven.kiddle@mrc-bsu.cam.ac.uk

CV has been previously submitted to ISAC ☒ **CV number:** 650_16S

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other 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 ☐

[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.*

11. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work

Dr Quint's research group has received funding from the MRC, Welcome Trust, BLF, Insmed and AZ for other projects, none of which relate to this work. Imperial College London will receive funding from GSK on behalf of Dr Quint's group for this project. Dr Quint has received funds from AZ, GSK, Chiesi and BI for Advisory board participation or travel. Dr. Müllerová is an employee of GSK R&D and owns shares and stock options of GSK plc.

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

12. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	**Publications using GPRD/CPRD data**
None	☐	☐
1-3	☐	☐
> 3	☒	☒

Experience/Expertise available	Yes	No
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint, Kiddle	☒	☐
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)* Quint, Whittaker, Mullerova	☒	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint	☒	☐

13. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

1. Quint JK *BMJOpen* 2014;23;4(7):e005540.
2. Vestbo, J., et al., *Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial.* The Lancet, 2016. 387(10030): p. 1817-1826.
3. Soriano, J.B., et al., *A pooled analysis of FEV1 decline in COPD patients randomized to inhaled corticosteroids or placebo.* Chest, 2007. 131(3): p. 682-689.

SECTION C: ACCESS TO THE DATA

14. Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry	☒	*Please specify name and country:* GSK, UK
Academia	☐	*Please specify name and country:*
Government / NHS	☐	*Please specify name and country:*
Charity	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*
None	☐	

15. Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	*Please specify name and country:* Imperial College London
Government Department	☐	*Please specify name and country:*
Research Service Provider	☐	*Please specify name and country:*
NHS	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*

16. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data ☐

The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data** ☒

A data set will be provided by the CPRD¥€ ☐

CPRD has been commissioned to extract the data and perform the analyses€ ☐

Other: ☐

If Other, please specify:

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*

***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 (enquiries@cprd.com) if a dataset of >300,000 patients is required.*

€*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

17. Primary care data

Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐

EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.

Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:

Name of CPRD Researcher Reference number (where available) Date of contact

SECTION D: INFORMATION ON DATA LINKAGES

18. Does this protocol seek access to linked data

Yes* ☒ No☐ If No, please move to section E.

Research groups which have not previously accessed CPRD linked data resources **must discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset PROMS data and the Pregnancy Register **must** also discuss this with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email enquiries@cprd.comto discuss your requirements **before** submitting your application.*

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

Name of CPRD Researcher: Reference number (where available) Date of contact

We have not discussed this proposal with a CPRD researcher as we are only asking to access data that we have previous experience of using.

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

19. Please select the source(s) of linked data being requested§

§Please note: This information will be published on the CPRD's website as part of its transparency policy.

☐ ONS Death Registration Data	☐ MINAP (Myocardial Ischaemia National Audit Project)
☒ HES Admitted Patient Care	☐ Cancer Registration Data*
☐ HES Outpatient	☐ PROMS (Patient Reported Outcomes Measure)**
☐ HES Accident and Emergency	☐ CPRD Mother Baby Link
☐ HES Diagnostic Imaging Dataset	☐ Pregnancy Register

☐ Practice Level Index of Multiple Deprivation (Standard)

☐ Practice Level Index of Multiple Deprivation (Bespoke)

☒ Patient Level Index of Multiple Deprivation***

☐ Patient Level Townsend Score ***

☐ Other**** *Please specify:*

**Applicants seeking access to cancer registration data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also 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.*

***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only accessible by academics*

**** 'Patient level IMD and Townsend scores will not be supplied for the same study*

*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

Name of CPRD Researcher Reference number (where available) Date of contact

20. Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **<u>not</u>** be included in this count): 2*

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

21. Is linkage to a <u>local</u>¥ dataset with <1 million patients being requested?

Yes* ☐ No ☒

**If yes, please provide further details:*

¥ *Data from defined geographical areas i.e. non-national datasets.*

22. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

23. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

24. Does this protocol describe a purely observational study using CPRD data?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*

*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

25. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐

Is the questionnaire a validated instrument? Yes ☐ No ☐

If yes, has permission been obtained to use the instrument? Yes ☐ No ☐

Please provide further information:

Other (please describe)

[ψ] Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

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: DECLARATION

28. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.
- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Jennifer Quint Date: 30/8/17 e-Signature (type name): JKQuint

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Inhaled corticosteroids, blood eosinophils and lung function (FEV1) decline over time in a primary care COPD cohort

B. Lay Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Lung function tests relate to how well our lungs work and measure such things as how much air our lungs can hold and how easily we can breathe in and out. All individuals have some decline in lung function over time, particularly in later life. People with chronic obstructive pulmonary disease (COPD) lose lung function faster than the general population, particularly those who continue to smoke. Lower lung function is associated with premature death and may lead to the inability to perform simple physical tasks such as walking short distances unaided. To date people with COPD are treated with short or long-acting bronchodilator inhalers at the first instance and with inhaled corticosteroids (ICS) if symptoms persist. However, over the last few years there has been debate over whether the benefits of ICS therapy outweigh the harms in COPD patients and whether these benefits vary by subgroups of COPD patients. A subgroup of interest is those with high blood eosinophils. Using statistical models, we will describe how lung function changes in COPD patients over time and see whether there is a difference in lung function decline between patients with high and low blood eosinophils who are on and not on ICS.

C. Technical Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

People with COPD are commonly treated with short or long-acting bronchodilator inhalers. If symptoms persist or patients experience exacerbations of COPD they are put onto inhaled corticosteroids (ICS). However, the risks and benefits of ICS in the treatment of COPD patients have long been debated. Randomized clinical and observational studies have shown that the use of ICS in COPD patients can increase the chances of respiratory infections as well as that they reduce rehospitalisation and exacerbations of COPD. More recently, it is thought that specific subgroups of COPD patients may benefit from ICS treatment more than others. High blood eosinophil counts in COPD patients is one subgroup of interest. This study aims to assess the effect of ICS on lung function decline, particularly FEV1, in a primary care COPD population, stratifying by blood eosinophil levels. Using a mixed effects linear model, we will investigate the decline in lung function in people with prevalent COPD over a 10 year period and compare the rates of decline in patients with high or low eosinophils, who are on and not on ICS to explore who may benefit more from ICS.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

D. Objectives, Specific Aims and Rationale

(i) The broad research objectives:

To investigate the rate of lung function decline in a population based representative cohort of COPD patients on ICS and not ICS with high and low blood eosinophil counts.

(ii) The specific aims are:

1. To investigate the rate of FEV_1 decline in COPD patients with high blood eosinophils and on ICS compared to :
   - COPD patients with high blood eosinophils not on ICS
   - COPD patients with low blood eosinophils on ICS
   - COPD patients with low blood eosinophils not on ICS
2. To investigate the rate of FEV_1 decline in COPD patients with low blood eosinophils and on ICS compared to
   - COPD patients with low blood eosinophils not on ICS
   - COPD patients with high blood eosinophils on ICS
   - COPD patients with high blood eosinophils not on ICS

(iii) Rationale:

Using routinely collected lung function data (measured every 15 months in people with COPD as part of QoF from 2004), we will describe the pattern of lung function decline in COPD patients, on and not on ICS and with high and low eosinophils, as mean rate of decline in FEV_1 per year in mLs and investigate factors that may influence the speed of lung function decline (see section M). This work will produce a better picture on the role of ICS and blood eosinophil counts on lung function decline in a generalizable UK population.

This work follows on from ISAC protocol 16_186R.

E. Study Background

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by the chronic obstruction of airflow in the airways and lungs. It is associated with pathological changes in the lungs, co-morbidities such as cardiovascular disease, diabetes, and musculoskeletal disorders, as well as extra-pulmonary manifestations such as systemic inflammation [237, 238]. In addition, it is well known that people with COPD have a faster decline in their lung function (FEV_1) than people without COPD[23].

In the UK it is estimated that 3 million people are living with COPD however, only one third of this population are currently diagnosed. COPD was ranked as the ninth leading cause of death worldwide in 2016 and is projected to be

not only the third leading cause of death globally by 2020 but the seventh leading cause of disability adjusted life years (DALYs) lost worldwide by 2030 and is one of the commonest causes of hospital admission [237, 239].

People with COPD are commonly treated with short or long-acting bronchodilator inhalers at the first instance and with inhaled corticosteroids (ICS) if symptoms persist or if patients experience exacerbations of COPD (AECOPD). It has been debated whether the harms of ICS outweigh the benefits and if specific subgroups of people with COPD may be more likely to benefit from them than others.

Studies have shown that ICS-containing therapy (hereafter referred to as 'ICS') reduces the rate of FEV_1 decline, GP-treated exacerbations and hospitalisation in COPD patients. Using data from the Study to Understand Mortality and Morbidity (SUMMIT) trial, one study showed that the rate of moderate/severe AECOPD was 29% (CI 22-35) lower in COPD patients on combined ICS therapy compared to the placebo group. In addition, the rate of hospitalisation was 27% (13-39) lower and rate of FEV_1 decline was slower (-38ml/year vs -46ml/year) in COPD patients on combined ICS therapy compared to those on placebo [86, 240]. A further study using the Inhaled Steroids Effect Evaluation in COPD (ISEEC) data found that compared to those on placebo, the mean FEV_1 was 2.42% (SE 0.19%) higher in COPD patients on ICS [241]. However, the difference in FEV_1 decline between those on ICS and those on placebo became non-significant after 6 months of ICS therapy.

On the other hand, studies have also shown that ICS therapy has no effect on mortality and can increase the rate of pneumonia and upper respiratory tract infections. Results from the SUMMIT trial and other clinical trials show that there was no significant difference between those on ICS therapy and those on the placebo in terms of mortality[86, 242]. Furthermore, COPD patients on ICS had a rate of first hospitalisation or death due to pneumonia (termed "serious pneumonia") 1.69 (CI 1.63-1.75) times higher than those on placebo. Patients who withdrew from ICS had a rate of "serious pneumonia" 1.08 (CI 0.99-1.17) times higher than the placebo group, illustrating the reversibility of the effect of ICS after withdrawal[41]. Similarly, a meta-analysis of 14 clinical trials found that the odds of upper respiratory tract infection (URTI) in COPD patients on ICS compared to those not on ICS was 1.16 (1.05-1.29) times higher. They additionally investigated the effect of high and low dose ICS on risk of URTI and found that high dose ICS increased this risk significantly[187].

Blood eosinophils were recently shows as a potential biomarker of response to interventions with ICS-containing medications among patients with COPD [40, 188, 189]. Most epidemiological work on blood eosinophil levels in COPD has focused on their distribution and the association of blood eosinophils and AECOPD risk [243] and few studies have investigated the role of eosinophils on lung function decline, specifically FEV_1 decline. One randomised control study found that COPD patients with high eosinophils had a slower rate of FEV_1 decline when on ICS compared to the placebo and those with low eosinophils had a similar rate of FEV_1 decline when on ICS compared to the placebo [40].

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

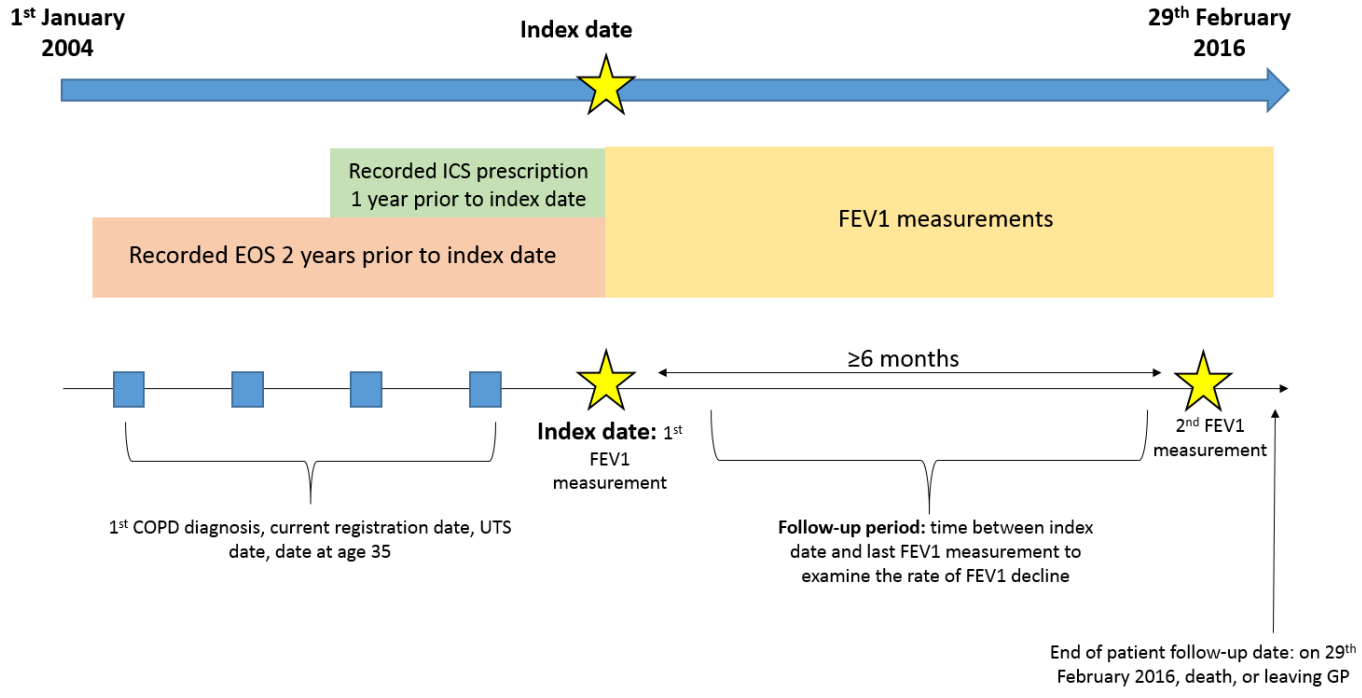
To date, evidence on the effect of ICS in COPD patients is conflicting and the majority of these studies are randomized clinical trials and external validity is needed [186]. It is therefore beneficial to investigate this further using "real world" data that is representative of the general UK population. This is because patients identified through "real world" data do not always meet the inclusion criteria for clinical trials and patients in these studies tend to have more severe disease states. By using CPRD data we can identify the effect of ICS in a cohort of primary care COPD patients on decline in their lung function (FEV1) over time further stratified by blood eosinophil phenotype.

F. Study Type

This will be a descriptive longitudinal cohort study. It is hypothesized that lung function decline among patients with higher levels of blood eosinophils is attenuated by use of ICS-containing medications.

G. Study Design

This will be a retrospective cohort study. A summary of the study design is illustrated below. See sections K and M for further detail.



Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

H. Feasibility counts

Initial feasibility calculations have been performed, and have confirmed that this study is adequately powered. The cohort comprises 61,104 COPD patients aged 35 or older, who are smokers or ex-smokers, have at least 2 spirometry measurements in their data at least 6 months apart, and have at least one eosinophil measurement recorded in their data. The mean follow-up time is 6.5 years.

I. Sample size considerations

We have undertaken previous work validating spirometry in CPRD in COPD patients (ISAC 12_065A) from 2004 onwards. From other COPD work undertaken in CPRD, in a cohort of 111,157 COPD patients aged 35 or older, and who are smokers or ex-smokers, 87,439 have FEV_1 recorded after 2004, 64,289 have more than two records, and 61,077 have more than two records 6 months apart. A formal power calculation has not been done.

J. Data Linkage Required (if applicable):§

§*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

IMD- to allow use of SES in the model

HES- to identify hospitalised exacerbations of COPD to determine exacerbation frequency and severity

K. Study population

The study population will include all individuals within CPRD over the age of 35 with a validated diagnosis of COPD [140][12] from 01/01/2004, who are smokers or ex-smokers, who have spirometry data (FEV_1) recorded more than once in their record at least 6 months apart, and have at least one blood eosinophil record in their data. Start of study will be the first FEV_1 date after the last date of: current registration at GP, up to standard date, date at age 35, first COPD diagnosis, or 01/01/2004. End of follow-up will be the first of: date of death, transfer out of GP date, last collection date, or 29/02/16 as this is the end of linked data availability.

We are aware that patients are only eligible for linkage if they (i) registered at a participating English practice prior to the transfer of identifiers to the trusted third party for matching (ii) had a valid identifier for linkage (either NHS number or postcode), (iii) had not opted out or dissented from CPRD or the linkage scheme.

L. Selection of comparison group(s) or controls

We will compare COPD patients with high eosinophils on ICS with:

- COPD patients with high eosinophils not on ICS
- COPD patients with low eosinophils on ICS
- COPD patients with low eosinophils and not on ICS

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

In addition, COPD patients with low eosinophils on ICS will be compared to:

- COPD patients with low eosinophils not on ICS
- COPD patients with high eosinophils on ICS
- COPD patients with high eosinophils and not on ICS

To identify those on ICS we will select patients who have been prescribed ICS-containing medication up to 1 year before their start of follow-up date. We will also look at incident ICS by identifying the first ICS prescription date during follow-up.

To identify patients with high or low eosinophils we will look at patient's last eosinophil measurement prior to their start of follow up and assign them to high or low eosinophil groups. We will consider several cut-off including 150, 300, and 500 cells/mm3.

M. Exposures, Health Outcomes§ and Covariates

§Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy

Exposure: The primary exposures of interest are COPD diagnosis (the COPD code list is published [140]), ICS-containing medication use and blood eosinophil level. ICS use will be determined through recordings for prescriptions of ICS monotherapy or fixed or open combinations one year prior to the patient's index date (see code list attached). The nearest blood eosinophil measurements will be taken two years prior to the patient's index date (using enttype 168 in test files). Blood eosinophil measurements recorded within 4 weeks of an exacerbation of COPD or an oral corticosteroid will not be used. Blood eosinophils will be split into high and low eosinophil levels defined at <150 vs ≥150 cells/mm3. Other eosinophil cut offs including <300 vs, ≥300, and <500 vs, ≥500 cells/mm3 will be explored in sensitivity analyses.

Outcome: The rate of lung function decline in mL/year, as determined by spirometry values, will be estimated by mixed linear regression (using enttype 394 in test files). Spirometry values are obtained from the additional file. Where more than one record is available on the same day, we will use the highest value.

Covariates:

Demographic: Age, sex, socioeconomic status (individual linked data from IMD), ethnicity, BMI, and smoking status (current smoker, ex-smoker,). These are all recorded in the Clinical/Additional files in the CPRD extract and the

group have extensive experience in defining them. Nearest BMI and smoking status prior to start of follow-up will be used.

Other co-morbid conditions: asthma, heart failure, bronchiectasis, emphysema, TB
COPD medications: These will include, long and short acting beta agonists, oral prednisolone, short and long acting anti-cholinergics, theophyllines, combination short acting beta agonists and short acting anti-cholinergics, combination long acting beta agonists and long acting anti-cholinergics nebulised therapy.

COPD severity: eosinophil level, neutrophil level, exacerbations of COPD (AECOPD) through linked HES data, MRC dyspnoea scale, and pneumonia. Statistical analyses will be stratified by GOLD grade.

N. Data/ Statistical Analysis

Analyses and data management will be performed in STATA 15. Multilevel linear models will be used to describe the rate of FEV_1 decline (mL/year) in a representative sample of COPD patients with high and low eosinophils on and not on ICS, stratified by GOLD grades. Multi-level mixed model will be used due to the nature of the study using repeated measures of FEV_1 within patients. The model will included FEV_1 as the dependent variable, time from last gold grade reached as the independent variable, an interaction term between time and eosinophil/ICS group, and patient ID as the level 2 variable to allow for random effects. The reference categories will be high blood eosinophils and ICS use and low blood eosinophils and ICS use.

Rate ratios (and 95% confidence intervals) will be estimated in eligible patients to compare the rates of FEV_1 decline. Rates of FEV_1 decline in ml/year will be derived from the coefficient for time and the interaction of time and blood eosinophil/ICS group in the mixed models. These coefficients illustrate the mean rate of FEV_1 decline in each group. Rate ratios will consequently be calculated by dividing the rate of each blood eosinophil/ICS group over the reference blood eosinophil/ICS group. Rates of FEV_1 decline can then be interpreted as being x times faster for a particular group compared to the reference group. Further multilevel linear models will adjust for any confounders mentioned in section M.

Further statistical analyses will use broken stick regression. Broken stick regression, also known as segmented or piecewise regression, is a regression method that divides the independent variable into intervals and fits a separate regression line to each interval. This method is useful if the outcome of interest differs over time between different time periods. In this study, broken stick regression will be used if rate of FEV_1 decline differs over time periods. For this analysis 3 FEV_1 measurements will be necessary and only patients with at least 3 FEV_1 measurements will be included.

We will investigate the differences in rates of FEV_1 decline between COPD patients with high eosinophils on ICS with: i) COPD patients with high eosinophils not on ICS; ii) COPD patients with low eosinophils on ICS, and COPD patients with low eosinophils on ICS with: i) low eosinophils not on ICS; and ii) high eosinophils and ICS.

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
In addition we will investigate the slope of FEV_1 decline in two populations. The first will be an intention to treat (ITT) population whereby patients are categorised into respective EOS/ICS groups at baseline and outcomes are analysed with respect to these groups. The second group of patients will also be categorised into respective EOS/ICS groups at baseline and patients not on ICS at baseline will be censored at date of first ICS prescription so that non-ICS users are those never on ICS. Further analyses will explore the effect of those starting ICS later in their follow-up. Exploratory analyses will investigate the rate of FEV_1 decline in an incident ICS cohort. Incident ICS will be defined as patients who have not been on ICS treatment in the year prior to their index date, and categorised as ICS and non-ICS patients based on their use of ICS within the first year of follow-up. Analyses described above will be performed using this incident ICS cohort further categorising by high and low eosinophil group as before. Initial analyses will investigate the rates of FEV_1 decline in high eosinophils, defined as ≥150 cells/mm3 and low eosinophils, defined as <150 cells/mm3 in ICS users and non-ICS users. Other eosinophil cut offs will include <300 vs, ≥300, and <500 vs, ≥500 cells/mm3[144]. Further exploratory analyses will explore the effect of dose and length of ICS therapy on the rate of FEV_1 in COPD patients with high and low eosinophils to investigate a potential dose-response effect of ICS and high/low eosinophils on FEV_1 decline.
O. Plan for addressing confounding This is a descriptive study. While we will adjust for demographic factors and look for other potential confounders in the stratified analyses we will not make causal statements.
P. Plans for addressing missing data We will consider the use of multiple imputation when using the mixed effects linear model if we are able to assume data are missing at random.
Q. Patient or user group involvement (if applicable) **N/A**

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The study findings will be submitted for publication in peer-reviewed scientific journals, and will be presented at appropriate conferences and other meetings; the latter will include scientific meetings externally, for example the American and European Respiratory Society Meetings and internally within Imperial College London. We plan to share our findings with patient/user groups via Breathe Easy (part of the British Lung Foundation).

S. Limitations of the study design, data sources, and analytic methods

Selection bias

The main aim of this analysis is to describe the average rate of FEV_1 over time in a representative primary care cohort of COPD patients with and without prevalent ICS therapy, further stratified by blood eosinophil phenotype. The generalizability of this work relies on the representativeness of COPD patients present in CPRD. GP practices are self-selecting into CPRD, and as such there is a potential for selection bias. We plan to stratify our results by GOLD grade of airflow limitation (one measure of COPD severity) as results are likely to be representative within each of these groups. In addition, the prevalence and severity of diagnosed COPD in CPRD is broadly similar to expected levels.

Survival bias

Stratifying by GOLD grade introduces an element of survival bias. This is because COPD patients are likely to have died before they reach severe and very severe GOLD grade groups. Patients left in these groups will be those who survived and their lung function will not represent the true lung function decline for severe and very severe COPD and results may be biased.

Misclassification

In our secondary analyses, we plan to stratify our main results by patient characteristics. Where possible we will use validated algorithms (such as for AECOPD). However it is possible that these patients may be misclassified due to undiagnosed of comorbidities in those with COPD. We will discuss the potential implications of this in any report. Blood eosinophil values are taken as analysed in respective local labs and recorded by the patient's general practice. An effort will be taken to remove any un-usual value and unit beyond expected range.

Data sources and quality

Only approximately 50% of the time is it stated that spirometry is done post bronchodilator. NICE guidance states that this is necessary for a diagnosis of COPD. We will carry out a sensitivity analysis by repeating the main analysis in both those in whom it is not stated as well as in those in whom it is clearly stated. We will assume that

subsequent readings after diagnosis are post bronchodilator if patients are prescribed long acting bronchodilator inhalers.

In addition, data quality between GPs may vary. Despite the implementation of the Quality and Outcomes Framework (QOF) in 2004, which encouraged GPs to record key data at a high level and lung function in COPD patients every 15 months, there is still some variation between GPs in terms of coding variables and recording data as free text, which researchers may miss. This therefore means not all available data is or can be used.

It is important to note that CPRD data is observational data and causality cannot be implied. Results should therefore be interpreted with caution.

Missingness

A further limitation commonly seen in studies using electronic health data is the problem of missing data. Including patients with only complete data may bias results and therefore methods to overcome missing values may be needed such as multiple imputation. We will report the numbers of patients with missing data and perform appropriate tests (e.g. chi-squared, t-tests, kruskal-wallis) between key variables and dummy variables (coded as missing/non-missing) for variables with substantial missingness. If missing data are random, methods to overcome missingness will be performed.

Statistical methods

Mixed linear regression will be used to estimate the linear slope of lung function decline in COPD patients. However, this assumes that lung function decline in COPD patients is continuously linear throughout follow up, which may not necessarily be the case. FEV_1 is more variable and Lung function in patients who initiate ICS medication can increase in the short period following drug initiation before returning back to a decline in lung function and it should not be assumed that lung function declines in a linear manner. Broken stick regression will be performed to help better model the natural decline in lung function in patients on COPD medication.

T. References

1. Vogelmeier, C.F., et al., *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary.* Am J Respir Crit Care Med, 2017. **195**(5): p. 557-582.

2. Gosker, H.R., et al., *Extrapulmonary manifestations of chronic obstructive pulmonary disease in a mouse model of chronic cigarette smoke exposure.* Am J Respir Cell Mol Biol, 2009. **40**(6): p. 710-6.

3. Fletcher, C. and R. Peto, *The natural history of chronic airflow obstruction.* British Medical Journal 1977. **1**: p. 1645-1648.

4. Collaborators, G.C.o.D., *Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016.* Lancet 2017. **390**(10100).

5. Martinez, F.J., et al., *Effect of Fluticasone Furoate and Vilanterol on Exacerbations of Chronic Obstructive Pulmonary Disease in Patients with Moderate Airflow Obstruction.* Am J Respir Crit Care Med, 2017. **195**(7): p. 881-888.

6. Vestbo, J., et al., *Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial.* The Lancet, 2016. **387**(10030): p. 1817-1826.

7. Soriano, J.B., et al., *A pooled analysis of FEV1 decline in COPD patients randomized to inhaled corticosteroids or placebo.* Chest, 2007. **131**(3): p. 682-689.

8. Drummond, M.B., et al., *Inhaled Corticosteroids in Patients With Stable Chronic Obstructive Pulmonary Disease*

A Systematic Review and Meta-analysis. JAMA, 2008. **300**(20): p. 2407-2416.

9. Suissa, S., et al., *Inhaled corticosteroids in COPD and the risk of serious pneumonia.* Thorax, 2013. **68**(11): p. 1029-36.

10. Yang, M., et al., *Long-term use of inhaled corticosteroids and risk of upper respiratory tract infection in chronic obstructive pulmonary disease: a meta-analysis.* Inhal Toxicol, 2017. **29**(5): p. 219-226.

11. Barnes, N.C., et al., *Blood eosinophils as a marker of response to inhaled corticosteroids in COPD.* Eur Respir J, 2016. **47**(5): p. 1374-82.

12. Pavord, I.D., et al., *Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD.* Thorax, 2016. **71**(2): p. 118-25.

13. Pascoe, S., et al., *Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials.* The Lancet Respiratory Medicine, 2015. **3**(6): p. 435-442.

14. Kerkhof, M., et al., *Blood eosinophil count and exacerbation risk in patients with COPD.* Eur Respir J, 2017. **50**(1).

15. Vestbo, J., et al., *Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice.* N Engl J Med, 2016. **375**(13): p. 1253-60.

16. Quint, J.K., et al., *Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD).* BMJ Open, 2014. **4**(7): p. e005540.

Applicants must complete all sections listed below Sections which do not apply should be completed as '***Not Applicable***'
17. Landis, S.H., et al., *Stability of Blood Eosinophil Count in Patients with COPD in the UK Clinical Practice Research Datalink.* COPD, 2017. **14**(4): p. 382-388.
List of Appendices (Submit all appendices as separate documents to this application) Codelist for inhaled corticosteroids

Approved Independent Scientific Advisory Committee (ISAC) protocol for chapter 7 (ISAC protocol 18_152RAR).

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

Study Title[§] (*Please state the study title below)*

Withdrawing inhaled corticosteroid (ICS) treatment in people with COPD: a real world study

[§]Please note: This information will be published on the CPRD's website as part of its transparency policy.

Has any part of this research proposal or a related proposal been previously submitted to ISAC?

Yes[*] ☐ No ☒

**If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.*

Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)

Yes[*] ☒ No ☐

**If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :* This project was submitted as an Investigator Initiated Study to Boehringer Ingelheim and has been reviewed and approved for funding by a Global Panel. As an IIS, BI will fund the work but have no input into the study itself.

Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☒
Drug Utilisation	☐	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐
Health care resource utilisation	☐	Methodological Research	☐
Health/Public Health Services Research	☐	Other[*]	☐

[*]If Other, please specify the type of study here and in the lay summary below:

Health Outcomes to be Measured[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy.*

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

- Time to first exacerbation of COPD (AECOPD)
- Time to first severe AECOPD
- Number of moderate or severe AECOPD
- Change from baseline in FEV1
- Adverse events (pneumonia, cardiac event, stroke)
- Change from baseline in dyspnoea (using modified Medical Research Council (mMRC))

[Please add more bullet points as necessary]

Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☒	Regulatory purposes	☐
Other[*]	☐		

**If Other, please provide further information:*

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

Chief Investigator[§]

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Dr Jennifer Quint, Clinical Senior lecturer in Respiratory epidemiology, Imperial College London, j.quint@imperial.ac.uk

[§]*Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy*

CV has been previously submitted to ISAC	☒ **CV number:**	042_15CEPSL
A new CV is being submitted with this protocol	☐	

An updated CV is being submitted with this protocol ☐

Affiliation of Chief Investigator (full address)

Respiratory Epidemiology, Occupational Medicine and Public Health

G48, Emmanuel Kaye Building

Manresa Road

National Heart and Lung Institute

Imperial College

London, SW3 6LR

Corresponding Applicant[§]
Please state the full name, affiliation(s) and e-mail address below:

Hannah Whittaker, h.whittaker@imperial.ac.uk

[§]*Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy*

Same as chief investigator ☐

CV has been previously submitted to ISAC ☒ **CV number:** 535_17

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

List of all investigators/collaborators[§]
Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

[§]*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator: Dr Steven Kiddle, Cambridge University, steven.kiddle@mrc-bsu.cam.ac.uk

CV has been previously submitted to ISAC ☒ **CV number:** 650_16S

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator: Dr Ian Douglas, LSHTM, Ian.douglas@lshtm.ac.uk

CV has been previously submitted to ISAC	☒	**CV number:**	157_15CESL
A new CV is being submitted with this protocol	☐		
An updated CV is being submitted with this protocol	☐		

Other investigator: Professor Deborah Jarvis, Imperial College London, d.jarvis@imperial.ac.uk

CV has been previously submitted to ISAC	☒	**CV number:**	256_18
A new CV is being submitted with this protocol	☐		
An updated CV is being submitted with this protocol	☐		

Other investigator: Dr Kevin Wing, LSHTM, kevin.wing@lshtm@ac.uk

CV has been previously submitted to ISAC	☒	**CV number:**	497_16ES
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.*

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

Dr Quint's research group has received funding from the MRC, Welcome Trust, BLF, Insmed, Bayer, GSK, the Health Foundation and AZ for other projects, none of which relate to this work. Imperial College London will receive funding from Boehringer Ingelheim on behalf of Dr Quint's group for this project. This is funded as an Investigator Initiated Study and BI have had no input into the study. Dr Quint has received funds from AZ, GSK, Chiesi, TEVA and BI for Advisory board participation or travel. Dr Kiddle has received funding from Janssen and Eli Lilly for other projects which do not relate to this work, and funds from Roche Diagnostics for Advisory board participation.

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☐	☐
> 3	☒	☒

Experience/Expertise available	Yes	No
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint, Kiddle, Whittaker, Douglas, Jarvis, Wing	☒	☐
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)* Quint, Whittaker, Douglas, Kiddle, Wing	☒	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint	☒	☐

References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

- Magnussen H, Tetzlaff K, Bateman ED, et al. Lung function changes over time following withdrawal of inhaled corticosteroids in patients with severe COPD. *The European respiratory journal* 2016; **47**(2): 651-4.
- Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *The New England journal of medicine* 2014; **371**(14): 1285-94.
- Wing K, Williamson E, Carpenter JR*, et al.* Real-world effects of medications for chronic obstructive pulmonary disease: protocol for a UK population-based non-interventional cohort study with validation against randomised trial results. *BMJOpen* 2018;**8:**e019475. doi: 10.1136/bmjopen-2017-019475

SECTION C: ACCESS TO THE DATA

Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry	☒	*Please specify name and country:* Boehringer Ingelheim, UK
Academia	☐	*Please specify name and country:*
Government / NHS	☐	*Please specify name and country:*
Charity	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*
None	☐	

Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	*Please specify name and country:* Imperial College London, UK
Government Department	☐	*Please specify name and country:*
Research Service Provider	☐	*Please specify name and country:*
NHS	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*

Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data	☐
The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data**	☒
A data set will be provided by the CPRD[¥€]	☐
CPRD has been commissioned to extract the data and perform the analyses[€]	☐
Other:	☐

If Other, please specify:

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*

***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 (enquiries@cprd.com) if a dataset of >300,000 patients is required.*

[€]*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

Name of CPRD Researcher	Reference number (where available)	Date of contact

Primary care data
Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies ☐ Both Vision and Aurum* ☒

Aurum only* ☐

Note: Vision and Aurum are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from Aurum is currently under evaluation prior to wider release.

Investigators requiring the use of Aurum data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for Aurum data:

Name of CPRD Researcher	Reference number (where available)	Date of contact

Site Location of Data

a) Processing location(s):

Location area - UK / EEA / Worldwide:

Organisation address:

Respiratory Epidemiology, Occupational Medicine and Public Health

G48, Emmanuel Kaye Building

Manresa Road

National Heart and Lung Institute

Imperial College

London, SW3 6LR

Note: Please enter the location details of where the data for this study will be used (processed).

b) Storage Location(s)

Location area - UK / EEA / Worldwide:

Organisation address:

Respiratory Epidemiology, Occupational Medicine and Public Health

G48, Emmanuel Kaye Building

Manresa Road

National Heart and Lung Institute

Imperial College

London, SW3 6LR

Note: Please enter the location details of where the data for this study will be stored.

c) Territory of analysis - UK / EEA / Worldwide:

UK

Note: Please enter the details of where the data for this study will be analysed.

SECTION D: INFORMATION ON DATA LINKAGES

Does this protocol seek access to linked data

Yes* ☒ No☐ If No, please move to section E.

Research groups which have not previously accessed CPRD linked data resources **must discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset, PROMS data, the Pregnancy Register, Cancer Registration, SACT and CPES data and the Mental Health Services Data Set **must** also discuss this with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email enquiries@cprd.comto discuss your requirements **before** submitting your application.*

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

We have not discussed linkage for this particular study but are only asking for access to datasets that we have previous experience of using and have had previous conversations with CPRD researchers about those data.

Name of CPRD Researcher Reference number (where available) Date of contact

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

Please select the source(s) of linked data being requested§
§Please note: This information will be published on the CPRD's website as part of its transparency policy.

☐ ONS Death Registration Data

☒ HES Admitted Patient Care

☐ HES Outpatient

☐ HES Accident and Emergency

☐ HES Diagnostic Imaging Dataset

☐ HES PROMS (Patient Reported Outcomes Measure)**

☐ CPRD Mother Baby Link

☐ Pregnancy Register

☐ NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data *

☐ NCRAS Cancer Patient Experience Survey (CPES) data*

☐ NCRAS Systemic Anti-Cancer Treatment (SACT) data*

☐ Mental Health Services Data Set (MHDS)

☐ Practice Level Index of Multiple Deprivation (Standard)

☐ Practice Level Index of Multiple Deprivation (Bespoke)

☒ Patient Level Index of Multiple Deprivation***

☐ Patient Level Townsend Score ***

**Applicants seeking access to NCRAS data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also 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.*

***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only available for non-commercial purposes, such as academic research, or in connection with delivering services to the NHS.*

**** 'Patient level IMD and Townsend scores will not be supplied for the same study*

*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

Name of CPRD Researcher	Reference number (where available)	Date of contact

Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **<u>not</u>** be included in this count)* 2

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

Is linkage to a <u>local</u>¥ dataset with <1 million patients being requested?

Yes* ☐ No ☒

**If yes, please provide further details:*

¥ *Data from defined geographical areas i.e. non-national datasets.*

If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

Does this protocol describe a purely observational study using CPRD data?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*

*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐

Is the questionnaire a validated instrument? Yes ☐ No ☐

If yes, has permission been obtained to use the instrument? Yes ☐ No ☐

Please provide further information:

Other (please describe)

[ψ] Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

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.*

Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected:*

SECTION F: DECLARATION

Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.
- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Jennifer Quint Date: 2/5/18 e-Signature (type name): JKQuint

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

D. Study Title[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Withdrawing inhaled corticosteroid (ICS) treatment in people with COPD: a real world study

E. Lay Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

People with chronic obstructive pulmonary disease (COPD) are treated with inhalers to alleviate symptoms and ease breathing (short and long-acting bronchodilator inhalers), and with inhalers that include steroids (inhaled corticosteroids (ICS)) if symptoms persist. A study in which people were randomly assigned to drug groups (randomised control trial), called "The Study to Understand Mortality and Morbidity in COPD" (SUMMIT), showed that ICS use slows down lung function decline and decreases the risk of periods of symptom worsening (exacerbations of COPD) in people with COPD. All individuals have some decline in lung function over time, particularly in later life, but people with COPD lose lung function faster than the general population, particularly in smokers. Recently another randomised control trial called "Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial" showed that people with COPD who started on medication including ICS but then stopped using ICS had the same lung function decline and risk of exacerbations as those who stayed on medication including ICS. This study included specific people with COPD and may not represent the true population of people with COPD. Using statistical models, we will replicate the WISDOM study using a more generalizable population of people with COPD.

F. Technical Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Chronic Obstructive Pulmonary Disease (COPD) patients are treated with short/long-acting bronchodilator inhalers. If symptoms persist or patients experience exacerbations of COPD (AECOPD) they are prescribed inhaled corticosteroids (ICS). The risks and benefits of ICS in the treatment of COPD is debated however, the Study to Understand Mortality and Morbidity in COPD (SUMMIT) suggested that ICS are associated with reduced lung function (FEV_1) decline, and decreased risk of AECOPD. In contrast, a recent randomised control trial (RCT), the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial, investigated whether FEV_1 decline in COPD patients on triple therapy, who withdrew from ICS, differed from those who remained on triple therapy. Results showed no difference in rate of FEV_1 decline between the two groups. Whilst well-performed RCTs allow causal effects of drug treatments to be inferred, they include very specific COPD populations and results may not be generalizable to the general COPD population. Observational studies are

therefore needed to assess associations in a wider population of COPD patients. Using mixed effects linear regression and Cox-proportional hazard regression we will investigate the association between risk of AECOPD and FEV_1 decline in COPD patients on triple therapy and those who withdraw from ICS.

U. Objectives, Specific Aims and Rationale

Our overarching objective is investigate the difference between COPD patients on triple therapy (LABA/LABA/ICS) and COPD patients who were on triple therapy but withdraw from ICS in terms of time to first AECOPD, time to first severe AECOPD, and time to first mild AECOPD over 14 years, number of AECOPD in first year of follow-up, rate of FEV1 decline over 14 years, and change in health status and dyspnoea over 14 years.

Our specific aims are:

1. To investigate the association between ICS withdrawal and the outcomes specified above in a COPD population similar to the WISDOM trial by following WISDOM's inclusion and exclusion criteria.

2. To investigate the association between ICS withdrawal and the same outcomes as aim 1 within a cohort of patients who would not have met the inclusion criteria for WISDOM.

3. To investigate the association between ICS withdrawal and the same outcomes as aim 1 within a cohort of patients who would have been specifically excluded from the WISDOM trial; i.e. patients with comorbidities or patients who did not experience an AECOPD prior to the study.

V. Study Background

Chronic obstructive pulmonary disease (COPD) affects 3 million people in the UK [1]. The most common cause is smoking, and patients exhibit airflow obstruction that is not fully reversible. The disease is progressive, with declining lung function and a worsening of symptoms. Most troublesome are acute exacerbations manifested as a sudden worsening of symptoms e.g. severe coughing, shortness of breath and chest congestion, requiring urgent treatment, and possibly hospitalisation. Whilst smoking cessation remains the most effective intervention, the rate of exacerbation can be reduced by regular medication such as combination long acting beta-adrenoceptor agonists (LABAs), and inhaled corticosteroids (ICS) or long-acting muscarinic antagonists (LAMAs).

Evidence of medication effects in routine care is vital for understanding the balance of treatment risks and benefits. RCTs have unique strengths, but results from trials are not always a good guide to the effects of drugs in routine clinical practice [2]. National drug licensing authorities are now demanding better real world evidence on which to make decisions and have introduced legislation mandating studies of both effectiveness and risk to be conducted in routine clinical care rather than the narrow and optimal confines of most randomised trials [3,4]. Whilst the conduct

of observational studies to investigate possible drug harms is well established, the use of these studies to estimate treatment effectiveness is in its infancy. Issues of treatment channelling and indication bias mean that measuring the intended benefit of a treatment is beset with difficulties. Whilst others have demonstrated it can be done in certain circumstances, we need more certainty about the methodology as it is applied in each disease area, since the issues of bias are likely to vary considerably [5]. Increasingly large quantities of electronic health records (EHR) have become available to researchers recently and links between sources of data are constantly developing. Over the next few years we will see more observational studies of drug effectiveness emerging; however, rigorous, validated methodology is needed to translate these complex data into reliable evidence. Here we propose a template for drug effectiveness research with inbuilt validation against a randomised trial.

COPD treatment guidelines are largely informed by randomised controlled trial (RCT) results [6], but we do not know if these findings apply to large patient populations not studied in trials. While randomised controlled trials (RCT) will continue to be the gold standard for assessing the efficacy of medical interventions, they are expensive to conduct, and for practical and ethical reasons usually involve testing treatments in patient populations and within contexts which are sometimes very different to real life. In particular, RCT participants usually have no comorbidities and are relatively healthy (apart from having COPD). Thus, often the very patients that are most commonly seen in a COPD outpatient clinic are those that would be excluded from clinical trials due to their co-morbidities. As patient populations with chronic diseases such as COPD become more complex, the studies used to generate clinical evidence must reflect this. Inevitably, this will require more and larger RCTs which may not always be feasible or ethical. Findings from the RCTs which are conducted, must therefore be extrapolated to other populations. The validity of this approach is uncertain as the balance of risks and benefits of a treatment may vary widely between subgroups. This uncertainty is rarely communicated alongside clinical guidelines. It also needs to be recognized that in many situations, such as when studying rare but important harms, it is rarely feasible to conduct adequately powered RCTs.

In this project therefore, we plan to study ICS withdrawal in people with COPD using individual patient data from the WISDOM study as the gold standard. Studying ICS withdrawal is important as there is increasing evidence that in some individuals with COPD the harm associated with being on them may outweigh the benefit. This will allow us to fine tune methodology to allow more accurate estimates of the effect of ICS withdraw in a real world population by comparing outcomes from WISDOM with routinely collected CPRD and linked HES data.

W. Study Type

Descriptive and hypothesis testing. The null hypotheses are that there is no association between ICS withdrawal and any of (i) the risk of AECOPD (ii) change in FEV1 or (iii) change from baseline mMRC

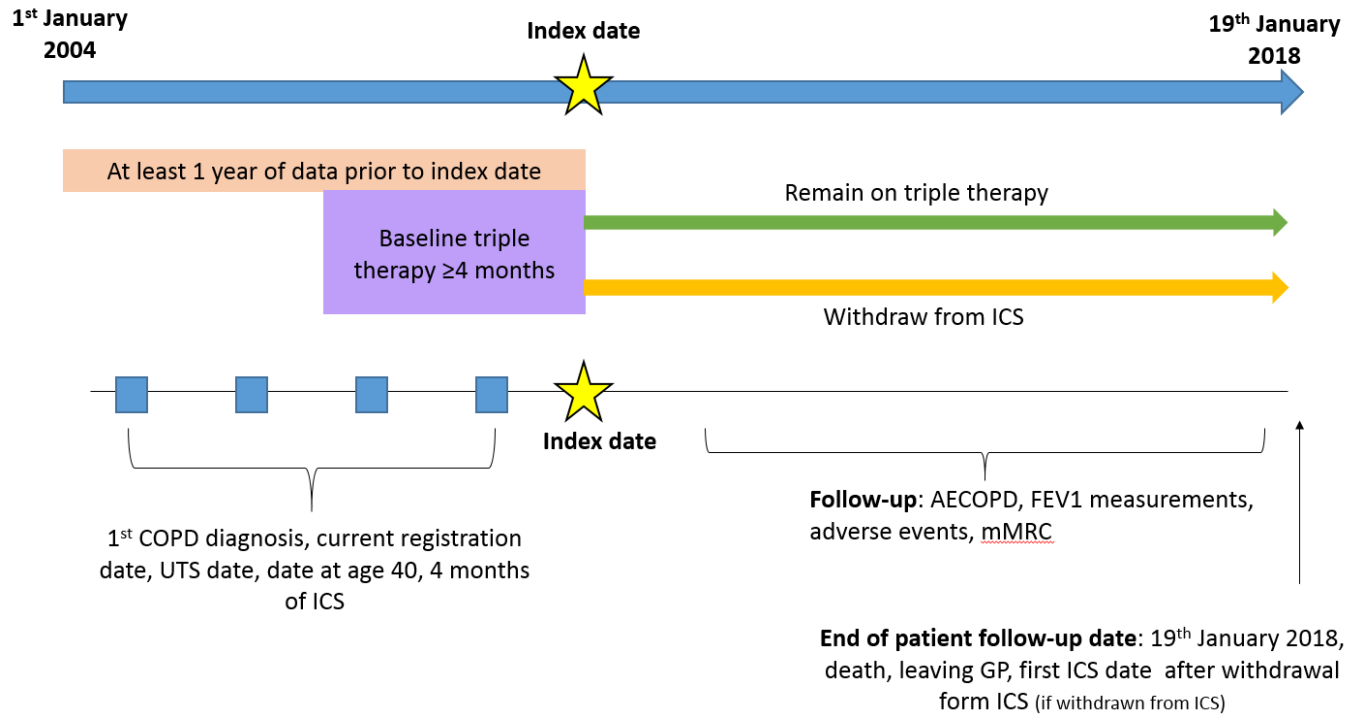
Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

X. Study Design

This will be a longitudinal cohort study.

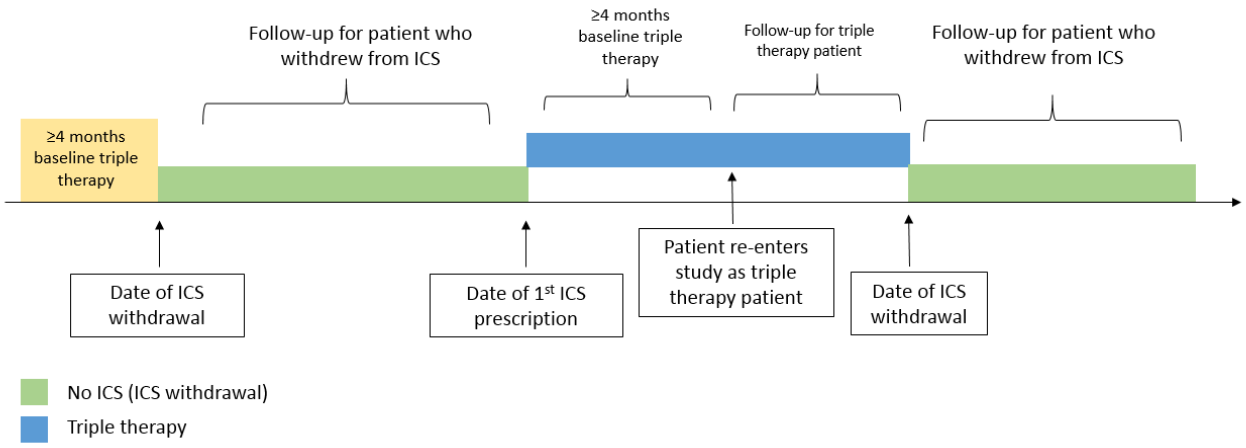
This study will use individual level patient data from WISDOM and prospectively collected routine electronic healthcare data from the Clinical Practice Research Datalink. We will replicate the study design of the WISDOM trial in CPRD patients. See the study design diagram for further information.



Due to immortal time bias we will conduct a sensitivity analysis whereby patients who withdraw from ICS but are prescribed an ICS later on will be censored and allowed to enter the cohort again as a patient on triple therapy following at least 4 months of ICS. Patients who are tripe therapy patients but withdraw from ICS later will be censored and allowed to enter the cohort again as an ICS-withdrawer. See figure below.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'



Y. Feasibility counts

Feasibility

Using a CPRD extract from July 2015 with a first COPD diagnosis from Jan 2004 to July 2015:

	Number of patients	**Excluded**
Acceptable patients	221,707	
Active in this study period	221,707	
COPD diagnosis 2004-2015	169,900 (COPD code & smoker)	
Patients with 1 year of data prior to index	132,785	37,045
Patient aged >= 40 at index	132,785	
Linkage to HES	79,714	53,071
FEV1/FVC < 70 ever confirmation of copd diagnosis	56,287	23,879
At least 1 exacerbation in study period	48,381	3,004

Current/exsmokers	done in COPD definition - all have smoking history	
Patients treated with triple therapy for at least 4 months anytime during follow up	23,002	25,379
Patients with incident ICS withdrawal during study period (after start of triple therapy, at least 6 months before end of follow up)	2,921	
Patients maintaining treatment during whole study period	20,081	
At least 1 exacerbation in year prior to withdrawal (withdrawal only pts)	2,491	430
At least 1 exacerbation during triple therpy time (non-withdrawal only pts)	19,645	436
Exclude Concurrent asthma in year prior to index triple therapy (withdrawal)	1,880	611
Exclude Concurrent asthma in year prior to index triple therapy (non-withdrawal)	12,783	6,862
Patients with incident ICS withdrawal during study period (after start of triple therapy, at least 6 months before end of follow up)	1,880	13%
Patients maintaining treatment 6 months after index	12,783	87%
Total patients	**14,663**	

The total number of patients who completed follow-up in the WISDOM trial was 2,485.

Z. Sample size considerations

From other COPD work undertaken in CPRD, in a cohort of 111,157 COPD patients aged 35 or older, and who are smokers or ex-smokers, 87,439 have FEV_1 recorded after 2004, 64,289 have more than two records, and 61,077 have more than two records 6 months apart. Following the power calculation in the WISDOM trial, 2,456 patients are needed in total to provide 90% power, with an alpha value of 0.025, in order to determine a non-inferiority hazard ratio for AECOPD in the withdrawal group vs triple therapy group.

AA. Data Linkage Required (if applicable):§

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

§*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

HES APC- to identify exacerbations of COPD to determine exacerbation frequency and severity

BB. Study population

1. For our first aim we will restrict patients to the WISDOM inclusion and exclusion criteria. This includes patients diagnosed with severe to very severe COPD (defined at <50% FEV1 predicted, <70% FEV1/FVC), aged older than 40 years, current or ex-smokers, and who have a history of at least one AECOPD 12 months before start of follow-up. In addition, patients must also have at least 2 FEV1 measurements across the follow-up period and be eligible for HES linkage. Excluded patients include those with: asthma; unstable cardiac arrhythmia; bronchiectasis; a respiratory tract infection or AECOPD within 6 weeks prior to start of follow-up; history of myocardial infarction within 3 months prior to start of follow-up; or hospitalisation for cardiac failure. We will use patient level data from WISDOM to match patients to the CPRD patients on age, sex, COPD GOLD grade, co-morbidities and if possible medications.

2. For our second aim we will include all COPD patients in CPRD meeting the following general inclusion criteria but not necessarily the exclusion criteria. These patients will not only include patients from aim 1 but will include many more who would not have been included in WISDOM because they would have met the exclusion criteria. Patients must have a COPD diagnosis [7] aged 35 years old or older, current or ex-smokers, who have at least 2 FEV1 measurements during their follow-up and be eligible for HES linkage.

3. For our third aim we will study only patients who would have been excluded from WISDOM. Here we will specifically create a cohort of patients who would have met the exclusion criteria. This will include mild to moderate COPD patients with any of the following: a current diagnosis of asthma; an MI within 3 months prior to study start; hospitalisation due to heart failure in the year prior to study start; a respiratory tract infection or AECOPD 6 weeks prior to start of follow-up; history of bronchiectasis; history of cardiac arrhythmia; or history of thoracotomy.

CC. Selection of comparison group(s) or controls

We will compare COPD patients on triple therapy (LAMA, LABA, ICS) with COPD patients who start on triple therapy but withdraw from the ICS. To select patients on a triple therapy we will identify prescriptions across patients follow-up and determine patients who remain on triple therapy for at least 4 months at any time in their follow-up. Patients who start on triple therapy and withdraw from ICS up to 6 months before the end of follow-up will be classed as patients who withdrew from ICS. The population will depend on the aim of interest as described in section K.

DD. Exposures, Health Outcomes§ and Covariates

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

§*Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy*

Exposure: The exposure of interest is withdrawal of ICS (see codelist) following long term triple therapy (LABA, LAMA, and ICS) for more than 4 months. This will be determined through prescription type and dates. Patients with LAMA, LABA and ICS prescriptions for at least 4 months who discontinue ICS before the last 6 months of follow-up will be classed as ICS withdrawal patients. Patients who are on triple therapy for at least 4 months and who do not withdraw from ICS will be considered the population who remain on triple therapy. Due to differences in the start of follow-up between the ICS and ICS withdrawal population, we will match on baseline ICS duration.

Outcomes: The primary outcome of interest is risk of moderate/severe AECOPD. Secondary outcomes are change in FEV1 (measured in ml/year), and change in dyspnoea (measured by the difference from baseline in mMRC scale). All outcomes are readily identifiable in CPRD/HES data and the algorithm that we will use for the detection of AECOPD has been previously validated [8].

Covariates:
(Depending on the aim the following covariates may also be part of the inclusion/exclusion criteria or as an outcome.)

Demographic: Age, sex, socioeconomic status (individual linked data from IMD), ethnicity, BMI, and smoking status (current smoker, ex-smoker,). These are all recorded in the Clinical/Additional files in the CPRD extract and the group have extensive experience in defining them. Nearest BMI and smoking status prior to start of follow-up will be used.

Other co-morbid conditions: asthma, heart failure, bronchiectasis, MI, stroke, respiratory tract infection, cardiac arrhythmia
COPD medications: These will include, long and short acting beta agonists, oral prednisolone, short and long acting anti-cholinergics, theophyllines, combination short acting beta agonists and short acting anti-cholinergics, combination long acting beta agonists and long acting anti-cholinergics nebulised therapy.

COPD severity: GOLD stage using airflow obstruction.

EE. Data/ Statistical Analysis

All analyses and data management will be performed in STATA 15. We will have access to individual level data from WISDOM (accessed through ClinicalStudyDataRequest.com) in order to match WISDOM patients with

CPRD patients on sex and age, COPD GOLD grade, co-morbidities and if possible medications in order to define the CPRD population needed for aim 1 [9]. The other two populations for aim 2 and 3 will not be matched with the WISDOM data. See section D for more detail. Furthermore, due to differences in the start of follow-up time between the ICS and ICS withdrawal population, we will match patients on baseline ICS duration for all aims.

Primary outcome: Risk of moderate/severe AECOPD

Cox proportional hazards regression will be used in order to investigate the association between ICS withdrawal and risk of first moderate/severe AECOPD. Baseline FEV1 and treatment will be incorporated into the model as well as the appropriate covariates listed in section M. In addition, time to first severe AEOCPD, first moderate AECOPD, and will be explored through sensitivity analyses using the same model and descriptive analyses. Number of AECOPD in the first year of follow-up will be explored using Poisson or negative binomial regression.

Secondary outcomes: Rate of FEV1, change in dyspnoea and health status

Multilevel linear models will be used to describe the rate of FEV_1 decline (mL/year). Multi-level mixed model will be used due to the nature of the study using repeated measures of FEV_1 within patients. The fixed part of the model (level 1) will include the exposure (ICS withdrawal), the outcome (FEV1 (ml) * time from start of follow-up (year)). The random effects (level 2) will include the patient identifier to allow for random intercepts and time from start of follow-up to allow for random slopes. The adjusted model will account for covariates listed in section M. Patients meeting the inclusion criteria and who have at least 2 FEV1 measurements will be included in the analysis.

In addition, changes in dyspnoea score (mMRC score 1-5) will be summarised using descriptive techniques.

In all analyses we will investigate the differences in outcomes between those who withdraw from ICS and those who do not and remain on the triple therapy throughout follow-up. In addition, we will treat analyses as an intention to treat (ITT) population whereby patients are categorised into the respective withdrawal/no withdrawal of ICS groups at baseline and outcomes are analysed with respect to these groups (even if they subsequently restart triple therapy).

FF. Plan for addressing confounding

A potential list of confounders of the association between ICS withdrawal and the COPD-related outcomes under study includes: age, sex, socioeconomic status, ethnicity, BMI, and smoking status (current smoker, ex-smoker), asthma, heart failure, stroke, bronchiectasis, MI, respiratory tract infection, cardiac arrhythmia, COPD medications, and airflow obstruction. Multivariable Cox regression will be applied and multi-level mixed effect linear models

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

prepared as detailed in section N.

GG. Plans for addressing missing data

We will consider the use of multiple imputation when using the mixed effects linear model or cox regression if we are able to assume data are missing at random. Variables that may include missing data include: MRC, FVC, IMD, and BMI.

HH. Patient or user group involvement (if applicable)

Study participants will not be contacted or involved in the planning or dissemination of the project. All participants will be pseudo-anonymised in order to keep their identify unknown, following blinding in RCTs.

II. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The study findings will be submitted for publication in peer-reviewed scientific journals, and will be presented at appropriate conferences and other meetings; the latter will include scientific meetings externally, for example the American and European Respiratory Society Meetings and internally within Imperial College London, University of Cambridge and LHSTM.

JJ.Limitations of the study design, data sources, and analytic methods

Misclassification COPD and asthma

Despite using a highly sensitive algorithm to identify patients with COPD, it is possible that GPs may have misdiagnosed asthma as COPD and vice versa, notably in patients over the age of forty [7, 10]. Based on findings from previous work on misclassification of asthma and COPD, we will include define history of asthma as an asthma diagnosis more than 2 years prior to study start.

Data sources and quality

Only approximately 50% of the time is it stated that spirometry is done post bronchodilator. NICE guidance states that this is necessary for a diagnosis of COPD. We will carry out a sensitivity analysis by repeating the main analysis in both those in whom it is not stated as well as in those in whom it is clearly stated. We will assume that

subsequent readings after diagnosis are post bronchodilator if patients are prescribed long acting bronchodilator inhalers.

In addition, data quality between GPs may vary. Despite the implementation of the Quality and Outcomes Framework (QOF) in 2004, which encouraged GPs to record key data at a high level and lung function in COPD patients every 15 months, there is still some variation between GPs in terms of coding variables and recording data as free text, which researchers may miss. This therefore means not all available data is or can be used.

It is important to note that CPRD data is observational data and causality cannot be implied. Results should therefore be interpreted with caution.

Missingness

A further limitation commonly seen in studies using electronic health data is the problem of missing data. Including patients with only complete data may bias results and therefore methods to overcome missing values may be needed such as multiple imputation. We will report the numbers of patients with missing data and perform appropriate tests (e.g. chi-squared, t-tests, kruskal-wallis) between key variables and dummy variables (coded as missing/non-missing) for variables with substantial missingness. If missing data are random (by analysing missing data patterns), methods to overcome missingness will be performed.

Difficulty mimicking WISDOM trial

Mimicking the WISDOM trial using electronic health records can have its difficulties and limitations. Unlike a RCT we cannot ensure that patients included in our study adhere to the medication they are prescribed by their GP. We must assume that they are, however, this may not be likely for all patients and is a limitation. This can lead to the misclassification of exposure groups in our study. A patient may be prescribed triple therapy (LABA, LAMA, and ICS) however, they only adhere to LABA/LAMA. Using their prescription data this patient would be grouped as a triple therapy user however, in reality they have withdrawn from the ICS and are therefore grouped into the wrong exposure group.

In addition, unlike WISDOM, patients will have different lengths of follow-up time. Whereas in the WISDOM trial patients were followed-up for a period of a year, we will be following patients for a longer maximum period of time, Depending on the patient's data, they may also have a follow-up less than a year. This is important for the change in FEV1 as follow-up time after withdrawal may influence the overall rate of change. As a sensitivity analysis we will restrict the length of follow-up to 1 year.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

KK. References

1. Healthcare Commission (2006) Clearing the air: a national study of chronic obstructive pulmonary disease. London: Healthcare Commission.
2. van Staa TP1, Leufkens HG, Zhang B, Smeeth L. (2009) A comparison of cost effectiveness using data from randomized trials or actual clinical practice: selective cox-2 inhibitors as an example. PLoS Med. 2009 Dec;6(12):e1000194. doi: 10.1371/journal.pmed.1000194. Epub 2009 Dec 8.
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4. Guidance for Industry Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, US FDA, April 2011
5. Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. Br J Clin Pharmacol 2009;67:99-109.
6. NICE (2010) Chronic obstructive pulmonary disease in over 16s: diagnosis and management; nice.org.uk/guidance/cg101
7. Quint, J. K., et al. (2014). "Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalin k (CPRD-GOLD)." BMJ Open **4**(7): e005540.
8. Rothnie, K. J., et al. (2016). "Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records." PLoS One **11**(3): e0151357.
9. Wing K, Williamson E, Carpenter JR*, et al.* Real-world effects of medications for chronic obstructive pulmonary disease: protocol for a UK population-based non-interventional cohort study with validation against randomised trial results. *BMJOpen* 2018;**8:**e019475. doi: 10.1136/bmjopen-2017-019475
10. Rothnie, K. J., et al. (2017). "Validity and interpretation of spirometric recordings to diagnose COPD in UK primary care." Int J Chron Obstruct Pulmon Dis **12**: 1663-1668.

List of Appendices (Submit all appendices as separate documents to this application)

Codelist for inhaled corticosteroids

Amendment 20th December 2019

Rationale:

We have started to define our cohorts using the inclusion and exclusion criteria described for each aim in section D&K however, the number of patients meeting these criteria are low (please see the flow diagrams below for further detail). In addition, ~2% of patients withdraw from ICS 6 months prior to the end of follow-up when using the first study design (see section G first figure). We think that few people in our dataset are withdrawing from ICS because the guidelines stating that ICS should be withdrawn from triple therapy only came into place in 2018. In addition, many previous CPRD GOLD practices are now likely to be contributing recent data to CPRD Aurum. This is why the feasibility numbers were higher in our ISAC because they were generated using GOLD data up until July 2015. Therefore, by using Aurum data we will be able to increase the number of patients in our population, increase power, and identify more patients withdrawing from ICS.

With this in mind, we would like to request a newer CPRD GOLD cut and additional CPRD Aurum data. This will help increase the number of patients meeting our inclusion criteria for each aim as well as help identify patients withdrawing from ICS. We acknowledge there may be differences between CPRD GOLD and CPRD Aurum and would perform the study separately in each database before combining the two.

N. Analyses will be performed in CPRD GOLD and Aurum separately at the first instance before combining the two databases.

S. We will be using both CPRD GOLD and Aurum data and differences between databases may exist. Therefore, we will perform the analyses separately in both databases before combining the two. Differences in patient characteristics and results between the two databases will be reported.

Approved Independent Scientific Advisory Committee (ISAC) protocol for chapter 8 (ISAC protocol 19_258).

GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY
Study Title (Max. 255 characters including spaces) Lung function decline and rate of cardiovascular disease in COPD patients in England

Research Area (place 'X' in all boxes that apply)

Drug Safety		Economics	
Drug Utilisation		Pharmacoeconomics	
Drug Effectiveness		Pharmacoepidemiology	
Disease Epidemiology	X	Methodological	
Health Services Delivery			

Chief Investigator

Title:	Dr
Full name:	Jennifer Quint
Job title:	Reader in Respiratory Epidemiology
Affiliation/organisation:	Imperial College London
Email address:	j.quint@imperial.ac.uk
CV Number (if applicable):	042_15CEPSL
Will this person be analysing the data? (Y/N)	N

Corresponding Applicant

Title:	Miss
Full name:	Hannah Whittaker
Job title:	Research Assistant and PhD student
Affiliation/organisation:	Imperial College London

Email address:	h.whittaker@imperial.ac.uk
CV Number (if applicable):	535_17
Will this person be analysing the data? (Y/N)	Y

List of all investigators/collaborators

Title:	Dr
Full name:	Steven Kiddle
Job title:	Research Fellow
Affiliation/organisation:	Imperial College London
Email address:	s.kiddle@imperial.ac.uk
CV Number (if applicable):	650_16S
Will this person be analysing the data? (Y/N)	N

Title:	Professor
Full name:	Deborah Jarvis
Job title:	Professor of Public Health
Affiliation/organisation:	Imperial College London
Email address:	d.jarvis@imperial.ac.uk
CV Number (if applicable):	256_18
Will this person be analysing the data? (Y/N)	N

Title:	Dr
Full name:	Ann Morgan
Job title:	Research Associate
Affiliation/organisation:	Imperial College London
Email address:	a.morgan15@imperial.ac.uk
CV Number (if applicable):	367_16
Will this person be analysing the data? (Y/N)	N

[Add more investigators/collaborators as necessary by copy and pasting a new table for each investigator/collaborator]

Experience/expertise available

List below the member(s) of the research team who have experience with CPRD data.

Name(s):

Whittaker

Quint

Kiddle

Morgan

List below the member(s) of the research team who have statistical expertise.

Name(s):

Quint

Kiddle

Jarvis

Whittaker

Morgan

List below the member(s) of the research team who have experience of handling large datasets (greater than 1 million records).

Name(s):

Quint

Kiddle

Whittaker

Morgan

List below the member(s) of the research team, or supporting the research team, who have experience of practicing in UK primary care.

Name(s):

Quint

ACCESS TO THE DATA

Sponsor of the study

Institution/Organisation:	Imperial
Address:	Emmanuel Kaye Building, 1b Manresa Road, London, SW3 6LR

Funding source for the study

Same as Sponsor?	Yes No X
Institution/Organisation:	British Lung Foundation
Address:	Goswell Rd, EC1V 7ER London

Institution conducting the research

Same as Sponsor?	Yes X No
Institution/Organisation:	Imperial College London
Address:	Emmanuel Kaye Building, 1b Manresa Road, London, SW3 6LR

Data Access Arrangements

Indicate with an '**X**' the method that will be used to access the data for this study:

Study-specific Dataset Agreement	
Institutional Multi-study Licence	X
Institution Name	Imperial College London
Institution Address	Emmanuel Kaye Building, 1b Manresa Road, London, SW3 6LR

Will the dataset be extracted by CPRD?

Yes No X

If yes, provide the reference number:

Data Processor(s):

Processing	X
Accessing	X
Storing	X

Processing area (UK/EEA/Worldwide)	
Organisation name	NHLI, Imperial College London
Organisation address	Emmanuel Kaye Building, 1b Manresa Road, London, SW3 6LR

INFORMATION ON DATA

Primary care data (place 'X' in all boxes that apply)

CPRD GOLD	X	CPRD Aurum	

Reference number (if applicable):

Please select any linked data or data products being requested

Patient Level Data (place '**X**' in all boxes that apply)

ONS Death Registration Data	X		
HES Admitted Patient Care	X		
HES Outpatient			
HES Accident and Emergency		NCRAS Cancer Registration Data	

HES Diagnostic Imaging Dataset		NCRAS Cancer Patient Experience Survey (CPES) data	
HES PROMS (Patient Reported Outcomes Measure)		NCRAS Systemic Anti-Cancer Treatment (SACT) data	
CPRD Mother Baby Link		NCRAS National Radiotherapy Dataset (RTDS) data	
Pregnancy Register		NCRAS Quality of Life Cancer Survivors Pilot (QOLP)	
Mental Health Data Set (MHDS)		NCRAS Quality of Life Colorectal Cancer Survivors (QOLC)	

Area Level Data (place '**X**' in <u>one</u> Practice / Patient level box that may apply)

Practice level (UK)		**Patient level (England only)**	
Practice Level Index of Multiple Deprivation		Patient Level Index of Multiple Deprivation	X
Practice Level Index of Multiple Deprivation (index other than the most recent)		Patient Level Index of Multiple Deprivation Domains	
Practice Level Index of Multiple Deprivation Domains		Patient Level Carstairs Index for 2011 Census	
Practice Level Carstairs Index for 2011 Census (Excluding Northern Ireland)		Patient Level Townsend Score	
2011 Rural-Urban Classification at LSOA level		2011 Rural-Urban Classification at LSOA level	

Reference / Protocol number (where applicable):

Are you requesting linkage to a dataset not listed above?

Yes No **X**

If yes, provide the Non-Standard Linkage reference number:

Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?

Yes No **X** If yes, provide further details:
VALIDATION/VERIFICATION
Does this protocol describe an observational study using purely CPRD data? Yes **X** No
Does this protocol involve requesting any additional information from GPs, or contact with patients? Yes No **X** If yes, provide the reference number:

Applicants must complete all sections listed below

Applications with sections marked 'Not applicable' without justification will be returned as invalid

Study Title (Max. 255 characters, including spaces)

Lung function decline and risk of cardiovascular disease in COPD patients in England

Lay Summary (Max. 250 words)

Lung function tests relate to how well our lungs are working and measure such things as how much air our lungs can hold and how easily we can breathe in and out. All individuals have some decline in their lung function over time, particularly in later life and people with chronic obstructive pulmonary disease (COPD) lose lung function faster than the general population. Low lung function and accelerated loss of lung function have been linked to cardiovascular disease in the general population. No studies have looked at this relationship in people with COPD. Using statistical models, we will investigate whether COPD patients who lose lung function faster are more likely to have cardiovascular disease compared to COPD patients who lose lung function at a slower rate.

Technical Summary (Max. 300 words)

People with chronic obstructive pulmonary disease (COPD) have a faster lung function decline compared to the general population. Accelerated lung function decline has been associated with mortality, and more recently with cardiovascular disease (CVD) in the general population. Specifically, accelerated lung function decline was associated with incident heart failure, stroke, death, and hospitalisations from heart failure. CVD is a common comorbidity of COPD and thus it is important to understand how lung function decline influences risk of incident cardiovascular disease in a population of COPD patients. Using survival analyses we will investigate rate of incident CVD in relation to rapid lung function decline over a 15 year period in a primary care population of COPD patients.

Outcomes to be Measured

Rate of incident cardiovascular disease including: stroke, heart failure (HF), myocardial infarction (MI), angina, atrial fibrillation (AF), and ischemic heart disease (IHD). We will include these CVD subtypes in order to pick up the whole spectrum of CVD.

Our outcome will primarily be a composite CVD variable (which includes HF, MI, stroke, angina, AF, IHD) and secondary outcomes will consist of HF, MI, stroke, angina, AF, and IHD individually.

Objectives, Specific Aims and Rationale

The aim of this study is to investigate the relationship between accelerated lung function decline and rate of incident CVD. Specifically, among COPD patients, we will:

1) Investigate the association between accelerated FEV1 decline and rate of CVD
2) Investigate the association between accelerated FVC decline and rate of CVD
3) Investigate the association between "active" disease (accelerated FEV1 decline & severe exacerbations (AECOPD) and risk of CVD

Accelerated lung function decline will be defined as patients in the fastest quartile of decline.

Using routinely collected lung function data (measured usually every 15 months in people with COPD as part of QoF from 2004), we will estimate the rate of lung function decline in COPD patients in FEV_1 and FVC per year in ml/year. Risk of incident CVD will be compared between patients with accelerated lung function decline and/or severe AECOPD and the remainder of the cohort. The main benefit of this work is to understand whether rate of lung function decline or "active" COPD is associated with subsequent CVD in COPD patients.

Study Background

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation that is not fully reversible, is progressive and is associated with a range of pathological changes in the lung, significant co-morbidities and extra-pulmonary manifestations [237]. It is estimated that 3 million individuals in the UK have COPD however, only 1/3 of them are currently diagnosed. COPD is both preventable and treatable and one of the commonest causes of hospital admission. The prevalence of COPD is increasing globally and it is projected to be not only the third leading cause of death, but also the seventh leading cause of disability adjusted life years (DALYs) lost worldwide by 2030.

A hallmark of COPD is accelerated lung function decline. Lung function includes forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). People with COPD have a faster decline in lung function than people without COPD. However, among people with COPD the speed with which lung function is lost varies [17]. Studies have shown that various factors are associated with rapid lung function decline in COPD. Studies have found that age, COPD medications, frequency and severity of exacerbations of COPD (AECOPD), smoking status, COPD severity, and BMI are all associated with accelerated FEV1 decline [32, 33, 38, 71, 72].

In addition, accelerated lung function decline is associated with other outcomes including increased risk of hospitalisations from COPD and mortality [244]. Furthermore, lower lung function and obstructive disease has been associated with increased incident CVD hospitalisations in the general population [64, 65]. Recently, incident cardiovascular disease (CVD) has also been associated with accelerated lung function decline in a general population study of people included in the ARIC study [218].

CVD is a common comorbidity of COPD [56]. Previous studies suggest risk of myocardial infarction (MI) is higher in COPD patients who experience moderate or severe AECOPD [142]. No studies have investigated the association between rate of lung function in COPD patients and risk of future CVD events. The aim of this study is to help understand the relationship between COPD and CVD more clearly by investigating the relationship between lung function decline and risk of incident CVD in a COPD population. The secondary aim of this study is to investigate the combined role of accelerated lung function decline and AECOPD on incident CVD in a COPD population.

This work will contribute to the greater understanding of lung function decline in primary care COPD patients which we are interested in. We have already investigated lung function decline thoroughly through protocols 17_229R and 18_249R and will apply our knowledge and skills to this study.

Study Type

This will be a descriptive longitudinal piece of work. We will use two cohorts of COPD patients in order to investigate the association between accelerated FEV1 and FVC decline and rate of CVD. Two cohorts may be required due to different patient numbers with valid recordings for each lung function measure.

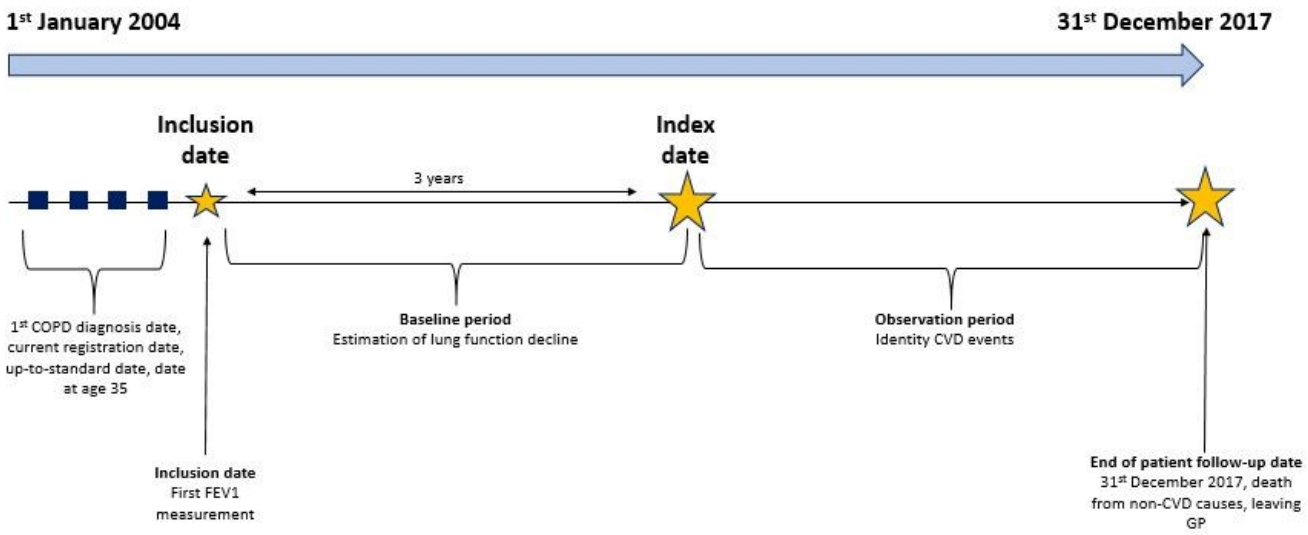
Study Design

This will be a retrospective cohort study using routinely collected primary care electronic health records (EHR) from the Clinical Practice Research Datalink (CPRD) and linked data from HES and ONS. The nature of this design will allow us to investigate the association between lung function decline, AECOPD and rate of CVD. Since 2004 as part of the QOF guidelines lung function should be measured every 15 months in COPD patients, which makes CPRD a reliable source of observational data for investigating lung function decline. Linked HES and ONS will allow us to identify hospitalized CVD events and death from CVD.

People with COPD will be identified based on a validated diagnosis of COPD [140] from the 1st of January 2004 to the 1st September 2019. COPD patients will be included if they meet the following inclusion criteria:

- COPD patients
- Aged 35 or over
- Have a current registration date and an up to standard GP date
- Smokers or ex-smokers
- Have at least two FEV_1 or FVC measurements at least 6 months apart in order to estimate rate lung function decline
- Have at least 3 years of follow-up in order to estimate rate of lung function decline. Previous work on lung function decline using CPRD has shown a high level of variability in lung function measurements and therefore a longer period of follow-up time is needed to more accurately estimate rate of lung function decline. We are aware this will introduce a selection bias. We will highlight this in our limitations and describe baseline characteristics in order to judge the populations generalizability).
- No previous MI, heart failure, stroke, angina, atrial fibrillation or IHD.

Patients meeting inclusion criteria will be followed up for 3 years at baseline in order to estimate lung function decline and patients will be categorized into those with accelerated lung function and those without accelerated lung function decline. Accelerated lung function will be defined as patients in the fastest quartile of decline. Patients will be followed up over the observation period in order to identify whether they experience hospitalization or death from CVD or a recorded GP event. CVD will include: MI, angina, heart failure, stroke, angina, and atrial fibrillation. Patients will be censored on the 1st September 2019 or beforehand if they transferred out of practice or died from non-CVD events. The figure below illustrates this further.



Feasibility counts

From our previous study (protocol 18_249) 72,683 and 50,649 COPD patients met the inclusion criteria and had at least 2 FEV1 or FVC measurements between 2004 and 2016, respectively. Of these patients, 59,185 and 41,529 patients had at least 3 years of follow-up, respectively. Of these patients, 50,609 and 35,618 had no previous heart failure, stroke, MI, or angina.

Sample size considerations

Previous literature on accelerated FEV1 decline and rate of CVD in the general population estimated a HR of 1.15. Following our sample size calculation we will need at least 3,200 patients with at least 3,083 events over the follow-up period in order to detect a HR of 1.15.

Following the feasibility counts in section I, the sample sizes of 50,609 and 35,618 for FEV1 and FVC cohorts will be more than sufficient for our survival analysis model.

Planned use of linked data (if applicable):

IMD- to allow use of SES

HES APC- to identify hospitalised CVD events as the outcome

ONS- to identify CVD related deaths as the outcome

Definition of the Study population

The study population will include all men and women who are registered with a GP in the UK and have data available in the CPRD-GOLD database. Patients will be included in the study if they meet the following eligibility criteria:

- are aged 35 or over
- have been diagnosed with COPD
- have FEV_1 measurements recorded twice or more in their data and at least 6 months apart (for FEV_1 cohort)
- have FVC measurements recorded twice or more in their data and at least 6 months apart (for FVC cohort)
- are ex or current smokers
- have up-to-standard (UTS) data available in CPRD-GOLD and are currently registered at a GP
- have at least 3 years follow-up
- have no previous CVD events (MI, HF, stroke, angina, AF, IHD)

Patients will also be included irrespective of any comorbidities or COPD severity.

For the FEV1 cohort, the study inclusion date will be the first FEV_1 measurement after the patient's first COPD diagnosis, UTS data and current registration date, date at which the patient turned 35, and the 1st January 2004. The baseline period of 3 years will be used to estimate patients' rate of FEV1 decline and patients will be categorized into those with accelerated FEV1 decline and those without accelerated lung function decline using the fastest quartile of decline as the cut-off. "Active" patients will be defined as patients with accelerated lung function decline and who had severe AECOPD at baseline. Patients will be followed up between the index date and the 1st September 2019. Patients will be censored at the 1st September 2019 or beforehand if they died from non-CVD causes or left the GP. CVD events will be identified during follow-up and will include GP recorded, hospitalisations and deaths from HF, stroke, MI, angina, AF, and IHD.

For the FVC cohort, the study inclusion date will be the first FVC measurement after the patient's first COPD diagnosis, UTS data and current registration date, date at which the patient turned 35, and the 1st January 2004. The baseline period of 3 years was used to estimate patients' rate of FVC decline and were categorized into those with accelerated FVC decline and those without accelerated decline using the fastest quartile of decline as the cut-off. Patients will be followed up between the index date and the 1st September 2019. Patient will be censored at the 1st September 2019 or beforehand if they died from non-CVD causes or left the GP. CVD events will be identified

during follow-up and will include GP recorded, hospitalisations and deaths from HF, stroke, MI, angina, AF, and IHD.

Selection of comparison group(s) or controls

Firstly, patients with accelerated lung function decline will be compared to patients without accelerated decline. Accelerated lung function will be defined as patients whose lung function falls in the fastest quartile of the population's decline. Patients without accelerated lung function decline will be defined as the remaining population i.e. patients whose lung function falls in the other 3 quartiles of the population's decline. A sensitivity analysis will compare patients with the fastest lung function decline to those in each of the other quartiles of decline separately.

Secondly, patients with "active" COPD (defined as those with accelerated FEV1 decline and severe AECOPD during the baseline period) will be compared to patients with accelerated FEV1 decline and no/moderate AECOPD and patients without accelerated decline in order to understand the combined association of lung function and AECOPD on CVD.

Results from our previous study suggest that severe AECOPD (defined as hospitalised AECOPD) were associated with increased FEV1 decline, not increased FVC decline (ISAC protocol: 18_249R, unpublished work). Therefore this will only be explored in the FEV1 population.

Exposures, Outcomes and Covariates

Exposure:

1) The primary exposure of interest is rate of lung function decline, specifically accelerated lung function decline compared to those without accelerated lung function decline.

2) The secondary exposure will be "active" COPD defined as patients with accelerated FEV1 and severe AECOPD at baseline. These patients will be compared to: i) patients with accelerated FEV1 decline and moderate or no AECOPD, and ii) patients without accelerated FEV1 decline.

Outcome: Rate of CVD events during follow-up will be the outcome of interest. This will defined as a composite CVD outcome that includes: stroke, MI, HF, angina, AF and IHD. These will be determined through GP recorded events, hospitalised events (using HES-APC) or death (using ONS). Secondary outcomes will consist of the individual CVD components. We will investigate both multiple CVD events over follow-up and first CVD event during follow-up.

Covariates:

-Age (years) at index date

- Gender

- BMI at baseline (normal: 18.5-24.9kg/m2; underweight: <18.5kg/m2; overweight: 25-29.9kg/m2; obese>30kg/m2). - smoking status (current or ex-smoking status) closest to index date

- airflow obstruction (mild: >80% predicted FEV1; moderate: 50-79% predicted FEV1; severe: 30-49% predicted FEV1; very severe: <30% predicted FEV1) using the last FEV1 measurement used to determine lung function decline

- AECOPD at baseline (none, 1 moderate (GP-treated) and 0 severe (hospitalised), 2 moderate and 0 severe, 3+ moderate and 0 severe, 1 severe and any moderate, 2+ severe and any moderate [12]

- mMRC dyspnoea score (0-4)

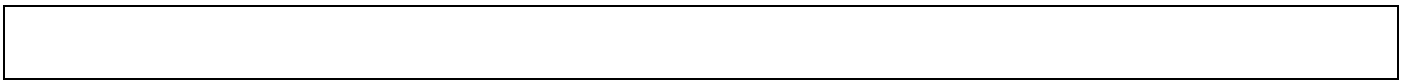
- hypertension (using medcodes and medication use) at baseline

- arrhythmia at baseline

- Statin use

- Inhaled corticosteroid use

- Diabetes



Data/ Statistical Analysis

Mixed linear regression will be used to generate individual rates of FEV1 decline for each patient in our sample. Patients will then be grouped into those with accelerated FEV1 decline, defined as patients in the fastest quartile of FEV1 decline, and those without accelerated FEV1 decline.

Baseline characteristics will be explored between: 1) patients with accelerated decline and in those without accelerated decline; and 2) patients with "active" COPD, patients with accelerated decline and no/moderate AECOPD, and patients without accelerated lung function decline.

Baseline characteristics include:

- Age
- Gender
- BMI
- smoking status
- airflow obstruction
- AECOPD
- mMRC
- hypertension
- arrhythmia
- Statin use
- Inhaled corticosteroid use
- Diabetes

Appropriate statistical testing will be used to highlight any statistically significant differences between patient groups. Missing data will be imputed if data are missing at random.

In order to investigate the association between patient groups and rate of CVD, survival analysis will be used. We will use Cox regression because we assume that rates of CVD events will vary over time. If rates of CVD events do not vary over time Poisson regression will be used to estimate the incidence rate ratio for CVD events between groups. We will test model assumptions. We will also test for effect modification by baseline covariates.

Secondary outcomes will include individual CVD components (MI, HF, stroke, AF, angina, IHD).

Sensitivity analyses will include:
- using -40ml/year as the cut off for accelerated lung function decline following previous literature [17].

- using relative change in lung function from baseline in order to determine accelerated lung function decline. This is because initial lung function will determine change in absolute lung function over time. Therefore we will use percentage change from baseline as the exposure and group patients into accelerated lung function using the fastest quartile of change.

- using change in FEV1 percent predicted to determine accelerate lung function decline. Previous work suggests that change in FEV1 percent predicted is a more reliable measure of spirometry in studies with follow-up less than 5 years [218].

Plan for addressing confounding

We will use results from our previous study (protocol 18_249) to determine confounders of interest (section N) which will be adjusted for in the analysis.

Plans for addressing missing data

We are not expecting missing data apart for the covariates BMI and MRC. If data is missing at random complete case analysis could be performed or multiple imputation. If the data is not missing at random, complete case analysis will be used.

Patient or user group involvement

This was discussed with patients as part of a British Lung Foundation grant submission.

Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The study findings will be submitted for publication in peer-reviewed scientific journals, and will be presented at appropriate conferences and other meetings; the latter will include scientific meetings externally, for example the American and European Respiratory Society Meetings and internally within Imperial College London.

Conflict of interest statement: Dr Quint's research group has received funding from The Health Foundation, MRC, Welcome Trust, BLF, Insmed, AZ, Bayer and BI for other projects, none of which relate to this work and from GSK for this work. Dr Quint has received funds from AZ, GSK, Chiesi, Teva and BI for Advisory board participation or travel. Professor Jarvis and Professor Burney's research group has received funding from MRC, European Union and Cystic Fibrosis Trust for other projects, none of which relate to this work. Her contribution to this work is not funded by GSK. Dr Kiddle has previously received research funding from EPSRC, BBSRC, MRC, NIHR, Alzheimer's Society, Eli Lily and Janssen for other projects, and funding from Roche Diagnostics for advisory board participation and travel. None of this relates to this work.

Limitations of the study design, data sources, and analytic methods

Observational studies allow understanding of disease progression and associations using real world data sources, in this case electronic health data. However, strengths and limitations are associated with this study design.

Firstly, it is important to note that although CRPD is broadly representative of the UK population in terms of age, sex, and socio-economic status, it may not be representative of all GPs across the UK [133]. Selection of patients into the study will be based on prospectively recorded diagnoses of COPD, FEV_1 and FVC measurements and may not be representative of COPD patients in the UK. In addition, it is important to note that studies using CPRD cannot prove causality, and merely find results that are consistent with casual hypotheses backed up by trials. Even when accounting for many confounders, there can always be residual confounding.

Patients will require at least 3 years of baseline follow-up in order to estimate rate of lung function decline which will introduce selection bias. Patients with longer follow-up may be different to those with less than 3 years of baseline follow-up. We will investigate whether these patients differ from those with less than 3 years of follow-up in terms of covariates listed in section N.

Algorithms used to identify patients with COPD have high sensitivity and PPV [140]: however, it could be possible that GPs misdiagnose asthma as COPD or COPD as asthma, particularly in patients aged over forty years [202]. To avoid misclassification of these diseases we will exclude COPD patients with asthma as a sensitivity analysis. In addition, CPRD only contains diagnosed COPD and symptomatic patients without a diagnosis of COPD would thus not be included. Furthermore, AECOPD frequency may be misclassified because those who have worse disease severity may meet with their GP more often and there would be more opportunity to report milder or self-managed exacerbations. To avoid this, the algorithm does not include patients who have self-managed an exacerbation using a rescue pack.

In addition, data quality between GPs may vary. Despite the implementation of the Quality and Outcomes Framework (QOF) in 2004, which encouraged GPs to record key data at a high level and lung function in COPD

patients every 15 months, there is still some variation between GPs in terms of coding variables and recording data as free text, which researchers may miss. This therefore means not all available data is or can be used.

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List of Appendices

Codes to identify COPD (CPRD GOLD)

medcode	Description
794	Emphysema
998	Chronic obstructive airways disease
1001	Chronic obstructive pulmonary disease
4084	Airways obstructn irreversible
5710	Chronic obstructive airways disease NOS
9520	Chronic obstructive pulmonary disease monitoring
9876	Severe chronic obstructive pulmonary disease
10802	Moderate chronic obstructive pulmonary disease
10863	Mild chronic obstructive pulmonary disease
10980	Centrilobular emphysema
11287	Chronic obstructive pulmonary disease annual review
12166	Other specified chronic obstructive airways disease
14798	Emphysematous bronchitis
16410	Other emphysema NOS
18476	COPD follow-up
18621	Chronic obstructive pulmonary disease follow-up
18792	Chronic obstructive pulmonary disease monitoring admin
23492	Chronic bullous emphysema NOS
26018	Chronic obstructive pulmonary disease monitoring by nurse
26306	Chronic bullous emphysema
28755	Chronic obstructive pulmonary disease monitoring 1st letter
33450	Emphysema NOS
34202	Chronic obstructive pulmonary disease monitoring 2nd letter
34215	Chronic obstructive pulmonary disease monitoring 3rd letter
37247	Chronic obstructive pulmonary disease NOS
37371	Chronic obstructive pulmonary disease monitoring due
38074	Chronic obstructive pulmonary disease monitor phone invite
42258	Chronic obstructive pulmonary disease monitoring verb invite
42313	Health education - chronic obstructive pulmonary disease
44525	Obstructive chronic bronchitis NOS
45770	Chronic obstructive pulmonary disease disturbs sleep

45771	Chronic obstructive pulmonary disease does not disturb sleep
45777	Chronic obstructive pulmonary disease clini management plan
45998	Chronic obstructive pulmonary disease monitoring by doctor
46578	Panlobular emphysema
60188	Giant bullous emphysema
65733	[X]Other specified chronic obstructive pulmonary disease
67040	Other specified chronic obstructive pulmonary disease
93568	Very severe chronic obstructive pulmonary disease
104608	End stage chronic obstructive airways disease
104710	On COPD (chr obstruc pulmonary disease) supportv cre pathway
104985	On chronic obstructive pulmonary disease supprtv cre pathway

Codes to identify COPD (CPRD-Aurum)

MedCodeId	Term
1823851000006119	Chronic obstructive pulmonary disease confirmed
301477019	Emphysema NOS
64049100000611	Emphysema
113497011	Centrilobular emphysema
1222334016	Other specified chronic obstructive pulmonary disease
1813871000006117	On chronic obstructive pulmonary disease supprtv cre pathway
1813881000006119	On COPD (chr obstruc pulmonary disease) supportv cre pathway
216596014	End stage chronic obstructive airways disease
2219551000000113	Seen in chronic obstructive pulmonary disease clinic
27096010	Giant bullous emphysema
285100019	Emphysematous bronchitis
301455018	Obstructive chronic bronchitis NOS
301460019	Chronic bullous emphysema
301468014	Chronic bullous emphysema NOS
301539010	Other specified chronic obstructive airways disease
301836011	[X]Other specified chronic obstructive pulmonary disease
396110016	Other emphysema NOS
405121000000111	Health education - chronic obstructive pulmonary disease
457168017	Mild chronic obstructive pulmonary disease
457169013	Moderate chronic obstructive pulmonary disease
457171013	Severe chronic obstructive pulmonary disease
516801000000112	Very severe chronic obstructive pulmonary disease
845451000006118	COPD follow-up
9337016	Panlobular emphysema
475431013	Chronic obstructive pulmonary disease
1484924013	Chronic obstructive pulmonary disease monitoring
1484971019	Chronic obstructive pulmonary disease monitoring due

1488423019	Chronic obstructive pulmonary disease follow-up
1488424013	Chronic obstructive pulmonary disease annual review
1780380013	Chronic obstructive pulmonary disease monitoring by nurse
1780381012	Chronic obstructive pulmonary disease monitoring by doctor
299001000000116	Chronic obstructive pulmonary disease disturbs sleep
299031000000110	Chronic obstructive pulmonary disease does not disturb sleep
1222335015	Chronic obstructive pulmonary disease NOS
189761000000117	Chronic obstructive pulmonary disease monitoring 1st letter
198471000000111	Chronic obstructive pulmonary disease monitoring 2nd letter
199481000000116	Chronic obstructive pulmonary disease monitoring 3rd letter
967531000006119	Chronic obstructive pulmonary disease monitoring admin
967571000006116	Chronic obstructive pulmonary disease monitoring verb invite
967581000006118	Chronic obstructive pulmonary disease monitor phone invite
966841000006111	Chronic obstructive pulmonary disease clini management plan
2199261000000110	Chronic obstructive pulmonary disease care pathway
264537018	Airways obstructn irreversible
301545019	Chronic obstructive airways disease
555471000006114	Chronic obstructive airways disease NOS

Codes to identify ex and current smoking status (CPRD GOLD)

medcode	description	Smoking status
203208	Current smoker	current smoker
221248	Ex-very heavy smoker (40+/day)	exsmoker
239315	Ex-heavy smoker (20-39/day)	exsmoker
230314	Ex-smoker - amount unknown	exsmoker
266944	Rolls own cigarettes	current smoker
257725	Keeps trying to stop smoking	current smoker
248528	Stopped smoking	exsmoker
294327	Trying to give up smoking	current smoker
285187	Cigarette smoker	current smoker
248526	Pipe smoker	current smoker
276051	Smoking started	current smoker
203207	Smoking restarted	current smoker
257726	Smoker	current smoker
276050	Cigar smoker	current smoker
309558	Smoking reduced	current smoker
276052	Date ceased smoking	exsmoker
266945	Ex pipe smoker	exsmoker
294328	Ex cigar smoker	exsmoker
12942	Smoker - amount smoked	current smoker
54	Tobacco consumption	current smoker
12941	Occasional smoker	current smoker
12958	Trivial smoker - < 1 cig/day	current smoker
12944	Light smoker - 1-9 cigs/day	current smoker
1878	Moderate smoker - 10-19 cigs/d	current smoker
3568	Heavy smoker - 20-39 cigs/day	current smoker
1822	Very heavy smoker - 40+cigs/d	current smoker
12961	Ex-trivial smoker (<1/day)	exsmoker
12957	Ex-light smoker (1-9/day)	exsmoker

12955	Ex-moderate smoker (10-19/day)	exsmoker
12956	Ex-heavy smoker (20-39/day)	exsmoker
12959	Ex-very heavy smoker (40+/day)	exsmoker
12964	Keeps trying to stop smoking	current smoker
12946	Ex-smoker - amount unknown	exsmoker
12240	Trying to give up smoking	current smoker
12947	Pipe smoker	current smoker
12943	Cigar smoker	current smoker
776	Stopped smoking	exsmoker
99838	Recently stopped smoking	exsmoker
60	Current non-smoker	exsmoker
12945	Rolls own cigarettes	current smoker
26470	Ex pipe smoker	exsmoker
19488	Ex cigar smoker	exsmoker
93	Cigarette smoker	current smoker
1823	Smoker	current smoker
12952	Smoking started	current smoker
12951	Smoking restarted	current smoker
10558	Current smoker	current smoker
90	Ex smoker	exsmoker
12878	Date ceased smoking	exsmoker
12966	Smoking reduced	current smoker
12965	Cigarette consumption	current smoker
12963	Cigar consumption	current smoker
12960	Tobacco consumption NOS	current smoker
12967	Pipe tobacco consumption	current smoker
31114	Ready to stop smoking	current smoker
30423	Thinking about stopping smoking	current smoker
30762	Not interested in stopping smoking	current smoker
41979	Smoking restarted	current smoker
46321	Reason for restarting smoking	current smoker

46300	Cigarette pack-years	current smoker
62686	Minutes from waking to first tobacco consumption	exsmoker
97210	Ex-cigarette smoker	exsmoker
100495	Ex roll-up cigarette smoker	exsmoker
101338	Failed attempt to stop smoking	exsmoker
105711	Total time smoked	exsmoker
105501	Waterpipe tobacco consumption	current smoker
26096	Smokes drugs	current smoker
34126	Negotiated date for cessation of smoking	current smoker
10898	Smoking free weeks	exsmoker
38112	Smoking cessation programme start date	current smoker
103955	Asthma trigger - tobacco smoke	exsmoker
11713	Pack years	current smoker
97973	Maternal tobacco abuse	exsmoker
2111	Health ed. - smoking	current smoker
10184	Pregnancy smoking advice	current smoker
18926	Lifestyle advice regarding smoking	current smoker
98137	Brief intervention for smoking cessation	current smoker
74907	Smoking cessation therapy	current smoker
94958	Smoking cessation drug therapy	current smoker
91708	Other specified smoking cessation therapy	current smoker
90522	Smoking cessation therapy NOS	current smoker
110692	Varenicline smoking cessation therapy offered	current smoker
7622	Smoking cessation advice	current smoker
41042	Smoking cessation advice provided by community pharmacist	current smoker
103507	Stop smoking service opportunity signposted	current smoker
18573	Referral to smoking cessation advisor	current smoker
10742	Referral to stop-smoking clinic	current smoker
98154	Referral to NHS stop smoking service	current smoker
100099	Smoking cessation advice declined	exsmoker

106391	Referral to smoking cessation service declined	current smoker
106359	Referral to smoking cessation service	current smoker
11356	Seen by smoking cessation advisor	current smoker
102361	Referral for smoking cessation service offered	exsmoker
7130	Stop smoking monitoring admin.	exsmoker
40418	Refuses stop smoking monitor	current smoker
53101	Stop smoking monitor verb.inv.	current smoker
103400	Referred for COPD structured smoking assessment	current smoker
98447	Ex-smoker annual review - enhanced services administration	exsmoker
100963	Ex-smoker annual review	exsmoker
104310	Current smoker annual review	current smoker
98347	Current smoker annual review - enhanced services admin	current smoker
32687	Tobacco dependence	current smoker
95610	Tobacco dependence, unspecified	current smoker
70746	Tobacco dependence, continuous	current smoker
108835	Tobacco dependence, episodic	current smoker
72706	Tobacco dependence in remission	exsmoker
68658	Tobacco dependence NOS	current smoker
16717	Smokers' cough	current smoker
43433	Toxic effect of tobacco and nicotine	exsmoker
9045	Advice on smoking	current smoker
42288	Pack years	current smoker
72700	[V]Personal history of tobacco abuse	exsmoker
12954	[V]Tobacco use	current smoker
35055	[V]Tobacco abuse counselling	current smoker

Codes to identify ex and current smoking status (CPRD Aurum)

Medcodeid	Term	Smoking status
909391000006117	[rfc] smoking cessation	current
461114016	[v]tobacco abuse counselling	current
460828018	[v]tobacco use	current
397911000006114	[x]mental and behav dis due to use of tobacco: harmful use	current
295951010	[x]mental and behavioural disorder due to use of tobacco	current
4939251000006118	advice on smoking	current
5495901000006112	amount and type of tobacco smoked	ex
1125741000000111	brief intervention for smoking cessation	current
904121000006117	carbon monoxide validation confirms smoker	current
904051000006110	carbon monoxide validation of smoking status	current
2636041000006110	cessation of smoking	ex
344794017	cigar consumption	current
99639019	cigar smoker	current
344793011	cigarette consumption	current
3256651000006113	cigarette cough	current
1780396011	cigarette pack-years	ex
854021000006115	cigarette smoker	current
3959121000006115	compulsive tobacco user syndrome	current
4765721000006119	continuous tobacco use	current
250374013	current non-smoker	ex
854071000006119	current smoker	current
1152111000000118	current smoker annual review	current
1714541000006110	current smoker annual review - enhanced services admin	current
604961000006114	current smoker nos	current
854151000006111	date stopped smoking	ex
649821000006115	ex cigar smoker	ex
649831000006117	ex pipe smoker	ex
1059701000000119	ex roll-up cigarette smoker	ex
649841000006110	ex smoker	ex

649851000006112	ex- rolled tobacco smoker	ex
852991000006114	ex-cigar smoker	ex
418914010	ex-cigarette smoker	ex
5496031000006112	ex-cigarette smoker amount unknown	ex
250366012	ex-heavy smoker (20-39/day)	ex
250364010	ex-light smoker (1-9/day)	ex
250365011	ex-moderate smoker (10-19/day)	ex
854051000006112	ex-pipe smoker	ex
250371017	ex-smoker - amount unknown	ex
1154471000000114	ex-smoker annual review	ex
1123951000000110	ex-smoker annual review - enhanced services administration	ex
903041000006110	ex-smoker nos	ex
250363016	ex-trivial smoker (<1/day)	ex
250367015	ex-very heavy smoker (40+/day)	ex
981841000006115	exposure to cigarette/cigar smoke	current
1592611000000110	failed attempt to stop smoking	current
854961000006110	grade b light smoker (1-10/day)	current
854981000006117	grade c moderate smoker (11-20/day)	current
855001000006114	grade d heavy smoker (>20 day)	current
852111000006118	gradual smoking reduction	current
819331000006110	heavy smoker - 20-39 cigs/day	current
250368013	keeps trying to stop smoking	current
743331000006116	light smoker - 1-9 cigs/day	current
2474719011	minutes from waking to first tobacco consumption	current
700121000006118	moderate smoker - 10-19 cigs/d	current
1488578010	not interested in stopping smoking	current
5495951000006111	occasional cigarette smoker (less than one cigarette/day)	current
397733018	occasional smoker	current
8153371000006117	occasional tobacco smoker	current
482871000000111	other specified smoking cessation therapy	ex
854111000006110	past smoker	ex

136515019	pipe smoker	current
344795016	pipe tobacco consumption	current
904021000006118	previous smoking quit attempts	current
2982426011	provision of smoking cessation leaflet	current
1488577017	ready to stop smoking	current
1780360012	reason for restarting smoking	current
1151791000000117	recently stopped smoking	ex
1704561000006112	refer copd structured smoking assessment - enhanc serv admin	current
1709641000000115	referral for smoking cessation service offered	current
8190531000006112	referral to nhs (national health service) stop smoking service	current
1715591000006117	referral to nhs stop smoking service	current
1489355012	referral to smoking cessation advisor	current
2251911000000114	referral to smoking cessation service	current
2251871000000112	referral to smoking cessation service declined	current
459722017	referral to stop-smoking clinic	current
1704551000006110	referred for copd structured smoking assessment	current
285792013	refuses stop smoking monitor	current
250375014	rolls own cigarettes	current
1538681000006118	smoke	current
128130017	smoker	current
137711000006111	smoker (read codes)	current
137721000006115	smoker - amount smoked	current
78013015	smokers' cough	current
342444018	smokes drugs in cigarette form	current
342445017	smokes drugs through a pipe	current
961581000006114	smokes/uses tobacco products	current
338608011	smoking cessation advice	current
1176421000000118	smoking cessation advice declined	current
904221000006110	smoking cessation bupropion therapy	current
482771000000118	smoking cessation drug therapy	ex
1175011000000112	smoking cessation programme declined	current

1591651000006110	smoking cessation referral declined	current
492511000000117	smoking cessation therapy	ex
489931000000114	smoking cessation therapy nos	ex
852121000006114	smoking cessation-maintain abstinence	ex
1704491000006115	smoking cessatn monitor template complet - enhanc serv admin	current
1488873010	smoking free weeks	current
1819411000006114	smoking increased	current
216212011	smoking reduced	current
2670126018	smoking restarted	current
2669652019	smoking started	current
1123541000000118	stop smoking face to face follow-up	current
1750931000000118	stop smoking service opportunity signposted	current
250373019	stopped smoking	ex
904031000006115	thinking about stopping smoking	current
3959141000006110	tobacco abuse	current
102921000006112	tobacco consumption	current
250387019	tobacco consumption nos	current
102951000006115	tobacco dependence	current
295259018	tobacco dependence in remission	ex
295260011	tobacco dependence nos	current
3959111000006111	tobacco dependence syndrome	current
295257016	tobacco dependence, continuous	current
295258014	tobacco dependence, episodic	current
4765751000006111	tobacco dependence, in remission	ex
295256013	tobacco dependence, unspecified	current
4180331000006118	tobacco use	current
4765711000006110	tobacco use, continuous	current
4180321000006116	tobacco user	current
1809131000006111	total time smoked	ex
88471000006112	trivial smoker - < 1 cig/day	current
250372012	trying to give up smoking	current

2462391000000119	varenicline smoking cessation therapy declined	current
2462431000000110	varenicline smoking cessation therapy offered	current
67621000006112	very heavy smoker - 40+cigs/d	current
904041000006113	waking time to first cigarette	current
2170961000000116	waterpipe tobacco consumption	current
108938018	cigarette smoker	current
503483019	current smoker	current
649861000006114	ex-cigarette smoker	ex
853001000006110	ex-smoker nos	ex
903981000006117	not interested in stopping smoking	current
5495941000006114	occasional smoker	current
8153381000006119	occasional smoker	current
904001000006111	ready to stop smoking	current
852981000006111	rolls own cigarettes	current
137791000006118	smoking restarted	current
1488576014	thinking about stopping smoking	current
342574011	total time smoked	ex
1809121000006113	waterpipe tobacco consumption	current

Codes to identify FEV1 (CPRD Aurum only)

Medcodeid	Description	FEV1	FEV1 % predicted
454110011	expected fev1	1	
453937018	expected fev1/fvc ratio		
5999141000006112	expected forced expiratory volume in one second/forced vital capacity ratio		
6000931000006116	expected forced expired volume in 1 second	1	
454111010	expected fvc		
4588671000006119	fev - forced expired volume	1	
3463571000006118	fev1 - forced expired volume in 1 second	1	
1821581000006113	fev1 60-80% of predicted		1
1821601000006115	fev1 < 60% of predicted		1
1821541000006119	fev1 > 80% of predicted		1
1761631000006119	fev1 after bronchial provocation test	1	
1780220014	fev1 after bronchodilation	1	
1865501000006114	fev1 after change of bronchodilator	1	
1761661000006111	fev1 before bronchial provocation test	1	
1780219015	fev1 before bronchodilation	1	
1780223011	fev1 post steroids	1	
1780316012	fev1 pre steroids	1	
1821561000006115	fev1 variability 20-30%		1
1821551000006117	fev1 variability < 20%		1
1821591000006111	fev1 variability > 30%		1
458838014	fev1/fvc < 70% of predicted		
458839018	fev1/fvc > 70% of predicted		
457080011	fev1/fvc percent		
1224805016	fev1/fvc ratio		
855141000006110	fev1/fvc ratio		
256690013	fev1/fvc ratio abnormal		

2163855015	fev1/fvc ratio after bronchodilator		
2163854016	fev1/fvc ratio before bronchodilator		
256689016	fev1/fvc ratio normal		
2163853010	fev1/fvc ratio post steroids		
2163852017	fev1/fvc ratio pre steroids		
1875691000006114	fev1/svc percent		
474781000000116	fev1/vc percent		
5308471000006114	fev1/vc ratio		
4588721000006111	forced expiratory volume (fev) normal	1	
764471000006117	forced expiratory volume - fev	1	
6749351000006110	forced expiratory volume 1 (fev1)/ forced vital capacity (fvc) ratio after bronchodilator		
951231000006116	forced expiratory volume 1 - fev1	1	
4588781000006110	forced expiratory volume in one second (fev1)/forced vital capacity (fvc) ratio abnormal		
4588751000006119	forced expiratory volume in one second (fev1)/forced vital capacity (fvc) ratio normal	1	
6046421000006115	forced expiratory volume in one second/forced vital capacity > 70% of predicted		
6046431000006117	forced expiratory volume in one second/forced vital capacity greater than 70% of predicted		
6046401000006113	forced expiratory volume in one second/forced vital capacity less than 70% of predicted		
6027621000006118	forced expiratory volume in one second/forced vital capacity percent		
4588791000006113	forced expiratory volume in one second/forced vital capacity ratio abnormal		
6749371000006117	forced expiratory volume in one second/forced vital capacity ratio after bronchodilator		
6749341000006113	forced expiratory volume in one second/forced vital capacity ratio before bronchodilator		

4588761000006117	forced expiratory volume in one second/forced vital capacity ratio normal		
6749311000006114	forced expiratory volume in one second/forced vital capacity ratio post steroids		
6749281000006112	forced expiratory volume in one second/forced vital capacity ratio pre steroids		
4588731000006114	forced expiratory volume normal	1	
764481000006119	forced expired volume in 1 second	1	
5308501000006119	forced expired volume in 1 second : forced vital capacity ratio		
6647421000006110	forced expired volume in 1 second after bronchodilation	1	
6647401000006117	forced expired volume in 1 second before bronchodilation	1	
6647481000006114	forced expired volume in 1 second post steroids	1	
6648701000006114	forced expired volume in 1 second pre steroids	1	
1141751000000110	forced expired volume in 1 second reversibility	1	
5308491000006110	forced expired volume in one sec/forced vital capacity ratio		
5308481000006112	forced expired volume in one second/forced vital capacity ratio		
375283017	forced expired volume in one second/vital capacity ratio		
6748961000006118	forced vital capacity (fvc) after bronchodilation		
764741000006116	forced vital capacity - fvc		
7256221000006111	fvc (forced vital capacity) before bronchodilation		
3323341000006118	fvc - forced vital capacity		
256686011	fvc - forced vital capacity abnormal		
256685010	fvc - forced vital capacity normal		
1761641000006112	fvc after bronchial provocation test		
2163847010	fvc after bronchodilation		
1865491000006118	fvc after change of bronchodilator		
1761671000006116	fvc before bronchial provocation test		
457081010	percent predicted fev1		1
6027641000006113	percent predicted forced expired volume in one second	1	
7337051000006118	percentage predicted fev1 (forced expiratory volume in 1 second) after bronchodilation		1

1752221000006118	percentage predicted fev1 after bronchodilation		1
1771021000006117	percentage predicted fev1 after exercise		1
459417016	spirometry reversibility	1	
459418014	spirometry reversibility negative	1	
459419018	spirometry reversibility positive	1	
6052331000006110	spirometry reversibility test	1	

Codes to Identify COPD medications (CPRD GOLD)

prodcode	productname	groups
67735	beclazone easi-breathe (roi) 250microgram/actuation pressurised inhalation (ivax pharmaceuticals ireland)	ICS
51234	qvar 100 inhaler (waymade healthcare plc)	ICS
49711	pulmicort 200micrograms/dose inhaler (astrazeneca uk ltd)	ICS
20812	pulmicort refill	ICS
4413	qvar 100 autohaler (teva uk ltd)	ICS
4132	fluticasone 125microgram/actuation pressurised inhalation	ICS
67253	flixotide 50micrograms/dose accuhaler (mawdsley-brooks & company ltd)	ICS
13037	pulvinal beclometasone dipropionate 200micrograms/dose dry powder inhaler (chiesi ltd)	ICS
3898	budesonide 3mg gastro-resistant modified-release capsules	ICS
1956	pulmicort 1mg respules (astrazeneca uk ltd)	ICS
15326	beclometasone 100micrograms/dose inhaler cfc free	ICS
1951	becodisks 400microgram disc (allen & hanburys ltd)	ICS
2600	beclometasone 250micrograms/dose breath actuated inhaler	ICS
5992	beclometasone 50micrograms/dose dry powder inhaler	ICS
64557	cortiment 9mg modified-release tablets (ferring pharmaceuticals ltd)	ICS
35288	beclometasone 400microgram inhalation powder blisters	ICS
71467	beclometasone 50micrograms/dose inhaler cfc free (j m mcgill ltd)	ICS
13815	beclazone 100microgram/actuation inhalation powder (actavis uk ltd)	ICS
909	budesonide 200micrograms/dose inhaler	ICS
39099	pulmicort 100micrograms/dose inhaler cfc free (astrazeneca uk ltd)	ICS
1551	beclazone 250 inhaler (teva uk ltd)	ICS
3442	pulmicort complete 200 mcg inh	ICS
71109	flixotide 250micrograms/dose accuhaler (de pharmaceuticals)	ICS
1734	beclometasone 100micrograms/dose breath actuated inhaler	ICS
19389	asmabec 50microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
4759	beclometasone 100microgram inhalation powder capsules	ICS
43074	flixotide 500micrograms/dose accuhaler (glaxosmithkline uk ltd)	ICS
2229	becodisks 100microgram disc (allen & hanburys ltd)	ICS
2335	qvar 100 inhaler (teva uk ltd)	ICS
1412	flixotide 250microgram/actuation inhalation powder (allen & hanburys ltd)	ICS

1642	budesonide 400micrograms/dose dry powder inhaler	ICS
51681	qvar 100 inhaler (sigma pharmaceuticals plc)	ICS
14567	asmabec 250 clickhaler (focus pharmaceuticals ltd)	ICS
71356	clenil modulite 250micrograms/dose inhaler (mawdsley-brooks & company ltd)	ICS
56484	flixotide 250micrograms/dose accuhaler (waymade healthcare plc)	ICS
1258	becotide 200 inhaler (glaxosmithkline uk ltd)	ICS
50287	qvar 100 inhaler (de pharmaceuticals)	ICS
35374	flixotide 500microgram disks (glaxosmithkline uk ltd)	ICS
70749	budesonide 400micrograms/dose turbohaler (dowelhurst ltd)	ICS
50037	pulmicort 0.5mg respules (waymade healthcare plc)	ICS
960	pulmicort 100 turbohaler (astrazeneca uk ltd)	ICS
32874	beclometasone 50microgram/actuation inhalation powder (actavis uk ltd)	ICS
35118	becodisks 400microgram with diskhaler (glaxosmithkline uk ltd)	ICS
27583	pulmicort	ICS
28761	spacehaler bdp 50microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
911	flixotide accuhaler 250 250microgram/inhalation inhalation powder (allen & hanburys ltd)	ICS
5885	fluticasone propionate 100micrograms/dose dry powder inhaler	ICS
4365	beclometasone 100micrograms disc	ICS
35113	beclometasone 200microgram inhalation powder blisters	ICS
5551	flixotide 0.5mg/2ml nebules (glaxosmithkline uk ltd)	ICS
40057	pulmicort 200micrograms/dose inhaler cfc free (astrazeneca uk ltd)	ICS
4499	aerobec 250microgram/actuation pressurised inhalation (meda pharmaceuticals ltd)	ICS
70015	beclometasone 100micrograms/dose inhaler (almus pharmaceuticals ltd)	ICS
51480	qvar 100 autohaler (de pharmaceuticals)	ICS
39102	budesonide 100micrograms/dose inhaler cfc free	ICS
5580	flixotide accuhaler 50 50microgram/inhalation inhalation powder (allen & hanburys ltd)	ICS
3993	filair forte 250micrograms/dose inhaler (meda pharmaceuticals ltd)	ICS
2125	pulmicort 200microgram refill canister (astrazeneca uk ltd)	ICS
3150	beclometasone 100micrograms/actuation extrafine particle cfc free inhaler	ICS
3743	filair 50 inhaler (meda pharmaceuticals ltd)	ICS
48088	budenofalk 9mg gastro-resistant granules sachets (dr. falk pharma uk ltd)	ICS
42928	flixotide 100micrograms/dose accuhaler (glaxosmithkline uk ltd)	ICS
5309	flixotide 50micrograms/dose evohaler (glaxosmithkline uk ltd)	ICS

3018	beclometasone 50micrograms/dose inhaler	ICS
16158	clenil modulite 50micrograms/dose inhaler (chiesi ltd)	ICS
3289	flixotide 25micrograms/dose inhaler (glaxosmithkline uk ltd)	ICS
99	becotide 100 inhaler (glaxosmithkline uk ltd)	ICS
2992	beclazone 50 inhaler (teva uk ltd)	ICS
8635	flixotide 50microgram disc (allen & hanburys ltd)	ICS
63585	beclometasone 50micrograms/dose inhaler (almus pharmaceuticals ltd)	ICS
42985	flixotide 50micrograms/dose accuhaler (glaxosmithkline uk ltd)	ICS
1406	becotide 50 inhaler (glaxosmithkline uk ltd)	ICS
71347	pulmicort 400 turbohaler (sigma pharmaceuticals plc)	ICS
2893	beclometasone 200micrograms disc	ICS
16305	flixotide 2mg/2ml nebules (glaxosmithkline uk ltd)	ICS
15706	beclometasone 100 micrograms/actuation vortex inhaler	ICS
27915	fluticasone prop disk refill	ICS
1424	flixotide 250microgram disc (allen & hanburys ltd)	ICS
9921	beclometasone 100micrograms/dose breath actuated inhaler cfc free	ICS
3075	becotide 400microgram rotacaps (glaxosmithkline uk ltd)	ICS
10090	beclometasone 50micrograms/actuation extrafine particle cfc free inhaler	ICS
1861	aerobec 100 autohaler (meda pharmaceuticals ltd)	ICS
20763	becloforte	ICS
53480	qvar 100 autohaler (stephar (u.k.) ltd)	ICS
3947	becotide 100microgram rotacaps (glaxosmithkline uk ltd)	ICS
19736	becotide susp for nebulisation	ICS
35580	beclometasone 100microgram inhalation powder blisters with device	ICS
34739	beclometasone 50micrograms/dose inhaler (teva uk ltd)	ICS
14524	bdp 250microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
8433	budesonide 100micrograms/actuation inhaler	ICS
2092	budesonide 200micrograms/dose dry powder inhaler	ICS
34794	beclometasone 200micrograms/dose inhaler (a a h pharmaceuticals ltd)	ICS
947	budesonide 50micrograms/actuation refill canister	ICS
56498	pulmicort 200 turbohaler (waymade healthcare plc)	ICS
62518	beclometasone 100micrograms/dose inhaler cfc free (ennogen healthcare ltd)	ICS
35225	flixotide 100microgram disks with diskhaler (glaxosmithkline uk ltd)	ICS

4131	fluticasone 100microgram disc	ICS
1259	beclometasone 200micrograms/dose inhaler	ICS
3220	qvar 50 autohaler (teva uk ltd)	ICS
4926	flixotide accuhaler 100 100microgram/inhalation inhalation powder (allen & hanburys ltd)	ICS
7724	betamethasone valerate 100micrograms/actuation inhaler	ICS
47225	budesonide 9mg gastro-resistant granules sachets	ICS
14736	pulvinal beclometasone dipropionate 400micrograms/dose dry powder inhaler (chiesi ltd)	ICS
5683	flixotide 250micrograms/dose evohaler (glaxosmithkline uk ltd)	ICS
19031	bdp 100microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
23675	pulmicort l.s. refil	ICS
1426	flixotide 500microgram disc (allen & hanburys ltd)	ICS
5521	beclometasone 200micrograms/dose dry powder inhaler	ICS
956	pulmicort 200 turbohaler (astrazeneca uk ltd)	ICS
67234	becotide 100 inhaler (waymade healthcare plc)	ICS
35461	flixotide 250microgram disks with diskhaler (glaxosmithkline uk ltd)	ICS
35772	fluticasone propionate 100microgram inhalation powder blisters	ICS
57555	flixotide 125micrograms/dose evohaler (dowelhurst ltd)	ICS
61664	clenil modulite 250micrograms/dose inhaler (waymade healthcare plc)	ICS
71427	budesonide 100micrograms/dose turbohaler (dowelhurst ltd)	ICS
7948	fluticasone propionate 250micrograms/dose dry powder inhaler	ICS
11497	beclometasone 400micrograms/dose dry powder inhaler	ICS
71366	flixotide 500micrograms/dose accuhaler (de pharmaceuticals)	ICS
883	becodisks 200microgram disc (allen & hanburys ltd)	ICS
9233	beclometasone 200microgram inhalation powder capsules	ICS
1236	becloforte 250micrograms/dose inhaler (glaxosmithkline uk ltd)	ICS
2723	fluticasone 25micrograms/dose inhaler	ICS
7653	beclometasone 400microgram inhalation powder capsules	ICS
5223	fluticasone 50micrograms/dose inhaler cfc free	ICS
35392	flixotide 500microgram disks with diskhaler (glaxosmithkline uk ltd)	ICS
52806	qvar 100 autohaler (lexon (uk) ltd)	ICS
8111	becloforte vm 250microgram/actuation vm pack (allen & hanburys ltd)	ICS
8251	pulmicort refil 50 mg inh	ICS
34315	beclometasone 250microgram/actuation inhalation powder (actavis uk ltd)	ICS

47943	beclazone easi-breathe (roi) 100microgram/actuation pressurised inhalation (ivax pharmaceuticals ireland)	ICS
14321	beclometasone 200micrograms/dose inhaler cfc free	ICS
9356	becotide rotahaler insufflator inhalation powder (allen and hanburys ltd)	ICS
2282	fluticasone propionate 500micrograms/dose dry powder inhaler	ICS
3570	budesonide 200micrograms/actuation refill canister	ICS
21005	beclometasone 250micrograms/dose inhaler cfc free	ICS
31774	beclometasone 50micrograms/dose inhaler (mylan)	ICS
3753	flixotide diskhaler-community pack 250 mcg	ICS
27525	becotide 50	ICS
1676	flixotide 125microgram/actuation inhalation powder (allen & hanburys ltd)	ICS
5975	fluticasone 125micrograms/dose inhaler cfc free	ICS
14700	budesonide 400micrograms/actuation inhaler	ICS
18394	bdp 50microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
2892	becloforte 400microgram disks (glaxosmithkline uk ltd)	ICS
35299	becodisks 400microgram (glaxosmithkline uk ltd)	ICS
16054	budesonide 200micrograms/actuation breath actuated powder inhaler	ICS
35106	becodisks 100microgram with diskhaler (glaxosmithkline uk ltd)	ICS
39879	budesonide 200micrograms/dose inhaler cfc free	ICS
16148	clenil modulite 250micrograms/dose inhaler (chiesi ltd)	ICS
34428	beclometasone 50microgram/actuation inhalation powder (neo laboratories ltd)	ICS
34919	beclometasone 50micrograms/dose inhaler (a a h pharmaceuticals ltd)	ICS
24898	spacehaler bdp 100microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
38	beclometasone 100micrograms/dose inhaler	ICS
36090	flixotide 100microgram disks (glaxosmithkline uk ltd)	ICS
67237	flixotide 125micrograms/dose evohaler (lexon (uk) ltd)	ICS
14590	asmabec 250microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
1959	pulmicort 0.5mg respules (astrazeneca uk ltd)	ICS
35631	budelin novolizer 200micrograms/dose inhalation powder (meda pharmaceuticals ltd)	ICS
895	beclazone 100 easi-breathe inhaler (teva uk ltd)	ICS
896	becotide easi-breathe 100microgram/actuation pressurised inhalation (allen & hanburys ltd)	ICS
20825	spacehaler bdp 250microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
62341	becotide 50 inhaler (dowelhurst ltd)	ICS
1725	beclazone 50 easi-breathe inhaler (teva uk ltd)	ICS

20707	becotide 100	ICS
51815	flixotide 250micrograms/dose evohaler (waymade healthcare plc)	ICS
33849	beclometasone 100microgram/actuation inhalation powder (neo laboratories ltd)	ICS
71337	qvar 100 inhaler (mawdsley-brooks & company ltd)	ICS
57589	becloforte 250micrograms/dose inhaler (dowelhurst ltd)	ICS
35700	fluticasone propionate 500microgram inhalation powder blisters with device	ICS
35986	flixotide 50microgram disks (glaxosmithkline uk ltd)	ICS
37447	fluticasone propionate 50microgram inhalation powder blisters	ICS
24660	betamethasone valerate	ICS
23741	novolizer budesonide 200microgram/actuation pressurised inhalation (meda pharmaceuticals ltd)	ICS
11198	beclometasons 50 micrograms/actuation vortex inhaler	ICS
36462	fluticasone propionate 500microgram inhalation powder blisters	ICS
48709	qvar 100micrograms/dose easi-breathe inhaler (sigma pharmaceuticals plc)	ICS
36021	fluticasone propionate 50microgram inhalation powder blisters with device	ICS
9577	asmabec 50 clickhaler (focus pharmaceuticals ltd)	ICS
17670	easyhaler budesonide 100micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	ICS
4688	fluticasone 50microgram/actuation pressurised inhalation	ICS
17654	easyhaler beclometasone 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	ICS
7602	fluticasone 50microgram disc	ICS
2440	flixotide accuhaler 500 500microgram/inhalation inhalation powder (allen & hanburys ltd)	ICS
35602	budesonide 200micrograms/dose dry powder inhalation cartridge	ICS
41269	beclometasone 400 cyclocaps (teva uk ltd)	ICS
4601	asmabec 100 clickhaler (focus pharmaceuticals ltd)	ICS
16151	clenil modulite 200micrograms/dose inhaler (chiesi ltd)	ICS
7788	budesonide 100micrograms/dose dry powder inhaler	ICS
35430	becodisks 200microgram with diskhaler (glaxosmithkline uk ltd)	ICS
54399	qvar 100 autohaler (sigma pharmaceuticals plc)	ICS
28640	beclometasone 100microgram/actuation inhalation powder (actavis uk ltd)	ICS
1518	flixotide 50microgram/actuation inhalation powder (allen & hanburys ltd)	ICS
9571	beclometasone 250micrograms/actuation vortex inhaler	ICS
1537	becotide 200microgram rotacaps (glaxosmithkline uk ltd)	ICS
1243	beclazone 250 easi-breathe inhaler (teva uk ltd)	ICS
3927	filair 100 inhaler (meda pharmaceuticals ltd)	ICS

3989	flixotide 100microgram disc (allen & hanburys ltd)	ICS
41412	beclometasone 400micrograms/actuation inhaler	ICS
67261	pulmicort 1mg respules (sigma pharmaceuticals plc)	ICS
1885	beclazone 200 inhaler (teva uk ltd)	ICS
10321	budesonide 400microgram inhalation powder capsules	ICS
959	budesonide 50micrograms/dose inhaler	ICS
1727	becotide easi-breathe 50microgram/actuation pressurised inhalation (allen & hanburys ltd)	ICS
13290	clenil modulite 100micrograms/dose inhaler (chiesi ltd)	ICS
67315	budesonide 400micrograms/dose turbohaler (waymade healthcare plc)	ICS
35905	fluticasone propionate 250microgram inhalation powder blisters	ICS
26063	beclometasone 100micrograms/dose inhaler (teva uk ltd)	ICS
35652	beclometasone 100microgram inhalation powder blisters	ICS
67265	becodisks 200microgram (lexon (uk) ltd)	ICS
3988	flixotide diskhaler-community pack 100 mcg	ICS
7891	fluticasone 500microgram disc	ICS
35611	flixotide 250microgram disks (glaxosmithkline uk ltd)	ICS
39200	aerobec forte 250 autohaler (meda pharmaceuticals ltd)	ICS
30210	beclometasone 250micrograms/dose inhaler (teva uk ltd)	ICS
8450	flixotide diskhaler-community pack 50 mcg	ICS
3546	qvar 50 inhaler (teva uk ltd)	ICS
19401	beclometasone 250micrograms/actuation inhaler and compact spacer	ICS
3363	becloforte 400microgram disks with diskhaler (glaxosmithkline uk ltd)	ICS
35510	budesonide 200micrograms/dose dry powder inhalation cartridge with device	ICS
57525	flixotide 250micrograms/dose accuhaler (stephar (u.k.) ltd)	ICS
3119	becloforte integra 250microgram/actuation inhaler with compact spacer (glaxo laboratories ltd)	ICS
5718	flixotide 125micrograms/dose evohaler (glaxosmithkline uk ltd)	ICS
50701	becotide rotahaler (glaxosmithkline uk ltd)	ICS
5522	beclometasone 100micrograms/dose dry powder inhaler	ICS
60946	entocort cr 3mg capsules (waymade healthcare plc)	ICS
33258	beclometasone 250micrograms/dose inhaler (a a h pharmaceuticals ltd)	ICS
51415	qvar 50 inhaler (mawdsley-brooks & company ltd)	ICS
1552	becloforte easi-breathe 250microgram/actuation pressurised inhalation (allen & hanburys ltd)	ICS
56477	flixotide 100micrograms/dose accuhaler (waymade healthcare plc)	ICS

1242	beclometasone 250micrograms/dose inhaler	ICS
39067	clipper 5mg gastro-resistant modified-release tablets (chiesi ltd)	ICS
11732	beclometasone 50micrograms/dose breath actuated inhaler cfc free	ICS
35638	fluticasone propionate 100microgram inhalation powder blisters with device	ICS
56475	flixotide 50micrograms/dose accuhaler (sigma pharmaceuticals plc)	ICS
35408	becodisks 100microgram (glaxosmithkline uk ltd)	ICS
18848	qvar 100micrograms/dose easi-breathe inhaler (teva uk ltd)	ICS
4803	beclazone 250microgram/actuation inhalation powder (actavis uk ltd)	ICS
56474	flixotide 125micrograms/dose evohaler (de pharmaceuticals)	ICS
27679	beclometasone 100microgram/actuation pressurised inhalation (approved prescription services ltd)	ICS
908	pulmicort 400 turbohaler (astrazeneca uk ltd)	ICS
48340	clenil modulite 100micrograms/dose inhaler (mawdsley-brooks & company ltd)	ICS
71368	pulmicort 200 turbohaler (lexon (uk) ltd)	ICS
56144	budenofalk 9mg gastro-resistant granules sachets (dr. falk pharma uk ltd)	ICS
1100	beclazone 100 inhaler (teva uk ltd)	ICS
54207	qvar 50 inhaler (de pharmaceuticals)	ICS
2159	aerobec 50 autohaler (meda pharmaceuticals ltd)	ICS
71345	budesonide 200micrograms/dose turbohaler (dowelhurst ltd)	ICS
24219	becotide rotacaps	ICS
9164	fluticasone propionate 50micrograms/dose dry powder inhaler	ICS
35071	becodisks 200microgram (glaxosmithkline uk ltd)	ICS
26665	pulmicort complete	ICS
16018	mometasone 200micrograms/dose dry powder inhaler	ICS
14757	pulvinal beclometasone dipropionate 100micrograms/dose dry powder inhaler (chiesi ltd)	ICS
35724	budelin novolizer 200micrograms/dose inhalation powder refill (meda pharmaceuticals ltd)	ICS
454	pulmicort 200microgram inhaler (astrazeneca uk ltd)	ICS
10254	mometasone 400micrograms/dose dry powder inhaler	ICS
27188	easyhaler budesonide 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	ICS
71338	pulmicort 200 turbohaler (de pharmaceuticals)	ICS
67319	flixotide 0.5mg/2ml nebules (waymade healthcare plc)	ICS
2148	beclometasone 400microgram disc	ICS
49412	clenil modulite 200micrograms/dose inhaler (mawdsley-brooks & company ltd)	ICS
5822	fluticasone 250micrograms/dose inhaler cfc free	ICS

67239	pulmicort 400 turbohaler (waymade healthcare plc)	ICS
36290	flixotide 50microgram disks with diskhaler (glaxosmithkline uk ltd)	ICS
28073	beclometasone 250microgram/actuation pressurised inhalation (approved prescription services ltd)	ICS
56493	qvar 50micrograms/dose easi-breathe inhaler (sigma pharmaceuticals plc)	ICS
9599	beclazone 50microgram/actuation inhalation powder (actavis uk ltd)	ICS
5804	beclometasone 250micrograms/dose dry powder inhaler	ICS
35293	beclometasone 200microgram inhalation powder blisters with device	ICS
3437	becotide rotahaler type 4 insufflator inhalation powder (allen and hanburys ltd)	ICS
21482	beclometasone 100micrograms/dose inhaler (mylan)	ICS
42994	flixotide 250micrograms/dose accuhaler (glaxosmithkline uk ltd)	ICS
34859	beclometasone 250microgram/actuation inhalation powder (neo laboratories ltd)	ICS
49367	clenil modulite 50micrograms/dose inhaler (mawdsley-brooks & company ltd)	ICS
6095	budesonide 3mg gastro-resistant capsules	ICS
14294	qvar 50micrograms/dose easi-breathe inhaler (teva uk ltd)	ICS
3188	pulmicort complete 50 mcg inh	ICS
25204	beclometasone 100micrograms/dose inhaler (a a h pharmaceuticals ltd)	ICS
2124	pulmicort refil 200 mcg inh	ICS
57579	flixotide 50micrograms/dose accuhaler (de pharmaceuticals)	ICS
30238	beclometasone 50microgram/actuation pressurised inhalation (approved prescription services ltd)	ICS
11149	betnelan 500microgram tablets (focus pharmaceuticals ltd)	ICS
56462	becodisks 400microgram (waymade healthcare plc)	ICS
37203	beclometasone 5mg gastro-resistant modified-release tablets	ICS
9477	asmabec 100microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
29325	beclometasone 250micrograms/dose inhaler (mylan)	ICS
67322	pulmicort 100 turbohaler (waymade healthcare plc)	ICS
56499	flixotide 500micrograms/dose accuhaler (waymade healthcare plc)	ICS
36401	fluticasone propionate 250microgram inhalation powder blisters with device	ICS
3065	bextasol inhalation powder (allen & hanburys ltd)	ICS
2160	beclometasone 50micrograms/dose breath actuated inhaler	ICS
71380	flixotide 250micrograms/dose accuhaler (necessity supplies ltd)	ICS
63893	budesonide 9mg modified-release tablets	ICS
51997	budesonide 9mg gastro-resistant granules sachets	ICS
2951	fluticasone 250microgram/actuation pressurised inhalation	ICS

60937	pulmicort 200 turbohaler (dowelhurst ltd)	ICS
30649	easyhaler budesonide 400micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	ICS
7638	fluticasone 250microgram disc	ICS
46157	beclometasone 200 cyclocaps (teva uk ltd)	ICS
4545	pulmicort ls 50microgram refill canister (astrazeneca uk ltd)	ICS
50129	qvar 100micrograms/dose easi-breathe inhaler (de pharmaceuticals)	ICS
35107	beclometasone 400microgram inhalation powder blisters with device	ICS
53057	flixotide 50micrograms/dose evohaler (lexon (uk) ltd)	ICS
16584	beclometasone 50micrograms/dose inhaler cfc free	ICS
18537	budesonide 200microgram inhalation powder capsules	ICS
71341	flixotide 100micrograms/dose accuhaler (necessity supplies ltd)	ICS
1680	pulmicort ls 50micrograms/dose inhaler (astrazeneca uk ltd)	ICS
49772	fluticasone 250micrograms/dose evohaler (sigma pharmaceuticals plc)	ICS
52732	pulmicort 0.5mg respules (necessity supplies ltd)	ICS
56471	becodisks 200microgram (mawdsley-brooks & company ltd)	ICS
465	salmeterol 25micrograms/dose inhaler	LABA
42103	tulobuterol 1mg/5ml sugar free syrup	LABA
7270	salmeterol 25micrograms/dose inhaler cfc free	LABA
35165	serevent 50microgram disks with diskhaler (glaxosmithkline uk ltd)	LABA
62662	olodaterol 2.5micrograms/dose solution for inhalation cartridge with device cfc free	LABA
719	salmeterol 50micrograms/dose dry powder inhaler	LABA
35503	salmeterol 50microgram inhalation powder blisters	LABA
1974	oxis 12 turbohaler (astrazeneca uk ltd)	LABA
45610	indacaterol 300microgram inhalation powder capsules with device	LABA
71394	serevent 50microgram disks with diskhaler (dowelhurst ltd)	LABA
19799	tulobuterol 2mg	LABA
910	serevent diskhaler 50microgram inhalation powder (glaxo wellcome uk ltd)	LABA
57694	vertine 25micrograms/dose inhaler cfc free (teva uk ltd)	LABA
9711	formoterol 6micrograms/dose dry powder inhaler	LABA
10968	foradil 12microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	LABA
43893	onbrez breezhaler 150microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	LABA
66547	oxis 12 turbohaler (de pharmaceuticals)	LABA
7268	serevent 25micrograms/dose evohaler (glaxosmithkline uk ltd)	LABA

68483	soltel 25micrograms/dose inhaler cfc free (kent pharmaceuticals ltd)	LABA
22663	respacal 2mg tablet (ucb pharma ltd)	LABA
43738	indacaterol 150microgram inhalation powder capsules with device	LABA
3297	salmeterol 50micrograms disc	LABA
2224	serevent 50micrograms/dose accuhaler (glaxosmithkline uk ltd)	LABA
35725	formoterol easyhaler 12micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	LABA
54742	salmeterol 25micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd)	LABA
67800	serevent 25micrograms/dose evohaler (lexon (uk) ltd)	LABA
6526	formoterol 12microgram inhalation powder capsules with device	LABA
57558	oxis 6 turbohaler (lexon (uk) ltd)	LABA
25784	atimos modulite 12micrograms/dose inhaler (chiesi ltd)	LABA
67823	salmeterol 50microgram diskhaler (dowelhurst ltd)	LABA
68260	serevent 50micrograms/dose accuhaler (mawdsley-brooks & company ltd)	LABA
57544	serevent 50micrograms/dose accuhaler (waymade healthcare plc)	LABA
44064	onbrez breezhaler 300microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	LABA
56482	oxis 12 turbohaler (waymade healthcare plc)	LABA
50051	serevent 25micrograms/dose evohaler (waymade healthcare plc)	LABA
14306	formoterol 12micrograms/dose inhaler cfc free	LABA
62739	indacaterol 85micrograms/dose / glycopyrronium bromide 54micrograms/dose inhalation powder capsules with device	LABA
26829	brelomax 2mg tablet (abbott laboratories ltd)	LABA
47638	neovent 25micrograms/dose inhaler cfc free (kent pharmaceuticals ltd)	LABA
35542	salmeterol 50microgram inhalation powder blisters with device	LABA
35825	serevent 50microgram disks (glaxosmithkline uk ltd)	LABA
549	serevent 25micrograms/dose inhaler (glaxosmithkline uk ltd)	LABA
67238	foradil 12microgram inhalation powder capsules with device (sigma pharmaceuticals plc)	LABA
7133	formoterol 12micrograms/dose dry powder inhaler	LABA
56478	serevent 50micrograms/dose accuhaler (de pharmaceuticals)	LABA
65431	striverdi respimat 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd)	LABA
62667	ultibro breezhaler 85microgram/43microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	LABA
1975	oxis 6 turbohaler (astrazeneca uk ltd)	LABA

65677	airflusal forspiro 50micrograms/dose / 500micrograms/dose dry powder inhaler (sandoz ltd)	LABA_ICS
6746	budesonide 400micrograms/dose / formoterol 12micrograms/dose dry powder inhaler	LABA_ICS
6616	salmeterol 25micrograms with fluticasone 50micrograms cfc free inhaler	LABA_ICS
48739	seretide 250 evohaler (de pharmaceuticals)	LABA_ICS
638	seretide 250 accuhaler (glaxosmithkline uk ltd)	LABA_ICS
51151	seretide 125 evohaler (lexon (uk) ltd)	LABA_ICS
61644	fostair nexthaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd)	LABA_ICS
7013	symbicort 100/6 turbohaler (astrazeneca uk ltd)	LABA_ICS
55677	seretide 500 accuhaler (lexon (uk) ltd)	LABA_ICS
6325	symbicort 200/6 turbohaler (astrazeneca uk ltd)	LABA_ICS
68453	seretide 125 evohaler (waymade healthcare plc)	LABA_ICS
68175	flutiform 50micrograms/dose / 5micrograms/dose inhaler (waymade healthcare plc)	LABA_ICS
66448	flutiform 250micrograms/dose / 10micrograms/dose inhaler (waymade healthcare plc)	LABA_ICS
66453	sirdupla 25micrograms/dose / 250micrograms/dose inhaler (waymade healthcare plc)	LABA_ICS
665	seretide 100 accuhaler (glaxosmithkline uk ltd)	LABA_ICS
67055	fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd)	LABA_ICS
63945	seretide 250 accuhaler (lexon (uk) ltd)	LABA_ICS
61666	duoresp spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (teva uk ltd)	LABA_ICS
70250	airflusal 25micrograms/dose / 125micrograms/dose inhaler (sandoz ltd)	LABA_ICS
63252	seretide 250 evohaler (lexon (uk) ltd)	LABA_ICS
5161	seretide 125 evohaler (glaxosmithkline uk ltd)	LABA_ICS
65596	fostair 200micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)	LABA_ICS
50886	seretide 250 evohaler (stephar (u.k.) ltd)	LABA_ICS
69827	airflusal 25micrograms/dose / 250micrograms/dose inhaler (sandoz ltd)	LABA_ICS
61782	duoresp spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (teva uk ltd)	LABA_ICS
71371	symbicort 100/6 turbohaler (waymade healthcare plc)	LABA_ICS
67958	budesonide 200micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	LABA_ICS
12994	fluticasone 50micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	LABA_ICS
5558	salmeterol 50micrograms with fluticasone 500micrograms cfc free inhaler	LABA_ICS
51570	symbicort 200/6 turbohaler (de pharmaceuticals)	LABA_ICS
62030	beclometasone 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	LABA_ICS
5172	seretide 250 evohaler (glaxosmithkline uk ltd)	LABA_ICS

53491	symbicort 200/6 turbohaler (sigma pharmaceuticals plc)	LABA_ICS
71354	symbicort 400/12 turbohaler (necessity supplies ltd)	LABA_ICS
59899	fluticasone furoate 184micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	LABA_ICS
71409	seretide 50 evohaler (waymade healthcare plc)	LABA_ICS
5942	salmeterol 50micrograms with fluticasone 250micrograms cfc free inhaler	LABA_ICS
65117	seretide 125 evohaler (mawdsley-brooks & company ltd)	LABA_ICS
69436	sereflo 25micrograms/dose / 125micrograms/dose inhaler (kent pharmaceuticals ltd)	LABA_ICS
37432	fostair 100micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)	LABA_ICS
6938	salmeterol 50micrograms with fluticasone 100micrograms dry powder inhaler	LABA_ICS
68034	symbicort 200/6 turbohaler (necessity supplies ltd)	LABA_ICS
51394	seretide 500 accuhaler (waymade healthcare plc)	LABA_ICS
51027	seretide 125 evohaler (de pharmaceuticals)	LABA_ICS
67677	symbicort 200micrograms/dose / 6micrograms/dose pressurised inhaler (astrazeneca uk ltd)	LABA_ICS
65658	fostair nexthaler 200micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd)	LABA_ICS
59327	relvar ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	LABA_ICS
51759	symbicort 200/6 turbohaler (mawdsley-brooks & company ltd)	LABA_ICS
13040	fluticasone propionate 250micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	LABA_ICS
49000	seretide 250 evohaler (waymade healthcare plc)	LABA_ICS
67101	fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler (a a h pharmaceuticals ltd)	LABA_ICS
3666	seretide 500 accuhaler (glaxosmithkline uk ltd)	LABA_ICS
50945	symbicort 100/6 turbohaler (mawdsley-brooks & company ltd)	LABA_ICS
65758	beclometasone 200micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	LABA_ICS
11618	fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	LABA_ICS
5864	salmeterol 25micrograms with fluticasone 250micrograms cfc free inhaler	LABA_ICS
59439	fluticasone furoate 92micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	LABA_ICS
51209	fluticasone 125micrograms/dose / formoterol 5micrograms/dose inhaler cfc free	LABA_ICS
51861	seretide 500 accuhaler (mawdsley-brooks & company ltd)	LABA_ICS
50689	flutiform 50micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)	LABA_ICS
6569	salmeterol 25micrograms with fluticasone 125micrograms cfc free inhaler	LABA_ICS
69538	sereflo 25micrograms/dose / 250micrograms/dose inhaler (kent pharmaceuticals ltd)	LABA_ICS
70711	trimbow 87micrograms/dose / 5micrograms/dose / 9micrograms/dose inhaler (chiesi ltd)	LABA_ICS
51909	seretide 250 evohaler (necessity supplies ltd)	LABA_ICS

59573	relvar ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	LABA_ICS
5143	seretide 50 evohaler (glaxosmithkline uk ltd)	LABA_ICS
53230	seretide 250 accuhaler (de pharmaceuticals)	LABA_ICS
6796	budesonide 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	LABA_ICS
64372	sirdupla 25micrograms/dose / 125micrograms/dose inhaler (mylan)	LABA_ICS
11588	fluticasone 125micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	LABA_ICS
50036	flutiform 125micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)	LABA_ICS
51593	seretide 500 accuhaler (de pharmaceuticals)	LABA_ICS
6780	symbicort 400/12 turbohaler (astrazeneca uk ltd)	LABA_ICS
50560	seretide 250 accuhaler (sigma pharmaceuticals plc)	LABA_ICS
37470	beclometasone 100micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	LABA_ICS
51270	fluticasone 50micrograms/dose / formoterol 5micrograms/dose inhaler cfc free	LABA_ICS
49868	fluticasone 250micrograms/dose / formoterol 10micrograms/dose inhaler cfc free	LABA_ICS
49114	symbicort 100/6 turbohaler (sigma pharmaceuticals plc)	LABA_ICS
48666	flutiform 250micrograms/dose / 10micrograms/dose inhaler (napp pharmaceuticals ltd)	LABA_ICS
71260	generic trimbow 87micrograms/dose / 5micrograms/dose / 9micrograms/dose inhaler	LABA_ICS
62126	seretide 100 accuhaler (de pharmaceuticals)	LABA_ICS
50739	symbicort 400/12 turbohaler (mawdsley-brooks & company ltd)	LABA_ICS
61280	seretide 250 accuhaler (waymade healthcare plc)	LABA_ICS
10218	budesonide 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	LABA_ICS
11410	fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	LABA_ICS
68983	aerivio spiromax 50micrograms/dose / 500micrograms/dose dry powder inhaler (teva uk ltd)	LABA_ICS
53283	seretide 100 accuhaler (waymade healthcare plc)	LABA_ICS
53237	symbicort 400/12 turbohaler (de pharmaceuticals)	LABA_ICS
64638	flutiform 125micrograms/dose / 5micrograms/dose inhaler (waymade healthcare plc)	LABA_ICS
65894	beclometasone 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	LABA_ICS
68495	seretide 500 accuhaler (necessity supplies ltd)	LABA_ICS
71284	fobumix easyhaler 320micrograms/dose / 9micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	LABA_ICS
13273	fluticasone propionate 100micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	LABA_ICS
64373	sirdupla 25micrograms/dose / 250micrograms/dose inhaler (mylan)	LABA_ICS
64523	spiolto respimat 2.5micrograms/dose / 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd)	LABA_LAMA
62838	aclidinium bromide 396micrograms/dose / formoterol 11.8micrograms/dose dry powder inhaler	LABA_LAMA

69556	aclidinium bromide 396micrograms/dose / formoterol 11.8micrograms/dose dry powder inhaler (colorama pharmaceuticals ltd)	LABA_LAMA
61490	umeclidinium bromide 65micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	LABA_LAMA
62535	duaklir 340micrograms/dose / 12micrograms/dose genuair (astrazeneca uk ltd)	LABA_LAMA
61176	anoro ellipta 55micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	LABA_LAMA
64509	tiotropium bromide 2.5micrograms/dose / olodaterol 2.5micrograms/dose solution for inhalation cartridge with device cfc free	LABA_LAMA
49228	eklira 322micrograms/dose genuair (astrazeneca uk ltd)	LAMA
35000	spiriva 18microgram inhalation powder capsules (boehringer ingelheim ltd)	LAMA
64232	tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device cfc free (am distributions (yorkshire) ltd)	LAMA
61582	spiriva respimat 2.5micrograms/dose solution for inhalation cartridge with device (waymade healthcare plc)	LAMA
68530	tiotropium bromide 10microgram inhalation powder capsules with device	LAMA
61879	incruse ellipta 55micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	LAMA
51967	spiriva 18microgram inhalation powder capsules (mawdsley-brooks & company ltd)	LAMA
746	tiotropium 18 microgram capsule	LAMA
62109	umeclidinium bromide 65micrograms/dose dry powder inhaler	LAMA
35011	tiotropium bromide 18microgram inhalation powder capsules	LAMA
69291	sialanar 320micrograms/ml oral solution (proveca ltd)	LAMA
36869	spiriva respimat 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd)	LAMA
49227	aclidinium bromide 375micrograms/dose dry powder inhaler	LAMA
50577	spiriva 18microgram inhalation powder capsules with handihaler (de pharmaceuticals)	LAMA
50103	spiriva 18microgram inhalation powder capsules with handihaler (waymade healthcare plc)	LAMA
63992	eklira 322micrograms/dose genuair (waymade healthcare plc)	LAMA
50292	spiriva 18microgram inhalation powder capsules (sigma pharmaceuticals plc)	LAMA
6050	spiriva 18 microgram capsule (boehringer ingelheim ltd)	LAMA
69109	glycopyrronium bromide 400micrograms/ml oral solution sugar free	LAMA
53982	seebri breezhaler 44microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	LAMA
59638	spiriva 18microgram inhalation powder capsules with handihaler (sigma pharmaceuticals plc)	LAMA
34995	spiriva 18microgram inhalation powder capsules with handihaler (boehringer ingelheim ltd)	LAMA
67531	glycopyrronium bromide 55microgram inhalation powder capsules with device (j m mcgill ltd)	LAMA

35014	tiotropium bromide 18microgram inhalation powder capsules with device	LAMA
68729	braltus 10microgram inhalation powder capsules with zonda inhaler (teva uk ltd)	LAMA
53761	glycopyrronium bromide 55microgram inhalation powder capsules with device	LAMA
36864	tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device cfc free	LAMA
63066	prednisolone 2.5mg tablets	OCS
25272	precortisyl 1mg tablet (hoechst marion roussel)	OCS
64128	pevanti 5mg tablets (amco)	OCS
64221	prednisolone 5mg/5ml oral suspension	OCS
54432	lodotra 1mg modified-release tablets (napp pharmaceuticals ltd)	OCS
62656	prednisone 5mg tablet (hillcross pharmaceuticals ltd)	OCS
44723	prednisone 5mg modified-release tablets	OCS
56891	prednisolone 1mg tablets (waymade healthcare plc)	OCS
64007	pevanti 10mg tablets (amco)	OCS
63214	prednisolone 5mg soluble tablets (alliance healthcare (distribution) ltd)	OCS
2044	prednisone 2.5 mg tab	OCS
53313	prednisolone 20mg/5ml oral suspension	OCS
43544	prednisone 5mg tablet (knoll ltd)	OCS
24716	prednisolone e/c	OCS
63082	prednisolone 20mg tablets	OCS
32803	prednisolone 5mg gastro-resistant tablets (actavis uk ltd)	OCS
3345	sintisone tablet (pharmacia ltd)	OCS
55480	prednisolone 2.5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	OCS
29333	prednisolone 5mg tablets (actavis uk ltd)	OCS
41745	prednisolone 25mg tablets (zentiva)	OCS
58000	prednisolone 5mg tablets (almus pharmaceuticals ltd)	OCS
13522	prednisolone 2 mg tab	OCS
31327	prednisolone steaglate 6.65mg tablet	OCS
66015	prednisolone dompe 5mg/5ml oral solution unit dose (logixx pharma solutions ltd)	OCS
7584	prednisolone 4 mg tab	OCS
69811	prednisolone 30mg tablets (actavis uk ltd)	OCS
44	prednisolone 5mg gastro-resistant tablets	OCS
2949	prednisone 5mg tablets	OCS
67076	prednisolone 20mg/5ml oral solution	OCS

2704	prednisolone 25mg tablets	OCS
1063	prednesol 5mg tablet (sovereign medical ltd)	OCS
21833	decortisyl 5mg tablet (roussel laboratories ltd)	OCS
3059	prednisolone 50 mg tab	OCS
38407	prednisolone 20mg tablet	OCS
64009	pevanti 20mg tablets (amco)	OCS
21417	prednisolone 5mg tablets (a a h pharmaceuticals ltd)	OCS
3557	prednisone 1mg tablets	OCS
2390	prednisolone e/c 1 mg tab	OCS
54118	prednisolone 25mg/5ml oral suspension	OCS
34631	prednisolone 1mg tablet (co-pharma ltd)	OCS
28376	prednisolone 2.5mg gastro-resistant tablet (biorex laboratories ltd)	OCS
67507	prednisolone 30mg tablets	OCS
2368	prednisolone 2.5mg tablet	OCS
45302	prednisolone 5mg tablet (biorex laboratories ltd)	OCS
30390	deltastab 2 mg tab	OCS
34978	prednisolone 1mg tablets (wockhardt uk ltd)	OCS
68497	prednisolone 2.5mg gastro-resistant tablets (waymade healthcare plc)	OCS
27962	deltastab 1mg tablet (waymade healthcare plc)	OCS
5913	deltacortril 2.5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	OCS
67559	prednisolone 5mg/5ml oral solution unit dose (a a h pharmaceuticals ltd)	OCS
47142	prednisolone 5mg soluble tablet (amdipharm plc)	OCS
7934	prednisone 30 mg tab	OCS
34660	prednisolone 1mg tablets (kent pharmaceuticals ltd)	OCS
63791	prednisolone 5mg/5ml oral solution unit dose	OCS
28859	deltastab 5mg tablet (waymade healthcare plc)	OCS
66645	prednisolone 5mg/5ml oral solution unit dose (logixx pharma solutions ltd)	OCS
19141	prednisolone 5mg soluble tablets (amco)	OCS
34748	prednisolone 1mg tablets (teva uk ltd)	OCS
41515	prednisolone 5mg tablets (teva uk ltd)	OCS
58061	prednisone 50mg tablets	OCS
955	prednisolone 5mg soluble tablets	OCS
34109	prednisolone 5 mg gastro-resistant tablet	OCS

66550	prednisolone 5mg gastro-resistant tablets (alliance healthcare (distribution) ltd)	OCS
59912	prednisolone 5mg gastro-resistant tablets (waymade healthcare plc)	OCS
65626	prednisolone 10mg/5ml oral suspension	OCS
65020	prednisolone 25mg/5ml oral solution	OCS
34461	prednisolone 2.5mg gastro-resistant tablets (actavis uk ltd)	OCS
20095	precortisyl forte 25mg tablet (aventis pharma)	OCS
66914	prednisolone 1mg gastro-resistant tablets	OCS
44802	lodotra 5mg modified-release tablets (napp pharmaceuticals ltd)	OCS
63172	prednisolone 10mg tablets	OCS
2799	prednisolone 10 mg tab	OCS
95	prednisolone 5mg tablets	OCS
63549	prednisolone 1mg/ml oral solution (logixx pharma solutions ltd)	OCS
61132	prednisolone 1mg tablets (boston healthcare ltd)	OCS
5490	deltacortril 5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	OCS
31532	prednisolone 5mg gastro-resistant tablets (a a h pharmaceuticals ltd)	OCS
9727	prednisolone 50mg tablets	OCS
61162	prednisolone 5mg tablets (waymade healthcare plc)	OCS
58369	prednisolone 5mg tablets (boston healthcare ltd)	OCS
58987	prednisolone 5mg gastro-resistant tablets (phoenix healthcare distribution ltd)	OCS
58384	prednisolone 1mg tablets (almus pharmaceuticals ltd)	OCS
23512	precortisyl 5mg tablet (hoechst marion roussel)	OCS
59338	prednisolone 1mg/5ml oral solution	OCS
13615	prednisone 10 mg tab	OCS
44803	lodotra 2mg modified-release tablets (napp pharmaceuticals ltd)	OCS
33988	prednisolone 5mg tablet (co-pharma ltd)	OCS
44380	prednisone 1mg modified-release tablets	OCS
32835	prednisolone 5mg tablets (wockhardt uk ltd)	OCS
33990	prednisolone 5mg tablet (ivax pharmaceuticals uk ltd)	OCS
27959	prednisolone	OCS
61689	prednisolone 5mg soluble tablets (a a h pharmaceuticals ltd)	OCS
59229	dilacort 5mg gastro-resistant tablets (auden mckenzie (pharma division) ltd)	OCS
7710	prednisolone 15 mg tab	OCS
33691	prednisolone 5mg gastro-resistant tablet (biorex laboratories ltd)	OCS

53336	prednisolone 25mg tablets (a a h pharmaceuticals ltd)	OCS
16724	prednisone 50 mg tab	OCS
58234	prednisolone 10mg/5ml oral solution	OCS
59283	dilacort 2.5mg gastro-resistant tablets (auden mckenzie (pharma division) ltd)	OCS
34404	prednisolone 1mg tablets (actavis uk ltd)	OCS
64416	prednisolone 10mg/ml oral solution sugar free	OCS
60421	prednisolone 5mg tablets (strides shasun (uk) ltd)	OCS
67107	prednisolone 5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	OCS
69686	pevanti 25mg tablets (amco)	OCS
70603	prednisolone 5mg soluble tablets (focus pharmaceuticals ltd)	OCS
34393	prednisolone 5mg gastro-resistant tablets (teva uk ltd)	OCS
30971	decortisyl 25 mg tab	OCS
34781	prednisolone 5mg tablets (kent pharmaceuticals ltd)	OCS
34914	prednisolone 1mg tablet (celltech pharma europe ltd)	OCS
578	prednisolone 1mg tablets	OCS
557	prednisolone 2.5mg gastro-resistant tablets	OCS
51753	prednisolone 1mg tablets (strides shasun (uk) ltd)	OCS
55024	prednisolone 5mg/5ml oral solution	OCS
27889	prednisolone	OCS
34452	prednisolone 1mg tablets (a a h pharmaceuticals ltd)	OCS
28375	prednisolone 2.5mg gastro-resistant tablets (a a h pharmaceuticals ltd)	OCS
64008	pevanti 2.5mg tablets (amco)	OCS
54434	prednisolone 2.5mg/5ml oral suspension	OCS
20670	prednisolone e/c	OCS
46711	prednisone 2mg modified-release tablets	OCS
21859	asmaven 100microgram inhalation powder (berk pharmaceuticals ltd)	SABA
987	ventolin 4mg tablet (allen & hanburys ltd)	SABA
14482	bricanyl 2.5 mg inj	SABA
4171	ventolin 2mg tablet (allen & hanburys ltd)	SABA
13038	pulvinal salbutamol 200micrograms/dose dry powder inhaler (chiesi ltd)	SABA
856	ventolin 2mg/5ml syrup (glaxosmithkline uk ltd)	SABA
33588	salbutamol 100micrograms/dose inhaler (mylan)	SABA
4665	salbulin 100micrograms/dose inhaler (3m health care ltd)	SABA

7935	maxivent 100microgram/inhalation inhalation powder (ashbourne pharmaceuticals ltd)	SABA
13575	bambec 20mg tablets (astrazeneca uk ltd)	SABA
1635	salbuvent 2mg/5ml oral solution (pharmacia ltd)	SABA
59409	salbutamol 100micrograms/dose inhaler cfc free (waymade healthcare plc)	SABA
22225	beclomethasone /salbutamol	SABA
40655	salbuvent 100microgram/actuation inhalation powder (pharmacia ltd)	SABA
22313	ventmax sr 8mg capsules (chiesi ltd)	SABA
2020	berotec 200micrograms/dose inhaler (boehringer ingelheim ltd)	SABA
8504	exirel 15 mg tab	SABA
15165	reproterol 500micrograms/dose inhaler	SABA
48809	ventodisks 400microgram with diskhaler (glaxosmithkline uk ltd)	SABA
67543	bricanyl 500micrograms/dose turbohaler (waymade healthcare plc)	SABA
4908	ventolin rotahaler (glaxosmithkline uk ltd)	SABA
3994	salbutamol 4mg modified-release tablets	SABA
1619	terbutaline 500micrograms/dose dry powder inhaler	SABA
41691	salbutamol 2mg/5ml oral solution sugar free (sandoz ltd)	SABA
696	salbutamol 8mg modified-release capsules	SABA
38416	salbutamol cyclocaps 400microgram inhalation powder (dupont pharmaceuticals ltd)	SABA
66972	salbutamol 100micrograms/dose inhaler cfc free (am distributions (yorkshire) ltd)	SABA
33373	salbutamol 200 cyclocaps (teva uk ltd)	SABA
12042	ventolin cr 8mg tablet (allen & hanburys ltd)	SABA
27573	ventolin	SABA
38419	terbutaline 1.5mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)	SABA
1628	terbutaline 250micrograms/actuation refill canister	SABA
882	salbutamol 200microgram inhalation powder capsules	SABA
13996	salamol 100microgram/inhalation inhalation powder (sandoz ltd)	SABA
235	bricanyl 250micrograms/dose inhaler (astrazeneca uk ltd)	SABA
1950	ventodisks 400microgram/blister disc (allen & hanburys ltd)	SABA
19732	cobutolin inh	SABA
5170	salamol 100micrograms/dose inhaler cfc free (teva uk ltd)	SABA
898	ventolin evohaler 100 100microgram/inhalation pressurised inhalation (glaxo wellcome uk ltd)	SABA
60923	salamol 100micrograms/dose easi-breathe inhaler (de pharmaceuticals)	SABA
15441	fenoterol hydrobromide .5 % sol	SABA

7954	bricanyl 250micrograms/dose spacer inhaler (astrazeneca uk ltd)	SABA
22790	reproterol 10mg/ml respirator solution	SABA
22430	spacehaler salbutamol 100microgram/inhalation spacehaler (celltech pharma europe ltd)	SABA
49370	ventodisks 200microgram (glaxosmithkline uk ltd)	SABA
31290	salbulin cfc free	SABA
7953	terbutaline 1.5mg/5ml oral solution sugar free	SABA
16577	easyhaler salbutamol sulfate 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	SABA
8339	fenoterol hydrobromide complete unit inh	SABA
1961	volmax 4mg modified-release tablets (glaxosmithkline uk ltd)	SABA
70750	ventolin 100micrograms/dose evohaler (dowelhurst ltd)	SABA
48742	ventodisks 400microgram (glaxosmithkline uk ltd)	SABA
42858	ventolin 200micrograms/dose accuhaler (glaxosmithkline uk ltd)	SABA
8636	ventolin s/r 8 mg spa	SABA
49368	ventodisks 200microgram with diskhaler (glaxosmithkline uk ltd)	SABA
31	ventolin 100microgram/inhalation inhalation powder (glaxo wellcome uk ltd)	SABA
3838	salbutamol 400mcg/beclometh.100mcg r/cap inh	SABA
5185	fenoterol 200micrograms/dose inhaler	SABA
25821	exirel 7.5mg/5ml oral solution (3m health care ltd)	SABA
510	ventolin 5mg/ml respirator solution (glaxosmithkline uk ltd)	SABA
20838	salbuvent 2mg tablet (pharmacia ltd)	SABA
12563	exirel inhalation powder (3m health care ltd)	SABA
4222	bricanyl 10mg/ml respirator solution (astrazeneca uk ltd)	SABA
38226	salbulin novolizer 100micrograms/dose inhalation powder refill (meda pharmaceuticals ltd)	SABA
4541	bricanyl sa 7.5mg tablets (astrazeneca uk ltd)	SABA
3163	salbutamol 200micrograms disc	SABA
10858	pulmadil auto inhalation powder (3m health care ltd)	SABA
8252	pirbuterol 15mg capsule	SABA
3758	pulmadil inhalation powder (3m health care ltd)	SABA
4497	ventolin accuhaler 200 200microgram/actuation inhalation powder (glaxo wellcome uk ltd)	SABA
2869	salbutamol 8mg modified-release tablets	SABA
50315	salbutamol 200microgram inhalation powder blisters with device	SABA
4055	salbulin 2mg/5ml oral solution (3m health care ltd)	SABA
34702	salbutamol 100microgram/inhalation inhalation powder (c p pharmaceuticals ltd)	SABA

674	ventolin 2.5mg nebules (glaxosmithkline uk ltd)	SABA
1093	salamol 100microgram/actuation inhalation powder (ivax pharmaceuticals uk ltd)	SABA
27793	salbutamol cyclohaler type 5 insufflator inhalation powder (bristol-myers squibb pharmaceuticals ltd)	SABA
7452	ventolin .25 mg inj	SABA
32812	numotac 10mg tablet (3m health care ltd)	SABA
282	salbutamol 2mg/5ml oral solution sugar free	SABA
862	salbulin inhalation powder (3m health care ltd)	SABA
19649	ventolin rotahaler	SABA
3764	bricanyl respules (5mg/2ml) 2.5 mg/ml inh	SABA
14527	bambec 10mg tablets (astrazeneca uk ltd)	SABA
7711	terbutaline 250micrograms/dose inhaler with spacer	SABA
13181	easyhaler salbutamol sulfate 100micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	SABA
46551	salbutamol 100microgram/inhalation inhalation powder (neo laboratories ltd)	SABA
3763	terbutaline respules inh	SABA
3189	salbuvent inh inh	SABA
12144	bambuterol 20mg tablets	SABA
28881	salbutamol 2mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)	SABA
42830	ventolin 100micrograms/dose evohaler (glaxosmithkline uk ltd)	SABA
1960	volmax 8mg modified-release tablets (glaxosmithkline uk ltd)	SABA
2655	airomir 100micrograms/dose inhaler (teva uk ltd)	SABA
5516	salamol 100micrograms/dose easi-breathe inhaler (teva uk ltd)	SABA
4842	fenoterol 100microgram/actuation inhaler	SABA
881	salbutamol 2mg tablets	SABA
28508	salbutamol 100microgram/inhalation inhalation powder (ivax pharmaceuticals uk ltd)	SABA
8572	rimiterol inhaler	SABA
19726	ventolin s/r	SABA
1957	ventolin 5mg nebules (glaxosmithkline uk ltd)	SABA
8	salbutamol 100micrograms/dose inhaler	SABA
1952	ventolin 400microgram rotacaps (glaxosmithkline uk ltd)	SABA
21102	salbutamol 2mg/5ml oral solution (lagap)	SABA
10458	ventolin cr 4mg tablet (allen & hanburys ltd)	SABA
12463	pirbuterol 15 mg tab	SABA
38097	salbutamol cyclocaps 200microgram inhalation powder (dupont pharmaceuticals ltd)	SABA

30212	salbutamol cyclohaler	SABA
57524	ventolin 200micrograms/dose accuhaler (dowelhurst ltd)	SABA
958	ventolin easi-breathe 100microgram/actuation pressurised inhalation (allen & hanburys ltd)	SABA
16236	pirbuterol acetate inhaler	SABA
860	salbutamol 4mg tablets	SABA
34311	salbutamol 100microgram/inhalation inhalation powder (berk pharmaceuticals ltd)	SABA
2758	bricanyl refill canister (astrazeneca uk ltd)	SABA
34619	salbutamol 100microgram/inhalation inhalation powder (kent pharmaceuticals ltd)	SABA
3584	bricanyl 1.5mg/5ml syrup (astrazeneca uk ltd)	SABA
5889	salamol 100microgram/inhalation inhalation powder (kent pharmaceuticals ltd)	SABA
907	bricanyl turbohaler 500 500microgram turbohaler (astrazeneca uk ltd)	SABA
48547	salamol 100micrograms/dose inhaler cfc free (arrow generics ltd)	SABA
69238	ventolin 200micrograms/dose accuhaler (waymade healthcare plc)	SABA
57249	asmavent 100micrograms/dose inhaler cfc free (kent pharmaceuticals ltd)	SABA
10353	salbuvent rondo	SABA
2978	salbutamol 200micrograms/dose dry powder inhaler	SABA
25820	bronchodil 10mg/5ml oral solution (viatris pharmaceuticals ltd)	SABA
9651	asmasal 100microgram/inhalation spacehaler (celltech pharma europe ltd)	SABA
17696	ventmax sr 4mg capsules (chiesi ltd)	SABA
26420	exirel 10 mg tab	SABA
32102	salbutamol 4mg tablets (a a h pharmaceuticals ltd)	SABA
20675	salbutamol rotahaler complete unit	SABA
26873	cobutolin 2mg tablet (actavis uk ltd)	SABA
25073	salbutamol	SABA
1794	berotec 100microgram/actuation inhalation powder (boehringer ingelheim ltd)	SABA
48490	ventolin 100micrograms/dose evohaler (de pharmaceuticals)	SABA
31845	salapin 2mg/5ml syrup (pinewood healthcare)	SABA
1882	ventodisks 200microgram/blister disc (allen & hanburys ltd)	SABA
34029	salbutamol 400micrograms inahalation capsules	SABA
15075	bronchodil 20mg tablet (viatris pharmaceuticals ltd)	SABA
49591	salbutamol 100micrograms/dose inhaler cfc free (sandoz ltd)	SABA
1741	salbutamol 100micrograms/dose breath actuated inhaler cfc free	SABA
26525	ventolin	SABA

2149	steri-neb salamol 2.5 mg inh	SABA
41549	salbutamol 2mg tablet (c p pharmaceuticals ltd)	SABA
23688	ventolin rotacaps	SABA
42497	salbutamol 8mg tablet	SABA
33089	salbutamol 100micrograms/dose inhaler (kent pharmaceuticals ltd)	SABA
22467	salbutamol respirator soln	SABA
42867	terbutaline 1.5mg/5ml oral solution (sandoz ltd)	SABA
41548	salbutamol 2mg tablets (approved prescription services ltd)	SABA
25218	salbutamol cfc/free b/a	SABA
19653	ventolin respirator	SABA
32050	salbutamol 400 cyclocaps (teva uk ltd)	SABA
2850	salbutamol 400microgram inhalation powder capsules	SABA
22550	duovent	SABA
53297	ventolin 200micrograms/dose accuhaler (sigma pharmaceuticals plc)	SABA
8522	terbutaline 7.5mg modified-release tablets	SABA
23787	exirel 10mg capsule (3m health care ltd)	SABA
67040	salbutamol 100micrograms/dose inhaler cfc free (alliance healthcare (distribution) ltd)	SABA
1620	terbutaline 250micrograms/dose inhaler	SABA
30230	salbutamol 100micrograms/actuation breath actuated inhaler	SABA
43085	bricanyl 5mg/2ml respules (astrazeneca uk ltd)	SABA
17901	bricanyl nebule 2.5 ml	SABA
30118	salbutamol 100micrograms/dose inhaler cfc free (teva uk ltd)	SABA
52543	salbutamol 400microgram inhalation powder blisters	SABA
34938	salbutamol 4mg tablets (actavis uk ltd)	SABA
34618	salbutamol 2mg tablets (actavis uk ltd)	SABA
49369	salbutamol 200microgram inhalation powder blisters	SABA
48519	ventolin 100micrograms/dose evohaler (waymade healthcare plc)	SABA
30204	salbutamol 200micrograms inahalation capsules	SABA
50956	ventolin 200micrograms/dose accuhaler (de pharmaceuticals)	SABA
10825	terbutaline 5mg tablets	SABA
26716	airomir autohaler cfc free b/a	SABA
6462	salbutamol 95micrograms/dose dry powder inhaler	SABA
42886	bricanyl 500micrograms/dose turbohaler (astrazeneca uk ltd)	SABA

50503	ventolin 200micrograms/dose accuhaler (mawdsley-brooks & company ltd)	SABA
38079	salbutamol 100micrograms/dose dry powder inhalation cartridge with device	SABA
66793	salbutamol rondo 100micrograms/actuation inhaler and spacer	SABA
3254	salbulin 4mg tablet (3m health care ltd)	SABA
66924	salbutamol 100micrograms/dose inhaler cfc free (de pharmaceuticals)	SABA
22512	salbutamol inhaler	SABA
10958	salbutamol .25 mg inj	SABA
67326	bricanyl 500micrograms/dose turbohaler (de pharmaceuticals)	SABA
1698	salbutamol 100micrograms/dose breath actuated inhaler	SABA
1087	asmasal 95micrograms/dose clickhaler (focus pharmaceuticals ltd)	SABA
58269	airsalb 100micrograms/dose inhaler cfc free (sandoz ltd)	SABA
48741	ventolin 100micrograms/dose evohaler (mawdsley-brooks & company ltd)	SABA
12486	bronchodil 500microgram/dose inhalation powder (viatris pharmaceuticals ltd)	SABA
7017	salbutamol 100micrograms/dose dry powder inhaler	SABA
64801	salbutamol 100micrograms/dose inhaler cfc free (mylan)	SABA
31082	salbuvent 5mg/ml respirator solution (pharmacia ltd)	SABA
3534	bricanyl 5mg tablets (astrazeneca uk ltd)	SABA
17	salbutamol 100micrograms/dose inhaler cfc free	SABA
66395	salbutamol 100micrograms/dose inhaler cfc free (mawdsley-brooks & company ltd)	SABA
22661	pirbuterol 10mg capsule	SABA
8012	exirel 15mg capsule (3m health care ltd)	SABA
17874	monovent 1.5mg/5ml oral solution (lagap)	SABA
3443	salbutamol 100microgram/inhalation spacehaler (celltech pharma europe ltd)	SABA
2851	ventolin 200microgram rotacaps (glaxosmithkline uk ltd)	SABA
29267	salbuvent 4mg tablet (pharmacia ltd)	SABA
65376	salbutamol 2mg/5ml oral solution sugar free (pinewood healthcare)	SABA
52799	salbutamol 400microgram inhalation powder blisters with device	SABA
2395	salbutamol 2 mg/5ml syr	SABA
38214	salbutamol 100micrograms/dose dry powder inhalation cartridge	SABA
34310	salbutamol 100micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd)	SABA
53019	ventolin 2.5mg nebules (mawdsley-brooks & company ltd)	SABA
5740	airomir 100micrograms/dose autohaler (teva uk ltd)	SABA
52410	bricanyl 500micrograms/dose turbohaler (necessity supplies ltd)	SABA

31933	salbutamol 100micrograms/dose inhaler (a a h pharmaceuticals ltd)	SABA
36677	reproterol 10mg/5ml oral solution	SABA
14525	salbutamol 100micrograms/inhalation vortex inhaler	SABA
8429	ventolin i/v 5 mg inj	SABA
33817	salbutamol 100micrograms/dose inhaler cfc free (actavis uk ltd)	SABA
19642	ventolin nebules	SABA
18622	salbulin 2mg tablet (3m health care ltd)	SABA
38136	salbulin novolizer 100micrograms/dose inhalation powder (meda pharmaceuticals ltd)	SABA
61591	salbutamol 100micrograms/dose inhaler cfc free (phoenix healthcare distribution ltd)	SABA
50557	ventolin 200micrograms/dose accuhaler (lexon (uk) ltd)	SABA
41832	monovent 1.5mg/5ml syrup (sandoz ltd)	SABA
9384	salbutamol 4mg modified-release capsules	SABA
44713	salbutamol 100microgram/inhalation inhalation powder (celltech pharma europe ltd)	SABA
25829	pirbuterol 7.5mg/5ml oral solution	SABA
5753	salbutamol 400micrograms disc	SABA
7192	bambuterol 10mg tablets	SABA
20781	salbutamol u.dose nebulising 2.5mg/2.5ml	SABA
957	salamol easi-breathe 100microgram/actuation pressurised inhalation (ivax pharmaceuticals uk ltd)	SABA
8267	sodium cromoglicate 1mg/dose / salbutamol 100micrograms/dose inhaler	SABA_CROMO
10360	aerocrom inhaler (castlemead healthcare ltd)	SABA_CROMO
18314	aerocrom syncroner with spacer (castlemead healthcare ltd)	SABA_CROMO
24380	sodium cromoglicate 1mg/dose / salbutamol 100micrograms/dose inhaler with spacer	SABA_CROMO
14561	salbutamol 400microgram / beclometasone 200microgram inhalation powder capsules	SABA_ICS
3556	beclometasone 50micrograms with salbutamol 100micrograms/inhalation inhaler	SABA_ICS
16625	ventide rotacaps (glaxosmithkline uk ltd)	SABA_ICS
18456	salbutamol 200microgram / beclometasone 100microgram inhalation powder capsules	SABA_ICS
19376	beclometasone 200micrograms with salbutamol 400micrograms inhalation capsules	SABA_ICS
1801	ventide inhaler (glaxosmithkline uk ltd)	SABA_ICS
18484	ventide paediatric rotacaps (glaxosmithkline uk ltd)	SABA_ICS
19121	beclometasone 100micrograms with salbutamol 200micrograms inhalation capsules	SABA_ICS
11307	salbutamol 100micrograms/dose / beclometasone 50micrograms/dose inhaler	SABA_ICS
27505	ipratropium bromide with fenoterol hydrobromide 40micrograms + 100micrograms/actuation	SABA_SAMA
556	combivent inhaler (boehringer ingelheim ltd)	SABA_SAMA

3786	fenoterol 100micrograms/dose / ipratropium 40micrograms/dose inhaler	SABA_SAMA
11046	ipratropium bromide with salbutamol 500micrograms + 2.5mg/2.5ml	SABA_SAMA
12808	fenoterol 100micrograms/dose / ipratropium bromide 40micrograms/dose breath actuated inhaler	SABA_SAMA
12822	salbutamol 2.5mg with ipratropium bromide 500micrograms/2.5ml unit dose nebuilser solution	SABA_SAMA
9270	ipratropium bromide with fenoterol hydrobromide 500micrograms + 1.25mg/4ml	SABA_SAMA
2152	ipratropium bromide with salbutamol 20mcg + 100mcg	SABA_SAMA
2722	duovent inhaler (boehringer ingelheim ltd)	SABA_SAMA
2862	duovent autohaler (boehringer ingelheim ltd)	SABA_SAMA
12909	salbutamol 100micrograms/dose / ipratropium 20micrograms/dose inhaler	SABA_SAMA
26616	ipratropium bromide with fenoterol hydrobromide 0micrograms + 100micrograms/actuation	SABA_SAMA
43090	atrovent 40microgram aerocaps (boehringer ingelheim ltd)	SAMA
9681	atrovent aerohaler 40microgram inhalation powder (boehringer ingelheim ltd)	SAMA
6081	ipratropium bromide 20micrograms/dose breath actuated inhaler	SAMA
6512	atrovent 20micrograms/dose inhaler cfc free (boehringer ingelheim ltd)	SAMA
3850	oxivent 100micrograms/dose autohaler (boehringer ingelheim ltd)	SAMA
11779	ipratropium bromide 40microgram inhalation powder capsules with device	SAMA
2994	atrovent aerocaps 40microgram inhalation powder (boehringer ingelheim ltd)	SAMA
19805	atrovent	SAMA
1410	ipratropium bromide 0.25mg/ml	SAMA
20720	atrovent forte	SAMA
1409	ipratropium bromide 20micrograms/dose inhaler	SAMA
534	atrovent 20micrograms/dose inhaler (boehringer ingelheim ltd)	SAMA
2437	oxitropium bromide 100micrograms/dose inhaler	SAMA
57557	atrovent 20micrograms/dose inhaler cfc free (lexon (uk) ltd)	SAMA
60920	atrovent 20micrograms/dose inhaler cfc free (sigma pharmaceuticals plc)	SAMA
1411	ipratropium bromide 250micrograms/ml	SAMA
18140	respontin 500micrograms/2ml nebules (glaxosmithkline uk ltd)	SAMA
23567	respontin 250micrograms/1ml nebules (glaxosmithkline uk ltd)	SAMA
50810	atrovent 20micrograms/dose inhaler cfc free (de pharmaceuticals)	SAMA
3039	oxivent 100micrograms/dose inhaler (boehringer ingelheim ltd)	SAMA
1697	atrovent 20micrograms/dose autohaler (boehringer ingelheim ltd)	SAMA
43105	atrovent 40microgram aerocaps with aerohaler (boehringer ingelheim ltd)	SAMA
9658	oxitropium bromide 100micrograms/dose breath actuated inhaler	SAMA

6522	ipratropium bromide 20micrograms/dose inhaler cfc free	SAMA
3306	atrovent forte 40micrograms/dose inhaler (boehringer ingelheim ltd)	SAMA
4268	ipratropium bromide 40micrograms/dose inhaler	SAMA
37791	ipratropium bromide 250microgram/ml	SAMA
8333	ipratropium bromide 40microgram inhalation powder capsules	SAMA
23961	ipratropium bromide 250microgram/ml inhalation vapour (galen ltd)	SAMA
25020	ipratropium bromide (forte)	SAMA
9	Amoxicillin 250mg capsules	ABX
48	Amoxicillin 500mg capsules	ABX
62	Amoxicillin 125mg/5ml oral suspension	ABX
63	Erythromycin 250mg gastro-resistant tablets	ABX
77	Oxytetracycline 250mg tablets	ABX
103	Erythromycin 250mg gastro-resistant capsules	ABX
105	Erythroped 250mg/5ml Liquid (Abbott Laboratories Ltd)	ABX
121	Tetracycline 250mg capsules	ABX
132	Oxytetracycline 250mg capsules	ABX
133	Amoxil 250mg capsules (GlaxoSmithKline UK Ltd)	ABX
155	Cefalexin 250mg capsules	ABX
163	Ciproxin 250mg/5ml oral suspension (Bayer Plc)	ABX
192	Ceporex 250mg Capsule (Galen Ltd)	ABX
264	Doxycycline 50mg capsules	ABX
268	Vibramycin 100mg capsules (Pfizer Ltd)	ABX
281	Ciprofloxacin 250mg tablets	ABX
318	Erymax 250mg Capsule (Elan Pharma)	ABX
319	Distaclor 500mg Capsule (Dista Products Ltd)	ABX
327	Erythroped a 500mg Tablet (Abbott Laboratories Ltd)	ABX
331	Clarithromycin 125mg/5ml oral suspension	ABX
366	Cefaclor 250mg capsules	ABX
386	Tetracycline 250mg tablets	ABX
397	Erythromycin 125mg/5ml oral suspension	ABX
399	Augmentin 375mg tablets (GlaxoSmithKline UK Ltd)	ABX
400	Cefalexin 500mg capsules	ABX
401	Erythromycin 500mg ec gastro-resistant tablets	ABX

415	Augmentin 125/31 SF oral suspension (GlaxoSmithKline UK Ltd)	ABX
427	Amoxicillin 250mg/5ml oral suspension	ABX
438	Erythromycin stearate 250mg tablets	ABX
439	Amoxicillin with Clavulanic acid dispersible tablets	ABX
480	Erythrocin 250mg Tablet (Abbott Laboratories Ltd)	ABX
485	Amoxicillin 125mg/1.25ml oral suspension paediatric	ABX
498	Ciprofloxacin 100mg tablets	ABX
503	Amoxicillin 125mg/5ml oral suspension sugar free	ABX
509	Augmentin 625mg tablets (GlaxoSmithKline UK Ltd)	ABX
524	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free	ABX
532	Erythroped 250mg/5ml Oral suspension (Abbott Laboratories Ltd)	ABX
537	Clarithromycin 250mg tablets	ABX
545	Co-amoxiclav 250mg/125mg tablets	ABX
553	Erythromycin 250mg.5ml oral suspension	ABX
569	Augmentin 250/62 SF oral suspension (GlaxoSmithKline UK Ltd)	ABX
583	Ciprofloxacin 500mg tablets	ABX
585	Amoxicillin 250mg/5ml oral suspension sugar free	ABX
641	Co-amoxiclav 500mg/125mg tablets	ABX
681	Clarithromycin 500mg tablets	ABX
728	Ciproxin 500mg tablets (Bayer Plc)	ABX
733	Erythromycin ethyl succinate 500mg tablets	ABX
765	Clarithromycin 250mg granules sachets	ABX
825	Erythroped pi 125mg/5ml Oral suspension (Abbott Laboratories Ltd)	ABX
829	Co-amoxiclav 250mg/125mg dispersible tablets sugar free	ABX
830	Keflex 250mg tablets (Flynn Pharma Ltd)	ABX
847	Amoxil 500mg capsules (GlaxoSmithKline UK Ltd)	ABX
865	Cefalexin 500mg tablets	ABX
870	Amoxicillin 250mg sugar free chewable tablets	ABX
970	Doxycycline (as hyclate) 100mg tablets	ABX
993	Erythroped forte 500mg/5ml Liquid (Abbott Laboratories Ltd)	ABX
997	Erythroped pi 125mg/5ml Liquid (Abbott Laboratories Ltd)	ABX
1037	ERYTHROMYCIN ETHYLSUCCINATE SF 125 MG/5ML SUS	ABX
1038	Cefaclor 125mg/5ml oral suspension	ABX

1046	Doxycycline 100mg capsules	ABX
1072	Erythrocin 500 500mg Tablet (Abbott Laboratories Ltd)	ABX
1140	Amoxicillin 3g oral powder sachets sugar free	ABX
1146	Cefalexin 250mg tablets	ABX
1202	Ciproxin 250mg tablets (Bayer Plc)	ABX
1376	ERYTHROMYCIN 100 MG SYR	ABX
1384	Cefalexin 125mg/5ml suspension	ABX
1391	Amoxicillin 250mg / Clavulanic acid 125mg tablets	ABX
1393	AMOXYCILLIN FIZTAB 250 MG TAB	ABX
1570	AMOXYCILLIN 500 MG TAB	ABX
1637	Amoxil fiztab 250mg Tablet (Bencard)	ABX
1638	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free	ABX
1693	Cefalexin 125mg/5ml oral suspension	ABX
1713	Cefalexin 250mg/5ml suspension	ABX
1722	Amoxicillin 500mg dispersible tablets	ABX
1812	Amoxil 250mg/5ml syrup sucrose free (GlaxoSmithKline UK Ltd)	ABX
1837	Ciprofloxacin 750mg tablets	ABX
1860	Cefalexin 250mg/5ml oral suspension	ABX
1969	ERYTHROMYCIN 250 MG MIX	ABX
2153	Amoxil 125mg/5ml syrup sucrose free (GlaxoSmithKline UK Ltd)	ABX
2171	Amoxil 125mg/1.25ml paediatric oral suspension (GlaxoSmithKline UK Ltd)	ABX
2174	Amoxil 3g oral powder sachets sucrose free (GlaxoSmithKline UK Ltd)	ABX
2225	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free	ABX
2226	Erythromycin ethyl succinate 500mg/5ml oral suspension	ABX
2227	Cefalexin 500mg/5ml oral suspension	ABX
2281	Amoxicillin 500mg sugar free chewable tablets	ABX
2326	Erythromycin 500mg/5ml oral suspension	ABX
2350	Erythromycin stearate 500mg tablets	ABX
2376	Erythromycin ethyl succinate 250mg/5ml oral suspension	ABX
2428	Distaclor 125mg/5ml Liquid (Dista Products Ltd)	ABX
2429	Erythromycin ethyl succinate 125mg/5ml oral suspension	ABX
2458	OXYTETRACYCLINE 100 MG TAB	ABX
2507	Augmentin 375mg dispersible tablets (GlaxoSmithKline UK Ltd)	ABX

2636	TETRACYCLINE 500 MG CAP	ABX
2661	Ceporex 500mg Capsule (Galen Ltd)	ABX
2719	Klaricid 250mg tablets (Abbott Laboratories Ltd)	ABX
2884	Doxycycline (as hyclate) 100mg dispersible tablets	ABX
2902	AMOXYCILLIN FIZTAB 125 MG TAB	ABX
2922	Tetracycline 250mg with nystatin 250000units tablets	ABX
2976	Cefaclor 500mg capsules	ABX
3042	Erythroped pi 125mg Sachets (Abbott Laboratories Ltd)	ABX
3152	Vibramycin 100mg Dispersible tablet (Pfizer Ltd)	ABX
3180	Cefaclor 375mg modified-release tablets	ABX
3209	Erythromid 250mg Tablet (Abbott Laboratories Ltd)	ABX
3408	ERYTHROMYCIN 500 MG CAP	ABX
3523	Distaclor 500mg Modified-release tablet (Dista Products Ltd)	ABX
3528	TETRACYCLINE 500 MG TAB	ABX
3572	Erythroped 250mg Powder (Abbott Laboratories Ltd)	ABX
3609	Ceporex 125mg/5ml Oral solution (Galen Ltd)	ABX
3669	Amoxymed 250mg Capsule (Medipharma Ltd)	ABX
3736	Klaricid 125mg/5ml Oral suspension (Abbott Laboratories Ltd)	ABX
3737	Cefaclor 250mg/5ml oral suspension	ABX
3742	Amoxicillin 125mg sugar free chewable tablets	ABX
3816	Tetrachel 250mg Tablet (Berk Pharmaceuticals Ltd)	ABX
3907	ERYTHROMYCIN SF sach 250 MG	ABX
4010	Amoxil 750mg Sachets (GlaxoSmithKline UK Ltd)	ABX
4091	Ciprofloxacin 250mg/5ml oral suspension	ABX
4153	Erythrolar 250mg/5ml Liquid (Lagap)	ABX
4154	Amoxil fiztab 125mg Tablet (Bencard)	ABX
4372	Erythroped forte 500mg Sachets (Abbott Laboratories Ltd)	ABX
4489	Erycen 250mg Tablet (Berk Pharmaceuticals Ltd)	ABX
4576	Distaclor 250mg Capsule (Dista Products Ltd)	ABX
4582	Amoxicillin 750mg soluble tablets	ABX
4596	Erythroped a 1g Sachets (Abbott Laboratories Ltd)	ABX
4610	Erythroped forte 500mg/5ml Oral suspension (Abbott Laboratories Ltd)	ABX
4672	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free	ABX

4689	Cefaclor 500mg Capsule (Lagap)	ABX
4895	Benzoyl peroxide 5% / Erythromycin 3% gel	ABX
4951	Tetralysal 300 capsules (Galderma (UK) Ltd)	ABX
5238	Levofloxacin 500mg tablets	ABX
5341	Augmentin-Duo 400/57 oral suspension (GlaxoSmithKline UK Ltd)	ABX
5357	Clarithromycin 250mg/5ml oral suspension	ABX
5662	Amoxicillin 500mg / Clarithromycin 500mg / Lansoprazole 30mg triple pack	ABX
5859	Ceporex 500mg/5ml Oral solution (Galen Ltd)	ABX
6121	Klaricid XL 500mg tablets (Mylan)	ABX
6206	Tavanic 500mg tablets (Sanofi)	ABX
6295	Levofloxacin 250mg tablets	ABX
6306	Moxifloxacin 400mg tablets	ABX
6396	Doxycycline 100mg dispersible tablets sugar free	ABX
6497	Clarithromycin 500mg with metronidazole 400mg with lansoprazole 30mg triple pack	ABX
6623	Klaricid 500 tablets (Abbott Laboratories Ltd)	ABX
6651	Cefalexin 125mg/5ml oral suspension sugar free	ABX
6671	Cefalexin 250mg/5ml oral suspension sugar free	ABX
6687	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free	ABX
6803	Clarithromycin 500mg modified-release tablets	ABX
7364	Co-amoxiclav 250mg/62mg/5ml oral suspension	ABX
7430	Keflex 250mg Capsule (Eli Lilly and Company Ltd)	ABX
7439	Ledermycin 150mg Capsule (Wyeth Pharmaceuticals)	ABX
7455	Terramycin 250mg Capsule (Pfizer Ltd)	ABX
7485	Keflex 125mg/5ml Liquid (Eli Lilly and Company Ltd)	ABX
7526	Cefaclor 125mg/5ml oral suspension sugar free	ABX
7560	Ceporex 125mg/5ml Liquid (Galen Ltd)	ABX
7581	AMOXYCILLIN 125MG/62MG CLAVULANIC ACID SYR	ABX
7592	AMOXYCILLIN 125 MG CAP	ABX
7636	Amoxicillin 250mg / Clavulanic acid 62mg/5ml oral suspension	ABX
7737	Amoxil fiztab 500mg Tablet (Bencard)	ABX
7752	Ciproxin 750mg tablets (Bayer Plc)	ABX
7792	ERYTHROMYCIN 12 MG SYR	ABX
7881	Chlortetracycline 250mg capsules	ABX

7889	Distaclor 375mg Modified-release tablet (Dista Products Ltd)	ABX
8008	Ceporex 250mg/5ml Oral solution (Galen Ltd)	ABX
8019	Ceporex 250mg Tablet (Galen Ltd)	ABX
8051	Cefaclor 500mg modified-release tablets	ABX
8085	Ceporex 500mg Tablet (Galen Ltd)	ABX
8219	Tetrachel 250mg Capsule (Berk Pharmaceuticals Ltd)	ABX
8284	Tetracycline 125mg/5ml syrup	ABX
8285	OXYTETRACYCLINE 250 MG SYR	ABX
8393	NOVOBIOCIN/TETRACYCLINE 125 MG CAP	ABX
8625	Ceporex 250mg/5ml Liquid (Galen Ltd)	ABX
8724	Doxycycline (as hyclate) 50mg/5ml oral solution	ABX
8906	Amoxicillin 125mg / Clavulanic acid 31mg/5ml oral suspension	ABX
9014	Tetrabid-organon 250mg Capsule (Organon Laboratories Ltd)	ABX
9034	Oxytetracycline 125mg/5ml syrup	ABX
9148	Erythromid ds 500mg Tablet (Abbott Laboratories Ltd)	ABX
9154	Ciproxin 100mg tablets (Bayer Plc)	ABX
9157	Keflex 250mg Tablet (Eli Lilly and Company Ltd)	ABX
9219	Distaclor 250mg/5ml Liquid (Dista Products Ltd)	ABX
9243	Amoram 250mg capsules (LPC Medical (UK) Ltd)	ABX
9267	Vibramycin Acne Pack 50mg capsules (Pfizer Ltd)	ABX
9293	Cefaclor 250mg/5ml oral suspension sugar free	ABX
9343	Amoxicillin 750mg sugar free powder	ABX
9361	Oxymycin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)	ABX
9434	Erymin 250mg/5ml Oral suspension (Elan Pharma)	ABX
9520	Cefaclor 250mg Capsule (Lagap)	ABX
9583	Klaricid 250mg/5ml Oral suspension (Abbott Laboratories Ltd)	ABX
9603	Keflex 500mg Tablet (Eli Lilly and Company Ltd)	ABX
9656	Erythromycin 2% gel	ABX
9664	Cefalexin 500mg capsules (IVAX Pharmaceuticals UK Ltd)	ABX
9689	Cefalexin 500mg tablets (Teva UK Ltd)	ABX
9690	Cefalexin 250mg capsules (Teva UK Ltd)	ABX
9698	Cefalexin 250mg tablets (Teva UK Ltd)	ABX
9903	Erythromycin estolate 250mg capsules	ABX

9925	Clavulanic acid 125mg with Amoxicillin 250mg tablets	ABX
10190	Erymax 250mg gastro-resistant capsules (Teva UK Ltd)	ABX
10200	Co-amoxiclav 125mg/31mg/5ml oral suspension	ABX
10304	Ciprofloxacin 2mg/ml infusion	ABX
10326	Clarithromycin 125mg granules straws	ABX
10454	Vibramycin 50mg/5ml Oral solution (Pfizer Ltd)	ABX
10455	Keflex 250mg/5ml Liquid (Eli Lilly and Company Ltd)	ABX
10542	OXYTETRACYCLINE HCL/HYDROCORTISONE .5 % EAR	ABX
11433	Clarithromycin 500mg with lansoprazole 30mg and amoxicillin 500mg triple pack	ABX
11611	Rommix 250 EC tablets (Ashbourne Pharmaceuticals Ltd)	ABX
11613	Amix 250 capsules (Ashbourne Pharmaceuticals Ltd)	ABX
11634	Amix 125 oral suspension (Ashbourne Pharmaceuticals Ltd)	ABX
11989	Keflex 250mg capsules (Flynn Pharma Ltd)	ABX
12016	Chymocyclar Capsule (Rorer Pharmaceuticals Ltd)	ABX
12235	Ceporex 1g Tablet (Galen Ltd)	ABX
12248	Cefalexin 125mg/1.25ml paediatric drops	ABX
12276	Keflex 500mg Capsule (Eli Lilly and Company Ltd)	ABX
12330	Erythromycin ethylsuccinate 1g sachets	ABX
12378	Amoram 125mg/5ml oral suspension (LPC Medical (UK) Ltd)	ABX
12504	Clomocycline 170mg capsules	ABX
12541	Imperacin 250mg Tablet (AstraZeneca UK Ltd)	ABX
12987	Doxycycline (as hyclate) 50mg capsules with microgranules	ABX
13120	Erythromycin ethyl succinate 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
13167	Erythromycin ethyl succinate 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
13216	Amoxicillin 500mg / Clavulanic acid 125mg tablets	ABX
13239	Clavulanic acid 125mg with Amoxicillin 500mg tablets	ABX
13262	Amoxicillin 250mg / Clavulanic acid 62mg/5ml oral suspension	ABX
13285	Amoxicillin 125mg / Clavulanic acid 31mg/5ml oral suspension	ABX
13635	Erythromycin ethylsuccinate 250mg sachets	ABX
13848	Amoxicillin 125mg sugar free powder	ABX
13910	Cefaclor 125mg/5ml Liquid (Generics (UK) Ltd)	ABX
14171	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free	ABX
14371	Galenamox 250mg capsules (Galen Ltd)	ABX

14386	Galenamox 125mg/5ml oral suspension (Galen Ltd)	ABX
14396	Galenamox 500mg capsules (Galen Ltd)	ABX
14407	Galenamox 250mg/5ml oral suspension (Galen Ltd)	ABX
14429	Erythromycin 125mg sprinkle capsules	ABX
14511	Erymax sprinkle 125mg Capsule (Elan Pharma)	ABX
14607	Cefaclor 125mg/5ml Liquid (Lagap)	ABX
14816	Klaricid Adult 250mg granules sachets (Mylan)	ABX
14904	Vibramycin-D 100mg dispersible tablets (Pfizer Ltd)	ABX
15071	Nordox 100mg Capsule (Sankyo Pharma UK Ltd)	ABX
15148	Amoxil 500mg Dispersible tablet (SmithKline Beecham Plc)	ABX
15192	Amoxicillin 400mg / Clavulanic acid 57mg/5ml sugar free oral suspension	ABX
15290	Lansoprazole with amoxicillin and clarithromycin 30mg + 500mg + 500mg Triple pack	ABX
15355	Tetracycline with chlortetracycline & demeclocycline tablets	ABX
15713	Erythromycin ethylsuccinate 500mg sachets	ABX
16612	Clavulanic acid 62mg with amoxicillin 250mg/5ml sugar free suspension	ABX
16613	Ledermycin 150mg capsules (Mercury Pharma Group Ltd)	ABX
16747	Erythroped 250mg Sachets (Abbott Laboratories Ltd)	ABX
17093	Bisolvomycin Capsule (Boehringer Ingelheim Ltd)	ABX
17150	Ceporex 125mg/1.25ml Drops (Glaxo Laboratories Ltd)	ABX
17207	Ilosone 250mg Capsule (Dista Products Ltd)	ABX
17222	Mysteclin Oral solution (Bristol-Myers Squibb Pharmaceuticals Ltd)	ABX
17226	Economycin 250mg Capsule (DDSA Pharmaceuticals Ltd)	ABX
17467	Terramycin 250mg tablets (Pfizer Ltd)	ABX
17645	Clarithromycin 250mg granules straws	ABX
17693	Tavanic 250mg tablets (Sanofi)	ABX
17703	Oxytetramix 250 tablets (Ashbourne Pharmaceuticals Ltd)	ABX
17711	Amopen 500mg Capsule (Yorkshire Pharmaceuticals Ltd)	ABX
17746	Amoxicillin 375mg soluble tablets	ABX
18109	Sebomin MR 100mg capsules (Actavis UK Ltd)	ABX
18243	Distaclor 500mg capsules (Flynn Pharma Ltd)	ABX
18451	Cefalexin 1g tablets	ABX
18643	Ilosone 500mg Tablet (Dista Products Ltd)	ABX
18682	Ilosone 125mg/5ml Liquid (Dista Products Ltd)	ABX

18786	Amix 500 capsules (Ashbourne Pharmaceuticals Ltd)	ABX
18930	Flemoxin 375mg Soluble tablet (Paines & Byrne Ltd)	ABX
19001	Megaclor 170mg Capsule (Pharmax Ltd)	ABX
19133	Cefalexin 250mg capsules (IVAX Pharmaceuticals UK Ltd)	ABX
19138	Cefalexin 500mg capsules (Actavis UK Ltd)	ABX
19144	Cefalexin 125mg/5ml oral suspension sugar free (Teva UK Ltd)	ABX
19152	Cefalexin 250mg capsules (Actavis UK Ltd)	ABX
19160	Cefalexin 250mg capsules (Mylan)	ABX
19161	Cefalexin 500mg capsules (Ranbaxy (UK) Ltd)	ABX
19184	Cefalexin 500mg capsules (Mylan)	ABX
19209	Co-amoxiclav 250mg/125mg tablets (Actavis UK Ltd)	ABX
19330	Ilosone 250mg/5ml Liquid (Dista Products Ltd)	ABX
19414	Co-amoxiclav 250mg/125mg tablets (Sandoz Ltd)	ABX
19693	Sustamycin 250mg Capsule (Boehringer Mannheim UK Ltd)	ABX
19795	AMOXYCILLIN 250MG/CLAVULANIC ACID 125MG	ABX
20054	Tetralysal 408mg Capsule (Pharmacia Ltd)	ABX
20409	Cefaclor 250mg/5ml Liquid (Lagap)	ABX
20420	Cefaclor 250mg/5ml Liquid (Generics (UK) Ltd)	ABX
20432	Clavulanic acid 57mg with amoxicillin 400mg/5ml sugar free suspension	ABX
20881	Cefaclor 375mg modified-release tablets (Ranbaxy (UK) Ltd)	ABX
20992	Distaclor MR 375mg tablets (Flynn Pharma Ltd)	ABX
21038	Doxatet 100mg Tablet (Manufacturer unknown)	ABX
21629	TETRACYCLINE EYE	ABX
21654	TETRACYCLINE EAR/EYE	ABX
21775	Clavulanic acid 31mg with amoxicillin 125mg/5ml sugar free oral suspension	ABX
21802	Berkmycen 250mg Tablet (Berk Pharmaceuticals Ltd)	ABX
21804	Tetracycline 125mg/5ml syrup	ABX
21808	Rommix 125mg/5ml Oral suspension sugar free (Ashbourne Pharmaceuticals Ltd)	ABX
21828	Demix 50 capsules (Ashbourne Pharmaceuticals Ltd)	ABX
21829	Zoxycil 250mg Capsule (Trinity Pharmaceuticals Ltd)	ABX
21835	Kiflone 250mg Capsule (Berk Pharmaceuticals Ltd)	ABX
21844	Amix 250 oral suspension (Ashbourne Pharmaceuticals Ltd)	ABX
21860	Cyclodox 100mg Capsule (Berk Pharmaceuticals Ltd)	ABX

21878	Demix 100 capsules (Ashbourne Pharmaceuticals Ltd)	ABX
21979	Kiflone 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	ABX
21982	AMOXYCILLIN TRIHYDRATE SACHET	ABX
22015	Respillin 125mg/5ml Oral solution (OPD Pharm)	ABX
22017	Respillin 125mg/5ml Oral solution (OPD Pharm)	ABX
22029	Amiclav 250mg/125mg tablets (Ashbourne Pharmaceuticals Ltd)	ABX
22042	Distaclor 250mg/5ml oral suspension (Flynn Pharma Ltd)	ABX
22076	Ledermycin 300mg Tablet (Wyeth Pharmaceuticals)	ABX
22293	AMOXYCILLIN TRIHYDRATE SACHET	ABX
22321	Cefalexin 500mg tablets (Mylan)	ABX
22415	Amoram 500mg capsules (LPC Medical (UK) Ltd)	ABX
22438	Amoram 250mg/5ml oral suspension (LPC Medical (UK) Ltd)	ABX
22469	AMOXYCILLIN 125mg/31mg CLAVULANIC ACID	ABX
23017	Erycen 500mg Tablet (Berk Pharmaceuticals Ltd)	ABX
23238	Amoxicillin 125mg/5ml oral suspension (IVAX Pharmaceuticals UK Ltd)	ABX
23244	Ilotycin 250mg Tablet (Eli Lilly and Company Ltd)	ABX
23405	Doxylar 100mg capsules (Sandoz Ltd)	ABX
23432	Doxylar 50mg capsules (Sandoz Ltd)	ABX
23740	Amoxicillin 500mg capsules (Mylan)	ABX
23819	Doxycycline (as hyclate) 50mg capsules with microgranules	ABX
23954	Erythrolar 500mg Tablet (Lagap)	ABX
23967	Amoxicillin 250mg capsules (Teva UK Ltd)	ABX
24006	Clavulanic acid 31mg with amoxcillin 125mg/5ml oral suspension	ABX
24090	Cefalexin 250mg capsules (PLIVA Pharma Ltd)	ABX
24093	Clavulanic acid with amoxicillin dispersible tablets	ABX
24097	Rondomycin 150mg Capsule (Pfizer Ltd)	ABX
24126	Doxycycline 100mg capsules (IVAX Pharmaceuticals UK Ltd)	ABX
24127	Erythromycin 250mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	ABX
24129	Erythromycin 250mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)	ABX
24149	Doxycycline 100mg capsules (A A H Pharmaceuticals Ltd)	ABX
24150	Amoxicillin 125mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	ABX
24200	Respillin 500mg Capsule (OPD Pharm)	ABX
24203	Respillin 250mg Capsule (OPD Pharm)	ABX

24220	Arpimycin 250mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)	ABX
24396	Flemoxin 750mg Soluble tablet (Paines & Byrne Ltd)	ABX
24618	Keflex 500mg capsules (Flynn Pharma Ltd)	ABX
25017	TETRACYCLINE	ABX
25034	AMOXYCILLIN 125mg/62mg CLAVULANIC ACID	ABX
25071	Tetracycline with nystatin capsules	ABX
25127	Avelox 400mg tablets (Bayer Plc)	ABX
25278	Rommix 500mg Tablet (Ashbourne Pharmaceuticals Ltd)	ABX
25280	Tiloryth 250mg gastro-resistant capsules (Tillomed Laboratories Ltd)	ABX
25370	Ranclav 375mg tablets (Ranbaxy (UK) Ltd)	ABX
25384	Distaclor 125mg/5ml oral suspension (Flynn Pharma Ltd)	ABX
25484	Amoxicillin 250mg capsules (A A H Pharmaceuticals Ltd)	ABX
25595	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	ABX
25751	Erythromycin ethylsuccinate (coated) 250mg/5ml oral suspension sugar free	ABX
25752	Nystatin with tetracycline hc Capsule	ABX
26059	Clarithromycin 187.5mg granules straws	ABX
26111	Economycin 250mg Tablet (DDSA Pharmaceuticals Ltd)	ABX
26157	Amoxicillin 500mg capsules (Actavis UK Ltd)	ABX
26207	Keftid 250mg capsules (Strides Pharma UK Ltd)	ABX
26233	Keftid 125mg/5ml oral suspension (Strides Pharma UK Ltd)	ABX
26236	Keftid 500mg capsules (Strides Pharma UK Ltd)	ABX
26262	Zoxycil 500mg Capsule (Trinity Pharmaceuticals Ltd)	ABX
26289	Bacticlor MR 375mg tablets (Ranbaxy (UK) Ltd)	ABX
26365	Erythromycin 500mg Tablet (IVAX Pharmaceuticals UK Ltd)	ABX
26392	Vibrox 100mg capsules (Kent Pharmaceuticals Ltd)	ABX
26747	Doxycycline 100mg Tablet (Neo Laboratories Ltd)	ABX
26989	Kiflone 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	ABX
26992	Kiflone 500mg Tablet (Berk Pharmaceuticals Ltd)	ABX
27016	CIPROFLOXACIN	ABX
27017	Kiflone 500mg Capsule (Berk Pharmaceuticals Ltd)	ABX
27072	Keflex 125mg/5ml oral suspension (Flynn Pharma Ltd)	ABX
27203	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Teva UK Ltd)	ABX
27254	Tenkorex 500mg Capsule (OPD Pharm)	ABX

27495	Arpimycin 125mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)	ABX
27504	Primacine 500mg/5ml Liquid (Pinewood Healthcare)	ABX
27681	Ranclav 125mg/31mg/5ml SF oral suspension (Ranbaxy (UK) Ltd)	ABX
27714	Amrit 250mg Capsule (BHR Pharmaceuticals Ltd)	ABX
27725	Amoxicillin 250mg/5ml oral suspension (Teva UK Ltd)	ABX
27768	Erythrolar 250mg Tablet (Lagap)	ABX
27886	AMOXYCILLIN 250/CLAVULANIC ACID 125 DISP	ABX
27897	AMOXYCILLIN	ABX
28130	Amoxicillin 3g oral powder sachets sugar free (Teva UK Ltd)	ABX
28291	OXYTETRACYCLINE 3%/HYDROCORTISONE 1%	ABX
28349	Clarosip 125mg granules for oral suspension straws (Grunenthal Ltd)	ABX
28544	Ciprofloxaxin 400mg/200ml in glucose 5% infusion	ABX
28722	Keflex 250mg/5ml oral suspension (Flynn Pharma Ltd)	ABX
28736	TETRACYCLINE HYDROCHLORIDE/AMPHOTERICIN SYR	ABX
28870	Amoxicillin 125mg/5ml oral suspension (Teva UK Ltd)	ABX
28871	Co-amoxiclav 250mg/125mg tablets (IVAX Pharmaceuticals UK Ltd)	ABX
28872	Amoxicillin 125mg/5ml Mixture (Crosspharma Ltd)	ABX
28874	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	ABX
28875	Amoxicillin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)	ABX
28882	Amoxicillin 250mg Capsule (Crosspharma Ltd)	ABX
29154	Erythromycin 250mg Capsule (Actavis UK Ltd)	ABX
29202	Cefalexin 500mg tablets (A A H Pharmaceuticals Ltd)	ABX
29281	Cefalexin 500mg capsules (Teva UK Ltd)	ABX
29337	Amoxicillin 125mg/5ml Oral solution (Neo Laboratories Ltd)	ABX
29343	Ciprofloxacin 250mg tablets (A A H Pharmaceuticals Ltd)	ABX
29344	Erythromycin 250mg gastro-resistant tablets (Actavis UK Ltd)	ABX
29353	Co-amoxiclav 500mg/125mg tablets (Teva UK Ltd)	ABX
29356	Co-amoxiclav 500mg/125mg tablets (IVAX Pharmaceuticals UK Ltd)	ABX
29458	Ciprofloxacin 500mg tablets (A A H Pharmaceuticals Ltd)	ABX
29463	Amoxicillin 500mg capsules (IVAX Pharmaceuticals UK Ltd)	ABX
29464	Cefalexin 250mg/5ml oral suspension (Mylan)	ABX
29472	Ciprofloxacin 750mg tablets (A A H Pharmaceuticals Ltd)	ABX
29697	Amopen 125mg/5ml Liquid (Yorkshire Pharmaceuticals Ltd)	ABX

29748	Cefalexin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
29858	Amoxicillin 125mg/5ml oral suspension sugar free (Sandoz Ltd)	ABX
30177	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	ABX
30234	Erythromycin ethylsuccinate 125mg sachets	ABX
30498	Amopen 250mg Capsule (Yorkshire Pharmaceuticals Ltd)	ABX
30520	Primacine 125mg/5ml Liquid (Pinewood Healthcare)	ABX
30528	Amoxicillin 250mg capsules (Kent Pharmaceuticals Ltd)	ABX
30705	Co-amoxiclav 500mg/125mg tablets (Mylan)	ABX
30707	Ciprofloxacin 500mg tablets (Mylan)	ABX
30739	Doxycycline 100mg capsules (Teva UK Ltd)	ABX
30743	Amoxicillin 250mg capsules (Ranbaxy (UK) Ltd)	ABX
30745	Amoxicillin 250mg capsules (Mylan)	ABX
30771	Cefaclor 500mg capsules (Ranbaxy (UK) Ltd)	ABX
30772	Cefaclor 250mg capsules (Ranbaxy (UK) Ltd)	ABX
30783	Co-amoxiclav 250mg/125mg tablets (Ranbaxy (UK) Ltd)	ABX
30786	Co-amoxiclav 250mg/125mg tablets (A A H Pharmaceuticals Ltd)	ABX
30980	Erythromycin ethyl succinate 500mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	ABX
31007	Aureomycin Powder (Wyeth Pharmaceuticals)	ABX
31014	Amoxicillin 125mg/5ml oral suspension sugar free (Mylan)	ABX
31110	Keflex 500mg tablets (Flynn Pharma Ltd)	ABX
31286	Amoxymed 125mg/5ml Oral solution (Medipharma Ltd)	ABX
31423	Amopen 250mg/5ml Liquid (Yorkshire Pharmaceuticals Ltd)	ABX
31425	TETRACYCLINE HCL/PANCREATIC CONCENTRATE CAP	ABX
31428	Retcin 250mg Tablet (DDSA Pharmaceuticals Ltd)	ABX
31514	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)	ABX
31530	Erythromycin 250mg gastro-resistant tablets (Ranbaxy (UK) Ltd)	ABX
31535	Amoxicillin 250mg/5ml oral suspension sugar free (Mylan)	ABX
31571	AMOXYCILLIN	ABX
31661	Amoxicillin 250mg Capsule (Co-Pharma Ltd)	ABX
31689	Clarosip 187.5mg granules for oral suspension straws (Grunenthal Ltd)	ABX
31690	Clarosip 250mg granules for oral suspension straws (Grunenthal Ltd)	ABX
31801	Amoxicillin 500mg capsules (Sandoz Ltd)	ABX
31825	Cefalexin 250mg tablets (IVAX Pharmaceuticals UK Ltd)	ABX

31827	Cefalexin 500mg tablets (IVAX Pharmaceuticals UK Ltd)	ABX
32066	Doxycycline 100mg capsules (Mylan)	ABX
32181	Cefalexin 125mg/5ml oral suspension (Actavis UK Ltd)	ABX
32235	Cefaclor 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)	ABX
32419	Doxycycline 50mg capsules (Teva UK Ltd)	ABX
32505	AMOXYCILLIN	ABX
32622	Amoxicillin 125mg/5ml oral suspension (Mylan)	ABX
32640	Amoxicillin 250mg/5ml oral suspension (IVAX Pharmaceuticals UK Ltd)	ABX
32642	Cefalexin 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	ABX
32643	Cefalexin 500mg capsules (A A H Pharmaceuticals Ltd)	ABX
32872	Amoxicillin 250mg Capsule (Mepra-Pharm)	ABX
32898	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	ABX
32902	Erythromycin ethyl succinate 250mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	ABX
32910	Co-amoxiclav 500mg/125mg tablets (Sandoz Ltd)	ABX
33109	Amrit 125mg/5ml Liquid (BHR Pharmaceuticals Ltd)	ABX
33110	Amrit 250mg/5ml Liquid (BHR Pharmaceuticals Ltd)	ABX
33112	Amrit 500mg Capsule (BHR Pharmaceuticals Ltd)	ABX
33165	Amoxicillin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
33222	Amoxicillin 250mg Capsule (Lagap)	ABX
33248	Erythromycin 125mg/5ml Liquid (IVAX Pharmaceuticals UK Ltd)	ABX
33304	Kerymax 250mg gastro-resistant capsules (Kent Pharmaceuticals Ltd)	ABX
33329	Cefalexin 125mg/5ml oral suspension (Teva UK Ltd)	ABX
33334	Cefalexin 250mg tablets (A A H Pharmaceuticals Ltd)	ABX
33343	Amoxicillin 250mg capsules (Actavis UK Ltd)	ABX
33383	Amoxicillin 3g oral powder sachets sugar free (A A H Pharmaceuticals Ltd)	ABX
33570	Amoxicillin 250mg/5ml Mixture (Crosspharma Ltd)	ABX
33671	Doxycycline 100mg capsules (Kent Pharmaceuticals Ltd)	ABX
33685	Erythromycin 250mg gastro-resistant tablets (Teva UK Ltd)	ABX
33686	Erythromycin 250mg gastro-resistant capsules (A A H Pharmaceuticals Ltd)	ABX
33689	Amoxicillin 250mg/5ml oral suspension (Mylan)	ABX
33690	Amoxicillin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
33692	Amoxicillin 500mg capsules (A A H Pharmaceuticals Ltd)	ABX
33693	Co-amoxiclav 250mg/125mg tablets (Kent Pharmaceuticals Ltd)	ABX

33694	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Mylan)	ABX
33695	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Mylan)	ABX
33696	Amoxicillin 125mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	ABX
33697	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	ABX
33699	Amoxicillin 250mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	ABX
33701	Co-amoxiclav 500mg/125mg tablets (A A H Pharmaceuticals Ltd)	ABX
33703	Erythromycin 250mg gastro-resistant tablets (Abbott Laboratories Ltd)	ABX
33705	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Teva UK Ltd)	ABX
33706	Amoxicillin 500mg capsules (Kent Pharmaceuticals Ltd)	ABX
33802	Cefalexin 250mg Capsule (Berk Pharmaceuticals Ltd)	ABX
33989	Ciprofloxacin 250mg tablets (Mylan)	ABX
34001	Amoxicillin 500mg capsules (Teva UK Ltd)	ABX
34011	Tetracycline 250mg capsules	ABX
34040	Oxytetracycline 250mg tablets (Actavis UK Ltd)	ABX
34042	Amoxicillin 250mg capsules (IVAX Pharmaceuticals UK Ltd)	ABX
34044	Oxytetracycline 250mg tablets (A A H Pharmaceuticals Ltd)	ABX
34133	Cefalexin 250mg/5ml oral suspension sugar free (Teva UK Ltd)	ABX
34141	Oxytetracycline 250mg tablets (Teva UK Ltd)	ABX
34175	Doxycycline 50mg capsules (A A H Pharmaceuticals Ltd)	ABX
34189	Erythromycin 250mg Tablet (C P Pharmaceuticals Ltd)	ABX
34231	Erythromycin 125mg/5ml Liquid (Berk Pharmaceuticals Ltd)	ABX
34232	Amoxicillin 250mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	ABX
34234	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Teva UK Ltd)	ABX
34253	Cefalexin 250mg capsules (A A H Pharmaceuticals Ltd)	ABX
34297	Co-amoxiclav 250mg/125mg tablets (Mylan)	ABX
34300	Doxycycline 100mg capsules (Actavis UK Ltd)	ABX
34308	Ciprofloxacin 250mg tablets (Actavis UK Ltd)	ABX
34322	Ciprofloxacin 500mg Tablet (Niche Generics Ltd)	ABX
34334	Erythromycin 250mg gastro-resistant tablets (Mylan)	ABX
34336	Oxytetracycline 250mg tablets (IVAX Pharmaceuticals UK Ltd)	ABX
34384	Amoxicillin 125mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	ABX
34394	Clarithromycin 250mg tablets (Mylan)	ABX
34423	Doxycycline 100mg Capsule (PLIVA Pharma Ltd)	ABX

34435	Amoxicillin 250mg Capsule (DDSA Pharmaceuticals Ltd)	ABX
34448	Ciprofloxacin 250mg tablets (Niche Generics Ltd)	ABX
34478	Ciprofloxacin 250mg tablets (Teva UK Ltd)	ABX
34479	Erythromycin 250mg gastro-resistant tablets (Sovereign Medical Ltd)	ABX
34493	Co-amoxiclav 500mg/125mg tablets (Ranbaxy (UK) Ltd)	ABX
34494	Ciprofloxacin 500mg tablets (Wockhardt UK Ltd)	ABX
34512	Erythromycin 250mg gastro-resistant capsules (Teva UK Ltd)	ABX
34533	Clarithromycin 250mg tablets (Teva UK Ltd)	ABX
34559	Ciprofloxacin 250mg tablets (Sandoz Ltd)	ABX
34594	Doxycycline 100mg Capsule (Neo Laboratories Ltd)	ABX
34605	Ciprofloxacin 500mg tablets (Actavis UK Ltd)	ABX
34608	Clarithromycin 500mg tablets (Mylan)	ABX
34638	Amoxicillin 125mg/5ml oral suspension sugar free (Teva UK Ltd)	ABX
34647	Ciprofloxacin 250mg Tablet (Neo Laboratories Ltd)	ABX
34650	Clarithromycin 250mg tablets (A A H Pharmaceuticals Ltd)	ABX
34655	Ciprofloxacin 250mg tablets (Wockhardt UK Ltd)	ABX
34679	Amoxicillin 125mg/5ml oral suspension sugar free (Actavis UK Ltd)	ABX
34680	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Ranbaxy (UK) Ltd)	ABX
34694	Ciprofloxacin 250mg tablets (PLIVA Pharma Ltd)	ABX
34714	Amoxicillin 250mg Capsule (Neo Laboratories Ltd)	ABX
34734	Co-amoxiclav 250mg/125mg tablets (Teva UK Ltd)	ABX
34760	Amoxicillin 250mg/5ml oral suspension (Actavis UK Ltd)	ABX
34765	Doxycycline 50mg capsules (Mylan)	ABX
34775	Amoxicillin 250mg/5ml oral suspension sugar free (Teva UK Ltd)	ABX
34779	Erythromycin ethyl succinate 125mg/5ml oral suspension (Sandoz Ltd)	ABX
34795	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	ABX
34811	Clarithromycin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)	ABX
34837	Erythromycin 250mg Gastro-resistant tablet (Co-Pharma Ltd)	ABX
34838	Cefaclor 375mg modified-release tablets (A A H Pharmaceuticals Ltd)	ABX
34852	Amoxicillin 500mg capsules (Ranbaxy (UK) Ltd)	ABX
34853	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Teva UK Ltd)	ABX
34855	Amoxicillin 250mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	ABX
34857	Amoxicillin 125mg/5ml oral suspension (Actavis UK Ltd)	ABX

34869	Erythromycin 500mg Tablet (C P Pharmaceuticals Ltd)	ABX
34873	Erythromycin 250mg Tablet (Berk Pharmaceuticals Ltd)	ABX
34885	Amoxicillin 500mg Capsule (DDSA Pharmaceuticals Ltd)	ABX
34888	Oxytetracycline 250mg Tablet (C P Pharmaceuticals Ltd)	ABX
34912	Amoxicillin 500mg Capsule (Neo Laboratories Ltd)	ABX
34913	Cefaclor 125mg/5ml Oral suspension (Genus Pharmaceuticals Ltd)	ABX
34972	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Sandoz Ltd)	ABX
34973	Ciprofloxacin 750mg Tablet (Niche Generics Ltd)	ABX
34974	Clarithromycin 500mg tablets (Teva UK Ltd)	ABX
35570	Amoxicillin 500mg Capsule (Crosspharma Ltd)	ABX
36054	Amoxicillin 125mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	ABX
36330	Cefalexin 250mg tablets (Actavis UK Ltd)	ABX
36514	Arpimycin 250mg/5ml Oral suspension (Rosemont Pharmaceuticals Ltd)	ABX
36544	Arpimycin 125mg/5ml Oral suspension (Rosemont Pharmaceuticals Ltd)	ABX
36569	Cefalexin 500mg capsules (Kent Pharmaceuticals Ltd)	ABX
36578	Cefalexin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)	ABX
36599	Cefalexin 250mg capsules (Ranbaxy (UK) Ltd)	ABX
36689	CHLORTETRACYCLINE HCl SYR	ABX
36701	Cefalexin 250mg tablets (Mylan)	ABX
37022	Arpimycin 500mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)	ABX
37304	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	ABX
37440	Sebren MR 100mg capsules (Teva UK Ltd)	ABX
37694	Erythromycin estolate 500mg tablets	ABX
37755	Amoxicillin 250mg/5ml Oral suspension (Sandoz Ltd)	ABX
37796	Erythromycin estolate 125mg/5ml suspension	ABX
38163	Clarithromycin 500mg tablets (A A H Pharmaceuticals Ltd)	ABX
38684	Amoxicillin 500mg Capsule (C P Pharmaceuticals Ltd)	ABX
38997	Klaricid Paediatric 125mg/5ml oral suspension (Mylan)	ABX
39010	Klaricid Paediatric 250mg/5ml oral suspension (Mylan)	ABX
39118	Primacine 250mg/5ml Liquid (Pinewood Healthcare)	ABX
39417	Cefalexin 125mg/5ml oral suspension (Mylan)	ABX
39613	Erythrocin 500 tablets (Advanz Pharma)	ABX
39616	Erythrocin 250 tablets (Advanz Pharma)	ABX

39623	Erythroped PI SF 125mg/5ml oral suspension (Advanz Pharma)	ABX
39632	Erythroped A 500mg tablets (Advanz Pharma)	ABX
39642	Erythroped Forte SF 500mg/5ml oral suspension (Advanz Pharma)	ABX
39669	Erythroped SF 250mg/5ml oral suspension (Advanz Pharma)	ABX
39703	Cefaclor 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
39913	Ciprofloxacin 100mg tablets (Sandoz Ltd)	ABX
40073	Erythromycin estolate 250mg/5ml suspension	ABX
40148	Co-amoxiclav 500mg/125mg tablets (Kent Pharmaceuticals Ltd)	ABX
40168	Amoxicillin 3g oral powder sachets sugar free (Kent Pharmaceuticals Ltd)	ABX
40238	Amoxicillin 250mg/5ml Mixture (Mepra-Pharm)	ABX
40243	Amoxicillin 250mg/5ml oral suspension sugar free (Actavis UK Ltd)	ABX
40320	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Ranbaxy (UK) Ltd)	ABX
40391	Doxycycline 50mg capsules (IVAX Pharmaceuticals UK Ltd)	ABX
40483	Oxytetracycline 250mg tablets (Sandoz Ltd)	ABX
40747	Cefalexin 250mg chewable tablets	ABX
40784	Clarithromycin 500mg tablets (Sandoz Ltd)	ABX
40796	Doxycycline 40mg modified-release capsules	ABX
40884	Ceporex 250mg capsules (Strides Pharma UK Ltd)	ABX
40914	Ceporex 500mg tablets (Strides Pharma UK Ltd)	ABX
40915	Ceporex 500mg capsules (Strides Pharma UK Ltd)	ABX
40945	Ceporex 250mg/5ml syrup (Strides Pharma UK Ltd)	ABX
40980	Efracea 40mg modified-release capsules (Galderma (UK) Ltd)	ABX
41049	Ceporex 250mg tablets (Strides Pharma UK Ltd)	ABX
41090	Amoxicillin 250mg/5ml oral suspension (Almus Pharmaceuticals Ltd)	ABX
41106	Ceporex 125mg/5ml syrup (Strides Pharma UK Ltd)	ABX
41192	Cefalexin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)	ABX
41230	Ceporex 500mg/5ml syrup (Strides Pharma UK Ltd)	ABX
41389	Erythoden 250mg/5ml Liquid (Stevenden Healthcare)	ABX
41453	Clarithromycin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)	ABX
41547	Tetracycline 250mg Capsule (Berk Pharmaceuticals Ltd)	ABX
41560	Doxycycline 100mg Capsule (IVAX Pharmaceuticals UK Ltd)	ABX
41561	Ciprofloxacin 250mg tablets (IVAX Pharmaceuticals UK Ltd)	ABX
41584	Erythromycin 250mg/5ml Liquid (IVAX Pharmaceuticals UK Ltd)	ABX

41604	Erythromycin 500mg Tablet (Hillcross Pharmaceuticals Ltd)	ABX
41605	Doxycycline 100mg Capsule (Sandoz Ltd)	ABX
41636	Tetracycline 250mg tablets (Actavis UK Ltd)	ABX
41734	Amoxicillin 3g Powder (Actavis UK Ltd)	ABX
41736	Cefalexin 250mg capsules (Kent Pharmaceuticals Ltd)	ABX
41818	Amoxicillin 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	ABX
41825	Cefalexin 250mg/5ml Oral solution (C P Pharmaceuticals Ltd)	ABX
41835	Amoxicillin 125mg Powder (IVAX Pharmaceuticals UK Ltd)	ABX
41853	Keftid 250mg/5ml oral suspension (Strides Pharma UK Ltd)	ABX
41968	Cefalexin 250mg/5ml oral suspension (Teva UK Ltd)	ABX
42008	Cefalexin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
42174	Ciprofloxacin 500mg tablets (IVAX Pharmaceuticals UK Ltd)	ABX
42227	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	ABX
42240	Amoxicillin 125mg/5ml Oral solution (Co-Pharma Ltd)	ABX
42296	Erythromycin 250mg gastro-resistant tablets (Dr Reddy's Laboratories (UK) Ltd)	ABX
42485	Clavulanic acid 62mg with amoxicillin 250mg/5ml oral suspension	ABX
42507	Ciprofloxacin 100mg tablets (A A H Pharmaceuticals Ltd)	ABX
42545	Amoxicillin 125mg/5ml oral suspension (Almus Pharmaceuticals Ltd)	ABX
42659	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)	ABX
42661	Erythromycin 250mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)	ABX
42732	Amoxicillin 250mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	ABX
42809	Amoxicillin 250mg Capsule (C P Pharmaceuticals Ltd)	ABX
42815	Amoxicillin 250mg/5ml Mixture (Celltech Pharma Europe Ltd)	ABX
42822	Amoxicillin 125mg/5ml Mixture (Celltech Pharma Europe Ltd)	ABX
43229	Amoxicillin 125mg/5ml Oral suspension (Sandoz Ltd)	ABX
43425	Cefaclor 500mg capsules (A A H Pharmaceuticals Ltd)	ABX
43517	Ciprofloxacin 750mg tablets (Actavis UK Ltd)	ABX
43538	Tetracycline 250mg tablets (A A H Pharmaceuticals Ltd)	ABX
43548	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	ABX
43557	Ciprofloxacin 500mg tablets (PLIVA Pharma Ltd)	ABX
43797	Ciprofloxacin 500mg tablets (Sandoz Ltd)	ABX
43814	Ciprofloxacin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)	ABX
44154	Co-amoxiclav 500mg/125mg tablets (Zentiva)	ABX

44755	Cefalexin 500mg Capsule (Berk Pharmaceuticals Ltd)	ABX
44854	Amoxicillin 500mg Capsule (Lagap)	ABX
45221	Cefalexin 250mg/5ml oral suspension (Actavis UK Ltd)	ABX
45267	Amoxicillin 250mg Capsule (Regent Laboratories Ltd)	ABX
45271	Tetracycline 250mg Tablet (Numark Management Ltd)	ABX
45285	Ciprofloxacin 500mg tablets (Teva UK Ltd)	ABX
45317	Amoxicillin 250mg/5ml Oral solution (Neo Laboratories Ltd)	ABX
45341	Ciprofloxacin 500mg Tablet (Neo Laboratories Ltd)	ABX
45591	Clarie XL 500mg tablets (Teva UK Ltd)	ABX
45795	Clarithromycin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
45870	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Pinewood Healthcare)	ABX
46154	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)	ABX
46488	Clarithromycin 500mg tablets (Ranbaxy (UK) Ltd)	ABX
46696	Erythromycin ethyl succinate 250mg/5ml oral suspension (Sandoz Ltd)	ABX
46807	Doxycycline 100mg capsules (Almus Pharmaceuticals Ltd)	ABX
46915	Co-amoxiclav 250mg/125mg tablets (Zentiva)	ABX
46918	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Sandoz Ltd)	ABX
46973	Cefaclor 250mg/5ml Oral suspension (Genus Pharmaceuticals Ltd)	ABX
47126	Erythromycin ethyl succinate 125mg/5ml oral suspension (Pinewood Healthcare)	ABX
47163	Cefalexin 250mg tablets (Arrow Generics Ltd)	ABX
47242	Erythromycin 250mg/5ml Liquid (C P Pharmaceuticals Ltd)	ABX
47582	Clarithromycin 250mg tablets (Sandoz Ltd)	ABX
47640	Amoxicillin 500mg capsules (Almus Pharmaceuticals Ltd)	ABX
47676	Erythromycin 500mg/5ml Liquid (C P Pharmaceuticals Ltd)	ABX
48006	Amoxicillin 250mg capsules (Sandoz Ltd)	ABX
48017	Erythoden 125mg/5ml Liquid (Stevenden Healthcare)	ABX
48023	Clarithromycin 500mg tablets (Actavis UK Ltd)	ABX
48025	Cefaclor 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)	ABX
48031	Ciprofloxacin 100mg tablets (Almus Pharmaceuticals Ltd)	ABX
48038	Amoxicillin 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	ABX
48095	Doxycycline 50mg capsules (Actavis UK Ltd)	ABX
48100	Tetracycline 250mg tablets (Teva UK Ltd)	ABX
48101	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Focus Pharmaceuticals Ltd)	ABX

48147	Co-amoxiclav 250mg/125mg tablets (Almus Pharmaceuticals Ltd)	ABX
48163	Clarithromycin 250mg tablets (Actavis UK Ltd)	ABX
48683	Augmentin 375mg tablets (Lexon (UK) Ltd)	ABX
49048	Augmentin 375mg tablets (Waymade Healthcare Plc)	ABX
49063	Augmentin 375mg tablets (DE Pharmaceuticals)	ABX
49065	Amoxicillin 250mg/5ml oral suspension sugar free (Bristol Laboratories Ltd)	ABX
49301	Erythrolar 500mg tablets (Ennogen Pharma Ltd)	ABX
49321	Augmentin 625mg tablets (Sigma Pharmaceuticals Plc)	ABX
49374	Augmentin 375mg tablets (Mawdsley-Brooks & Company Ltd)	ABX
49445	Ciprofloxacin 500mg tablets (Almus Pharmaceuticals Ltd)	ABX
49590	Amoxil 500mg capsules (Lexon (UK) Ltd)	ABX
49610	Co-amoxiclav 500mg/125mg tablets (Medreich Plc)	ABX
49656	Augmentin 625mg tablets (Lexon (UK) Ltd)	ABX
49683	Augmentin 625mg tablets (Waymade Healthcare Plc)	ABX
49737	Doxycycline 100mg capsules (Alliance Healthcare (Distribution) Ltd)	ABX
49839	Ciproxin 500mg tablets (Waymade Healthcare Plc)	ABX
49939	Clarithromycin 500mg tablets (Alliance Healthcare (Distribution) Ltd)	ABX
49952	Erythromycin 250mg gastro-resistant capsules (Phoenix Healthcare Distribution Ltd)	ABX
49978	Erythromycin ethyl succinate 125mg/5ml oral suspension (Focus Pharmaceuticals Ltd)	ABX
50002	Amoxicillin 125mg/5ml oral suspension (Bristol Laboratories Ltd)	ABX
50055	Ciprofloxacin 500mg tablets (DE Pharmaceuticals)	ABX
50205	Erythrolar 250mg tablets (Ennogen Pharma Ltd)	ABX
50223	Erythrocin 500 tablets (Stephar (U.K.) Ltd)	ABX
50279	Augmentin 625mg tablets (DE Pharmaceuticals)	ABX
50341	Co-amoxiclav 500mg/125mg tablets (Alliance Healthcare (Distribution) Ltd)	ABX
50446	Co-amoxiclav 250mg/125mg tablets (Phoenix Healthcare Distribution Ltd)	ABX
50580	Erythromycin 250mg gastro-resistant capsules (Actavis UK Ltd)	ABX
50595	Augmentin 125/31 SF oral suspension (Mawdsley-Brooks & Company Ltd)	ABX
50601	Ciprofloxacin 250mg tablets (Accord Healthcare Ltd)	ABX
50693	Erythrocin 500 tablets (Sigma Pharmaceuticals Plc)	ABX
50694	Erythromycin 250mg gastro-resistant capsules (Alliance Healthcare (Distribution) Ltd)	ABX
50742	Co-amoxiclav 500mg/125mg tablets (Actavis UK Ltd)	ABX
50946	Clarithromycin 250mg tablets (Sigma Pharmaceuticals Plc)	ABX

50948	Erythromycin ethyl succinate 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)	ABX
51154	Clarithromycin 250mg tablets (Kent Pharmaceuticals Ltd)	ABX
51164	Augmentin 125/31 SF oral suspension (Waymade Healthcare Plc)	ABX
51194	Augmentin-Duo 400/57 oral suspension (Sigma Pharmaceuticals Plc)	ABX
51382	Amoxicillin 250mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)	ABX
51426	Clarithromycin 500mg tablets (Accord Healthcare Ltd)	ABX
51436	Amoxil 500mg capsules (Mawdsley-Brooks & Company Ltd)	ABX
51536	Amoxicillin 250mg capsules (Milpharm Ltd)	ABX
51537	Ciprofloxacin 250mg tablets (Alliance Healthcare (Distribution) Ltd)	ABX
51623	Co-amoxiclav 250mg/125mg tablets (Alliance Healthcare (Distribution) Ltd)	ABX
51637	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	ABX
51678	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	ABX
51831	Clarithromycin 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)	ABX
51984	Erythrocin 500 tablets (Mawdsley-Brooks & Company Ltd)	ABX
52058	Amoxicillin 500mg capsules (Medreich Plc)	ABX
52099	Ciprofloxacin 750mg tablets (Bristol Laboratories Ltd)	ABX
52122	Amoxicillin 125mg/5ml oral suspension sugar free (Bristol Laboratories Ltd)	ABX
52158	Clarithromycin 250mg tablets (Alliance Healthcare (Distribution) Ltd)	ABX
52177	Ciproxin 500mg tablets (Sigma Pharmaceuticals Plc)	ABX
52207	Augmentin 625mg tablets (Mawdsley-Brooks & Company Ltd)	ABX
52282	Cefalexin 250mg capsules (Milpharm Ltd)	ABX
52283	Cefalexin 250mg capsules (Arrow Generics Ltd)	ABX
52309	Ciprofloxacin 100mg tablets (Sigma Pharmaceuticals Plc)	ABX
52353	Ciproxin 250mg tablets (DE Pharmaceuticals)	ABX
52411	Klaricid 250mg tablets (Necessity Supplies Ltd)	ABX
52428	Erythromycin 250mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)	ABX
52501	Ciprofloxacin 500mg tablets (Accord Healthcare Ltd)	ABX
52616	Ciprofloxacin 500mg tablets (Arrow Generics Ltd)	ABX
52666	Augmentin 250/62 SF oral suspension (Sigma Pharmaceuticals Plc)	ABX
52685	Amoxicillin 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)	ABX
52719	Clarithromycin 250mg tablets (Apotex UK Ltd)	ABX
52771	Amoxicillin 500mg capsules (Bristol Laboratories Ltd)	ABX
52807	Ciproxin 500mg tablets (Mawdsley-Brooks & Company Ltd)	ABX

52820	Amoxicillin 500mg capsules (Alliance Healthcare (Distribution) Ltd)	ABX
52851	Cefalexin 500mg capsules (Alliance Healthcare (Distribution) Ltd)	ABX
52857	Amoxicillin 125mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	ABX
52860	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	ABX
52906	Erythromycin 250mg gastro-resistant tablets (Alliance Healthcare (Distribution) Ltd)	ABX
52945	Ciprofloxacin 200mg/100ml solution for infusion vials	ABX
52952	Erythromycin 250mg gastro-resistant tablets (Strides Pharma UK Ltd)	ABX
52967	Vibramycin-D 100mg dispersible tablets (Stephar (U.K.) Ltd)	ABX
53004	Erythrocin 500 tablets (Necessity Supplies Ltd)	ABX
53078	Amoxicillin 125mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	ABX
53086	Clarithromycin 250mg tablets (DE Pharmaceuticals)	ABX
53088	Ciprofloxacin 500mg tablets (Dr Reddy's Laboratories (UK) Ltd)	ABX
53109	Clarithromycin 500mg tablets (Somex Pharma)	ABX
53117	Tetracycline 250mg tablets (Almus Pharmaceuticals Ltd)	ABX
53135	Vibramycin-D 100mg dispersible tablets (Waymade Healthcare Plc)	ABX
53144	Clarithromycin 250mg tablets (Wockhardt UK Ltd)	ABX
53153	Clarithromycin 250mg tablets (Phoenix Healthcare Distribution Ltd)	ABX
53168	Clarithromycin 125mg/5ml oral suspension (Sandoz Ltd)	ABX
53179	Clarithromycin 250mg/5ml oral suspension (Sandoz Ltd)	ABX
53310	Doxycycline 100mg capsules (Sigma Pharmaceuticals Plc)	ABX
53449	Erythrocin 500 tablets (Lexon (UK) Ltd)	ABX
53519	Ciproxin 250mg tablets (Lexon (UK) Ltd)	ABX
53609	Co-amoxiclav 500mg/125mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)	ABX
53627	Amoxicillin 500mg capsules (Accord Healthcare Ltd)	ABX
53641	Ciprofloxacin 500mg tablets (Strides Pharma UK Ltd)	ABX
53673	Levofloxacin 500mg/100ml infusion bags	ABX
53688	Clarithromycin 250mg tablets (Ranbaxy (UK) Ltd)	ABX
53703	Clarithromycin 500mg tablets (Kent Pharmaceuticals Ltd)	ABX
53715	Clarithromycin 500mg tablets (Almus Pharmaceuticals Ltd)	ABX
53776	Clarithromycin 500mg tablets (DE Pharmaceuticals)	ABX
53875	Clarithromycin 500mg tablets (Tillomed Laboratories Ltd)	ABX
53878	Ciprofloxacin 500mg tablets (Ranbaxy (UK) Ltd)	ABX
53924	Amoxicillin 250mg/5ml oral suspension (Sigma Pharmaceuticals Plc)	ABX

53942	Amoxicillin 125mg / Clavulanic acid 62.5mg/5ml oral suspension	ABX
53945	Cefalexin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	ABX
53973	Doxycycline 50mg capsules (Alliance Healthcare (Distribution) Ltd)	ABX
53986	Erythromycin 250mg gastro-resistant tablets (Medreich Plc)	ABX
53996	Co-amoxiclav 500mg/125mg tablets (Aurobindo Pharma Ltd)	ABX
54052	Co-amoxiclav 125mg/31mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
54098	Erythroped A 500mg tablets (Lexon (UK) Ltd)	ABX
54185	Amoxicillin 250mg capsules (Wockhardt UK Ltd)	ABX
54208	Clarithromycin 250mg/5ml oral suspension (Sigma Pharmaceuticals Plc)	ABX
54214	Tetracycline 250mg tablets (Alliance Healthcare (Distribution) Ltd)	ABX
54222	Amoxicillin 250mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	ABX
54241	Clarithromycin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
54269	Clarithromycin 250mg tablets (Somex Pharma)	ABX
54271	Amoxicillin 250mg capsules (Mawdsley-Brooks & Company Ltd)	ABX
54302	Ciprofloxacin 250mg tablets (Medreich Plc)	ABX
54324	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Actavis UK Ltd)	ABX
54393	Ciprofloxacin 250mg tablets (Arrow Generics Ltd)	ABX
54452	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	ABX
54472	Clarithromycin 250mg tablets (Accord Healthcare Ltd)	ABX
54491	Amoxicillin 250mg capsules (Bristol Laboratories Ltd)	ABX
54529	Clarithromycin 500mg Modified-release tablet (Hillcross Pharmaceuticals Ltd)	ABX
54555	Ciprofloxacin 100mg tablets (DE Pharmaceuticals)	ABX
54591	Co-amoxiclav 500mg/125mg tablets (Phoenix Healthcare Distribution Ltd)	ABX
54674	Ciprofloxacin 100mg tablets (Phoenix Healthcare Distribution Ltd)	ABX
54701	Ciprofloxacin 250mg tablets (Bristol Laboratories Ltd)	ABX
54708	Co-amoxiclav 250mg/62mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	ABX
54725	Amoxicillin 500mg capsules (Milpharm Ltd)	ABX
54732	Co-amoxiclav 125mg/31mg/5ml oral suspension (Mylan)	ABX
54780	Co-amoxiclav 250mg/62mg/5ml oral suspension (Mylan)	ABX
54796	Amoxicillin 250mg capsules (Boston Healthcare Ltd)	ABX
54808	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	ABX
54864	Cefalexin 250mg capsules (Alliance Healthcare (Distribution) Ltd)	ABX
54882	Clarithromycin 250mg tablets (Almus Pharmaceuticals Ltd)	ABX

54897	Clarithromycin 250mg tablets (Tillomed Laboratories Ltd)	ABX
54903	Clarithromycin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	ABX
54955	Cefalexin 500mg capsules (Milpharm Ltd)	ABX
55018	Amoxicillin 250mg/5ml oral suspension (Bristol Laboratories Ltd)	ABX
55047	Amoxicillin 125mg/5ml oral suspension (Sandoz Ltd)	ABX
55133	Erythromycin 250mg gastro-resistant capsules (Kent Pharmaceuticals Ltd)	ABX
55148	Clarithromycin 250mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	ABX
55211	Cefaclor 500mg capsules (Kent Pharmaceuticals Ltd)	ABX
55300	Erythromycin 500mg Tablet (Teva UK Ltd)	ABX
55312	Co-amoxiclav 250mg/125mg tablets (Waymade Healthcare Plc)	ABX
55394	Amoxicillin 500mg capsules (Wockhardt UK Ltd)	ABX
55397	Erythromycin 250mg gastro-resistant capsules (Waymade Healthcare Plc)	ABX
55428	Clarithromycin 250mg/5ml oral suspension (Waymade Healthcare Plc)	ABX
55483	Erythromycin 250mg gastro-resistant tablets (Milpharm Ltd)	ABX
55499	Amoxicillin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)	ABX
55519	Doxycycline 100mg capsules (Waymade Healthcare Plc)	ABX
55527	Amoxicillin 500mg capsules (Boston Healthcare Ltd)	ABX
55589	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	ABX
55626	Amoxicillin 125mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	ABX
55708	Levofloxacin 250mg tablets (Actavis UK Ltd)	ABX
55917	Ciprofloxacin 500mg tablets (Medreich Plc)	ABX
56012	Levofloxacin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)	ABX
56044	Tetracycline 125mg/5ml oral solution	ABX
56181	Tetracycline 250mg Tablet (Celltech Pharma Europe Ltd)	ABX
56198	Vibramycin-D 100mg dispersible tablets (Mawdsley-Brooks & Company Ltd)	ABX
56203	Erythroped A 500mg tablets (Sigma Pharmaceuticals Plc)	ABX
56223	Amoxicillin 250mg/5ml oral suspension (Sandoz Ltd)	ABX
56381	Ciprofloxacin 250mg tablets (Strides Pharma UK Ltd)	ABX
56439	Ciprofloxacin 200mg/100ml solution for infusion vials (A A H Pharmaceuticals Ltd)	ABX
56561	Amoxicillin 125mg/5ml oral suspension (Waymade Healthcare Plc)	ABX
56578	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	ABX
56591	Augmentin-Duo 400/57 oral suspension (Lexon (UK) Ltd)	ABX
56610	Cefaclor 125mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	ABX

56700	Amoxil 500mg capsules (Necessity Supplies Ltd)	ABX
56789	Ciprofloxacin 500mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)	ABX
56856	Ciprofloxacin 750mg tablets (Ranbaxy (UK) Ltd)	ABX
56884	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	ABX

Codes to identify COPD medications (CPRD Aurum)

prodcodeid	termfromemis	groups
88541000033116	atrovent 20micrograms/dose autohaler (boehringer ingelheim ltd)	sama
88241000033118	atrovent 20micrograms/dose inhaler (boehringer ingelheim ltd)	sama
3075541000033113	atrovent 20micrograms/dose inhaler cfc free (boehringer ingelheim ltd)	sama
88341000033111	atrovent 40microgram aerocaps (boehringer ingelheim ltd)	sama
88441000033117	atrovent 40microgram aerocaps with aerohaler (boehringer ingelheim ltd)	sama
89441000033110	atrovent forte 40micrograms/dose inhaler (boehringer ingelheim ltd)	sama
772841000033113	ipratropium bromide 20micrograms/dose breath actuated inhaler	sama
772641000033112	ipratropium bromide 20micrograms/dose inhaler	sama
3075441000033112	ipratropium bromide 20micrograms/dose inhaler cfc free	sama
772941000033117	ipratropium bromide 40microgram inhalation powder capsules	sama
773041000033110	ipratropium bromide 40microgram inhalation powder capsules with device	sama
772541000033111	ipratropium bromide 40micrograms/dose inhaler	sama
1714241000033112	airomir 100micrograms/dose autohaler (teva uk ltd)	saba
22741000033118	airomir 100micrograms/dose inhaler (teva uk ltd)	saba
8491641000033114	airsalb 100micrograms/dose inhaler cfc free (sandoz ltd)	saba
158441000033117	bricanyl 250micrograms/dose inhaler (astrazeneca uk ltd)	saba
160941000033118	bricanyl 250micrograms/dose spacer inhaler (astrazeneca uk ltd)	saba
163641000033116	bricanyl 500micrograms/dose turbohaler (astrazeneca uk ltd)	saba
160241000033110	bricanyl refill canister 250 micrograms/puff	saba
1579541000033118	bricanyl turbohaler breath-actuated dry powder inhaler 500 micrograms/dose	saba
330241000033113	combivent inhaler (boehringer ingelheim ltd)	saba
3198541000033119	easyhaler salbutamol sulfate 100micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	saba
3198641000033118	easyhaler salbutamol sulfate 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	saba
4499041000033118	novolizer salbulin inhalation cartridge + device 100 micrograms/dose	saba
4499141000033119	novolizer salbulin inhalation cartridge refill 100 micrograms/dose	saba
2622741000033114	pulvinal salbutamol 200micrograms/dose dry powder inhaler (chiesi ltd)	saba
2588241000033119	salamol 100micrograms/dose easi-breathe inhaler (teva uk ltd)	saba
2086541000033119	salamol 100micrograms/dose inhaler cfc free (teva uk ltd)	saba

1221341000033118	salamol easi-breathe breath-actuated inhaler 100 micrograms/puff	saba
1241241000033114	salamol inhaler 100 micrograms/puff	saba
1241341000033116	salbulin 100micrograms/dose inhaler (3m health care ltd)	saba
1768141000033111	salbulin cfc-free inhaler 100 micrograms/puff	saba
5393141000033116	salbulin novolizer 100micrograms/dose inhalation powder (mylan)	saba
5393241000033111	salbulin novolizer 100micrograms/dose inhalation powder refill (mylan)	saba
3163441000033113	salbutamol 100micrograms/dose / ipratropium 20micrograms/dose inhaler	saba
1221441000033112	salbutamol 100micrograms/dose breath actuated inhaler	saba
1751341000033111	salbutamol 100micrograms/dose breath actuated inhaler cfc free	saba
4498941000033110	salbutamol 100micrograms/dose dry powder inhalation cartridge	saba
4498841000033119	salbutamol 100micrograms/dose dry powder inhalation cartridge with device	saba
3343941000033118	salbutamol 100micrograms/dose dry powder inhaler	saba
1241441000033110	salbutamol 100micrograms/dose inhaler	saba
1222341000033110	salbutamol 100micrograms/dose inhaler cfc free	saba
3163541000033114	salbutamol 2.5mg/2.5ml / ipratropium bromide 500micrograms/2.5ml nebuliser liquid unit dose vials	saba
2726241000033113	salbutamol 200 cyclocaps (teva uk ltd)	saba
1250141000033112	salbutamol 200microgram inhalation powder blisters	saba
1228841000033115	salbutamol 200microgram inhalation powder blisters with device	saba
1905641000033119	salbutamol 200microgram inhalation powder capsules	saba
1907541000033112	salbutamol 200micrograms/dose dry powder inhaler	saba
2726341000033115	salbutamol 400 cyclocaps (teva uk ltd)	saba
1250241000033117	salbutamol 400microgram inhalation powder blisters	saba
1228941000033111	salbutamol 400microgram inhalation powder blisters with device	saba
1905741000033111	salbutamol 400microgram inhalation powder capsules	saba
2174141000033117	salbutamol 95micrograms/dose dry powder inhaler	saba
1206041000033115	salbutamol accuhaler 200 micrograms/dose	saba
1206241000033111	salbutamol aerosol inhalation 100 micrograms/metered inhalation	saba
1207741000033115	salbutamol autohaler 100 micrograms/puff	saba
2864041000033119	salbutamol breath actuated pressurised inhalation 100 micrograms/actuation	saba
2952141000033110	salbutamol breath actuated pressurised inhalation, cfc-free 100 micrograms/actuation	saba
1221541000033113	salbutamol breath-actuated inhaler 95 micrograms/dose	saba

1228341000033112	salbutamol cyclocaps 200 micrograms	saba
1228441000033118	salbutamol cyclocaps 400 micrograms	saba
1913441000033115	salbutamol dry powder breath-actuated inhaler 200 micrograms	saba
1903141000033113	salbutamol dry powder breath-actuated inhaler 95 micrograms/dose	saba
1907341000033117	salbutamol dry powder disks + disk inhaler 200 micrograms	saba
1907441000033111	salbutamol dry powder disks + disk inhaler 400 micrograms	saba
1907641000033113	salbutamol dry powder for inhalation 400 micrograms/dose	saba
3344041000033116	salbutamol dry powder inhaler 200 micrograms/actuation, 200 dose	saba
1241941000033117	salbutamol inhaler with vortex generating actuator 100 micrograms/dose	saba
1905441000033116	salbutamol insufflator type 4	saba
1252241000033118	salbutamol rotacaps 200 micrograms	saba
1252341000033111	salbutamol rotacaps 400 micrograms	saba
1252441000033117	salbutamol rotahaler 1	saba
1255041000033118	salbutamol spacehaler 100 micrograms/puff	saba
1419341000033114	terbutaline 250micrograms/dose inhaler	saba
1423441000033112	terbutaline 250micrograms/dose inhaler with spacer	saba
1699041000033114	terbutaline 500micrograms/dose dry powder inhaler	saba
1422541000033119	terbutaline sulfate refill canister 250 micrograms/puff	saba
1429441000033110	terbutaline sulfate turbohaler 500 micrograms/dose	saba
1705441000033110	ventolin 100micrograms/dose evohaler (glaxosmithkline uk ltd)	saba
1510541000033116	ventolin 200microgram rotacaps (glaxosmithkline uk ltd)	saba
1505741000033119	ventolin 200micrograms/dose accuhaler (glaxosmithkline uk ltd)	saba
1510641000033115	ventolin 400microgram rotacaps (glaxosmithkline uk ltd)	saba
1505941000033116	ventolin easi-breathe breath-actuated inhaler 100 micrograms/puff	saba
1508041000033110	ventolin inhaler 100 micrograms/puff	saba
1510741000033112	ventolin rotahaler (glaxosmithkline uk ltd)	saba
8056941000033114	aclidinium bromide 375micrograms/dose dry powder inhaler	lama
9995641000033112	aclidinium bromide 396micrograms/dose / formoterol 11.8micrograms/dose dry powder inhaler	lama_laba
11789041000033118	braltus 10microgram inhalation powder capsules with zonda inhaler (teva uk ltd)	lama
8057341000033112	eklira 322micrograms/dose genuair (astrazeneca uk ltd)	lama

8141741000033112	glycopyrronium bromide 55microgram inhalation powder capsules with device	lama
9703641000033117	incruse ellipta 55micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	lama
9851941000033115	indacaterol 85micrograms/dose / glycopyrronium bromide 54micrograms/dose inhalation powder capsules with device	lama_laba
8141841000033119	seebri breezhaler 44microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	lama
2793841000033111	spiriva 18microgram inhalation powder capsules (boehringer ingelheim ltd)	lama
2793741000033118	spiriva 18microgram inhalation powder capsules with handihaler (boehringer ingelheim ltd)	lama
4270741000033115	spiriva respimat 2.5micrograms/dose inhalation solution cartridge with device (boehringer ingelheim ltd)	lama
13178841000033113	spiriva respimat 2.5micrograms/dose inhalation solution refill cartridge (boehringer ingelheim ltd)	lama
11788941000033110	tiotropium bromide 10microgram inhalation powder capsules with device	lama
2793641000033110	tiotropium bromide 18microgram inhalation powder capsules	lama
2793541000033114	tiotropium bromide 18microgram inhalation powder capsules with device	lama
13178541000033111	tiotropium bromide 2.5micrograms/dose / olodaterol 2.5micrograms/dose inhalation solution cartridge cfc free	lama_laba
10589141000033112	tiotropium bromide 2.5micrograms/dose / olodaterol 2.5micrograms/dose solution for inhalation cartridge with device cfc free	lama_laba
13178741000033115	tiotropium bromide 2.5micrograms/dose inhalation solution cartridge cfc free	lama
4270641000033112	tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device cfc free	lama
9293341000033116	anoro ellipta 55micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	lama_laba
3347141000033113	atimos modulite 12micrograms/dose inhaler (chiesi ltd)	laba
9995741000033115	duaklir 340micrograms/dose / 12micrograms/dose genuair (astrazeneca uk ltd)	lama_laba
3163841000033111	fluticasone 125micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	laba_ics
3163941000033115	fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	laba_ics

3163741000033118	fluticasone 50micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	laba_ics
8946841000033112	fluticasone furoate 184micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	laba_ics
8946941000033116	fluticasone furoate 92micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	laba_ics
3164041000033118	fluticasone propionate 100micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	laba_ics
3164141000033119	fluticasone propionate 250micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	laba_ics
3164241000033114	fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	laba_ics
599641000033111	foradil 12microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	laba
3089841000033115	formoterol 12microgram inhalation powder capsules with device	laba
3089741000033113	formoterol 12micrograms/dose dry powder inhaler	laba
3347041000033114	formoterol 12micrograms/dose inhaler cfc free	laba
3089641000033116	formoterol 6micrograms/dose dry powder inhaler	laba
4063341000033111	formoterol dry powder inhaler 12 micrograms/actuation, 120 dose	laba
4063241000033118	formoterol dry powder inhaler 12 micrograms/actuation, 60 dose	laba
4063541000033116	formoterol easyhaler 12micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	laba
5707041000033111	indacaterol 150microgram inhalation powder capsules with device	laba
5707141000033110	indacaterol 300microgram inhalation powder capsules with device	laba
6456541000033118	neovent 25micrograms/dose inhaler cfc free (kent pharmaceuticals ltd)	laba
13178941000033117	olodaterol 2.5micrograms/dose inhalation solution cartridge cfc free	laba
9299341000033119	olodaterol 2.5micrograms/dose solution for inhalation cartridge with device cfc free	laba
5707241000033115	onbrez breezhaler 150microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	laba
5707341000033113	onbrez breezhaler 300microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	laba
1022341000033117	oxis 12 turbohaler (astrazeneca uk ltd)	laba

1022441000033111	oxis 6 turbohaler (astrazeneca uk ltd)	laba
5140041000033112	oxis turbuhaler 4.5 micrograms/dose	laba
5140141000033111	oxis turbuhaler 9 micrograms/dose	laba
1206341000033118	salmeterol 25micrograms/dose inhaler	laba
3855941000033115	salmeterol 25micrograms/dose inhaler cfc free	laba
1252041000033114	salmeterol 50microgram inhalation powder blisters	laba
1914241000033119	salmeterol 50microgram inhalation powder blisters with device	laba
1914141000033114	salmeterol 50micrograms/dose dry powder inhaler	laba
1205941000033113	salmeterol xinafoate accuhaler 50 micrograms/dose	laba
1228741000033113	salmeterol xinafoate disks with diskhaler 50 micrograms/blister	laba
3856041000033113	serevent 25micrograms/dose evohaler (glaxosmithkline uk ltd)	laba
1267641000033111	serevent 25micrograms/dose inhaler (glaxosmithkline uk ltd)	laba
1272941000033113	serevent 50microgram disks (glaxosmithkline uk ltd)	laba
1268941000033117	serevent 50microgram disks with diskhaler (glaxosmithkline uk ltd)	laba
1267441000033114	serevent 50micrograms/dose accuhaler (glaxosmithkline uk ltd)	laba
11782841000033117	soltel 25micrograms/dose inhaler cfc free (cipla eu ltd)	laba
10589241000033117	spiolto respimat 2.5micrograms/dose / 2.5micrograms/dose inhalation solution cartridge with device (boehringer ingelheim ltd)	lama_laba
13178641000033112	spiolto respimat 2.5micrograms/dose / 2.5micrograms/dose inhalation solution refill cartridge (boehringer ingelheim ltd)	lama_laba
9299441000033113	striverdi respimat 2.5micrograms/dose inhalation solution cartridge with device (boehringer ingelheim ltd)	laba
13179041000033114	striverdi respimat 2.5micrograms/dose inhalation solution refill cartridge (boehringer ingelheim ltd)	laba
9852041000033114	ultibro breezhaler 85microgram/43microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	lama_laba
9293241000033114	umeclidinium bromide 65micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	lama_laba
8536141000033111	vertine 25micrograms/dose inhaler cfc free (teva uk ltd)	laba
12197841000033113	airflusal 25micrograms/dose / 125micrograms/dose inhaler (sandoz ltd)	laba_ics
12197941000033117	airflusal 25micrograms/dose / 250micrograms/dose inhaler (sandoz ltd)	laba_ics
10715041000033111	airflusal forspiro 50micrograms/dose / 500micrograms/dose dry powder inhaler (sandoz ltd)	laba_ics

12370841000033110	aloflute 25micrograms/dose / 125micrograms/dose inhaler (mylan)	laba_ics
12370941000033119	aloflute 25micrograms/dose / 250micrograms/dose inhaler (mylan)	laba_ics
4823341000033115	alvesco 160 inhaler (astrazeneca uk ltd)	ics
3227641000033114	alvesco 80 inhaler (astrazeneca uk ltd)	ics
3227741000033117	alvesco cfc-free inhaler 160 micrograms/actuation, 120 doses	ics
3267741000033112	alvesco cfc-free inhaler 160 micrograms/actuation, 60 doses	ics
5811441000033112	asmanex 200micrograms/dose twisthaler (merck sharp & dohme ltd)	ics
5811541000033113	asmanex 400micrograms/dose twisthaler (merck sharp & dohme ltd)	ics
2873041000033114	asmanex twisthaler dry powder inhaler 200 micrograms/dose, 30 doses	ics
2873141000033113	asmanex twisthaler dry powder inhaler 200 micrograms/dose, 60 doses	ics
2873241000033118	asmanex twisthaler dry powder inhaler 400 micrograms/dose, 30 doses	ics
2873341000033111	asmanex twisthaler dry powder inhaler 400 micrograms/dose, 60 doses	ics
2725541000033116	beclometasone 100 cyclocaps (teva uk ltd)	ics
3081341000033111	beclometasone 100microgram inhalation powder blisters	ics
3081041000033114	beclometasone 100microgram inhalation powder blisters with device	ics
3082041000033116	beclometasone 100microgram inhalation powder capsules	ics
9531441000033113	beclometasone 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	laba_ics
4418141000033112	beclometasone 100micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	laba_ics
3080741000033119	beclometasone 100micrograms/dose breath actuated inhaler	ics
3083041000033113	beclometasone 100micrograms/dose breath actuated inhaler cfc free	ics
3082341000033119	beclometasone 100micrograms/dose dry powder inhaler	ics
3081741000033112	beclometasone 100micrograms/dose inhaler	ics
3082841000033111	beclometasone 100micrograms/dose inhaler cfc free	ics
2725641000033115	beclometasone 200 cyclocaps (teva uk ltd)	ics
3081441000033117	beclometasone 200microgram inhalation powder blisters	ics
3081141000033113	beclometasone 200microgram inhalation powder blisters with device	ics
3082141000033117	beclometasone 200microgram inhalation powder capsules	ics
10735041000033115	beclometasone 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	laba_ics
10740041000033111	beclometasone 200micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	laba_ics

3082641000033110	beclometasone 200micrograms/dose dry powder inhaler	ics
3081641000033115	beclometasone 200micrograms/dose inhaler	ics
3942841000033114	beclometasone 200micrograms/dose inhaler cfc free	ics
3080541000033110	beclometasone 250micrograms/dose breath actuated inhaler	ics
3082441000033113	beclometasone 250micrograms/dose dry powder inhaler	ics
3080441000033114	beclometasone 250micrograms/dose inhaler	ics
3942941000033118	beclometasone 250micrograms/dose inhaler cfc free	ics
2725741000033112	beclometasone 400 cyclocaps (teva uk ltd)	ics
3081541000033116	beclometasone 400microgram inhalation powder blisters	ics
3081241000033118	beclometasone 400microgram inhalation powder blisters with device	ics
3081941000033110	beclometasone 400microgram inhalation powder capsules	ics
3082541000033114	beclometasone 400micrograms/dose dry powder inhaler	ics
3080641000033111	beclometasone 50micrograms/dose breath actuated inhaler	ics
3082941000033115	beclometasone 50micrograms/dose breath actuated inhaler cfc free	ics
3082241000033112	beclometasone 50micrograms/dose dry powder inhaler	ics
3081841000033119	beclometasone 50micrograms/dose inhaler	ics
3082741000033118	beclometasone 50micrograms/dose inhaler cfc free	ics
5393341000033118	budelin novolizer 200micrograms/dose inhalation powder (mylan)	ics
5393441000033112	budelin novolizer 200micrograms/dose inhalation powder refill (mylan)	ics
3164341000033116	budesonide 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	laba_ics
3871541000033110	budesonide 100micrograms/dose dry powder inhaler	ics
4815041000033111	budesonide 100micrograms/dose inhaler cfc free	ics
2726041000033117	budesonide 200 cyclocaps (teva uk ltd)	ics
2725841000033119	budesonide 200microgram inhalation powder capsules	ics
3164441000033110	budesonide 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	laba_ics
11707241000033115	budesonide 200micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	laba_ics
3256341000033119	budesonide 200micrograms/dose dry powder inhalation cartridge	ics
3141341000033112	budesonide 200micrograms/dose dry powder inhalation cartridge with device	ics
3871641000033111	budesonide 200micrograms/dose dry powder inhaler	ics
163741000033113	budesonide 200micrograms/dose inhaler	ics

4815141000033110	budesonide 200micrograms/dose inhaler cfc free	ics
169341000033114	budesonide 3mg gastro-resistant modified-release capsules	ics
2726141000033118	budesonide 400 cyclocaps (teva uk ltd)	ics
2725941000033110	budesonide 400microgram inhalation powder capsules	ics
3164541000033111	budesonide 400micrograms/dose / formoterol 12micrograms/dose dry powder inhaler	laba_ics
3871741000033119	budesonide 400micrograms/dose dry powder inhaler	ics
163841000033115	budesonide 50micrograms/dose inhaler	ics
1579841000033116	budesonide breath-actuated dry powder inhaler 100 micrograms/dose	ics
1579941000033112	budesonide breath-actuated dry powder inhaler 200 micrograms/dose	ics
1580041000033111	budesonide breath-actuated dry powder inhaler 400 micrograms/dose	ics
2798441000033118	budesonide inhaler with spacer device 200 micrograms/dose	ics
171241000033113	budesonide refill canister 200 micrograms/dose	ics
171341000033115	budesonide refill canister 50 micrograms/dose	ics
171741000033119	budesonide spacer inhaler 200 micrograms/dose	ics
171641000033111	budesonide spacer inhaler 50 micrograms/dose	ics
174641000033114	budesonide turbohaler 100 micrograms/dose	ics
174441000033112	budesonide turbohaler 200 micrograms/dose	ics
174541000033113	budesonide turbohaler 400 micrograms/dose	ics
4823241000033113	ciclesonide 160micrograms/dose inhaler cfc free	ics
3227441000033112	ciclesonide 80micrograms/dose inhaler cfc free	ics
3227541000033113	ciclesonide cfc-free inhaler 160 micrograms/actuation, 120 doses	ics
3267641000033115	ciclesonide cfc-free inhaler 160 micrograms/actuation, 60 doses	ics
3943341000033113	clenil modulite 100micrograms/dose inhaler (chiesi ltd)	ics
3943441000033119	clenil modulite 200micrograms/dose inhaler (chiesi ltd)	ics
3943641000033117	clenil modulite 250micrograms/dose inhaler (chiesi ltd)	ics
3943041000033111	clenil modulite 50micrograms/dose inhaler (chiesi ltd)	ics
12579441000033119	combisal 25micrograms/dose / 125micrograms/dose inhaler (aspire pharma ltd)	laba_ics
12579541000033118	combisal 25micrograms/dose / 250micrograms/dose inhaler (aspire pharma ltd)	laba_ics
12579341000033113	combisal 25micrograms/dose / 50micrograms/dose inhaler (aspire pharma ltd)	laba_ics

9342741000033111	duoresp spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (teva uk ltd)	laba_ics
9342841000033118	duoresp spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (teva uk ltd)	laba_ics
3343041000033119	easyhaler beclometasone 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	ics
3871841000033112	easyhaler budesonide 100micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	ics
3871941000033116	easyhaler budesonide 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	ics
3872041000033110	easyhaler budesonide 400micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	ics
590841000033115	flixotide 100microgram disks (glaxosmithkline uk ltd)	ics
581241000033110	flixotide 100microgram disks with diskhaler (glaxosmithkline uk ltd)	ics
576741000033118	flixotide 100micrograms/dose accuhaler (glaxosmithkline uk ltd)	ics
2067541000033118	flixotide 125micrograms/dose evohaler (glaxosmithkline uk ltd)	ics
590941000033111	flixotide 250microgram disks (glaxosmithkline uk ltd)	ics
581341000033117	flixotide 250microgram disks with diskhaler (glaxosmithkline uk ltd)	ics
576841000033111	flixotide 250micrograms/dose accuhaler (glaxosmithkline uk ltd)	ics
2067641000033117	flixotide 250micrograms/dose evohaler (glaxosmithkline uk ltd)	ics
585741000033118	flixotide 25micrograms/dose inhaler (glaxosmithkline uk ltd)	ics
591441000033110	flixotide 500microgram disks (glaxosmithkline uk ltd)	ics
581841000033114	flixotide 500microgram disks with diskhaler (glaxosmithkline uk ltd)	ics
577041000033119	flixotide 500micrograms/dose accuhaler (glaxosmithkline uk ltd)	ics
591041000033118	flixotide 50microgram disks (glaxosmithkline uk ltd)	ics
581441000033111	flixotide 50microgram disks with diskhaler (glaxosmithkline uk ltd)	ics
576941000033115	flixotide 50micrograms/dose accuhaler (glaxosmithkline uk ltd)	ics
2148541000033119	flixotide 50micrograms/dose evohaler (glaxosmithkline uk ltd)	ics
585641000033110	flixotide inhaler 125 micrograms/puff	ics
586241000033117	flixotide inhaler 250 micrograms/puff	ics
585841000033111	flixotide inhaler 50 micrograms/puff	ics
12634941000033116	fluticasone 125micrograms/dose / formoterol 5micrograms/dose breath actuated inhaler cfc free	laba_ics

8101741000033115	fluticasone 125micrograms/dose / formoterol 5micrograms/dose inhaler cfc free	laba_ics
2067741000033114	fluticasone 125micrograms/dose inhaler cfc free	ics
8101841000033113	fluticasone 250micrograms/dose / formoterol 10micrograms/dose inhaler cfc free	laba_ics
2067841000033116	fluticasone 250micrograms/dose inhaler cfc free	ics
586041000033113	fluticasone 25micrograms/dose inhaler	ics
12635041000033116	fluticasone 50micrograms/dose / formoterol 5micrograms/dose breath actuated inhaler cfc free	laba_ics
8101641000033112	fluticasone 50micrograms/dose / formoterol 5micrograms/dose inhaler cfc free	laba_ics
2148441000033115	fluticasone 50micrograms/dose inhaler cfc free	ics
591141000033119	fluticasone propionate 100microgram inhalation powder blisters	ics
1914841000033115	fluticasone propionate 100microgram inhalation powder blisters with device	ics
1914441000033118	fluticasone propionate 100micrograms/dose dry powder inhaler	ics
591241000033114	fluticasone propionate 250microgram inhalation powder blisters	ics
1914941000033111	fluticasone propionate 250microgram inhalation powder blisters with device	ics
1914541000033117	fluticasone propionate 250micrograms/dose dry powder inhaler	ics
591541000033111	fluticasone propionate 500microgram inhalation powder blisters	ics
1915041000033111	fluticasone propionate 500microgram inhalation powder blisters with device	ics
1914641000033116	fluticasone propionate 500micrograms/dose dry powder inhaler	ics
591341000033116	fluticasone propionate 50microgram inhalation powder blisters	ics
1914741000033113	fluticasone propionate 50microgram inhalation powder blisters with device	ics
1914341000033112	fluticasone propionate 50micrograms/dose dry powder inhaler	ics
577141000033115	fluticasone propionate accuhaler 100 micrograms/dose	ics
577241000033110	fluticasone propionate accuhaler 250 micrograms/dose	ics
577341000033117	fluticasone propionate accuhaler 50 micrograms/dose	ics
577441000033111	fluticasone propionate accuhaler 500 micrograms/dose	ics
4164541000033114	fluticasone propionate aqueous nasal spray 50 micrograms/dose, 60 doses	ics
581541000033112	fluticasone propionate disks with diskhaler 100 micrograms/dose	ics
581641000033113	fluticasone propionate disks with diskhaler 250 micrograms/dose	ics
581741000033116	fluticasone propionate disks with diskhaler 50 micrograms/dose	ics
581941000033118	fluticasone propionate disks with diskhaler 500 micrograms/puff	ics

585941000033115	fluticasone propionate inhaler 125 micrograms/puff	ics
586341000033110	fluticasone propionate inhaler 250 micrograms/puff	ics
586141000033112	fluticasone propionate inhaler 50 micrograms/puff	ics
8102041000033111	flutiform 125micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)	laba_ics
8102141000033110	flutiform 250micrograms/dose / 10micrograms/dose inhaler (napp pharmaceuticals ltd)	laba_ics
8101941000033117	flutiform 50micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)	laba_ics
12635141000033117	flutiform k-haler 125micrograms/dose / 5micrograms/dose breath actuated inhaler (napp pharmaceuticals ltd)	laba_ics
12635241000033112	flutiform k-haler 50micrograms/dose / 5micrograms/dose breath actuated inhaler (napp pharmaceuticals ltd)	laba_ics
12430741000033111	fobumix easyhaler 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	laba_ics
12403741000033110	fobumix easyhaler 320micrograms/dose / 9micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	laba_ics
12434441000033111	fobumix easyhaler 80micrograms/dose / 4.5micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	laba_ics
4418241000033117	fostair 100micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)	laba_ics
10740141000033110	fostair 200micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)	laba_ics
9537441000033115	fostair nexthaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd)	laba_ics
10735141000033116	fostair nexthaler 200micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd)	laba_ics
12529241000033119	fusacomb easyhaler 50micrograms/dose / 250micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	laba_ics
12529341000033112	fusacomb easyhaler 50micrograms/dose / 500micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	laba_ics
12530441000033112	kelhale 100micrograms/dose inhaler (cipla eu ltd)	ics
12530541000033113	kelhale 50micrograms/dose inhaler (cipla eu ltd)	ics
5811241000033111	mometasone 200micrograms/dose dry powder inhaler	ics
5811341000033118	mometasone 400micrograms/dose dry powder inhaler	ics

2872641000033111	mometasone furoate dry powder inhaler 200 micrograms/dose, 30 doses	ics
2872841000033112	mometasone furoate dry powder inhaler 200 micrograms/dose, 60 doses	ics
2872941000033116	mometasone furoate dry powder inhaler 400 micrograms/dose, 30 doses	ics
2872741000033119	mometasone furoate dry powder inhaler 400 micrograms/dose, 60 doses	ics
3141441000033118	novolizer budesonide inhalation cartridge + device 200 micrograms/dose, 100 doses	ics
3256441000033113	novolizer budesonide inhalation cartridge refill 200 micrograms/dose, 100 doses	ics
1145341000033116	pulmicort 100 turbohaler (astrazeneca uk ltd)	ics
4815241000033115	pulmicort 100micrograms/dose inhaler cfc free (astrazeneca uk ltd)	ics
1145141000033119	pulmicort 200 turbohaler (astrazeneca uk ltd)	ics
1143041000033117	pulmicort 200micrograms/dose inhaler (astrazeneca uk ltd)	ics
4815341000033113	pulmicort 200micrograms/dose inhaler cfc free (astrazeneca uk ltd)	ics
2798341000033112	pulmicort 200micrograms/dose inhaler with nebuchamber (astrazeneca uk ltd)	ics
1145241000033114	pulmicort 400 turbohaler (astrazeneca uk ltd)	ics
1143141000033118	pulmicort ls 50micrograms/dose inhaler (astrazeneca uk ltd)	ics
1144341000033117	pulmicort ls refill canister 50 micrograms/dose	ics
1144241000033110	pulmicort refill canister 200 micrograms/dose	ics
1144841000033114	pulmicort spacer inhaler 200 micrograms/dose	ics
1144941000033118	pulmicort spacer inhaler 50 micrograms/dose	ics
1670741000033111	pulmicort turbohaler breath-actuated dry powder inhaler 100 micrograms/dose	ics
1670841000033118	pulmicort turbohaler breath-actuated dry powder inhaler 200 micrograms/dose	ics
1670941000033114	pulmicort turbohaler breath-actuated dry powder inhaler 400 micrograms/dose	ics
2623141000033115	pulvinal beclometasone dipropionate 100micrograms/dose dry powder inhaler (chiesi ltd)	ics
2623241000033110	pulvinal beclometasone dipropionate 200micrograms/dose dry powder inhaler (chiesi ltd)	ics
2623341000033117	pulvinal beclometasone dipropionate 400micrograms/dose dry powder inhaler (chiesi ltd)	ics

1671341000033119	qvar 100 autohaler (teva uk ltd)	ics
1671141000033117	qvar 100 inhaler (teva uk ltd)	ics
3199341000033119	qvar 100micrograms/dose easi-breathe inhaler (teva uk ltd)	ics
1671241000033112	qvar 50 autohaler (teva uk ltd)	ics
1671041000033116	qvar 50 inhaler (teva uk ltd)	ics
3199241000033112	qvar 50micrograms/dose easi-breathe inhaler (teva uk ltd)	ics
8947041000033115	relvar ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	laba_ics
8947141000033116	relvar ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	laba_ics
12046641000033114	sereflo 25micrograms/dose / 125micrograms/dose inhaler (cipla eu ltd)	laba_ics
12046741000033117	sereflo 25micrograms/dose / 250micrograms/dose inhaler (cipla eu ltd)	laba_ics
1752141000033117	seretide 100 accuhaler (glaxosmithkline uk ltd)	laba_ics
2147341000033110	seretide 125 evohaler (glaxosmithkline uk ltd)	laba_ics
1752241000033112	seretide 250 accuhaler (glaxosmithkline uk ltd)	laba_ics
2147441000033116	seretide 250 evohaler (glaxosmithkline uk ltd)	laba_ics
2147241000033117	seretide 50 evohaler (glaxosmithkline uk ltd)	laba_ics
1752341000033119	seretide 500 accuhaler (glaxosmithkline uk ltd)	laba_ics
10387141000033115	sirdupla 25micrograms/dose / 125micrograms/dose inhaler (mylan)	laba_ics
10387241000033110	sirdupla 25micrograms/dose / 250micrograms/dose inhaler (mylan)	laba_ics
12901441000033118	soprobec 100micrograms/dose inhaler (glenmark pharmaceuticals europe ltd)	ics
12901541000033117	soprobec 200micrograms/dose inhaler (glenmark pharmaceuticals europe ltd)	ics
12901641000033116	soprobec 250micrograms/dose inhaler (glenmark pharmaceuticals europe ltd)	ics
12901341000033112	soprobec 50micrograms/dose inhaler (glenmark pharmaceuticals europe ltd)	ics
12901741000033113	stalpex 50micrograms/dose / 500micrograms/dose dry powder inhaler (glenmark pharmaceuticals europe ltd)	laba_ics
2587541000033118	symbicort 100/6 turbohaler (astrazeneca uk ltd)	laba_ics
2587641000033117	symbicort 200/6 turbohaler (astrazeneca uk ltd)	laba_ics
11707341000033113	symbicort 200micrograms/dose / 6micrograms/dose pressurised inhaler (astrazeneca uk ltd)	laba_ics
2905641000033115	symbicort 400/12 turbohaler (astrazeneca uk ltd)	laba_ics
5140741000033110	symbicort turbuhaler 160/4.5 micrograms/dose	laba_ics
8028941000033114	symbicort turbuhaler 320/9 micrograms/dose	laba_ics

5140541000033119	symbicort turbuhaler 80/4.5 micrograms/dose	laba_ics
12431141000033117	trelegy ellipta 92micrograms/dose / 55micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	triple
12364641000033110	trimbow 87micrograms/dose / 5micrograms/dose / 9micrograms/dose inhaler (chiesi ltd)	triple
2509441000033112	*prednisolone granules	ocs
2509541000033113	*prednisolone liquid	ocs
2509741000033117	*prednisolone pills (sucrose)	ocs
2509641000033114	*prednisolone powder	ocs
2509341000033118	*prednisolone tablets	ocs
429141000033119	decortisyl tablets 5 mg	ocs
431541000033114	deltacortril 2.5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	ocs
431641000033110	deltacortril 5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	ocs
429441000033110	deltastab tablets 1 mg	ocs
429541000033111	deltastab tablets 5 mg	ocs
8494441000033110	dilacort 2.5mg gastro-resistant tablets (crescent pharma ltd)	ocs
8494541000033111	dilacort 5mg gastro-resistant tablets (crescent pharma ltd)	ocs
10212641000033118	pevanti 10mg tablets (advanz pharma)	ocs
10212441000033115	pevanti 2.5mg tablets (advanz pharma)	ocs
10212741000033110	pevanti 20mg tablets (advanz pharma)	ocs
10212941000033113	pevanti 25mg tablets (advanz pharma)	ocs
10212541000033119	pevanti 5mg tablets (advanz pharma)	ocs
10212141000033111	prednisolone 10mg tablets	ocs
10494341000033117	prednisolone 10mg/ml oral solution sugar free	ocs
9119141000033118	prednisolone 15mg/5ml oral solution	ocs
11507841000033115	prednisolone 1mg gastro-resistant tablets	ocs
1131741000033117	prednisolone 1mg tablets	ocs
1114241000033116	prednisolone 2.5mg gastro-resistant tablets	ocs
1131841000033110	prednisolone 2.5mg tablets	ocs
10212341000033114	prednisolone 20mg tablets	ocs
1130741000033110	prednisolone 25mg tablets	ocs
11664841000033116	prednisolone 30mg tablets	ocs
1114341000033114	prednisolone 5mg gastro-resistant tablets	ocs

1127341000033111	prednisolone 5mg soluble tablets	ocs
1131941000033119	prednisolone 5mg tablets	ocs
10266841000033117	prednisolone 5mg/5ml oral solution unit dose	ocs
1130841000033117	prednisolone steaglate tablets 6.65 mg	ocs
5990141000033115	prednisone 1mg modified-release tablets	ocs
5990241000033110	prednisone 2mg modified-release tablets	ocs
5990341000033117	prednisone 5mg modified-release tablets	ocs
1132041000033113	prednisone tablets 1 mg	ocs
1132141000033112	prednisone tablets 5 mg	ocs
2494441000033116	*penicillin granules	abx
2494541000033115	*penicillin liquid	abx
2494741000033111	*penicillin pills (sucrose)	abx
2494641000033119	*penicillin powder	abx
2494341000033110	*penicillin tablets	abx
3079841000033112	amoxicillin 125mg/1.25ml oral suspension paediatric	abx
3079641000033111	amoxicillin 125mg/5ml oral suspension	abx
3080041000033117	amoxicillin 125mg/5ml oral suspension sugar free	abx
3079141000033118	amoxicillin 250mg capsules	abx
3079741000033119	amoxicillin 250mg/5ml oral suspension	abx
3080141000033118	amoxicillin 250mg/5ml oral suspension sugar free	abx
3079941000033116	amoxicillin 3g oral powder sachets sugar free	abx
3079241000033113	amoxicillin 500mg capsules	abx
52841000033110	amoxil 125mg/1.25ml paediatric oral suspension (glaxosmithkline uk ltd)	abx
55941000033112	amoxil 125mg/5ml syrup sucrose free (glaxosmithkline uk ltd)	abx
44041000033113	amoxil 250mg capsules (glaxosmithkline uk ltd)	abx
56041000033119	amoxil 250mg/5ml syrup sucrose free (glaxosmithkline uk ltd)	abx
44141000033112	amoxil 500mg capsules (glaxosmithkline uk ltd)	abx
46841000033112	amoxil dispersible tablets 500 mg	abx
47241000033111	amoxil fiztabs 125 mg	abx
47341000033118	amoxil fiztabs 250 mg	abx
47441000033112	amoxil fiztabs 500 mg	abx
54041000033110	amoxil sachets sf 750 mg	abx
52041000033115	ampicillin 125mg/5ml oral suspension	abx

44441000033116	ampicillin 250mg capsules	abx
52141000033116	ampicillin 250mg/5ml oral suspension	abx
44541000033115	ampicillin 500mg capsules	abx
53341000033114	ampicillin paediatric suspension 125 mg/1.25 ml	abx
53441000033115	ampicillin paediatric tablets 125 mg	abx
56541000033112	ampicillin syrup 125 mg/5 ml	abx
56641000033113	ampicillin syrup forte 250 mg/5 ml	abx
1572541000033110	augmentin 1 g tablets	abx
94641000033110	augmentin 125/31 sf oral suspension (glaxosmithkline uk ltd)	abx
94741000033118	augmentin 250/62 sf oral suspension (glaxosmithkline uk ltd)	abx
93141000033115	augmentin 375mg dispersible tablets (glaxosmithkline uk ltd)	abx
94941000033115	augmentin 375mg tablets (glaxosmithkline uk ltd)	abx
95041000033115	augmentin 625mg tablets (glaxosmithkline uk ltd)	abx
93941000033118	augmentin junior suspension	abx
94441000033113	augmentin paediatric suspension	abx
5331141000033112	augmentin sr m/r tablets 1000 mg + 62.5 mg	abx
95141000033116	augmentin tablets	abx
94841000033111	augmentin-duo 400/57 oral suspension (glaxosmithkline uk ltd)	abx
2890341000033112	avelox 400mg tablets (bayer plc)	abx
98441000033116	azithromycin 200mg/5ml oral suspension	abx
96941000033113	azithromycin 250mg capsules	abx
3955441000033115	azithromycin 250mg tablets	abx
1572841000033112	azithromycin 500mg tablets	abx
230941000033110	cefaclor 125mg/5ml oral suspension	abx
230741000033112	cefaclor 125mg/5ml oral suspension sugar free	abx
220441000033115	cefaclor 250mg capsules	abx
231741000033119	cefaclor 250mg/5ml oral suspension	abx
230841000033119	cefaclor 250mg/5ml oral suspension sugar free	abx
227741000033114	cefaclor 375mg modified-release tablets	abx
219741000033111	cefaclor 500mg capsules	abx
227841000033116	cefaclor m/r tablets 500 mg	abx
231041000033117	cefadroxil 125mg/5ml oral suspension	abx
231541000033110	cefadroxil 250mg/5ml oral suspension	abx

220541000033119	cefadroxil 500mg capsules	abx
231641000033111	cefadroxil 500mg/5ml oral suspension	abx
3084441000033119	cefalexin 125mg/5ml oral suspension	abx
5747941000033119	cefalexin 125mg/5ml oral suspension sugar free	abx
3084041000033111	cefalexin 250mg capsules	abx
3084241000033115	cefalexin 250mg tablets	abx
3084541000033118	cefalexin 250mg/5ml oral suspension	abx
4373141000033119	cefalexin 250mg/5ml oral suspension sugar free	abx
3084141000033110	cefalexin 500mg capsules	abx
3084341000033113	cefalexin 500mg tablets	abx
3084641000033117	cefalexin 500mg/5ml oral suspension	abx
230041000033114	cefixime 100mg/5ml oral suspension	abx
232741000033113	cefixime 200mg tablets	abx
12395841000033112	cefixime 400mg tablets	abx
3084741000033114	cefradine 250mg capsules	abx
3085141000033111	cefradine 250mg/5ml oral solution	abx
3084841000033116	cefradine 500mg capsules	abx
228941000033111	cefuroxime 125mg granules sachets	abx
235441000033111	cefuroxime 125mg tablets	abx
230141000033113	cefuroxime 125mg/5ml oral suspension	abx
233041000033118	cefuroxime 250mg tablets	abx
2831741000033110	cefuroxime tablets 500 mg	abx
220741000033110	cephalexin capsules 250 mg	abx
220841000033117	cephalexin capsules 500 mg	abx
221241000033111	cephalexin chewable tablets 125 mg	abx
221341000033118	cephalexin chewable tablets 250 mg	abx
227941000033112	cephalexin mixture 125 mg/5 ml	abx
228041000033110	cephalexin mixture 250 mg/5 ml	abx
228141000033114	cephalexin mixture 500mg/5 ml	abx
228541000033117	cephalexin paediatric drops 125 mg/1.25 ml	abx
231141000033118	cephalexin suspension 125 mg/5 ml	abx
231241000033113	cephalexin suspension 250 mg/5 ml	abx
232041000033110	cephalexin syrup 125 mg/5 ml	abx

232141000033114	cephalexin syrup 250 mg/5 ml	abx
232241000033119	cephalexin syrup 500 mg/5 ml	abx
232641000033116	cephalexin syrup 500mg/5 ml	abx
1581441000033111	cephalexin tablets 1 gram	abx
234941000033119	cephalexin tablets 250 mg	abx
235041000033119	cephalexin tablets 500 mg	abx
259341000033118	ciprofloxacin 100mg tablets	abx
260241000033112	ciprofloxacin 250mg tablets	abx
1582941000033113	ciprofloxacin 250mg/5ml oral suspension	abx
3834741000033115	ciprofloxacin 3mg/g eye ointment	abx
258841000033116	ciprofloxacin 500mg tablets	abx
259041000033115	ciprofloxacin 750mg tablets	abx
259441000033112	ciproxin 100mg tablets (bayer plc)	abx
259641000033114	ciproxin 250mg tablets (bayer plc)	abx
1582841000033117	ciproxin 250mg/5ml oral suspension (bayer plc)	abx
258741000033114	ciproxin 500mg tablets (bayer plc)	abx
258941000033112	ciproxin 750mg tablets (bayer plc)	abx
3838541000033117	clarithromycin 125mg granules straws	abx
278241000033118	clarithromycin 125mg/5ml oral suspension	abx
3838641000033116	clarithromycin 187.5mg granules straws	abx
282141000033118	clarithromycin 250mg granules sachets	abx
3838741000033113	clarithromycin 250mg granules straws	abx
287441000033111	clarithromycin 250mg tablets	abx
1830541000033112	clarithromycin 250mg/5ml oral suspension	abx
277841000033115	clarithromycin 500mg modified-release tablets	abx
285341000033110	clarithromycin 500mg tablets	abx
330541000033110	co-amoxiclav 1000mg/200mg powder for solution for injection vials	abx
5697041000033116	co-amoxiclav 125mg/31mg/5ml oral suspension	abx
366941000033113	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free	abx
317741000033113	co-amoxiclav 250mg/125mg dispersible tablets sugar free	abx
370041000033115	co-amoxiclav 250mg/125mg tablets	abx
5697141000033117	co-amoxiclav 250mg/62mg/5ml oral suspension	abx
367041000033114	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free	abx

367541000033116	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free	abx
330441000033114	co-amoxiclav 500mg/100mg powder for solution for injection vials	abx
370141000033116	co-amoxiclav 500mg/125mg tablets	abx
1594141000033117	co-amoxiclav 875mg/125mg tablets	abx
317241000033119	co-amoxiclav dispersible tablets	abx
359141000033110	co-amoxiclav s/f junior suspension	abx
359241000033115	co-amoxiclav s/f paediatric suspension	abx
369241000033113	co-amoxiclav tablets	abx
3089341000033112	doxycycline 100mg capsules	abx
3089441000033118	doxycycline 100mg dispersible tablets sugar free	abx
3089541000033117	doxycycline 20mg tablets	abx
5150141000033114	doxycycline 40mg modified-release capsules	abx
1603241000033119	doxycycline 50mg capsules	abx
7871241000033116	doxycycline 50mg/5ml oral suspension	abx
472341000033113	doxycycline capsules 100 mg	abx
472541000033118	doxycycline capsules 50 mg	abx
473641000033113	doxycycline dispersible tablets 100 mg	abx
7860041000033110	doxycycline hyclate oral suspension 50 mg/5 ml	abx
479441000033114	doxycycline syrup 50 mg/5 ml	abx
481941000033110	doxycycline tablets 100 mg	abx
2637041000033111	doxycycline tablets 20 mg	abx
534241000033118	erythromycin 250mg gastro-resistant capsules	abx
1924941000033118	erythromycin 250mg gastro-resistant tablets	abx
1846041000033116	erythromycin 40mg/ml / zinc acetate 12mg/ml lotion	abx
537641000033110	erythromycin ethyl succinate 125mg/5ml oral suspension	abx
537441000033113	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free	abx
537741000033118	erythromycin ethyl succinate 250mg/5ml oral suspension	abx
537541000033114	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free	abx
538841000033112	erythromycin ethyl succinate 500mg tablets	abx
537841000033111	erythromycin ethyl succinate 500mg/5ml oral suspension	abx
537941000033115	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free	abx
534341000033111	erythromycin ethyl succinate granules 1 gram/sachet	abx
534441000033117	erythromycin ethyl succinate granules 125 mg/sachet	abx

534541000033116	erythromycin ethyl succinate granules 250 mg/sachet	abx
534641000033115	erythromycin ethyl succinate granules 500 mg/sachet	abx
535741000033113	erythromycin ethyl succinate mixture 125 mg/5 ml	abx
535841000033115	erythromycin ethyl succinate mixture 250 mg/5 ml	abx
535941000033111	erythromycin ethyl succinate mixture 500 mg/5 ml	abx
536241000033114	erythromycin paediatric suspension 125 mg/5 ml	abx
536941000033117	erythromycin stearate 250mg tablets	abx
13300741000033118	erythromycin stearate 500mg tablets	abx
536841000033113	erythromycin stearate tablets 500 mg	abx
538341000033115	erythromycin sugar free granules 250 mg/sachet	abx
538541000033110	erythromycin sugar free suspension 125mg/5ml	abx
538641000033111	erythromycin sugar free suspension 250mg/5ml	abx
538441000033114	erythromycin suspension 250 mg/5 ml	abx
537041000033116	erythromycin suspension 500 mg/5 ml	abx
536741000033115	erythromycin tablets 250 mg	abx
540041000033119	erythromycin tablets 500 mg	abx
540141000033115	erythroped a 500mg tablets (advanz pharma)	abx
536541000033111	erythroped a sachets 1 gram/sachet	abx
537241000033112	erythroped forte sf 500mg/5ml oral suspension (advanz pharma)	abx
534741000033112	erythroped granules forte 500 mg/sachet	abx
536041000033118	erythroped p.i. sachets 125 mg/sachet	abx
536341000033116	erythroped p.i. suspension 125 mg/5 ml	abx
536141000033119	erythroped pi sf 125mg/5ml oral suspension (advanz pharma)	abx
536441000033110	erythroped sachets 250 mg/sachet	abx
537341000033119	erythroped sf 250mg/5ml oral suspension (advanz pharma)	abx
538241000033113	erythroped sugar free granules 250 mg/sachet	abx
537141000033117	erythroped suspension 250 mg/5 ml	abx
805741000033118	klaricid 250mg tablets (abbott laboratories ltd)	abx
805441000033113	klaricid 500 tablets (abbott laboratories ltd)	abx
805341000033119	klaricid adult 250mg granules sachets (mylan)	abx
805141000033117	klaricid paediatric 125mg/5ml oral suspension (mylan)	abx
1830641000033113	klaricid paediatric 250mg/5ml oral suspension (mylan)	abx
804941000033116	klaricid xl 500mg tablets (mylan)	abx

1626241000033115	levofloxacin 250mg tablets	abx
1626341000033113	levofloxacin 500mg tablets	abx
1626141000033110	levofloxacin 500mg/100ml solution for infusion vials	abx
857741000033118	magnapen 250mg/250mg capsules (wockhardt uk ltd)	abx
867741000033114	magnapen syrup (wockhardt uk ltd)	abx
2890241000033119	moxifloxacin 400mg tablets	abx
1044541000033118	penicillin v capsules 250 mg	abx
1051141000033110	penicillin v elixir 125 mg/5 ml	abx
1051241000033115	penicillin v elixir 250 mg/5 ml	abx
1051341000033113	penicillin v elixir 62.5 mg/5 ml	abx
1067741000033113	penicillin v tablets 250 mg	abx
1064641000033111	penicillin vk tablets 250 mg	abx
3914841000033111	suprax capsules 400 mg	abx
1698741000033115	tavanic 250mg tablets (sanofi)	abx
1698841000033113	tavanic 500mg tablets (sanofi)	abx
1698641000033112	tavanic 500mg/100ml solution for infusion vials (sanofi)	abx
1558241000033114	zinnat 125mg tablets (glaxosmithkline uk ltd)	abx
1557041000033117	zinnat 125mg/5ml oral suspension (glaxosmithkline uk ltd)	abx
1557341000033115	zinnat 250mg tablets (glaxosmithkline uk ltd)	abx
1556241000033110	zinnat suspension 125mg granules sachets (glaxosmithkline uk ltd)	abx
2831841000033117	zinnat tablets 500 mg	abx
1557141000033118	zithromax 200mg/5ml oral suspension (pfizer ltd)	abx
1553141000033111	zithromax 250mg capsules (pfizer ltd)	abx
1713741000033116	zithromax 500mg tablets (pfizer ltd)	abx
8029141000033118	zithromax sd oral suspension 2 gram/unit dose	abx

Codes to Identify Heart Failure (CPRD GOLD)

medcode	description
398	congestive heart failure
884	left ventricular failure
2062	heart failure
2906	congestive cardiac failure
12627	seen in heart failure clinic
8966	Left ventricular systolic dysfunction
4024	heart failure nos
17851	heart failure follow-up
12366	congestive heart failure monitoring
30779	heart failure annual review
1223	cardiac failure
9913	heart failure confirmed
13189	New York Heart Association classification - class II
11284	Echocardiogram shows left ventricular systolic dysfunction
5942	impaired left ventricular function
7251	Impaired Left Ventricular Function
18853	New York Heart Association classification - class I
19066	New York Heart Association classification - class III
12550	Left ventricular diastolic dysfunction
5255	acute left ventricular failure
83502	heart failure 6 month review
32671	chronic congestive heart failure
32945	heart failure care plan discussed with patient
11351	Echocardiogram shows left ventricular diastolic dysfunction
24503	Cardiac failure therapy
27884	decompensated cardiac failure
107397	Left ventricular cardiac dysfunction
103732	has heart failure management plan
17278	cardiac failure nos
23707	acute congestive heart failure
27964	acute heart failure
26242	New York Heart Assoc classification heart failure symptoms
51214	New York Heart Association classification - class IV
101138	heart failure with normal ejection fraction
32898	admit heart failure emergency
11424	compensated cardiac failure
106897	heart failure with preserved ejection fraction
101137	hfnef - heart failure with normal ejection fraction
94870	congestive heart failure due to valvular disease
106008	heart failure clinical pathway
62718	hypertensive heart disease nos with ccf
21837	hypertensive heart&renal dis wth (congestive) heart failure
52127	benign hypertensive heart disease with ccf
57987	Hyperten heart&renal dis+both(congestv)heart and renal fail

105542	preferred place of care for next exacerbation heart failure
72668	malignant hypertensive heart disease with ccf
66306	heart failure as a complication of care
22262	Rheumatic left ventricular failure
9524	Biventricular failure
10079	Right heart failure
10154	Right ventricular failure
104275	Right ventricular failure
5695	Chronic cor pulmonale
8464	Acute cor pulmonale

Codes to identify Myocardial Infraction (CPRD GOLD)

medcode	description
241	Acute myocardial infarction
1204	Heart attack
1677	MI - acute myocardial infarction
1678	Inferior myocardial infarction NOS
2491	Coronary thrombosis
3704	Acute subendocardial infarction
4017	Old myocardial infarction
5387	Other specified anterior myocardial infarction
8935	Acute inferolateral infarction
9507	Acute non-Q wave infarction
10562	Acute non-ST segment elevation myocardial infarction
12139	Acute anterolateral infarction
12229	Acute ST segment elevation myocardial infarction
13566	Attack - heart
13571	Thrombosis - coronary
14658	Acute myocardial infarction NOS
14897	Anterior myocardial infarction NOS
14898	Lateral myocardial infarction NOS
17464	Personal history of myocardial infarction
17689	Silent myocardial infarction
17872	Acute anteroseptal infarction
18842	Subsequent myocardial infarction
23708	Atrial septal defect/curr comp folow acut myocardal infarct
23892	Posterior myocardial infarction NOS
28736	Acute atrial infarction
29553	Thrombosis atrium,auric append&vent/curr comp foll acute MI
29643	Acute inferoposterior infarction
29758	Acute transmural myocardial infarction of unspecif site
30330	Acute Q-wave infarct
30421	Cardiac rupture following myocardial infarction (MI)
32272	Postoperative myocardial infarction
32854	Acute posterolateral myocardial infarction
34803	Other acute myocardial infarction
36423	Certain current complication follow acute myocardial infarct
37657	Ventric septal defect/curr comp fol acut myocardal infarctn
38609	Subsequent myocardial infarction of inferior wall
40429	Acute anteroapical infarction
41221	Acute septal infarction
41835	Postoperative subendocardial myocardial infarction
45809	Subsequent myocardial infarction of anterior wall
46017	Other acute myocardial infarction NOS
46112	Postoperative transmural myocardial infarction anterior wall

46166	Subsequent myocardial infarction of unspecified site
46276	Postoperative transmural myocardial infarction inferior wall
50372	H/O: Myocardial infarction in last year
59189	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
59940	Ruptur chordae tendinae/curr comp fol acute myocard infarct
62626	Acute papillary muscle infarction
63467	True posterior myocardial infarction
68748	Postoperative myocardial infarction, unspecified
69474	Rupture papillary muscle/curr comp fol acute myocard infarct
72562	Subsequent myocardial infarction of other sites
96838	[X]Acute transmural myocardial infarction of unspecif site
99991	[X]Subsequent myocardial infarction of unspecified site
100139	History of myocardial infarction
109035	[X]Subsequent myocardial infarction of other sites
21844	Transient myocardial ischaemia
33650	percut transluminal coronary thrombolysis with streptokinase

Codes to identify Myocardial Infraction (CPRD Aurum)

Medcodeid	Term
905351000006113	[rfc] myocardial infarction (mi)
362461000006119	[x]acute transmural myocardial infarction of unspecif site
300881018	[x]subsequent myocardial infarction of other sites
300882013	[x]subsequent myocardial infarction of unspecified site
3343471000006116	acute anteroapical myocardial infarction
3699921000006110	acute inferior myocardial infarction
94884017	acute myocardial infarction
299721019	acute myocardial infarction nos
3381601000006117	acute myocardial infarction of anterior wall
3641641000006116	acute myocardial infarction of anterolateral wall
4775891000006119	acute myocardial infarction of atrium
3699911000006119	acute myocardial infarction of diaphragmatic wall
3565871000006113	acute myocardial infarction of inferolateral wall
3745741000006117	acute myocardial infarction of inferoposterior wall
3452181000006112	acute myocardial infarction of lateral wall
3784911000006111	acute myocardial infarction of septum
3784921000006115	acute myocardial infarction of septum alone
1780501013	acute non-st segment elevation myocardial infarction
967931000006114	acute posterolateral myocardial infarction
5935321000006111	acute q wave myocardial infarction
1780491019	acute st segment elevation myocardial infarction
460681000006116	acute transmural myocardial infarction of unspecif site
3427201000006111	ami - acute myocardial infarction
299709018	anterior myocardial infarction nos
1576301000006115	cause of death- acute myocardial infarction
1576271000006117	cause of death- myocardial infarction
256452010	ecg: myocardial infarction
4586051000006118	ekg: myocardial infarction
4586041000006115	electrocardiographic myocardial infarction
932081000006118	first myocardial infarction
299714019	inferior myocardial infarction nos
299711010	lateral myocardial infarction nos
219531000000117	mi - acute myocardial infarction
2855341000006114	mi - myocardial infarction
5056461000006113	mi - silent myocardial infarction
884151000006119	myocardial infarction
2855301000006112	myocardial infarction
6348651000006112	myocardial infarction with complication
299718016	other acute myocardial infarction
299720018	other acute myocardial infarction nos
299707016	other specified anterior myocardial infarction
299710011	posterior myocardial infarction nos
208365015	postoperative myocardial infarction
455423016	postoperative myocardial infarction, unspecified
455422014	postoperative subendocardial myocardial infarction
212061000006119	postoperative transmural myocardial infarction anterior wall
212071000006114	postoperative transmural myocardial infarction inferior wall
212081000006112	postoperative transmural myocardial infarction other sites

212091000006110	postoperative transmural myocardial infarction unspec site
350376014	silent myocardial infarction
6651221000006117	stemi - st elevation myocardial infarction
299808017	subsequent myocardial infarction
299811016	subsequent myocardial infarction of anterior wall
299812011	subsequent myocardial infarction of inferior wall
299813018	subsequent myocardial infarction of other sites
118831000006118	subsequent myocardial infarction of unspecified site
299712015	true posterior myocardial infarction

Codes to identifysstroke (CPRD GOLD)

medcode	description
93459	[x]other lacunar syndromes
29939	ruptured berry aneurysm
5051	intracerebral haemorrhage
6960	cva - cerebrovascular accid due to intracerebral haemorrhage
18604	stroke due to intracerebral haemorrhage
31595	cortical haemorrhage
40338	internal capsule haemorrhage
46316	basal nucleus haemorrhage
13564	cerebellar haemorrhage
7912	pontine haemorrhage
62342	bulbar haemorrhage
30202	intracerebral haemorrhage, intraventricular
57315	intracerebral haemorrhage, multiple localized
107440	lobar cerebral haemorrhage
31060	intracerebral haemorrhage in hemisphere, unspecified
28314	left sided intracerebral haemorrhage, unspecified
19201	right sided intracerebral haemorrhage, unspecified
3535	intracerebral haemorrhage nos
31805	other and unspecified intracranial haemorrhage
20284	intracranial haemorrhage nos
45781	precerebral arterial occlusion
57495	infarction - precerebral
32447	basilar artery occlusion
4240	carotid artery occlusion
4152	thrombosis, carotid artery
40847	vertebral artery occlusion
98642	multiple and bilateral precerebral arterial occlusion
51326	other precerebral artery occlusion
23671	cerebral infarct due to thrombosis of precerebral arteries
24446	cerebral infarction due to embolism of precerebral arteries
71585	precerebral artery occlusion nos
8837	cerebral arterial occlusion
5363	cva - cerebral artery occlusion
569	infarction - cerebral
6155	stroke due to cerebral arterial occlusion
16517	cerebral thrombosis
36717	cerebral infarction due to thrombosis of cerebral arteries
15019	cerebral embolism
34758	cerebral embolus
27975	cerebral infarction due to embolism of cerebral arteries
3149	cerebral infarction nos
15252	brainstem infarction nos
5602	cerebellar infarction

25615	brainstem infarction
9985	left sided cerebral infarction
10504	right sided cerebral infarction
26424	infarction of basal ganglia
1469	stroke and cerebrovascular accident unspecified
1298	cva unspecified
6253	stroke unspecified
6116	cva - cerebrovascular accident unspecified
18689	middle cerebral artery syndrome
19280	anterior cerebral artery syndrome
19260	posterior cerebral artery syndrome
8443	brain stem stroke syndrome
17322	cerebellar stroke syndrome
33499	pure motor lacunar syndrome
51767	pure sensory lacunar syndrome
7780	left sided cva
12833	right sided cva
40053	generalised ischaemic cerebrovascular disease nos
70536	acute cerebrovascular insufficiency nos
12555	generalised ischaemic cerebrovascular disease nos
39344	cereb infarct due cerebral venous thrombosis, nonpyogenic
51759	occlusion and stenosis of middle cerebral artery
57527	occlusion and stenosis of anterior cerebral artery
65770	occlusion and stenosis of posterior cerebral artery
55602	occlusion and stenosis of cerebellar arteries
71274	occlusion+stenosis of multiple and bilat cerebral arteries
98188	small vessel cerebrovascular disease
34117	other cerebrovascular disease os
37493	other cerebrovascular disease nos
40758	cereb infarct due unsp occlus/stenos precerebr arteries
33543	cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
51311	other specified cerebrovascular disease
10062	cerebrovascular disease nos
73901	[x]cerebrovascular diseases
53810	[x]other intracerebral haemorrhage
91627	[x]cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
53745	[x]other cerebral infarction
90572	[x]occlusion and stenosis of other precerebral arteries
92036	[x]occlusion and stenosis of other cerebral arteries
96630	[x]intracerebral haemorrhage in hemisphere, unspecified
94482	[x]cereb infarct due unsp occlus/stenos precerebr arteries
47607	cva - cerebrovascular accident in the puerperium

Codes to identify Coronary Heart Disease/Ischemic Heart Disease (CPRD GOLD)

medcode	description
1430	angina pectoris
240	Ischaemic heart disease
241	acute myocardial infarction
1792	IHD - Ischaemic heart disease
68357	Microinfarction of heart
66388	Status anginosus
19542	angina control - good
737	Coronary artery bypass graft operations
1344	Coronary artery disease
1431	unstable angina
1676	Ischaemic heart disease NOS
2901	Transluminal balloon angioplasty of coronary artery
11983	acute coronary syndrome
7347	Unstable angina
8942	Insertion of coronary artery stent
5904	Coronary artery operations
28554	angina pectoris nos
7137	Saphenous vein graft replacement of coronary artery OS
43939	Perc translumin balloon angioplasty stenting coronary artery
1655	Triple vessel disease of the heart
5413	Coronary atherosclerosis
105184	Percutaneous coronary intervention
1414	angina on effort
25842	angina pectoris nos
12804	stable angina
3999	Single coronary vessel disease
4656	crescendo angina
5744	Open angioplasty of coronary artery
732	Transluminal balloon angioplasty of coronary artery NOS
5254	Double coronary vessel disease
2491	Coronary thrombosis
12734	Coronary artery bypass graft occlusion
36523	preinfarction syndrome
7442	Saphenous vein graft replacement of three coronary arteries
18118	worsening angina
15373	angina control - poor
9276	Acute coronary insufficiency
18249	Saphenous vein graft replacement of coronary artery
5030	[V]Presence of coronary artery bypass graft
20095	angina decubitus
20416	Atherosclerotic heart disease
7320	Ischaemic cardiomyopathy
42304	Insertion of drug-eluting coronary artery stent

15349	Angina control NOS
17307	angina at rest
11610	Saphenous vein graft replacement of four+ coronary arteries
18670	Percut transluminal balloon angioplasty one coronary artery
7634	Saphenous vein graft replacement of two coronary arteries
8312	Saphenous vein graft bypass of coronary artery
36854	coronary artery spasm
23078	Chronic myocardial ischaemia
10603	Coronary artery operations NOS
32450	ischaemic chest pain
18889	Asymptomatic coronary heart disease
22828	Percutaneous transluminal laser coronary angioplasty
60067	Perc translum ball angio insert 1-2 drug elut stents cor art
12986	prinzmetal's angina
33471	Other bypass of coronary artery NOS
24783	Arteriosclerotic heart disease
34963	Other bypass of coronary artery
22383	Other specified ischaemic heart disease
23892	posterior myocardial infarction nos
28138	Other chronic ischaemic heart disease
19655	angina at rest
17133	mural thrombosis
29421	Silent myocardial ischaemia
15661	Dressler's syndrome
26863	new onset angina
8679	Saphenous vein graft replacement of one coronary artery
33461	Revision of bypass for coronary artery
33735	Percut translum balloon angioplasty mult coronary arteries
15754	Other chronic ischaemic heart disease NOS
9414	Other autograft replacement of coronary artery
51515	Saphenous vein graft replacement coronary artery NOS
36609	Atherosclerotic cardiovascular disease
18125	nocturnal angina
9555	Post infarct angina
85947	Perc translum balloon angioplasty insert 1-2 stents cor art
3159	Other specified other bypass of coronary artery
31571	Other specified operations on coronary artery
61208	Perc translum balloon angioplasty stenting coronary art NOS
30421	Cardiac rupture following myocardial infarction (MI)
27951	Other acute and subacute ischaemic heart disease
10209	Autograft replacement of three coronary arteries NEC
32651	Allograft bypass of coronary artery
34328	refractory angina
11048	variant angina pectoris
57062	H/O: Angina in last year
87849	Perc tran ball angio ins 3 or more drug elut stents cor art

24540	Chronic coronary insufficiency
9413	Other acute and subacute ischaemic heart disease
23579	Postmyocardial infarction syndrome
39693	Subendocardial ischaemia
27977	Other acute and subacute ischaemic heart disease NOS
34633	Other specified chronic ischaemic heart disease
42462	Percut translum balloon angioplasty bypass graft coronary a
45809	Subsequent myocardial infarction of anterior wall
37657	Ventric septal defect/curr comp fol acut myocardal infarctn
38609	subsequent myocardial infarction of inferior wall
44585	Repair of coronary artery NOS
7696	Syncope anginosa
35713	Other specified chronic ischaemic heart disease NOS
29553	Thrombosis atrium,auric append&vent/curr comp foll acute MI
18913	[V]Presence of aortocoronary bypass graft
23708	Atrial septal defect/curr comp folow acut myocardal infarct
36423	Certain current complication follow acute myocardial infarct
59189	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI

Codes to identify Atrial Fibrillation (CPRD GOLD)

medcode	description
1268	Paroxysmal atrial fibrillation
1664	Atrial fibrillation
1757	Atrial flutter
2212	Atrial fibrillation and flutter
3757	ECG: atrial fibrillation
23437	Atrial fibrillation and flutter NOS
35127	Non-rheumatic atrial fibrillation
45773	Atrial fibrillation annual review
96076	Persistent atrial fibrillation
96277	Permanent atrial fibrillation
107472	Paroxysmal atrial flutter

Codes to identify HF, MI, AF, stroke, and CAD in HES and ONS

HF	stroke	MI	AF	stroke	CAD
I09.9	I61	I21.0	I48.0	I60	I20
I11.0	I693	I21.1	I48.1	I60.0	I20.0
I11.9	G463	I21.2	I48.2	I60.1	I20.1
I13.0	G464	I21.3	I48.3	I60.2	I20.8
I13.1	G465	I21.4	I48.4	I60.3	I20.9
I13.2	G466	I21.9	I48.9	I60.4	I23
I50	G467	I22.0		I60.5	I23.0
I50.0	I64	I22.1		I60.6	I23.1
I50.1	I63.0	I22.8		I60.7	I23.2
I50.20	I63.1	I22.9		I60.8	I23.3
I50.21	I63.2			I60.9	I23.4
I50.22	I63.3			I61	I23.5
I50.23	I63.4			I61.0	I23.6
I50.30	I63.5			I61.1	I23.8
I50.31	I63.8			I61.2	I24
I50.32	I63.9			I61.3	I24.0
I50.33				I61.4	I24.1
I50.40				I61.5	I24.8
I50.41				I61.6	I24.9
I50.42				I61.8	I25
I50.43				I61.9	I25.0
I50.810				I62	I25.1
I50.811				I62.0	I25.2
I50.812				I62.1	I25.5
I50.813				I62.9	I25.6
I50.814				I63	I25.8
I50.82				I63.0	I25.9
I50.83				I63.1	T82.2
I50.84				I63.2	Z95.5
I50.89				I63.3	
I50.9				I63.4	
				I63.5	
				I63.6	
				I63.8	
				I63.9	
				I64	

Codes to identify AECOPD events (CPRD GOLD)

medcode	Term
68	Chest infection
148	Bronchitis unspecified
152	Wheezy bronchitis
312	Acute bronchitis
556	Influenza
1019	Acute bronchiolitis
1382	Acute viral bronchitis unspecified
1446	Acute exacerbation of chronic obstructive airways disease
2157	Flu like illness
2476	Chest cold
2581	Chest infection NOS
3163	Tracheobronchitis NOS
3358	Lower resp tract infection
3480	Bronchitis NOS
4899	Recurrent chest infection
5947	Influenza like illness
5978	Acute wheezy bronchitis
6124	Acute lower respiratory tract infection
6181	Obliterating fibrous bronchiolitis
7092	Recurrent wheezy bronchitis
7884	Chron obstruct pulmonary dis wth acute exacerbation, unspec
8980	Influenza-like symptoms
9043	Acute pneumococcal bronchitis
9389	Chest infection - viral pneumonia
11019	Admit COPD emergency
11072	Acute purulent bronchitis
11101	Acute tracheobronchitis
11150	Mucopurulent chronic bronchitis
14791	Influenza with gastrointestinal tract involvement
14798	Emphysematous bronchitis
15626	Chronic catarrhal bronchitis
15774	Influenza with laryngitis
16287	Chest infection - unspecified bronchopneumonia
16388	Influenza NOS
17185	Acute bronchiolitis with bronchospasm
17359	Chest infection - unspecified bronchitis
17917	Acute bronchiolitis NOS
18207	Allergic bronchitis NEC
18451	Acute bronchiolitis due to respiratory syncytial virus
20198	Acute bronchitis NOS
21061	Chronic obstruct pulmonary dis with acute lower resp infectn
21145	Acute croupous bronchitis
21492	Acute haemophilus influenzae bronchitis
22795	Chest infection - other bacterial pneumonia
23488	Influenza with respiratory manifestations NOS
24248	Mixed simple and mucopurulent chronic bronchitis

24316	Chest infection with infectious disease EC
24800	Acute bacterial bronchitis unspecified
26125	Bronchiolitis obliterans
29166	Chest infection - pneumococcal pneumonia
29273	Acute bronchitis due to parainfluenza virus
29457	Chest infection - influenza with pneumonia
29617	Influenza with pharyngitis
29669	Acute bronchitis and bronchiolitis
30653	Chest infection - pneumonia organism OS
31363	Influenza with other manifestations NOS
31886	Acute bronchitis due to mycoplasma pneumoniae
37447	Acute lower respiratory tract infection
40159	Purulent chronic bronchitis
41137	Acute bronchitis or bronchiolitis NOS
41589	Acute obliterating bronchiolitis
43362	Acute streptococcal bronchitis
43625	Influenza with other respiratory manifestation
46157	Influenza with encephalopathy
47472	Influenza with other manifestations
48593	Acute bronchitis due to respiratory syncytial virus
49794	Acute neisseria catarrhalis bronchitis
50396	Acute fibrinous bronchitis
54533	Acute capillary bronchiolitis
54830	Acute bronchitis due to chemical fumes
55391	Subacute bronchitis unspecified
61513	Mucopurulent chronic bronchitis NOS
63216	Obliterative bronchiolitis due to chemical fumes
63697	Avian influenza virus nucleic acid detection
64890	Acute bronchitis due to rhinovirus
65916	Acute bronchitis due to echovirus
66228	Acute bronchiolitis due to other specified organisms
66397	[X]Other acute lower respiratory infections
69192	Acute exudative bronchiolitis
71370	Acute pseudomembranous bronchitis
73100	[X]Acute bronchitis due to other specified organisms
91123	Parainfluenza type 3 nucleic acid detection
93153	Acute bronchitis due to coxsackievirus
94130	Parainfluenza type 1 nucleic acid detection
94858	Parainfluenza type 2 nucleic acid detection
94930	Avian influenza
96017	Influenza B virus detected
96018	Influenza H3 virus detected
96019	Influenza H1 virus detected
96286	Human parainfluenza virus detected
97062	Influenza A virus, other or untyped strain detected
97279	[X]Influenza+other manifestations, virus not identified
97605	[X]Influenza+oth respiratory manifestatns,virus not identifd
97936	[X]Influenza+other manifestations,influenza virus identified
98102	Influenza A (H1N1) swine flu

98103	Possible influenza A virus H1N1 subtype
98115	Suspected swine influenza
98125	Suspected influenza A virus subtype H1N1 infection
98129	Influenza due to Influenza A virus subtype H1N1
98143	Influenza A virus H1N1 subtype detected
98156	Influenza H5 virus detected
98257	[X]Flu+oth respiratory manifestations,'flu virus identified
99214	[X]Acute bronchiolitis due to other specified organisms
100650	Aspergillus bronchitis
101775	Acute membranous bronchitis
102918	Influenza H2 virus detected

Codes to identify AECOPD events (CPRD Aurum)

medcodeid	description
1173471000000110	Antibiotic therapy for acute pulmonary exacerbation
1765431000000114	Preferred place of care for next exacerbation of COPD
1882421000006113	1 COPD exacerbation in past year
1882431000006111	3+ COPD exacerbations in past year
1882441000006118	2 COPD exacerbations in past year
1882451000006116	No COPD exacerbations in past year
2192591000000114	Dyspnoea, obstruction, smoking, exacerbation frequency index
2196421000000114	Acute non-infective exacerbation of chronic obstructive pulmonary disease
2533538014	Chronic obstructive pulmonary disease accident and emergency attendance since last visit
2533539018	Emergency chronic obstructive pulmonary disease admission since last appointment
300201000000114	Multiple chronic obstructive pulmonary disease emergency hospital admissions
301453013	Acute exacerbation of chronic obstructive airways disease
3335171010	Number of chronic obstructive pulmonary disease exacerbations in past year
424365019	Acute infective exacerbation of chronic obstructive pulmonary disease
756761000000112	At risk of chronic obstructive pulmonary diseas exacerbation

Codes to identify LRTI (CPRD GOLD)

medcode	readterm
68	chest infection
312	acute bronchitis
1382	acute viral bronchitis unspecified
2476	chest cold
2581	chest infection nos
3358	lower resp tract infection
5978	acute wheezy bronchitis
6124	acute lower respiratory tract infection
9043	acute pneumococcal bronchitis
11072	acute purulent bronchitis
17359	chest infection - unspecified bronchitis
20198	acute bronchitis nos
21061	chronic obstruct pulmonary dis with acute lower resp infectn
21492	acute haemophilus influenzae bronchitis
24316	chest infection with infectious disease ec
24800	acute bacterial bronchitis unspecified
29273	acute bronchitis due to parainfluenza virus
37447	acute lower respiratory tract infection
43362	acute streptococcal bronchitis
48593	acute bronchitis due to respiratory syncytial virus
49794	acute neisseria catarrhalis bronchitis
64890	acute bronchitis due to rhinovirus
65916	acute bronchitis due to echovirus
71370	acute pseudomembranous bronchitis
73100	[x]acute bronchitis due to other specified organisms
93153	acute bronchitis due to coxsackievirus
101775	acute membranous bronchitis
556	influenza
1019	acute bronchiolitis
2157	flu like illness
5947	influenza like illness
6181	obliterating fibrous bronchiolitis
8980	influenza-like symptoms
14791	influenza with gastrointestinal tract involvement
15774	influenza with laryngitis
16388	influenza nos
17185	acute bronchiolitis with bronchospasm
17917	acute bronchiolitis nos
18451	acute bronchiolitis due to respiratory syncytial virus
21145	acute croupous bronchitis
23488	influenza with respiratory manifestations nos
26125	bronchiolitis obliterans
29617	influenza with pharyngitis

29669	acute bronchitis and bronchiolitis
31363	influenza with other manifestations nos
41137	acute bronchitis or bronchiolitis nos
41589	acute obliterating bronchiolitis
43625	influenza with other respiratory manifestation
46157	influenza with encephalopathy
47472	influenza with other manifestations
54533	acute capillary bronchiolitis
63697	avian influenza virus nucleic acid detection
66228	acute bronchiolitis due to other specified organisms
66397	[x]other acute lower respiratory infections
69192	acute exudative bronchiolitis
91123	parainfluenza type 3 nucleic acid detection
94130	parainfluenza type 1 nucleic acid detection
94858	parainfluenza type 2 nucleic acid detection
94930	avian influenza
96017	influenza b virus detected
96018	influenza h3 virus detected
96019	influenza h1 virus detected
96286	human parainfluenza virus detected
97062	influenza a virus, other or untyped strain detected
97279	[x]influenza+other manifestations, virus not identified
97605	[x]influenza+oth respiratory manifestatns,virus not identifd
97936	[x]influenza+other manifestations,influenza virus identified
98102	influenza a (h1n1) swine flu
98103	possible influenza a virus h1n1 subtype
98115	suspected swine influenza
98125	suspected influenza a virus subtype h1n1 infection
98129	influenza due to influenza a virus subtype h1n1
98143	influenza a virus h1n1 subtype detected
98156	influenza h5 virus detected
98257	[x]flu+oth respiratory manifestations,'flu virus identified
99214	[x]acute bronchiolitis due to other specified organisms
102918	influenza h2 virus detected

Codes to identify LRTI (CPRD Aurum)

medcodeid	term
843921000033117	*influenza & common cold
907511000006114	[rfc] chest infection
301821013	[x]acute bronchiolitis due to other specified organisms
301820014	[x]acute bronchitis due to other specified organisms
387051000006110	[x]flu+oth respiratory manifestations,'flu virus identified
288067017	[x]haemophilus influenzae infection, unspecified
389891000006119	[x]influenza+other manifestations, virus not identified
389901000006115	[x]influenza+other manifestations,influenza virus identified
301819015	[x]other acute lower respiratory infections
301121011	acute bacterial bronchitis unspecified
10187013	acute bronchiolitis
7302851000006115	acute bronchiolitis caused by human metapneumovirus
4780571000006115	acute bronchiolitis caused by respiratory syncytial virus
1816261000006119	acute bronchiolitis due to human metapneumovirus
301129013	acute bronchiolitis due to other specified organisms
301128017	acute bronchiolitis due to respiratory syncytial virus
301130015	acute bronchiolitis nos
25801011	acute bronchiolitis with bronchospasm
18268014	acute bronchitis
301095014	acute bronchitis and bronchiolitis
12717061000006114	acute bronchitis and/or bronchiolitis
4780471000006119	acute bronchitis caused by coxsackievirus
4780511000006112	acute bronchitis caused by rhinovirus
455991000006112	acute bronchitis due to coxsackievirus
456001000006113	acute bronchitis due to echovirus
4780541000006111	acute bronchitis due to echovirus
350044014	acute bronchitis due to mycoplasma pneumoniae
456021000006115	acute bronchitis due to parainfluenza virus
456031000006117	acute bronchitis due to respiratory syncytial virus
301116013	acute bronchitis due to rhinovirus
301122016	acute bronchitis nos
301132011	acute bronchitis or bronchiolitis nos
885041000006119	acute bronchitis/bronchiolitis
4780461000006114	acute coxsackieviral bronchitis
4780451000006112	acute coxsackievirus bronchitis
2475602011	acute croupous bronchitis
4780531000006118	acute echoviral bronchitis
4780521000006116	acute echovirus bronchitis
301126018	acute exudative bronchiolitis
301108016	acute haemophilus influenzae bronchitis
457801000006117	acute lower respiratory tract infection
579878017	acute lower respiratory tract infection
4780421000006115	acute moraxella catarrhalis bronchitis
5053331000006119	acute mycoplasmal bronchitis
301109012	acute neisseria catarrhalis bronchitis
4780481000006116	acute parainfluenza virus bronchitis
301105018	acute pneumococcal bronchitis

301103013	acute purulent bronchitis
885051000006117	acute resp. infection nos
12726371000006114	acute respiratory infection nos
301145010	acute respiratory infection nos
300997012	acute respiratory infections
4780491000006118	acute respiratory syncytial virus bronchitis
301106017	acute streptococcal bronchitis
58909014	acute tracheobronchitis
5053371000006116	acute viral bronchiolitis
301120012	acute viral bronchitis unspecified
411490016	acute wheezy bronchitis
4780011000006115	ari - acute respiratory infections
92429016	avian influenza
312571000000119	avian influenza virus nucleic acid detection
2564641000006110	bronchiolitis
7302861000006118	bronchiolitis caused by human metapneumovirus
7302821000006112	bronchiolitis due to human metapneumovirus
546411000006111	chest infection
1222333010	chest infection - pneumonia organism os
350041018	chest infection - unspecified bronchitis
396090018	chest infection nos
546511000006112	chest infection with infectious disease ec
5992751000006117	encephalitis due to influenza
906821000033118	haemophilus influenzae (lyophilized bacterial lysates)
151462017	haemophilus influenzae infection
7649691000006115	haemophilus influenzae type b infection
7649701000006115	hib (haemophilus influenzae type b) infection
689941000000115	human parainfluenza virus detected
11203012	influenza
885261000006111	influenza + encephalopathy
885251000006114	influenza + pneumonia
7267051000006117	influenza a (h1n1)
1128141000000118	influenza a (h1n1) swine flu
1126371000000114	influenza a virus h1n1 subtype detected
677021000000113	influenza a virus, other or untyped strain detected
2175841000000116	influenza b nucleic acid detection
677081000000114	influenza b virus detected
7267061000006115	influenza caused by influenza a virus subtype h1n1
2820795016	influenza due to influenza a virus subtype h1n1
2608951000000113	influenza due to pandemic influenza virus
2608991000000117	influenza due to seasonal influenza virus
2608911000000114	influenza due to zoonotic influenza virus
676781000000110	influenza h1 virus detected
676841000000114	influenza h2 virus detected
676901000000115	influenza h3 virus detected
676961000000116	influenza h5 virus detected
4063911000006112	influenza like illness
778711000006116	influenza like illness
2397631000033114	influenza myl
396106019	influenza nos
301416019	influenza with laryngitis

301421016	influenza with other manifestations
1988661000006110	influenza with other manifestations due to seasonl inf virus
301424012	influenza with other manifestations nos
301415015	influenza with other respiratory manifestation
1988651000006113	influenza with othr resp manifestation due to seasonal virus
301417011	influenza with pharyngitis
778871000006116	influenza with pneumonia
301414016	influenza with pneumonia nos
301418018	influenza with respiratory manifestations nos
460161011	influenza-like symptoms
733471000006110	lower resp tract infection
3316381000006114	lower respiratory infection
3316401000006114	lrti - lower respiratory tract infection
301144014	other specified acute respiratory infections
301430012	other specified pneumonia or influenza
353561000000111	parainfluenza type 1 nucleic acid detection
353591000000117	parainfluenza type 2 nucleic acid detection
353621000000119	parainfluenza type 3 nucleic acid detection
2115571000000116	parainfluenza type 4 nucleic acid detection
3555891000006119	pneumonia due to parainfluenza virus
1232627018	pneumonia due to parainfluenza virus
301431011	pneumonia or influenza nos
12721231000006111	pneumonia or influenza nos
175471000006116	respiratory infection nos
92677014	respiratory syncytial virus infection
411488017	respiratory tract infection
3405411000006114	rsv - respiratory syncytial virus infection
5573831000006110	rti - respiratory tract infection
301119018	subacute bronchitis unspecified
1707241000006115	swine influenza

Codes to identify cough (CPRD GOLD)

medcode	readterm
92	cough
292	chesty cough
1025	bronchial cough
1160	[d]cough
1234	productive cough nos
1273	c/o - cough
3068	night cough present
3645	coughing up phlegm
4070	morning cough
4836	nocturnal cough / wheeze
4931	dry cough
7706	productive cough -clear sputum
7707	cough symptom nos
7708	productive cough-yellow sputum
7773	productive cough -green sputum
8239	[d]cough with haemorrhage
18907	cough with fever
22318	difficulty in coughing up sputum
29318	evening cough
60903	cough aggravates symptom
100515	cough swab

Codes to identify cough (CPRD Aurum)

medcodeid	term
317403015	[d]cough
2168391000000116	[d]episodic dry cough
30371011	barking cough
252360013	bronchial cough
407081018	c/o - cough
252359015	chesty cough
113213012	chronic cough
3256651000006113	cigarette cough
5533011000006112	complaining of cough
1970531000006111	copd assessment test score - cough
961781000006119	cough
479311018	cough on exercise
1935491000006116	cough stress test positive
252366019	cough symptom nos
216653013	cough with fever
1763631000006115	cough with physiotherapy
598431000006113	coughing up phlegm
1780331000006117	daytime cough
20419011	dry cough
8260311000006113	episodic dry cough
252364016	evening cough
1819551000006111	history of productive cough
2961951000006114	moist cough
252363010	morning cough
252357018	night cough present
252406018	nocturnal cough / wheeze
11823221000006114	non-productive cough
3304991000006116	observation of cough
2011321000006113	oh respiratory questionnaire: > 1 cough/phlegm episode in past 3 years - yes
2011101000006118	oh respiratory questionnaire: cough first thing in morning in winter - yes
2011181000006110	oh respiratory questionnaire: cough most days as much as 3 months/year - yes
2010881000006111	oh respiratory questionnaire: cough when climb stairs fast - yes
2010821000006112	oh respiratory questionnaire: cough when run fast - yes
2011301000006115	oh respiratory questionnaire: increased cough/phlegm > 3 weeks in past 3 years - yes
2011121000006111	oh respiratory questionnaire: usually cough during the day - yes
2011141000006116	oh respiratory questionnaire: usually cough during the night - yes
2011161000006117	oh respiratory questionnaire: usually cough in winter - yes
423230012	persistent cough
252351017	productive cough -clear sputum
252352012	productive cough -green sputum
397882011	productive cough nos
252353019	productive cough-yellow sputum
295349016	psychogenic cough
806931000033118	robitussin chesty cough
78013015	smokers' cough
459738011	unexplained cough

2688441000006111	unproductive cough
82824016	cough
1709331000006110	cough on exercise

Codes to identify breathlessness (CPRD GOLD)

medcode	readterm
735	[d]breathlessness
741	[d]shortness of breath
1429	breathlessness
2563	[d]respiratory distress
2575	short of breath on exertion
2737	respiratory distress syndrome
2931	difficulty breathing
3092	[d]dyspnoea
4822	shortness of breath
5175	breathlessness symptom
5349	shortness of breath symptom
5896	dyspnoea - symptom
6326	breathless - moderate exertion
6434	paroxysmal nocturnal dyspnoea
7000	o/e - dyspnoea
7534	o/e - respiratory distress
7683	breathless - lying flat
7932	breathless - mild exertion
9297	[d]respiratory insufficiency
18116	nocturnal dyspnoea
21801	breathlessness nos
22094	short of breath dressing/undressing
24889	breathless - strenuous exertion
31143	breathless - at rest
53771	dyspnoea on exertion
40813	Unable to complete a sentence in one breath

Codes to identify sputum (CPRD GOLD)

medcode	readterm
292	chesty cough
1025	bronchial cough
1234	productive cough nos
1251	[d]abnormal sputum
3645	Coughing up phlegm
3727	sputum sent for c/s
7706	productive cough -clear sputum
7708	productive cough-yellow sputum
7773	productive cough -green sputum
8287	sputum sample obtained
8760	[d]positive culture findings in sputum
9807	sputum - symptom
11072	acute purulent bronchitis
14271	sputum culture
14272	sputum microscopy
14273	sputum appearance
14804	sputum appears infected
15430	[d]sputum abnormal - colour
16026	sputum examination: abnormal
18964	sputum clearance
20086	[d]sputum abnormal - amount
22318	difficulty in coughing up sputum
23252	sputum microscopy nos
23582	[d]abnormal sputum nos
24181	sputum: mucopurulent
30754	yellow sputum
30904	sputum sent for examination
36515	[d]abnormal sputum - tenacious
36880	green sputum
43270	sputum evidence of infection
44214	[d]sputum abnormal - odour
49144	sputum: pus cells present
49694	sputum: organism on gram stain
54177	sputum: excessive - mucoid
100484	volume of sputum
100524	moderate sputum
100629	white sputum
100647	copious sputum
100931	brown sputum
101782	profuse sputum
103209	grey sputum

Codes to identify sputum (CPRD Aurum)

medcodeid	term
317414017	[d]abnormal sputum
317420016	[d]abnormal sputum - tenacious
317421017	[d]abnormal sputum nos
317415016	[d]sputum abnormal - amount
317417012	[d]sputum abnormal - colour
317418019	[d]sputum abnormal - odour
961811000006117	abnormal sputum
301103013	acute purulent bronchitis
5606201000006111	appearance of sputum
252360013	bronchial cough
414649011	brown sputum
252359015	chesty cough
371091012	clear sputum
371086011	copious sputum
598431000006113	coughing up phlegm
2226161000000119	dark green sputum
3201001000006118	fetid sputum
5606181000006110	gray sputum
414647013	green sputum
414638017	grey sputum
301456017	mixed simple and mucopurulent chronic bronchitis
1709281000006118	moderate sputum
2961951000006114	moist cough
411653012	mucoid sputum - o/e
885281000006118	mucopurulent chr. bronchitis
123588010	mucopurulent chronic bronchitis
301448015	mucopurulent chronic bronchitis nos
2011321000006113	oh respiratory questionnaire: > 1 cough/phlegm episode in past 3 years - yes
2011301000006115	oh respiratory questionnaire: increased cough/phlegm > 3 weeks in past 3 years - yes
1838091000006112	other sputum isolate identified
1834121000006118	pale green sputum
2961961000006111	producing sputum
252351017	productive cough -clear sputum
252352012	productive cough -green sputum
252353019	productive cough-yellow sputum
371085010	profuse sputum
506053014	purulent chronic bronchitis
806931000033118	robitussin chesty cough
1709301000006119	scanty sputum
371081018	sputum - symptom
5530031000006111	sputum abnormal - color
11989411000006117	sputum abnormal - odor
414639013	sputum appearance
131721000006111	sputum appears infected
131741000006116	sputum culture
411654018	sputum evidence of infection
260949018	sputum examination: abnormal

1717261000006118	sputum specimen
5259651000006111	sputum volume
260954010	sputum: excessive - mucoid
493627015	sputum: fetid/offensive
12451331000006110	sputum: frothy/watery
132001000006112	sputum: mucopurulent
260965017	sputum: pus cells present
1803511000006110	test request : sputum microscopy
371084014	volume of sputum
2694247010	white sputum
414646016	yellow sputum
1709311000006116	brown sputum
1709271000006116	copious sputum
1834111000006114	dark green sputum
371087019	moderate sputum
2226201000000110	pale green sputum
371088012	scanty sputum
11905721000006116	sputum abnormal - odor
260955011	sputum: frothy/watery
1709321000006112	white sputum

Codes to identify AECOPD events in HES

ICD10 code	Term
J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory infection
J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation
J44.9	Chronic obstructive pulmonary disease, unspecified

Codes to identify MRC dyspnoea (CPRD Aurum)

Medcodeid	Term
55910017	malocclusion due to mouth breathing
112574019	adult respiratory distress syndrome
198599018	paroxysmal nocturnal dyspnoea
252384017	no breathlessness
252385016	breathless - moderate exertion
252386015	breathless - mild exertion
252419019	breath symptom
253357012	breathing aggravates symptom
253615013	o/e - distressed
253889014	o/e - dyspnoea
253892013	o/e - respiratory distress
253909010	o/e - breathing method
253911018	o/e - thoracic breathing
253912013	o/e - mouth breathing
253960011	o/e - breath sounds
253961010	o/e - breath sounds normal
253965018	o/e - cavernous breathing
254295013	o/e - smell of breath
254296014	o/e - breath smell normal
254298010	o/e - bad breath
254300010	o/e-breath offensive-halitosis
254301014	o/e - breath sweet - acetone
254303012	o/e - breath urinose - uraemic
256352014	breath test
261495013	helicobacter breath test negative
307536010	maternal distress with postnatal problem
316268018	fetal distress before labour - liveborn
316278015	liveborn with labour fetal distress
316279011	fetal distress in labour - liveborn
371012016	nocturnal dyspnoea
371051014	noisy breathing
375668015	hydrogen breath test
376352012	c14 triolein breath test
397888010	breathlessness
397890011	shortness of breath
398408017	fetal distress - affecting management
402454016	o/e - breathing description
456095019	o/e - breath sounds abnormal
481328013	painful breathing -pleurodynia
498862013	dyspnoea on exertion
1232138017	short of breath on exertion
1234408015	bad breath - halitosis
1485144011	mrc breathlessness scale: grade 1
1485148014	mrc breathlessness scale: grade 3
1485150018	mrc breathlessness scale: grade 5
1780468018	borg breathlessness score: 1 very slight
1780469014	borg breathlessness score: 2 slight
1780471014	borg breathlessness score: 4 somewhat severe

1780473012	borg breathlessness score: 5 severe
1780480014	borg breathlessness score: 8 very severe (+)
2692059016	helicobacter breath test equivocal
369461000000119	urea breath test
371401000000111	c14 urea helicobacter pylori breath test
468531000033119	beclazone easi-breathe
523231000033113	cromogen easi-breathe
544531000033111	becotide 50 easi-breathe
544631000033110	becotide 100 easi-breathe
908571000006118	[rfc] breath holding
947231000033110	qvar easi-breathe
961761000006112	abnormal breathing patterns
961771000006117	unable to breathe independently
961841000006118	abnormal breath sounds
1042191000006113	adverse reaction to qvar easi-breathe
1071661000006119	adverse reaction to cromogen easi-breathe
1075581000006111	adverse reaction to beclazone easi-breathe
1127851000000111	breath ethanol level
1141031000006113	adverse reaction to helicobacter pylori breath
1269531000033112	hiline breathable
1621021000006111	helicobacter breath test equivocal
1706441000000112	buteyko breathing exercises
1707321000006115	ethanol measurement, breath
1709491000006116	active cycle of breathing technique
1749761000006111	austoms learning & knowledge: client distress/wellbeing score
1749821000006112	austoms walk & mobility: client distress/wellbeing score
1749881000006111	austoms upper limb use: client distress/wellbeing score
1749891000006114	austoms upper limb use: carer distress/wellbeing score
1749951000006112	austoms life tasks & routines: carer distress/wellbeing score
1750061000006117	austoms using transport: client distress/wellbeing score
1750071000006112	austoms using transport: carer distress/wellbeing score
1750131000006110	austoms self care: carer distress/wellbeing score
1750241000006114	austoms domestic life-resources: client distress/wellbeing score
1750251000006111	austoms domestic life-resources: carer distress/wellbeing score
1750301000006116	austoms relationships: client distress/wellbeing score
1750311000006118	austoms relationships: carer distress/wellbeing score
1750371000006110	austoms work & education: carer distress/wellbeing score
1750431000006117	austoms life & leisure: carer distress/wellbeing score

1763721000006114	mod. shuttle walk test-objective breathlessness at end of test
1807851000006117	o/e - dyspnoea on exertion
1809281000006116	distress
1831781000006116	physiotherapy treatment modality: breathing exercises
1852931000006110	dva compensation mrca impairment points
1857611000006112	subjective breathlessness score at end of exercise test
1864271000006119	test request : helicobacter breath test
1878131000006112	adverse reaction to colobreathe
1893001000006119	able to complete a sentence in one breath
1909981000006119	adverse reaction to free breath
1913151000006114	dva compensation determination - vrb/mrcc claim number
1970561000006119	copd assessment test score - breathless walking up hill/stairs
1979061000006119	fit for emergency breathing system training (ebst)
1981131000006118	keele taps trial - comorbidity, distress & frailty assessed
2012131000033117	colobreathe
2287071000000115	anxiety about breathlessness
2287881000000112	breathlessness causing difficulty eating
2011001000006117	oh respiratory questionnaire: wake up ever with difficulty in breathing - yes
2010971000006119	oh respiratory questionnaire: sleep ever broken by difficulty in breathing - no
2013101000006119	on examination no dyspnoea present
2324431000033113	ami medical suportx breathable skin
2007881000006113	adverse reaction to ami medical suportx breathable black
2010811000006116	oh respiratory questionnaire: have to stop for breath walking own pace level ground - no
2324631000033111	ami medical suportx breathable easy peel black
2008031000006117	adverse reaction to ami medical suportx breathable skin
2011011000006119	oh respiratory questionnaire: wake up ever with difficulty in breathing - no
2010801000006119	oh respiratory questionnaire: have to stop for breath walking own pace level ground - yes
2007991000006115	adverse reaction to ami medical suportx breathable white
2011661000006110	oh monitoring report - asbestos: number of years used breathing protection
2324831000033110	ami medical suportx breathable easy peel white
2001721000006110	clinical outcomes in routine evaluation outcome measure global distress score
252412011	breathlessness nos
253913015	o/e - breathing method nos
256353016	helicobacter pylori breath test
306703019	fetal distress nos
316897013	[x]other respiratory distress of newborn

317322013	[d]mouth breathing
17281000000115	mrc treatment lost to followup
273881000006117	o/e - tubular breathing
371381000000111	breath tests nos
428721000006118	[x]threat breath due cave-in fall earth+oth substn occ farm
428751000006110	[x]thret breath due cave-in fall erth+oth sub sprt/athl area
463141000006111	adult respiratory distress syndrome
484981000000114	urea helicobacter pylori breath test nec
525691000006114	breathless - lying flat
525741000006111	breathlessness symptom
633381000006111	dyspnoea - symptom
1559721000006118	breath tests
11932801000006116	ipos staff score : degree pt affected by breathlessness past week
11932841000006119	ipos patient score : degree pt affected by breathlessness past 3 days
406028015	o/e - breathing depth
2338051000000112	diabetes distress scale 17 item
17291000000118	mrc coronary trial nos
1865641000006112	dyspnoea,obstruction, smoking, exacerbation frequency index
11875971000006117	not breathing in newborn infant
3971751000006112	fetal intrauterine distress, not clear if noted before or after onset of labour in liveborn infant
4559181000006114	on examination - breath smell
4550871000006113	on examination - distressed
4836741000006111	liveborn with labour foetal distress
3256151000006119	respiratory distress syndrome of newborn
8285801000006111	dyspnoea, airflow obstruction, smoking status, exacerbation frequency index score
3971741000006110	fetal intrauterine distress, not clear if noted before or after onset of labor in liveborn infant
3256041000006115	cardiorespiratory distress syndrome of newborn
4836671000006113	foetal distress before labour - liveborn
11999461000006115	clasp (cardiovascular limitations and symptoms profile) shortness of breath score
3602451000006118	acquired respiratory distress syndrome
4554091000006110	on examination - orthopnea
3410121000006117	asthmatic breath sounds
2514681000006117	not breathing
5891401000006112	observation of breathing
4836641000006117	fetal distress before labor - liveborn
3488361000006114	dyspnea on effort
4545441000006113	sobar - shortness of breath at rest
8285811000006114	dose (dyspnoea, airflow obstruction, smoking status, exacerbation frequency) index score
5319571000006115	breath test using radiolabelled bile salts
4555211000006111	on examination - cavernous breathing
4545451000006110	dyspnea at rest
4559361000006118	on examination - breath - alcohol smell

8324991000006112	diabetes distress scale 17 item score
4836631000006110	liveborn with prelabor fetal distress
3602471000006111	ards - adult respiratory distress syndrome
4554441000006112	on examination - mouth breathing
3799111000006114	foul breath
4554111000006118	on examination - respiratory distress
4555131000006111	on examination - breath sounds
5499421000006112	foetal distress-affecting care
6519301000006117	medical research council breathlessness scale: grade 3
3488371000006119	dyspnoea on effort
3545921000006110	relaxation/breathing techniques treatments and procedures
3488351000006112	breathlessness on exertion
4554381000006110	on examination - breathing method
3400211000006117	pnd - paroxysmal nocturnal dyspnea
6015731000006113	on examination - breath sounds abnormal
3256051000006118	idiopathic respiratory distress syndrome of newborn
4545421000006118	dyspnoea at rest
4554061000006119	on examination - dyspnea
2527521000006118	alcohol measurement, breath
3903091000006113	breathing rate
4554421000006117	on examination - thoracic breathing
7486681000006119	chronic respiratory disease questionnaire dyspnea subscale score
4554051000006116	o/e - dyspnea
3400201000006115	pnd - paroxysmal nocturnal dyspnoea
3488381000006116	exertional dyspnoea
3153771000006119	mechanically assisted breathing
5497741000006119	breathless
2704841000006111	physiotherapeutic breathing exercise
5004081000006113	dib - difficulty in breathing
7698591000006118	breath holding attack
5985361000006110	cheyne-stokes breathing
3488341000006110	exertional dyspnea
4559311000006116	on examination - breath urinose - uremic
5497761000006115	sob - shortness of breath
4559281000006118	on examination - breath sweet - acetone
4836651000006115	liveborn with prelabour fetal distress
5258891000006111	short of breath at night
5499401000006119	fetal distress-affecting care
3602361000006110	acute respiratory distress syndrome
8323631000006117	diabetes distress scale 2 item score
4554591000006116	on examination - shallow breathing
3971721000006115	foetal distress, in liveborn infant
4554191000006111	on examination - stertorous breathing
4836771000006115	liveborn with labor fetal distress
5319541000006111	breath test using radiolabelled fats
12476731000006118	[x]other specified threats to breathing, occurrence on street and highway

12704651000006111	foetal distress, in liveborn infant
12476711000006112	[x]other specified threats to breathing, occurrence at school, other institution and public administrative area
12481271000006113	[x]unspecified threat to breathing, occurrence at trade and service area
12477691000006111	[x]other specified threats to breathing, occurrence on farm
12723841000006118	perinatal respiratory distress nos
12481261000006118	[x]unspecified threat to breathing, occurrence at sports and athletics area
11932081000006117	mrc (medical research council) breathlessness scale grade 5b
12481211000006116	[x]unspecified threat to breathing, occurrence at industrial and construction area
12481221000006112	[x]unspecified threat to breathing, occurrence at other specified place
12476741000006111	[x]other specified threats to breathing, occurrence at other specified place
12481251000006115	[x]unspecified threat to breathing, occurrence at school, other institution and public administrative area
316277013	liveborn with prelabour fetal distress nos
316290018	liveborn with fetal distress, unspecified
333697014	[x]other specified threats to breathing
333708018	[x]unspecified threat to breathing
333709014	[x]unspecified threat to breathing, occurrence at home
333716010	[x]unspecified threat to breathing, occurrence on farm
405301000006112	[x]oth specif threat to breath occ sch oth inst/pub adm area
405321000006119	[x]oth specif threat to breathing occurrn on street/highway
405341000006114	[x]oth specif threat to breathing occurrn sport/athlet area
430711000006113	[x]unspecif threat to breathing occurrence oth specif place
430731000006119	[x]unspecif threat to breathing occurrnce on street/highway
430741000006112	[x]unspecif threat to breathng occ sch oth ins/pub adm area
430761000006111	[x]unspecif threat to breathng occurrn at trade/servce area
430771000006116	[x]unspecif threat to breathng occurrn in resident instit'n
2002191000006115	mrc (medical research council) breathlessness scale grade 5a
12715411000006114	mrc coronary screen dna
12715911000006117	mrc treatment phase
12715421000006118	mrc treatment phase refused

394711000006118	[x]labour+delivery complicat/oth evidence of fetal distress
405311000006110	[x]oth specif threat to breathing occurrn at unspecif place
405371000006118	[x]oth specif threats to breathng occurrn resident instit'n
894281000006118	perinatal resp. distress nos
12758921000006112	mrc treatment lost to followup
1222462010	fetal distress, unspecified when, liveborn
41791000006118	orthopnoea symptom
175421000006117	respiratory distress syndrome
316267011	liveborn with prelabour fetal distress
317390011	[d]respiratory distress
317392015	[d]shortness of breath
2324731000033116	ami medical suportx breathable easy peel skin
2008051000006112	adverse reaction to ami medical suportx breathable easy peel white
253967014	o/e - breath sounds nos
254307013	o/e - breath smell nos
2001731000006113	core-om - global distress average score
2098131000033115	free breath
2379631000000117	able to complete sentence in one breath
1964621000006111	ipos-5 staff score: breathlessness last 3 days - cannot assess
1857671000006115	subjective breathlessness score at start of exercise test
1861171000006111	breathlessness causing difficulty eating
1875731000006118	chronic resp. disease questionnaire dyspnoea subscale score
1749771000006116	austoms learning & knowledge: carer distress/wellbeing score
1749831000006110	austoms walk & mobility: carer distress/wellbeing score
1759571000006112	adverse reaction to drug desensitisation therapy - dyspnoea
1127841000000113	breath alcohol level
894211000006113	fetal distress - in labour
939911000006119	troubled / distressed
730921000033113	tracheostomy breathing aid
738321000033114	helicobacter pylori breath
544431000033112	ventolin easi-breathe
1485149018	mrc breathlessness scale: grade 4
1488810017	substance level in breath
306682018	fetal distress - delivered
252420013	breath normal
132523019	bad breath
428761000006112	[x]thret breath due cave-in fall erth+oth sub trad/serv area
4559201000006110	on examination - breath smell normal
911011000006110	borg breathlessness score: 9 very, very sev (almost maximal)
252421012	breath symptom nos

11933371000006111	ipos patient score : degree pt affected by breathlessness past week
6462341000006118	breathing problem
3410131000006119	asthmatic breathing
4554401000006110	on examination - abdominal breathing
5312771000006119	h-bt - hydrogen breath test
4766181000006112	psychogenic overbreathing
2520221000006115	breathing treatment
4585291000006113	helicobacter pylor breath test
3903071000006112	br - breathing rate
7295721000006116	nitric oxide breath test
11905591000006110	orthopnea
3488411000006118	soboe - shortness of breath on exertion
3799081000006115	smelly breath
8325001000006117	dds17 (diabetes distress scale 17) score
6519351000006118	medical research council (mrc) breathlessness scale: grade 5
6519221000006115	medical research council (mrc) breathlessness scale: grade 1
3971731000006117	fetal distress, in liveborn infant
3971761000006114	foetal intrauterine distress, not clear if noted before or after onset of labour in liveborn infant
11932071000006115	mrc (medical research council) breathlessness scale grade 5a
5731141000006112	fetal distress - in labour
140461000006116	shortness of breath symptom
451467013	[d]breathlessness
17241000000111	mrc coronary screen dna
307532012	maternal distress unspecified
317395018	[d]dyspnoea
317453014	[d]breath-holding spell
317994012	[x]other and unspecified abnormalities of breathing
2011641000006111	oh monitoring report - asbestos: wears breathing protection at work - no
1984321000006116	manchester triage - shortness of breath in adult
1984331000006118	manchester triage - shortness of breath in child
1943631000033118	ultrabreathe
1807841000006119	o/e - dyspnoea at rest
1834611000006117	dyspnoea, airflow obstn, smoking stat, exacerbatn freq index
1861181000006114	breathlessness causing anxiety
1748881000006119	adverse reaction to hiline breathable
1749941000006110	austoms life tasks & routines: client distress/welbeing score
1750011000006115	austoms transfers: carer distress/wellbeing score
1750191000006114	austoms domestic life - home: carer distress/wellbeing score
1750361000006115	austoms work & education: client distress/wellbeing score
1750421000006115	austoms life & leisure: client distress/wellbeing score
1100271000006116	adverse reaction to powerbreathe medic

1140981000006116	adverse reaction to tracheostomy breathing aid
1076341000006116	adverse reaction to salamol easi-breathe
1084621000006115	adverse reaction to becloforte easi-breathe
894201000006110	fetal distress - prelabour
819531000006116	helicobacter breath test
544731000033115	becloforte easi-breathe
1495637015	breathing exercises
1780479011	borg breathlessness score: 7 very severe
17231000000119	mrc coronary prevention trial
307534013	maternal distress - delivered with postnatal problem
253890017	o/e - orthopnoea
253896011	o/e - stertorous breathing
253910017	o/e - abdominal breathing
254294012	o/e - breath smell
144882018	maternal distress
252387012	breathless - at rest
428711000006114	[x]threat breath due cave-in fall earth+oth subs strt/h'way
910921000006114	borg breathlessness score: 0.5 very, very slight
1559741000006113	c14 glycocholic acid breath test
1812891000006110	referr to british lung foundation breathe easy support group
253916011	o/e - breathing rate
2337941000000112	diabetes distress scale 2 item
3256161000006117	irds - idiopathic respiratory distress syndrome
5312781000006116	h2bt - hydrogen breath test
5258881000006113	nocturnal dyspnea
5731151000006114	fetal distress - in labor
4798211000006113	foetal distress with antenatal problem
3256111000006115	idiopathic respiratory distress syndrome
5530001000006115	distressed breathing
7486671000006117	chronic respiratory disease questionnaire dyspnoea subscale score
3799101000006111	breath smells offensive
7563281000006118	difficulty eating due to breathlessness
5731131000006119	foetal distress - in labour
4559261000006111	on examination - breath offensive-halitosis
3256131000006114	rds - respiratory distress syndrome of newborn
5529931000006118	rapid breathing
4559301000006119	o/e - breath urinose - uremic
6519231000006117	medical research council breathlessness scale grade 1
12715921000006113	mrc treatment lost to follow-up
13045891000006117	recently performed oxygen administration by non-rebreather mask
12481241000006117	[x]unspecified threat to breathing, occurrence on street and highway
12481371000006116	[x]unspecified threat to breathing, occurrence at home
12476761000006110	[x]other specified threats to breathing, occurrence at trade and service area

12481281000006111	[x]unspecified threat to breathing, occurrence in residential institution
12477681000006113	[x]other specified threats to breathing, occurrence at home
316288019	liveborn with labour fetal distress nos
316294010	liveborn with unspecified fetal distress nos
333619011	[x]other accidental threats to breathing
405331000006116	[x]oth specif threat to breathing occurrn oth specif place
430721000006117	[x]unspecif threat to breathing occurrnce at unspecif place
430751000006114	[x]unspecif threat to breathng occurrn at sport/athlet area
2002201000006117	mrc (medical research council) breathlessness scale grade 5b
4555201000006113	on examination - amphoric breathing
371361000000119	other specified breath tests
1222501019	[d]foul breath
17251000000114	mrc treatment phase
307537018	maternal distress nos
2619871000000116	howrthey rating score - pain and/or distress
2010961000006114	oh respiratory questionnaire: sleep ever broken by difficulty in breathing - yes
2008011000006111	adverse reaction to ami medical suportx breathable easy peel black
2324531000033112	ami medical suportx breathable white
2001181000006113	mhip risk factor - level of distress
1959181000006110	breath sound monitoring
1964611000006115	ipos-5 staff score:degree pt affect by breathlessness last 3 day
1964891000006112	equipment in use - positive pressure breathing ventilator
1750121000006112	austoms self care: client distress/wellbeing score
1750181000006111	austoms domestic life - home: client distress/wellbeing score
1761521000006116	modified shuttle walk test - borg breathlessness score at rest
1763711000006118	mod. shuttle walk test-objective breathlessness at start of test
1075591000006114	adverse reaction to beclazone 250 easi-breathe
1084601000006113	adverse reaction to becotide 50 easi-breathe
951841000006113	unfit breathing apparatus/agr
960871000006117	relaxation/breathing techniques
474231000033116	salamol easi-breathe
1780475017	borg breathlessness score: 6 severe (+)
2159189012	unable to complete a sentence in one breath
343671018	active cycle of breathing technique
344917018	difficulty breathing
306683011	fetal distress with antenatal problem
307533019	maternal distress - delivered
307535014	maternal distress with antenatal problem
254297017	o/e - breath smell unpleasant

261494012	helicobacter breath test positive
77969012	neonatal respiratory distress syndrome
525611000006116	breath holder
11933211000006111	ipos staff score: degree pt affected by breathlessness past 3 days
460916013	[v]breathing exercises
317383018	[d]orthopnoea
11905201000006117	o/e - breathing depth
4559221000006117	on examination - breath smell unpleasant
4451931000006118	fetal distress
4555171000006114	on examination - tubular breathing
3400191000006118	paroxysmal nocturnal dyspnea
4798191000006112	foetal distress - delivered
4836791000006119	foetal distress in labour - liveborn
4559331000006110	on examination - breath musty - hepatic
405351000006111	[x]oth specif threat to breathng occurrn at trade/serv area
430701000006110	[x]unspecif threat to breathing occ at industr/constr area
2527511000006114	ethanol measurement, breath
3757591000006111	breathing orally
5497731000006112	dyspnea
3727481000006113	breathing painful
4555151000006116	on examination - breath sounds normal
6519361000006116	medical research council breathlessness scale grade 5
3645081000006116	stridulous breathing
11905211000006119	o/e - breathing rate
7774861000006116	core-om (clinical outcomes in routine evaluation outcome measure) global distress score
12481361000006111	[x]unspecified threat to breathing
12476781000006117	[x]other specified threats to breathing, occurrence in residential institution
12476771000006115	[x]other specified threats to breathing, occurrence at industrial and construction area
12476751000006113	[x]other specified threats to breathing, occurrence at sports and athletics area
306681013	fetal distress unspecified
6048351000006116	mrcp - magnetic resonance cholangiopancreatography
3488391000006118	dyspnea on exertion
13045901000006118	recently performed oxygen administration by non-rebreathing mask
5319561000006110	breath test of small intestine using radiolabelled bile salts
4836781000006117	fetal distress in labor - liveborn
4991651000006114	acbt - active cycle of breathing technique
316376018	perinatal respiratory distress nos
468631000033115	beclazone 250 easi-breathe
1484903015	short of breath dressing/undressing
1484904014	breathless - strenuous exertion
1485147016	mrc breathlessness scale: grade 2

1780464016	borg breathlessness score: 0 none at all
1780470010	borg breathlessness score: 3 moderate
1780482018	borg breathlessness score: 10 maximal
6519321000006110	medical research council (mrc) breathlessness scale: grade 4
3621831000006111	overbreathing
3455891000006110	decreased breath sounds
253929011	o/e - shallow breathing
253962015	o/e - bronchial breathing
254304018	o/e - breath musty - hepatic
254305017	o/e - breath - alcohol smell
254306016	o/e - alcoholic breath
216593018	clasp shortness of breath score
8323641000006110	dds2 (diabetes distress scale 2) score
1852781000006114	dva compensation determination legislation - mrca
1857341000006118	adverse reaction to ultrabreathe
1084571000006118	adverse reaction to ventolin easi-breathe
1084611000006111	adverse reaction to becotide 100 easi-breathe
973721000006112	** book pack b - mrcgp candidates
973731000006110	** notes for the mrcgp
973741000006117	** mrcgp practice papers: mcqs & emqs
982351000006118	dyspnoea
1002031000033115	powerbreathe medic
1750001000006118	austoms transfers: client distress/wellbeing score
1761541000006111	modified shuttle walk test - borg breathlessness score end test
1222513012	[d]mouth breather
11932811000006118	ipos staff score : cannot assess degree pt affected by breathlessness past week
11933271000006119	ipos staff score: cannot assess degree pt affected by breathlessness past 3 days
17261000000112	mrc treatment phase refused
911541000006119	hydrogen breath test
428701000006111	[x]threat breath due cave-in fall earth+oth subs resid inst
428731000006115	[x]threat breath due cave-in fall earth+oth substn occ home
428741000006113	[x]threat to breathng due cave-in fallng earth + oth substn
428771000006117	[x]thret breath due cave-in fall erth+oth sub unspecif place
291761000006114	o/e - amphoric breathing
1913061000006112	dva compensation determination - determining authority - mrcc
2005421000006119	oxygen administration by non rebreather mask
2011631000006118	oh monitoring report - asbestos: wears breathing protection at work - yes
2011651000006113	oh monitoring report - asbestos: wears breathing protection at work - sometimes
2008081000006116	adverse reaction to ami medical suportx breathable easy peel skin
2324331000033115	ami medical suportx breathable black

6462331000006111	breathing abnormal
4991721000006113	bc - breathing control technique
4555181000006112	on examination - bronchial breathing
3256171000006112	respiratory distress syndrome in neonate
4554081000006112	o/e - orthopnea
6519281000006116	medical research council breathlessness scale grade 2
405361000006113	[x]oth specif threat to breathng occurrn indust/constr area
12715901000006115	mrc coronary prevention trial
12715431000006115	mrc coronary trial nos
12476721000006116	[x]other specified threats to breathing, occurrence at unspecified place
333698016	[x]other specified threats to breathing, occurrence at home
333705015	[x]other specified threats to breathing, occurrence on farm
6519271000006119	medical research council (mrc) breathlessness scale: grade 2
2514671000006115	has stopped breathing
6519331000006113	medical research council breathlessness scale grade 4
12477671000006110	[x]other specified threats to breathing
12481231000006110	[x]unspecified threat to breathing, occurrence at unspecified place
12481381000006118	[x]unspecified threat to breathing, occurrence on farm

Codes to identify anxiety (CPRD GOLD)

medcode	readterm
131	Anxiousness
462	Panic attack
514	Tension - nervous
636	Anxiety states
655	Anxiety with depression
791	Nervous breakdown
962	[X]Anxiety neurosis
1582	Nervous exhaustion
1758	Chronic anxiety
2509	[D]Nervousness
2524	Worried
3076	Agoraphobia with panic attacks
3328	General nervous symptoms
4069	Panic disorder
4081	[X]Panic state
4534	Anxiety state NOS
4634	Recurrent anxiety
4659	Generalised anxiety disorder
5385	[X]Other anxiety disorders
5902	Anxiousness - symptom
6221	Separation anxiety disorder
6408	[X]Panic attack
6939	Anxiety state unspecified
7749	[X]Mild anxiety depression
7999	Anxiety counselling
8205	[X]Panic disorder [episodic paroxysmal anxiety]
8424	[X]Anxious [avoidant] personality disorder
8725	O/E - nervous
10344	[X]Generalized anxiety disorder
10390	Fear of death
10723	[D]Nervous tension
11890	C/O - panic attack
11913	[X]Mixed anxiety and depressive disorder
11940	Acute panic state due to acute stress reaction
12838	Agoraphobia without mention of panic attacks
13124	O/E - anxious
14890	[X]Panic disorder with agoraphobia
16729	[X]Agoraphobia without history of panic disorder
17687	[X]Dream anxiety disorder
19000	O/E - panic attack
20089	General nervous symptom NOS
20163	Apprehension
23838	[X]Anxiety disorder, unspecified
24066	[X]Other specified anxiety disorders
25638	[X]Anxiety NOS

26331	O/E - fearful mood
28167	[X]Anxiety hysteria
28381	Alleviating anxiety
28925	Referral for guided self-help for anxiety
29608	
34064	[X]Phobic anxiety disorder, unspecified
35825	[X]Anxiety reaction
38155	O/E - afraid
40431	Cries easily
44321	[X]Other mixed anxiety disorders
50191	[X]Anxiety state
56924	Adjustment reaction with anxious mood
93401	Anxious
101422	Feeling low or worried

Codes to identify depression (CPRD GOLD)

medcode	readterm
324	Depressive disorder NEC
543	[X]Depression NOS
595	Endogenous depression
655	Anxiety with depression
1055	Agitated depression
1131	Neurotic depression reactive type
1533	Brief depressive reaction
2560	Depressive psychoses
2639	Postnatal depression
2923	Puerperal depression
2970	[X]Depressive episode, unspecified
2972	Postviral depression
3291	[X]Depressive disorder NOS
3292	[X]Recurrent depressive disorder
4323	Chronic depression
4639	[X]Depressive episode
4979	[X]Postpartum depression NOS
5879	Agitated depression
5987	[X] Reactive depression NOS
6482	Recurrent depression
6546	Endogenous depression first episode
6854	[X]Other depressive episodes
6932	Endogenous depression - recurrent
6950	Endogenous depression first episode
7011	Single major depressive episode NOS
7604	[X]Single episode of reactive depression
7737	[X]Neurotic depression
7749	[X]Mild anxiety depression
7953	[X]Dysthymia
8478	Reactive depressive psychosis
8584	[X]Depressive neurosis
8826	[X]SAD - Seasonal affective disorder
8851	[X]Recurrent episodes of depressive reaction
8902	[X]Recurrent episodes of reactive depression
9055	[X]Single episode of depressive reaction
9183	Masked depression
9211	[X]Moderate depressive episode
9667	[X]Severe depressive episode without psychotic symptoms
10290	[X]Depressive personality disorder
10455	Depressive personality disorder
10610	Single major depressive episode
10667	[X]Mild depression
10720	[X]Atypical depression
10825	Seasonal affective disorder
11055	[X]Schizoaffective disorder, depressive type
11252	[X]Major depression, recurrent without psychotic symptoms
11329	[X]Endogenous depression without psychotic symptoms
11717	[X]Mild depressive episode

11913	[X]Mixed anxiety and depressive disorder
12099	[X]Severe depressive episode with psychotic symptoms
12122	Depression medication review
12399	Depression annual review
13307	[X]Postnatal depression NOS
14709	Recurrent major depressive episodes, moderate
15099	Recurrent major depressive episode
15155	Single major depressive episode, moderate
15219	Single major depressive episode, severe, without psychosis
15220	[X]Persistant anxiety depression
16506	Single major depressive episode, mild
16632	Prolonged depressive reaction
16861	[X]Recurrent severe episodes of psychotic depression
17770	Psychotic reactive depression
18510	[X]Single episode of psychogenic depression
19054	[X]Recurrent brief depressive episodes
19696	[X]Recurrent episodes of psychogenic depression
20785	[X]Post-schizophrenic depression
21887	Senile dementia with depression
22806	[X]Single episode major depression w'out psychotic symptoms
23731	[X]Endogenous depression with psychotic symptoms
24112	[X]Single episode of psychotic depression
24117	[X]Single episode of major depression and psychotic symptoms
24171	Recurrent major depressive episodes, severe, with psychosis
25563	Recurrent major depressive episode NOS
25697	Recurrent major depressive episodes, severe, no psychosis
27491	Atypical depressive disorder
27677	Presenile dementia with depression
27759	[X] Senile dementia, depressed or paranoid type
28248	[X]Prolonged single episode of reactive depression
28677	[X]Manic-depress psychosis,depressed type+psychotic symptoms
28756	[X]Seasonal depressive disorder
28863	[X]Single episode of reactive depressive psychosis
29342	Recurrent major depressive episodes, mild
29451	[X]Manic-depress psychosis,depressd,no psychotic symptoms
29520	[X]Recurrent depressive disorder, current episode moderate
29527	[D]Postoperative depression
29784	[X]Recurrent depressive disorder, current episode mild
30405	Depression interim review
31757	[X]Recurr severe episodes/psychogenic depressive psychosis
32159	Single major depressive episode, severe, with psychosis
32941	[X]Recurr severe episodes/major depression+psychotic symptom
33469	[X]Recurr depress disorder cur epi severe without psyc sympt
34390	Single major depressive episode, unspecified
35274	[X]Schizoaffective psychosis, depressive type
35671	Recurrent major depressive episodes, unspecified
36246	Brief depressive reaction NOS
36616	[X]Monopolar depression NOS
37764	[X]Recurrent severe episodes/reactive depressive psychosis
41022	[X]Schizophreniform psychosis, depressive type
41089	Senile dementia with depressive or paranoid features NOS

41989	[X]Single episode agitated depressn w'out psychotic symptoms
43292	Arteriosclerotic dementia with depression
44300	[X]Recurrent depressive disorder, unspecified
44674	Senile dementia with depressive or paranoid features
44848	Depression management programme
47009	[X]Recurrent depress disorder cur epi severe with psyc symp
47731	[X]Other recurrent depressive disorders
52678	[X]Single episode of psychogenic depressive psychosis
56609	[X]Single episode of masked depression NOS
59386	[X]Single episode vital depression w'out psychotic symptoms
73991	[X]Vital depression, recurrent without psychotic symptoms
98252	[X]Major depression, moderately severe
98346	[X]Major depression, mild
98414	[X]Major depression, severe without psychotic symptoms
98417	[X]Major depression, severe with psychotic symptoms

Codes to identify GORD (CPRD GOLD)

medcode	desc
592	oesophagitis
984	gastro-oesophageal reflux
1327	oesophageal reflux
2281	acid reflux
2535	reflux oesophagitis
7104	gastro-oesophageal reflux with oesophagitis
7577	gastric reflux
14760	oesophagitis nos
15054	acid reflux
15579	peptic oesophagitis
16450	regurgitant oesophagitis
16605	oesophageal reflux with oesophagitis
19470	reflux cough
25610	oesopheal reflux without mention of oesophagitis

Codes to identify bronchiectasis (CPRD GOLD)

medcode	description
2195	bronchiectasis
15693	tuberculous bronchiectasis
20364	recurrent bronchiectasis
32679	bronchiectasis nos
41491	post-infective bronchiectasis
56427	congenital bronchiectasis
109816	h/o: bronchiectasis

Codes to identify bronchiectasis (CPRD Aurum)

Medcodeid	Terms
21163015	bronchiectasis
3183591000006116	bronchiectasis, chronic sinusitis and dextrocardia syndrome
3901501000006113	polynesian bronchiectasis
4781641000006119	postinfectious bronchiectasis
301524014	recurrent bronchiectasis
301525010	post-infective bronchiectasis
3762481000006115	developmental bronchiectasis
301526011	bronchiectasis nos
38677017	tuberculous bronchiectasis
2867041000006113	post-tuberculous bronchiectasis

Codes to identify lung cancer (CPRD GOLD)

medcode	description
2587	lung cancer
3903	malignant neoplasm of bronchus or lung nos
4137	secondary malignant neoplasm of lung
10358	malignant neoplasm of upper lobe, bronchus or lung
12582	malignant neoplasm of lower lobe of lung
12870	malignant neoplasm of main bronchus
13243	malignant neoplasm of trachea, bronchus and lung
17391	malignant neoplasm of carina of bronchus
18678	malignant neoplasm of lower lobe bronchus
21698	malignant neoplasm of main bronchus nos
25886	malignant neoplasm of upper lobe of lung
29284	[v]personal history of malignant neoplasm of lung
31188	malignant neoplasm of lower lobe, bronchus or lung
31268	malignant neoplasm of middle lobe, bronchus or lung
31700	malignant neoplasm of upper lobe bronchus
32246	[v]personal history of malignant neoplasm of bronchus
33444	malignant neoplasm of hilus of lung
36371	malignant neoplasm of overlapping lesion of bronchus & lung
38961	malignant neoplasm of other sites of bronchus or lung
39923	malignant neoplasm of middle lobe of lung
40595	[x]malignant neoplasm of bronchus or lung, unspecified
41523	malignant neoplasm of middle lobe bronchus
42566	malignant neoplasm of lower lobe, bronchus or lung nos
44169	malignant neoplasm of upper lobe, bronchus or lung nos
54134	malignant neoplasm of middle lobe, bronchus or lung nos

Codes to identify hypertension (CPRD GOLD)

medcode	description
799	Essential hypertension
204	Hypertensive disease
351	High blood pressure
10818	Essential hypertension NOS
11056	Patient on maximal tolerated antihypertensive therapy
3712	Hypertension NOS
3425	On treatment for hypertension
27511	Poor hypertension control
7057	Hypertensive disease NOS
1894	Benign essential hypertension
13188	Hypertensive treatm.changed
8732	BP - hypertensive disease
4372	Systolic hypertension
18057	Antihypertensive therapy
21826	Hypertension treatm. started
18590	Moderate hypertension control
16292	Hypertensive heart disease
15377	Malignant essential hypertension
7329	Secondary hypertension
105316	Stage 1 hypertension
4668	Hypertensive heart disease
105274	Stage 2 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)
8857	Cardiomegaly - hypertensive
105371	Stage 1 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)
83473	Diastolic hypertension
16059	Secondary hypertension NOS
16173	Hypertensive heart disease NOS
31341	Hypertension secondary to drug
105487	Severe hypertension
42229	Secondary hypertension NOS
31464	Hypertensive heart disease NOS
69753	[X]Hypertensive diseases
108136	Stage 1 hypertension (NICE 2011) without evidence of end organ damage
31755	Secondary malignant hypertension
57288	Secondary benign hypertension
61166	Hypertensive heart disease NOS without CCF
62718	Hypertensive heart disease NOS with CCF
51635	Secondary benign hypertension NOS
105989	Severe hypertension (NICE - National Institute for Health and Clinical Excellence 2011)
109797	Stage 1 hypertension (NICE 2011) with evidence of end organ damage
73293	Secondary malignant hypertension NOS
102458	[X]Other secondary hypertension

Codes to identify hypertension related medications (CPRD GOLD)

These include ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, vasodilators, and beta blockers

prodcode	productname
2	Bendroflumethiazide 2.5mg tablets
6	Furosemide 40mg tablets
55	Furosemide 20mg tablets
56	Co-amilofruse 5mg/40mg tablets
58	Bendroflumethiazide 5mg tablets
65	Lisinopril 10mg tablets
69	Lisinopril 20mg tablets
78	Lisinopril 5mg tablets
80	Ramipril 5mg capsules
82	Ramipril 10mg capsules
91	Isosorbide mononitrate 20mg tablets
97	Perindopril erbumine 4mg tablets
119	Doxazosin 1mg tablets
147	Ramipril 1.25mg capsules
193	Co-amilofruse 2.5mg/20mg tablets
196	Enalapril 5mg tablets
211	Frumil 40mg+5mg Tablet (Helios Healthcare Ltd)
214	HYDRALAZINE 1 MG SYR
217	CAPTOPRIL 4 MG/ML LIQ
219	Diltiazem 120mg modified-release tablets
269	Nifedipine 5mg capsules
277	Lisinopril 2.5mg tablets
338	Clonidine 25microgram tablets
348	Moduretic Tablet (Bristol-Myers Squibb Pharmaceuticals Ltd)
410	Nifedipine 10mg modified-release tablets
445	Prazosin 1mg tablets and Prazosin 500microgram tablets
448	Enalapril 2.5mg tablets
452	Nifedipine 10mg capsules
491	Felodipine 2.5mg modified-release tablets
493	Doxazosin 2mg tablets
501	Felodipine 5mg modified-release tablets
504	Hydralazine 20mg powder for solution for injection ampoules
517	Adizem sr 120mg Modified-release capsule (Napp Pharmaceuticals Ltd)
520	Losartan 25mg tablets
521	Isosorbide mononitrate 25mg modified-release capsules
529	Candesartan 2mg tablets
531	Candesartan 4mg tablets
536	Tildiem la 200mg Modified-release capsule (Sanofi)
541	Adalat LA 20mg tablets (Bayer Plc)
542	Hydrochlorothiazide 25mg tablets
562	Furosemide 10mg/ml Injection
568	Felodipine 10mg modified-release tablets
573	Hydralazine 25mg tablets
575	Valsartan 40mg capsules
581	Atenolol 50mg with Chlortalidone 12.5mg tablets
582	Doxazosin 4mg modified-release tablets

591	Prazosin 1mg tablets
593	Perindopril erbumine 2mg tablets
605	Chlortalidone 50mg tablets
621	Isosorbide mononitrate 60mg modified-release tablets
624	Losartan 100mg tablets
632	Imdur 60mg modified-release tablets (TopRidge Pharma (Ireland) Ltd)
633	Fosinopril 10mg tablets
636	Diltiazem 60mg modified-release capsules
654	Ramipril 2.5/5mg/10mg capsule
662	Adalat 5mg capsules (Bayer Plc)
692	Spironolactone 25mg tablets
700	Vera-Til SR 120mg tablets (Tillomed Laboratories Ltd)
708	Spironolactone 50mg tablets
709	Ramipril 2.5mg capsules
726	Prazosin 2mg tablets
737	Nifedipine 20mg modified-release capsules
755	Cardura XL 4mg tablets (Upjohn UK Ltd)
756	Ramipril 10mg tablets
761	Ramipril 1.25mg tablets
764	Co-Diovan 80mg/12.5mg tablets (Novartis Pharmaceuticals UK Ltd)
776	Isosorbide mononitrate 60mg modified-release capsules
779	Isosorbide mononitrate 10mg tablets
787	Spironolactone 100mg capsule
793	Adizem xl 240mg Capsule (Napp Pharmaceuticals Ltd)
814	Bumetanide 1mg tablets
828	Irbesartan 75mg tablets
923	Co-amilozide 5mg/50mg tablets
924	Co-amilozide 2.5mg/25mg tablets
939	Tildiem Retard 90mg tablets (Sanofi)
1021	Innozide 20mg/12.5mg tablets (Merck Sharp & Dohme Ltd)
1060	Amiloride 5mg tablets
1118	Verapamil 40mg tablets
1120	Verapamil 80mg tablets
1121	Captopril 12.5mg tablets
1124	Tenoretic 100mg/25mg tablets (AstraZeneca UK Ltd)
1125	Navidrex -k Tablet (Novartis Pharmaceuticals UK Ltd)
1130	Viazem XL 300mg capsules (Thornton & Ross Ltd)
1143	Captopril 25mg tablets
1144	Capoten 25mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
1170	Cyclopenthiazide 500microgram tablets
1209	Neo-Naclex 5mg tablets (Mercury Pharma Group Ltd)
1211	Bendroflumethiazide 2.5mg / Potassium chloride 630mg (potassium 8.4mmol) modified-release tablets
1213	Neo-Naclex-K modified-release tablets (Mercury Pharma Group Ltd)
1251	Moduret 25 tablets (Merck Sharp & Dohme Ltd)
1262	Nifedipine 12 20mg Modified-release tablet
1288	Tenoret 50mg/12.5mg tablets (AstraZeneca UK Ltd)
1289	Tildiem Retard 120mg tablets (Sanofi)
1292	Hypovase 1mg tablets (Pfizer Ltd)
1293	Irbesartan 150mg tablets
1294	Doxazosin 4mg tablets

1296	Hydralazine 50mg tablets
1297	Aldactide 50 tablets (Pfizer Ltd)
1298	Verapamil 240mg modified-release tablets
1299	Enalapril 10mg tablets
1300	Nifensar xl 20mg Modified-release tablet (Rhone-Poulenc Rorer Ltd)
1301	Frumil ls 20mg+2.5mg Tablet (Helios Healthcare Ltd)
1369	Furosemide with amiloride 40mg+5mg Tablet
1449	Nifedipine 24 30mg Modified-release tablet
1455	Prazosin 500microgram tablets
1520	Capozide 25mg/50mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
1538	Diltiazem 60mg tablets
1574	Verapamil 120mg modified-release capsules
1684	Beta-Adalat modified-release capsules (Bayer Plc)
1686	Diltiazem 90mg modified-release capsules
1707	Methyldopa 250mg tablets
1721	Dyazide 50mg/25mg tablets (Advanz Pharma)
1747	Verapamil 120mg tablets
1748	Cordilox 120mg tablets (IVAX Pharmaceuticals UK Ltd)
1753	Isordil 10mg tablets (Shire Pharmaceuticals Ltd)
1754	Isosorbide dinitrate 10mg tablets
1776	Burinex K modified-release tablets (LEO Pharma)
1780	Losartan 50mg tablets
1782	ISOSORBIDE MONONITRATE 60 MG CAP
1788	Atenolol 100mg with Chlortalidone 25mg tablets
1807	Captopril 50mg tablets
1836	Diltiazem 60mg modified-release tablets
1854	Adalat la 30mg Tablet (Bayer Plc)
1904	Enalapril 20mg tablets
1993	ISOSORBIDE MONONITRATE 40 MG CAP
1994	Isosorbide mononitrate 40mg tablets
1995	Diltiazem 12hr 120mg modified-release capsules
2001	Aldactide 25 tablets (Pfizer Ltd)
2002	Amiloride 5mg / hydrochlorothiazide 50mg tablets
2046	Navidrex 500microgram tablets (Advanz Pharma)
2142	Spironolactone 100mg tablets
2255	Navispare 2.5mg/250microgram tablets (Advanz Pharma)
2280	Adalat retard 10mg tablets (Bayer Plc)
2343	Adalat retard 20mg tablets (Bayer Plc)
2362	Apresoline 25mg tablets (Advanz Pharma)
2389	Aldactone 25mg tablets (Pfizer Ltd)
2453	Diltiazem 60mg modified-release capsules
2493	Burinex A 5mg/1mg tablets (LEO Pharma)
2495	Bumetanide with Amiloride tablets
2521	Adalat 10mg capsules (Bayer Plc)
2528	Slozem 120mg capsules (Merck Serono Ltd)
2592	Viazem XL 120mg capsules (Thornton & Ross Ltd)
2605	Nifedipine 10mg modified-release capsules
2612	Indapamide 2.5mg tablets
2619	Isosorbide mononitrate 40mg modified-release tablets
2630	Dixarit 25microgram tablets (Boehringer Ingelheim Ltd)
2633	Ismo 10- Tablet (Roche Products Ltd)

2649	METHYLDOPA 250 MG CAP
2663	Diltiazem 240mg modified-release capsules
2680	Apresoline 50mg Tablet (Sovereign Medical Ltd)
2681	AMILORIDE 10 MG TAB
2686	Dilzem xl mr 240mg Modified-release capsule (Elan Pharma)
2746	Coracten SR 10mg capsules (UCB Pharma Ltd)
2772	Lasoride 5mg/40mg tablets (Sanofi)
2788	Burinex 1mg tablets (LEO Pharma)
2811	Adizem sr 180mg Modified-release capsule (Napp Pharmaceuticals Ltd)
2833	CYCLOPENTHIAZIDE -K tablets
2878	Clonidine 100microgram tablets
2888	Tildiem 60mg modified-release tablets (Sanofi)
2926	Nicardipine 20mg capsules
2927	PERINDOPRIL/TERT-BUTYLAMINE 2 MG TAB
2933	Isosorbide dinitrate 20mg tablets
2961	Frusene 50mg/40mg tablets (Orion Pharma (UK) Ltd)
2967	Minoxidil 5mg tablets
2968	Minoxidil 10mg tablets
2970	Minoxidil 2.5mg tablets
2971	Irbesartan 300mg tablets
2979	Centyl k Tablet (Edwin Burgess Ltd)
2982	Zestoretic 20- 20mg+12.5mg Tablet (AstraZeneca UK Ltd)
3049	Methyldopa 125mg tablets
3050	Furosemide with triamterene 40mgwith50mg Tablet
3054	Hygroton 100mg Tablet (Alliance Pharmaceuticals Ltd)
3056	Natrilix SR 1.5mg tablets (Servier Laboratories Ltd)
3057	Securon 120mg tablets (Abbott Laboratories Ltd)
3061	Diltiazem 12hr 180mg modified-release capsules
3069	Acepril 25mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
3070	Methyldopa 500mg tablets
3118	Adizem sr 90mg Modified-release capsule (Napp Pharmaceuticals Ltd)
3203	Capozide LS Tablet (E R Squibb and Sons Ltd)
3222	Valsartan 80mg capsules
3248	Furosemide 500mg tablets
3285	AMILORIDE S/F 5 MG/5ML SOL
3287	Furosemide 1mg/ml Oral solution
3293	Moduretic Oral solution (Bristol-Myers Squibb Pharmaceuticals Ltd)
3302	Cardene SR 30mg capsules (Astellas Pharma Ltd)
3310	Capoten 12.5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
3342	Securon SR 240mg tablets (Mylan)
3343	Half Securon SR 120mg tablets (Mylan)
3370	Dilzem xl mr 120mg Modified-release capsule (Elan Pharma)
3509	ENALAPRIL MALEATE 40 MG TAB
3517	Hydrochlorothiazide 50mg tablets
3526	Amiloride with atenolol with hydrochlorothiazide capsules
3548	Chlortalidone 100mg tablets
3676	Dilzem xl mr 180mg Modified-release capsule (Elan Pharma)
3691	Sotalol 160mg with hydrochlorothiazide 25mg tablet
3701	Amiloride 2.5mg / hydrochlorothiazide 25mg tablets
3711	Adipine MR 20 tablets (Chiesi Ltd)
3712	Coracten XL 30mg capsules (UCB Pharma Ltd)

3715	Prazosin 5mg tablets
3720	Zestril 2.5mg tablets (AstraZeneca UK Ltd)
3793	Co-amilofruse 10mg/80mg tablets
3839	Capoten 50mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
3902	FRUSEMIDE 20MG/SPIRONOLACTONE 50MG MG CAP
3929	Quinapril 10mg tablets
3930	Nifedipine 60mg modified-release tablets
3943	Verapamil 240mg modified-release capsules
3962	TRIAMTERENE 50MG HYDROCHLOROTHIAZIDE25MG TAB
3997	Hygroton 50mg tablets (Alliance Pharmaceuticals Ltd)
4034	Amiloride 5mg / hydrochlorothiazide 50mg/5ml solution
4044	Diurexan 20mg tablets (Mylan)
4111	Hypovase 500microgram tablets (Pfizer Ltd)
4155	Amias 2mg tablets (Takeda UK Ltd)
4161	Spiroctan 25mg Tablet (Roche Products Ltd)
4182	Lasix 5mg/5ml oral solution (Borg Medicare)
4211	Furosemide with amiloride 20mg+2.5mg Tablet
4215	Catapres 100microgram tablets (Boehringer Ingelheim Ltd)
4226	Cozaar 25mg tablets (Merck Sharp & Dohme Ltd)
4227	Adalat la 60mg Tablet (Bayer Plc)
4239	Adipine MR 10 tablets (Chiesi Ltd)
4258	Lasix 20mg/2ml solution for injection ampoules (Sanofi)
4308	Dilzem sr 90mg Capsule (Elan Pharma)
4332	Metolazone 5mg tablets
4334	Metolazone 500microgram low dose Tablet
4408	Slozem 240mg capsules (Merck Serono Ltd)
4429	Trasidrex modified-release tablets (Mercury Pharma Group Ltd)
4449	Cardura 1mg tablets (Upjohn UK Ltd)
4507	HYDRALAZINE HCl 12.5 MG TAB
4508	Isosorbide dinitrate 30mg tablets
4540	Cozaar-Comp 50mg/12.5mg tablets (Merck Sharp & Dohme Ltd)
4542	Atenolol 50mg / Nifedipine 20mg modified-release capsules
4571	Staril 10mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
4605	Moducren tablets (Merck Sharp & Dohme Ltd)
4609	Isosorbide mononitrate 40mg modified-release capsules
4635	Diltiazem 200mg modified-release capsules
4645	Valsartan 160mg capsules
4661	Spironolactone 50mg / Furosemide 20mg capsules
4685	Amias 4mg tablets (Takeda UK Ltd)
4705	Furosemide 20mg/2ml Injection
4732	Diltiazem 90mg modified-release tablets
4741	Candesartan 16mg tablets
4796	Inderetic 80mg/2.5mg capsules (AstraZeneca UK Ltd)
4802	Cardura 2mg tablets (Upjohn UK Ltd)
4808	Diltiazem 240mg modified-release capsules
4818	Candesartan 8mg tablets
4843	Isosorbide dinitrate 20mg modified-release capsules
4852	Adizem sr 120mg Modified-release tablet (Napp Pharmaceuticals Ltd)
4856	Coracten SR 20mg capsules (UCB Pharma Ltd)
4873	Fru-Co 5mg/40mg tablets (Teva UK Ltd)
4923	Diltiazem 24hr 180mg modified-release capsules

4939	Coracten XL 60mg capsules (UCB Pharma Ltd)
4960	Aldactone 50mg tablets (Pfizer Ltd)
4983	Atenolol with amiloride and hydrochlorothiazide capsules
4993	Moxonidine 200microgram tablets
5004	Isosorbide dinitrate 20mg modified-release tablets
5013	Amias 8mg tablets (Takeda UK Ltd)
5054	Angitil SR 180 capsules (Ethypharm UK Ltd)
5112	Indapamide 1.5mg modified-release tablets
5117	Amias 16mg tablets (Takeda UK Ltd)
5159	Quinapril 20mg tablets
5162	Nifedipine 30mg modified-release capsules
5181	Angiopine MR 20mg tablets (Ashbourne Pharmaceuticals Ltd)
5183	Hypovase 2mg tablets (Pfizer Ltd)
5189	Enalapril 20mg / Hydrochlorothiazide 12.5mg tablets
5194	Dilzem sr 120mg Capsule (Elan Pharma)
5218	Bumetanide 1mg/5ml oral solution sugar free
5220	Furosemide with amiloride 80mg+10mg Tablet
5234	Slozem 180mg capsules (Merck Serono Ltd)
5249	Furosemide 50mg/5ml oral solution sugar free
5275	Tritace 2.5mg capsules (Sanofi)
5277	Fortipine LA 40 tablets (Advanz Pharma)
5289	Clonidine 250microgram modified-release capsules
5296	Tildiem la 300mg Modified-release capsule (Sanofi)
5326	Diltiazem 24hr 300mg modified-release capsules
5330	Corgaretic 40mg tablets (Sanofi-Synthelabo Ltd)
5348	Diltiazem 300mg modified-release capsules
5416	Co-triamterzide 50mg/25mg tablets
5477	Nicardipine 30mg modified-release capsules
5496	Doxazosin 8mg modified-release tablets
5513	Dilzem sr 60mg Capsule (Elan Pharma)
5570	Zanidip 10mg tablets (Recordati Pharmaceuticals Ltd)
5593	Lercanidipine 10mg tablets
5612	Coversyl 2mg tablets (Servier Laboratories Ltd)
5618	Cardura XL 8mg tablets (Upjohn UK Ltd)
5721	Co-tenidone 100mg/25mg tablets
5723	Cozaar 50mg tablets (Merck Sharp & Dohme Ltd)
5727	Amiloride 2.5mg / Cyclopenthiazide 250microgram tablets
5728	Furosemide 40mg/5ml oral solution sugar free
5735	Tritace 5mg capsules (Sanofi)
5800	Coversyl 4mg tablets (Servier Laboratories Ltd)
5806	Tensipine MR 20 tablets (Genus Pharmaceuticals Ltd)
5861	Fosinopril 20mg tablets
5868	Frusol 20mg/5ml oral solution (Rosemont Pharmaceuticals Ltd)
5988	Telmisartan 40mg tablets
6078	Perindopril erbumine 8mg tablets
6099	Monosorb XL 60 tablets (Teva UK Ltd)
6111	Isosorbide dinitrate 40mg modified-release tablets
6118	Furosemide 20mg/5ml oral solution sugar free
6159	Nyzamac SR 60mg capsules (Ethypharm UK Ltd)
6160	Bumetanide 500microgram / Potassium chloride 573mg (potassium 7.7mmol) modified-release tablets

6217	Olmesartan medoxomil 10mg tablets
6243	Telmisartan 20mg tablets
6261	Tritace 1.25mg tablets (Sanofi)
6285	Olmesartan medoxomil 20mg tablets
6288	Ramipril 5mg tablets
6309	Adizem xl 300mg Capsule (Napp Pharmaceuticals Ltd)
6314	Ramipril 2.5mg tablets
6343	Monomax XL 60mg tablets (Chiesi Ltd)
6351	Olmesartan medoxomil 40mg tablets
6359	Zestoretic 10- 10mg+12.5mg Tablet (AstraZeneca UK Ltd)
6362	Tritace 5mg tablets (Sanofi)
6364	Tritace 2.5mg tablets (Sanofi)
6408	Tanatril 5mg tablets (Mitsubishi Tanabe Pharma Europe Ltd)
6437	Losartan 50mg / Hydrochlorothiazide 12.5mg tablets
6468	Lisinopril 20mg / Hydrochlorothiazide 12.5mg tablets
6510	Univer 120mg modified-release capsules (Teva UK Ltd)
6518	Diovan 160mg capsules (Novartis Pharmaceuticals UK Ltd)
6694	Clonidine 300microgram tablets
6765	Quinapril 5mg tablets
6786	Lisinopril 10mg / Hydrochlorothiazide 12.5mg tablets
6794	Perindopril erbumine 4mg / Indapamide 1.25mg tablets
6806	Zestril 10mg tablets (AstraZeneca UK Ltd)
6807	Zestril 5mg tablets (AstraZeneca UK Ltd)
6815	Spironolactone 50mg/5ml oral suspension sugar free
6821	Isotard 60XL tablets (Kyowa Kirin Ltd)
6877	Co-Diovan 160mg/12.5mg tablets (Novartis Pharmaceuticals UK Ltd)
6939	Eprosartan 300mg tablets
7043	Candesartan 32mg tablets
7066	Metoprolol 100mg / Hydrochlorothiazide 12.5mg tablets
7174	Moxonidine 400microgram tablets
7280	Plendil 10mg modified-release tablets (AstraZeneca UK Ltd)
7314	Accupro 5mg tablets (Pfizer Ltd)
7327	Isosorbide mononitrate 25mg modified-release tablets
7338	Aprovel 75mg tablets (Sanofi)
7351	Bendroflumethiazide 2.5mg/5ml oral suspension
7398	Viazem XL 360mg capsules (Thornton & Ross Ltd)
7416	Aldomet 50mg/ml Injection (Merck Sharp & Dohme Ltd)
7433	Monit LS 10mg tablets (Sanofi-Synthelabo Ltd)
7441	Lasilactone 20mg/50mg capsules (Sanofi)
7541	Nifopress Retard 20mg tablets (Advanz Pharma)
7543	Kalten capsules (M & A Pharmachem Ltd)
7547	Doxadura 2mg tablets (Dexcel-Pharma Ltd)
7549	Doxadura 1mg tablets (Dexcel-Pharma Ltd)
7562	Cardene 30mg capsules (Astellas Pharma Ltd)
7582	Lasikal modified-release tablets (Borg Medicare)
7606	Lasix 40mg tablets (Sanofi)
7618	Xipamide 20mg tablets
7626	Aldomet 250mg Tablet (Merck Sharp & Dohme Ltd)
7641	Natrilix 2.5mg tablets (Servier Laboratories Ltd)
7642	Aldomet 500mg Tablet (Merck Sharp & Dohme Ltd)
7698	Aprinox 5mg tablets (Amdipharm Plc)

7702	Sorbitrate 10mg Tablet (AstraZeneca UK Ltd)
7734	Diumide-K Continus tablets (Teofarma)
7746	Ismo 20- Tablet (Roche Products Ltd)
7762	Elantan 10 tablets (UCB Pharma Ltd)
7790	MINOXIDIL 1 % LOT
7799	Lasix 20mg tablets (Borg Medicare)
7806	Bumetanide 5mg tablets
7823	NIFEDIPINE TAB 5 mg
7952	Aldactone 100mg tablets (Pfizer Ltd)
7961	Spironolactone 50mg with hydroflumethiazide 50mg tablet
7991	Spiroctan 100mg Capsule (Roche Products Ltd)
8024	DILTIAZEM HCl XL 300 MG CAP
8033	Aldomet 125mg Tablet (Merck Sharp & Dohme Ltd)
8037	Monit 20mg tablets (Sanofi-Synthelabo Ltd)
8052	Torasemide 5mg tablets
8058	Normetic Tablet (Abbott Laboratories Ltd)
8061	Sotalol 80mg with hydrochlorothiazide 12.5mg tablet
8086	Cardura 4mg Tablet (Pfizer Ltd)
8102	Furosemide 40mg / Potassium chloride 600mg (potassium 8mmol) modified-release tablets
8105	Innovace 20mg tablets (Merck Sharp & Dohme Ltd)
8106	Innovace 2.5mg tablets (Merck Sharp & Dohme Ltd)
8147	Lopresoretic Tablet (Novartis Pharmaceuticals UK Ltd)
8189	Secadrex 200mg/12.5mg tablets (Sanofi)
8198	Hypovase 5mg Tablet (Pfizer Ltd)
8201	Nicardipine 30mg capsules
8213	Nifedipine 24 20mg Modified-release tablet
8257	Prescal 2.5mg tablets (Novartis Pharmaceuticals UK Ltd)
8268	Zestril 20mg tablets (AstraZeneca UK Ltd)
8296	Catapres PL Perlongets 250microgram capsules (Boehringer Ingelheim Ltd)
8303	Tenavoid Tablet (Edwin Burgess Ltd)
8310	Isradipine 2.5mg tablets
8324	Isosorbide mononitrate 50mg modified-release capsules
8369	Inderex 160mg/5mg modified-release capsules (AstraZeneca UK Ltd)
8428	Sorbid-40 SA capsules (AstraZeneca UK Ltd)
8464	Meprobamate with bendroflumethiazide Tablet
8521	Spironolactone 25mg with hydroflumethiazide 25mg tablet
8524	Securon 40mg Tablet (Abbott Laboratories Ltd)
8526	Aprinox 2.5mg tablets (Advanz Pharma)
8539	Sorbichew 5mg Tablet (AstraZeneca UK Ltd)
8558	Adizem xl 120mg Capsule (Napp Pharmaceuticals Ltd)
8602	Metenix 5mg tablets (Sanofi)
8623	Prestim Tablet (ICN Pharmaceuticals France S.A.)
8642	Tenif 50mg/20mg modified-release capsules (AstraZeneca UK Ltd)
8673	Oxprenolol with cyclopenthiazide 160mg+0.25mg Modified-release tablet
8759	Verapamil hcl 120mg modified release tablets
8765	ATENOLOL/CHLORTHALIDONE 50 MG TAB
8790	Isosorbide dinitrate 5mg Sublingual tablet
8793	Monit SR 40mg tablets (Sanofi-Synthelabo Ltd)
8800	Innovace 5mg tablets (Merck Sharp & Dohme Ltd)
8830	Innovace 10mg tablets (Merck Sharp & Dohme Ltd)

8863	Hypovase benign prostatic hyperplasia 1mg Tablet (Pfizer Ltd)
8884	Cordilox 40mg tablets (IVAX Pharmaceuticals UK Ltd)
8891	Hygroton -k Tablet (Novartis Pharmaceuticals UK Ltd)
8897	Triam-Co 50mg/25mg tablets (IVAX Pharmaceuticals UK Ltd)
8902	Elantan la 25mg Capsule (UCB Pharma Ltd)
8923	CAPTOPRIL 100 MG TAB
8940	Ismo 40 tablets (Roche Products Ltd)
8945	Univer 240mg modified-release capsules (Teva UK Ltd)
8975	Verapamil 180mg modified-release capsules
8987	Propranolol 160mg modified-release / Bendroflumethiazide 5mg capsules
9088	Ismo retard 40mg Tablet (Roche Products Ltd)
9094	DILTIAZEM HCl SR 300 MG CAP
9178	Atenolol 25mg / Bendroflumethiazide 1.25mg capsules
9196	Aprovel 150mg tablets (Sanofi)
9223	Triamterene with hydrochlorothiazide 50mg + 25mg Tablet
9225	Methyldopa 250mg Capsule
9240	Adizem xl 180mg Capsule (Napp Pharmaceuticals Ltd)
9269	Nifedipine 40mg modified-release tablets
9282	Nyzamac SR 40mg capsules (Ethypharm UK Ltd)
9295	Elantan la 50mg Capsule (UCB Pharma Ltd)
9334	Plendil 2.5mg modified-release tablets (AstraZeneca UK Ltd)
9335	Isosorbide dinitrate 5mg tablets
9374	Adizem 60mg Modified-release tablet (Napp Pharmaceuticals Ltd)
9386	Nicardipine 45mg modified-release capsules
9410	Angitil SR 120 capsules (Ethypharm UK Ltd)
9431	Frusemek 40mg+5mg Tablet (Approved Prescription Services Ltd)
9437	Plendil 5mg modified-release tablets (AstraZeneca UK Ltd)
9456	Amiloride 5mg / furosemide 40mg tablets
9463	Loniten 5mg tablets (Pfizer Ltd)
9485	Hypolar Retard 20 tablets (Sandoz Ltd)
9492	Modisal 60 XL tablets (Sandoz Ltd)
9497	Isosorbide dinitrate 40mg modified-release capsules
9553	Slofedipine XL 60 tablets (Zentiva)
9569	Verapamil 120mg modified-release tablets
9573	Slofedipine XL 30mg tablets (Zentiva)
9622	Cedocard Retard 40 tablets (Pfizer Ltd)
9646	Tritace 1.25mg capsules (Aventis Pharma)
9660	Isotard 40XL tablets (Kyowa Kirin Ltd)
9680	Frusol 40mg/5ml oral solution (Rosemont Pharmaceuticals Ltd)
9693	Tritace 10mg capsules (Sanofi)
9697	Loniten 2.5mg tablets (Pfizer Ltd)
9703	Isotard 25XL tablets (Kyowa Kirin Ltd)
9708	Diltiazem 24hr 120mg modified-release capsules
9719	Isib 60XL tablets (Alliance Pharmaceuticals Ltd)
9723	Calcicard CR 90mg tablets (Teva UK Ltd)
9731	Quinapril 40mg tablets
9744	Isoket Retard 40 tablets (Forum Health Products Ltd)
9745	Teveten 300mg tablets (Mylan)
9749	Physiotens 400microgram tablets (Mylan)
9750	Nifedipine 60mg modified-release capsules
9764	Carace 20 Tablet (Bristol-Myers Squibb Pharmaceuticals Ltd)

9783	Co-tenidone 50mg/12.5mg tablets
9876	Physiotens 300microgram tablets (Mylan)
9908	Chemydur 60XL tablets (Advanz Pharma)
9915	Tritace 10mg tablets (Sanofi)
9919	Diltiazem 2% cream
9935	Amiloride 5mg/5ml oral solution sugar free
10066	Torem 5mg tablets (Mylan)
10088	Doxadura 4mg tablets (Dexcel-Pharma Ltd)
10135	Nifedipress mr 10mg Modified-release tablet (Sandoz Ltd)
10136	Nifedipress MR 20 tablets (Dexcel-Pharma Ltd)
10147	Trangina XL 60mg tablets (Accord Healthcare Ltd)
10153	Felendil xl 5mg Modified-release tablet (Ratiopharm UK Ltd)
10214	Spironolactone 5mg/5ml oral suspension sugar free
10246	Adipine XL 60mg tablets (Chiesi Ltd)
10251	Eplerenone 25mg tablets
10253	Moxonidine 300microgram tablets
10267	Adizem-XL 200mg capsules (Napp Pharmaceuticals Ltd)
10316	CoAprovel 150mg/12.5mg tablets (Sanofi)
10323	Losartan 100mg / Hydrochlorothiazide 25mg tablets
10392	Lasix 500mg tablets (Sanofi)
10422	Lasix 50mg/5ml Injection (Hoechst UK Ltd)
10459	Cedocard 5 tablets (Pfizer Ltd)
10587	Cedocard Retard 20 tablets (Pfizer Ltd)
10607	Isordil 5mg tablets (Shire Pharmaceuticals Ltd)
10627	Co-Betaloc tablets (Pfizer Ltd)
10688	Verapamil 160mg tablets
10700	Isordil 30mg tablets (Shire Pharmaceuticals Ltd)
10781	Lasix with k Tablet (Hoechst Marion Roussel)
10796	CHLORTHALIDONE 25MG/POTASSIUM6.7MMOL S/R MG TAB
10832	Securon 80mg Tablet (Abbott Laboratories Ltd)
10882	Carace 2.5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
10902	Captopril 50mg with Hydrochlorothiazide 25mg tablets
11133	Hydrochlorothiazide with captopril 25mg with 50mg Tablet
11156	Spirolone 25mg Tablet (Berk Pharmaceuticals Ltd)
11177	Physiotens 200microgram tablets (Mylan)
11197	Innovace melt 5mg Wafer (Merck Sharp & Dohme Ltd)
11223	Angitil SR 90 capsules (Ethypharm UK Ltd)
11251	Diovan 40mg capsules (Novartis Pharmaceuticals UK Ltd)
11252	Diovan 80mg capsules (Novartis Pharmaceuticals UK Ltd)
11265	Triamterene 50mg / Furosemide 40mg tablets
11268	Torem 2.5mg tablets (Mylan)
11338	Bendroflumethiazide 5mg with Nadolol 40mg tablets
11348	Aprovel 300mg tablets (Sanofi)
11351	Co-zidocapt 25mg/50mg tablets
11384	Co-flumactone 50mg/50mg tablets
11448	Irbesartan 150mg / Hydrochlorothiazide 12.5mg tablets
11469	Irbesartan 300mg / Hydrochlorothiazide 12.5mg tablets
11487	Torasemide 2.5mg tablets
11512	Nifedipress MR 10 tablets (Dexcel-Pharma Ltd)
11519	Spironolactone 25mg/5ml oral suspension sugar free
11526	CoAprovel 300mg/12.5mg tablets (Sanofi)

11561	Co-zidocapt 12.5mg/25mg tablets
11567	Ramipril 5mg with felodipine 5mg modified-release tablet
11596	Xismox XL 60 tablets (Genus Pharmaceuticals Ltd)
11616	Isosorbide mononitrate 50mg modified-release tablets
11641	Captopril 25mg with Hydrochlorothiazide 12.5mg tablets
11769	Calchan MR 20 tablets (Ranbaxy (UK) Ltd)
11770	Dilzem SR 60 capsules (Teva UK Ltd)
11777	Verapamil 40mg/5ml oral solution sugar free
11864	Valsartan 160mg / Hydrochlorothiazide 12.5mg tablets
11922	Diltiazem 60mg/5ml oral suspension
11937	Ramipril 2.5mg/5ml oral suspension
11943	Cardene 20mg capsules (Astellas Pharma Ltd)
11957	Isosorbide dinitrate 100mg/100ml solution for infusion bottles
11965	Ramipril 2.5mg with felodipine 2.5mg modified-release tablet
11972	Vertab SR 240 tablets (Chiesi Ltd)
11973	Calcicard CR 120mg tablets (Teva UK Ltd)
11978	Isosorbide dinitrate 25mg/50ml infusion bottles
11983	Perindopril erbumine 4mg/5ml oral suspension
11987	Lisinopril 5mg/5ml oral solution
12017	Sorbitrate 20mg Tablet (AstraZeneca UK Ltd)
12054	Propranolol 80mg / Bendroflumethiazide 2.5mg capsules
12063	Isordil Tembids 40mg modified-release capsules (Shire Pharmaceuticals Ltd)
12104	Cordilox 160mg tablets (IVAX Pharmaceuticals UK Ltd)
12151	Vascardin 10mg Tablet (Nicholas Laboratories Ltd)
12226	Burinex 1mg/5ml Oral solution (LEO Pharma)
12284	Mono-cedocard -40 Tablet (Pharmacia Ltd)
12294	Burinex 5mg tablets (LEO Pharma)
12313	Carace 20mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
12318	Lasix 250mg/25ml Injection (Hoechst Marion Roussel)
12392	Univer 180mg modified-release capsules (Teva UK Ltd)
12440	Hydrosaluric 25mg tablets (Merck Sharp & Dohme Ltd)
12456	Sotazide Tablet (Bristol-Myers Squibb Pharmaceuticals Ltd)
12517	Timolol maleate with bendroflumethiazide 20mg + 5mg Tablet
12546	Kalspare Tablet (Dominion Pharma)
12547	Triamterene 50mg / Chlortalidone 50mg tablets
12606	Nifelease 20mg Modified-release tablet (Eastern Pharmaceuticals Ltd)
12613	Unipine xl 30mg Modified-release tablet (Genus Pharmaceuticals Ltd)
12639	Diltiazem HCl 90mg Modified-release tablet (Actavis UK Ltd)
12651	Timolol 10mg / Bendroflumethiazide 2.5mg tablets
12705	Angiozem CR 90mg tablets (Ashbourne Pharmaceuticals Ltd)
12804	MCR-50 modified-release capsules (Pfizer Ltd)
12815	Tanatril 10mg tablets (Mitsubishi Tanabe Pharma Europe Ltd)
12836	Eprosartan 600mg tablets
12858	Imidapril 10mg tablets
12874	Telmisartan 80mg tablets
12875	Cardene SR 45mg capsules (Astellas Pharma Ltd)
12946	Spironolactone 10mg/5ml oral suspension sugar free
13027	Viazem XL 240mg capsules (Thornton & Ross Ltd)
13033	Angitil XL 240 capsules (Ethypharm UK Ltd)
13075	Dilzem XL 180 capsules (Teva UK Ltd)
13090	Isosorbide dinitrate 1.25mg/dose sublingual spray sugar free

13123	Eprosartan 400mg tablets
13127	Dilzem XL 240 capsules (Teva UK Ltd)
13139	Adipine XL 30mg tablets (Chiesi Ltd)
13240	Dilzem XL 120 capsules (Teva UK Ltd)
13243	Lercanidipine 20mg tablets
13251	Vera-Til SR 240mg tablets (Tillomed Laboratories Ltd)
13264	Spironolactone 15mg/5ml oral suspension
13302	Dilzem SR 90 capsules (Teva UK Ltd)
13317	Apresoline 20mg powder for solution for injection ampoules (Advanz Pharma)
13352	Midamor 5mg Tablet (MSD Thomas Morson Pharmaceuticals)
13363	Esidrex 50mg Tablet (Novartis Pharmaceuticals UK Ltd)
13410	Angiozem 60mg modified-release tablets (Ashbourne Pharmaceuticals Ltd)
13435	Frumil Forte 10mg/80mg tablets (Sanofi)
13446	Elantan 20mg Tablet (UCB Pharma Ltd)
13526	Atenix Co 100 tablets (Ashbourne Pharmaceuticals Ltd)
13589	Staril 20mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
13610	Alphavase 2 tablets (Ashbourne Pharmaceuticals Ltd)
13672	Angiopine MR 10mg tablets (Ashbourne Pharmaceuticals Ltd)
13699	Angiopine la 40mg Tablet (Ashbourne Pharmaceuticals Ltd)
13755	Enalapril 10mg wafer
13821	Micardis 40mg tablets (Boehringer Ingelheim Ltd)
13856	Verapress MR 240mg tablets (Actavis UK Ltd)
13871	Co-prenozide 160mg/0.25mg modified-release tablets
13882	Imazin XL tablets (Napp Pharmaceuticals Ltd)
13926	Diltiazem 360mg modified-release capsules
13965	Cordilox MR 240mg tablets (Teva UK Ltd)
14109	Spironolactone 100mg/5ml oral solution sugar free
14126	Acebutolol 200mg / Hydrochlorothiazide 12.5mg tablets
14144	Inspra 25mg tablets (Upjohn UK Ltd)
14228	Coversyl Plus tablets (Servier Laboratories Ltd)
14283	Valsartan 160mg / Hydrochlorothiazide 25mg tablets
14300	Zanidip 20mg tablets (Recordati Pharmaceuticals Ltd)
14305	Vascalpha 10mg modified-release tablets (Accord Healthcare Ltd)
14387	Carace 5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
14390	Aldomet 250mg/5ml Liquid (Merck Sharp & Dohme Ltd)
14438	Corgaretic 80mg tablets (Sanofi-Synthelabo Ltd)
14477	Accupro 10mg tablets (Pfizer Ltd)
14478	Accupro 20mg tablets (Pfizer Ltd)
14495	Loniten 10mg tablets (Pfizer Ltd)
14587	Amiloride 5mg / Bumetanide 1mg tablets
14679	Cibral xl 60mg Tablet (Ranbaxy (UK) Ltd)
14685	Monit xl 60 60mg Modified-release tablet (Sterwin Medicines)
14731	Isodur 25XL capsules (Galen Ltd)
14738	Hydrochlorothiazide with losartan 12.5mg with 50mg Tablet
14761	Frusid 40mg tablets (Dr Reddy's Laboratories (UK) Ltd)
14837	Frusol 50mg/5ml oral solution (Rosemont Pharmaceuticals Ltd)
14861	Calchan MR 10 tablets (Ranbaxy (UK) Ltd)
14870	Telmisartan 40mg / Hydrochlorothiazide 12.5mg tablets
14892	Anoheal 2% Cream (S.L.A. Pharma (UK) Ltd)
14896	Cibral 10 tablets (Ranbaxy (UK) Ltd)
14943	Valsartan 40mg tablets

14960	Coversyl 8mg tablets (Servier Laboratories Ltd)
14965	Cozaar 100mg tablets (Merck Sharp & Dohme Ltd)
14983	Olmetec 10mg tablets (Daiichi Sankyo UK Ltd)
15031	Accuretic 10mg/12.5mg tablets (Pfizer Ltd)
15034	Cedocard -10 Tablet (Pharmacia Ltd)
15042	Tolerzide Tablet (Bristol-Myers Squibb Pharmaceuticals Ltd)
15052	Spiroctan 50mg Tablet (Roche Products Ltd)
15053	SPIRONOLACTONE 10 MG/5ML LIQ
15069	Elantan 40mg Tablet (UCB Pharma Ltd)
15083	Ismo Starter pack (Roche Products Ltd)
15085	Innovace Titration pack (Merck Sharp & Dohme Ltd)
15096	Accupro 40mg tablets (Pfizer Ltd)
15108	Quinapril 10mg / Hydrochlorothiazide 12.5mg tablets
15117	Nifedipine with atenolol 20mg + 50mg Capsule
15127	Hydrochlorothiazide with triamterene 25mgwith50mg Tablet
15135	Hydrochlorothiazide with captopril 12.5mg with 25mg Tablet
15221	Dilcardia xl 180mg Modified-release capsule (Generics (UK) Ltd)
15288	Angitil XL 300 capsules (Ethypharm UK Ltd)
15341	Burinex 0.5mg/ml Injection (LEO Pharma)
15488	Metoprolol tartrate with chlortalidone Tablet
15493	Reserpine with hydrochlorothiazide tablet
15577	HYDROCHLOROTHIAZIDE 12.5MG/K 8.1MMOL S/R 12.5 MG TAB
15659	DILTIAZEM HCL S/R 180 CAP
15715	Genalat retard 20mg Modified-release tablet (Wyeth Pharmaceuticals)
15811	Co-flumactone 25mg/25mg tablets
15874	Amiloride 2.5mg / furosemide 20mg tablets
15958	Captopril 2mg tablets
15998	Eumon xl 40mg Tablet (Neo Laboratories Ltd)
16038	Dilzem SR 120 capsules (Teva UK Ltd)
16060	Valsartan 80mg / Hydrochlorothiazide 12.5mg tablets
16073	Nifedipress MR 10 tablets (Teva UK Ltd)
16161	Telmisartan 80mg / Hydrochlorothiazide 12.5mg tablets
16206	Froop 40mg tablets (Ashbourne Pharmaceuticals Ltd)
16248	Clonidine 150micrograms/1ml solution for injection ampoules
16256	Modisal LA25 capsules (Sandoz Ltd)
16285	Teveten 400mg tablets (Abbott Healthcare Products Ltd)
16328	Verapress MR 240mg tablets (Dexcel-Pharma Ltd)
16371	Teveten 600mg tablets (Mylan)
16498	Kalspare tablets (DHP Healthcare Ltd)
16531	Eplerenone 50mg tablets
16630	Mono-cedocard -10 Tablet (Pharmacia Ltd)
16632	Hydrosaluric 50mg tablets (Merck Sharp & Dohme Ltd)
16677	Cordilox 80mg tablets (IVAX Pharmaceuticals UK Ltd)
16701	Carace 10mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
16708	Enalapril titration pack
16786	Chlortalidone 25mg with Atenolol 100mg tablets
16850	Angiozem CR 120mg tablets (Ashbourne Pharmaceuticals Ltd)
16924	Imidapril 5mg tablets
16940	Zemon 60 XL tablets (Fannin UK Ltd)
17006	Triapin 5mg/5mg modified-release tablets (Sanofi)
17149	Monozide 10 tablets (Wyeth Pharmaceuticals)

17252	Esidrex 25mg Tablet (Novartis Pharmaceuticals UK Ltd)
17256	Isoket -20 Tablet (Schwarz Pharma Ltd)
17325	Cardilate MR 10mg tablets (Teva UK Ltd)
17338	Nifedotard 20 mr 20mg Modified-release tablet (Galen Ltd)
17342	Nivaten retard 10mg Modified-release tablet (Actavis UK Ltd)
17406	Zemtard 180 XL capsules (Galen Ltd)
17425	Zemtard 120 XL capsules (Galen Ltd)
17448	Nifedipress mr 10mg Modified-release tablet (Sterwin Medicines)
17462	Bisoprolol 10mg / Hydrochlorothiazide 6.25mg tablets
17474	Felodipine 5mg modified-release / Ramipril 5mg tablets
17492	Zemtard 300 XL capsules (Galen Ltd)
17545	Micardis 80mg tablets (Boehringer Ingelheim Ltd)
17557	Felotens XL 5mg tablets (Thornton & Ross Ltd)
17561	Bendroflumethiazide 2.5mg / Potassium chloride 573mg (potassium 7.7mmol) modified-release tablets
17566	Felotens XL 10mg tablets (Thornton & Ross Ltd)
17586	Slozem 300mg capsules (Merck Serono Ltd)
17599	Verapress MR 240mg tablets (Sandoz Ltd)
17624	Captopril 5mg/5ml oral suspension
17633	Captopril 3mg/5ml oral solution
17655	Carace 10 Tablet (Bristol-Myers Squibb Pharmaceuticals Ltd)
17666	Viazem XL 180mg capsules (Thornton & Ross Ltd)
17686	Micardis 20mg tablets (Boehringer Ingelheim Ltd)
17689	MicardisPlus 80mg/12.5mg tablets (Boehringer Ingelheim Ltd)
17783	Spiroprop Tablet (Pharmacia Ltd)
17867	Imtack 1.25mg/actuation Spray (AstraZeneca UK Ltd)
17902	Spirolone 100mg Tablet (Berk Pharmaceuticals Ltd)
17950	Spirolone 50mg Tablet (Berk Pharmaceuticals Ltd)
17960	Furosemide 20mg / Potassium chloride 750mg (potassium 10mmol) modified-release tablets
18030	Imazin XL forte tablets (Napp Pharmaceuticals Ltd)
18096	Torasemide 10mg tablets
18200	Olmesartan medoxomil 20mg / Hydrochlorothiazide 12.5mg tablets
18202	MicardisPlus 40mg/12.5mg tablets (Boehringer Ingelheim Ltd)
18219	Imidapril 20mg tablets
18223	Trandolapril with verapamil 2mg + 180mg Modified-release capsule
18252	Metalpha 250mg Tablet (Ashbourne Pharmaceuticals Ltd)
18263	Acezide 25mg/50mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
18269	Acepril 12.5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
18287	Co-Betaloc SA tablets (Pfizer Ltd)
18325	Acepril 50mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
18332	Aridil 20mg+2.5mg Tablet (C P Pharmaceuticals Ltd)
18361	Amilmaxco 5mg/50mg tablets (Ashbourne Pharmaceuticals Ltd)
18379	Dilcardia SR 90mg capsules (Mylan)
18403	Diltiazem HCl 180mg Modified-release capsule (Hillcross Pharmaceuticals Ltd)
18404	Diltiazem 60mg modified-release capsules (A A H Pharmaceuticals Ltd)
18497	Amiloride 10mg / furosemide 80mg tablets
18606	Diltiazem and hydrochlorothiazide 150mg+12.5mg modified-release capsules
18716	Dryptal 10mg/ml Injection (Berk Pharmaceuticals Ltd)
18726	Triamaxco 50mg/25mg tablets (Ashbourne Pharmaceuticals Ltd)
18733	Co-amilozide 5mg with 50mg/ml oral solution

18743	Tenben 25mg/1.25mg capsules (Galen Ltd)
18787	Angeze sr 40mg Modified-release capsule (Opus Pharmaceuticals Ltd)
18830	Disogram SR 90mg capsules (Ranbaxy (UK) Ltd)
18834	Disogram SR 60mg capsules (Ranbaxy (UK) Ltd)
18852	Disogram SR 120mg capsules (Ranbaxy (UK) Ltd)
18861	Hydralazine 10mg/5ml oral suspension
18874	Disogram SR 180mg capsules (Ranbaxy (UK) Ltd)
18889	Isoket Retard 20 tablets (Forum Health Products Ltd)
18903	Olmesartan medoxomil 20mg / Hydrochlorothiazide 25mg tablets
18910	Olmetec 20mg tablets (Daiichi Sankyo UK Ltd)
18938	MINOXIDIL 1 % TAB
18964	Sorbid-20 SA capsules (AstraZeneca UK Ltd)
18973	Centyl 2.5mg Tablet (Edwin Burgess Ltd)
18975	Calcicard 60mg Tablet (3M Health Care Ltd)
19003	SPIRONOLACTONE/PROPRANOLOL 50 MG TAB
19055	Chlortalidone 12.5mg with Atenolol 50mg tablets
19056	Furosemide 50mg/5ml sugar free Oral solution (Rosemont Pharmaceuticals Ltd)
19142	Bendroflumethiazide 2.5mg with Timolol maleate 10mg tablets
19170	Tensipine MR 10 tablets (Genus Pharmaceuticals Ltd)
19175	Verapamil 40mg tablets (IVAX Pharmaceuticals UK Ltd)
19192	Furosemide 40mg Tablet (M & A Pharmachem Ltd)
19193	Doxazosin 2mg tablets (Teva UK Ltd)
19194	Furosemide 20mg tablets (Teva UK Ltd)
19195	Spironolactone 50mg Tablet (Wyeth Pharmaceuticals)
19198	Lisinopril 20mg tablets (Teva UK Ltd)
19204	Lisinopril 5mg tablets (Teva UK Ltd)
19208	Enalapril 10mg tablets (Actavis UK Ltd)
19216	Doxazosin 4mg tablets (IVAX Pharmaceuticals UK Ltd)
19223	Lisinopril 10mg tablets (Teva UK Ltd)
19258	Furosemide 50mg/5ml solution for injection ampoules
19300	Bumetanide 2mg/4ml solution for injection ampoules
19325	Cordilox 2.5mg/ml Injection (IVAX Pharmaceuticals UK Ltd)
19352	Xuret 0.5mg Tablet (Galen Ltd)
19426	Disogram SR 240mg capsules (Ranbaxy (UK) Ltd)
19440	Disogram SR 300mg capsules (Ranbaxy (UK) Ltd)
19457	Ranvera MR 240mg tablets (Ranbaxy (UK) Ltd)
19459	Verapamil 240mg modified-release tablets (A A H Pharmaceuticals Ltd)
19611	AMILORIDE 5MG/HYDROCHLORTHIAZIDE 50MG
19690	Verapamil 180mg modified-release / Trandolapril 2mg capsules
19695	AMILORIDE HYDROCHLORIDE
19721	AMILORIDE 5MG/HYDROCHLORTHIAZIDE 50MG
19823	Alphavase 5 tablets (Ashbourne Pharmaceuticals Ltd)
19839	Eumon xl 60mg Tablet (Neo Laboratories Ltd)
19890	Hydrochlorothiazide with amiloride 25mgwith2.5mg Tablet
19892	Serpasil -esidrex Tablet (Novartis Pharmaceuticals UK Ltd)
20066	Amil-Co 5mg/50mg tablets (IVAX Pharmaceuticals UK Ltd)
20093	Metoprolol 200mg modified-release / Hydrochlorothiazide 25mg tablets
20117	Olmetec 40mg tablets (Daiichi Sankyo UK Ltd)
20160	CHLORTHALIDONE 500 MG TAB
20188	Enalapril 2.5mg wafer
20257	Cardilate MR 20mg tablets (IVAX Pharmaceuticals UK Ltd)

20311	Nifedipress mr 20mg Modified-release tablet (Generics (UK) Ltd)
20322	Monomil XL 60mg tablets (Teva UK Ltd)
20369	Doxazosin 1mg/5ml oral suspension
20426	Centyl k 2.5mg+7.7mmol Tablet (Edwin Burgess Ltd)
20431	Centyl K modified-release tablets (LEO Pharma)
20459	Felendil xl 10mg Modified-release tablet (Ratiopharm UK Ltd)
20500	Soni-Slo SR 20mg capsules (Lipha Pharmaceuticals Ltd)
20513	LASIX 10 MG INJ
20530	Cedocard -20 Tablet (Pharmacia Ltd)
20538	Frumax 40mg Tablet (Ashbourne Pharmaceuticals Ltd)
20579	Tarka modified-release capsules (Abbott Laboratories Ltd)
20591	Nifedipress MR 20 tablets (Teva UK Ltd)
20642	Bi-carzem sr 60mg Modified-release capsule (Tillomed Laboratories Ltd)
20849	Tensopril 12.5mg tablets (Teva UK Ltd)
20878	Angiopine 10 capsules (Ashbourne Pharmaceuticals Ltd)
20879	Isotard 50XL tablets (Kyowa Kirin Ltd)
20890	Zemtard 240 XL capsules (Galen Ltd)
20975	Lisinopril 7.5mg/5ml oral suspension
21025	Prestim forte Tablet (LEO Pharma)
21066	Mono-cedocard -20 Tablet (Pharmacia Ltd)
21145	Dilcardia SR 60mg capsules (Mylan)
21162	Felodipine 2.5mg modified-release / Ramipril 2.5mg tablets
21182	Hydrochlorothiazide with timolol and amiloride 25mg with 10mg with 2.5mg Tablet
21216	Hypolar Retard 10mg tablets (Sandoz Ltd)
21231	Caralpha 20mg/12.5mg tablets (Actavis UK Ltd)
21245	Nifedipress mr 10mg Modified-release tablet (Actavis UK Ltd)
21346	Hydromet Tablet (MSD Thomas Morson Pharmaceuticals)
21380	Aspirin 75mg / Isosorbide mononitrate 60mg modified-release tablets
21382	Aspirin 150mg / Isosorbide mononitrate 60mg modified-release tablets
21423	Cozaar-Comp 100mg/25mg tablets (Merck Sharp & Dohme Ltd)
21749	HYDRALAZINE HCl 100 MG TAB
21763	Diltiazem 60mg modified-release tablets (A A H Pharmaceuticals Ltd)
21764	Monodur 60mg Modified-release tablet (Waymade Healthcare Plc)
21773	Diltiazem HCl 60mg Tablet (Generics (UK) Ltd)
21778	Diltiazem 60mg modified-release tablets (Teva UK Ltd)
21795	Retalzem 60 modified-release tablets (Kent Pharmaceuticals Ltd)
21803	Berkozide 2.5mg Tablet (Berk Pharmaceuticals Ltd)
21849	Dryptal 40mg Tablet (Berk Pharmaceuticals Ltd)
21867	Berkozide 5mg Tablet (Berk Pharmaceuticals Ltd)
21872	Angiopine 5mg Capsule (Ashbourne Pharmaceuticals Ltd)
21873	Atenix Co 50 tablets (Ashbourne Pharmaceuticals Ltd)
21886	Nifedipress MR 20 tablets (Actavis UK Ltd)
21911	Spirospare 25mg Tablet (Ashbourne Pharmaceuticals Ltd)
21918	Optil 60mg modified-release tablets (Opus Pharmaceuticals Ltd)
21938	Froop Co 5mg/40mg tablets (Ashbourne Pharmaceuticals Ltd)
21943	Kaplon 12.5mg tablets (Teva UK Ltd)
22019	Calanif 10mg Capsule (Berk Pharmaceuticals Ltd)
22142	Calcilat 10mg Capsule (Eastern Pharmaceuticals Ltd)
22151	METOPROLOL 100MG/CHLORTHALIDONE 12.5MG
22217	Nimodrel 10mg modified-release tablet (Opus Pharmaceuticals Ltd)
22358	Monigen XL 60 tablets (Mylan)

22427	Isosorbide dinitrate 30mg/dose transdermal spray
22439	Ednyt 20mg Tablet (Dominion Pharma)
22539	LASIX (2ML)
22619	Britiazim 60mg Modified-release tablet (Thames Laboratories Ltd)
22658	Torem 10mg tablets (Mylan)
22696	Slofedipine 20mg tablets (Sterwin Medicines)
22708	Enalapril 5mg wafer
22726	Monosorb xl 60mg Modified-release tablet (Generics (UK) Ltd)
22752	Isodur 50XL capsules (Galen Ltd)
22826	Securon 160mg Tablet (Abbott Laboratories Ltd)
22876	Cedocard -40 Tablet (Pharmacia Ltd)
22882	RAMIPRIL
22912	Bendroflumethiazide 2.5mg with Propanolol 80mg capsules
22923	Hydrochlorothiazide with amiloride 50mg with 5mg Tablet
23011	Isotrate 20mg Tablet (Bioglan Laboratories Ltd)
23091	Spirospare 100 tablets (Ashbourne Pharmaceuticals Ltd)
23131	Bendroflumethiazide 5mg with Propanolol 160mg modified-release capsules
23134	Nadolol 40mg / Bendroflumethiazide 5mg tablets
23233	Bi-carzem sr 90mg Modified-release capsule (Tillomed Laboratories Ltd)
23252	Pralenal 10 tablets (Opus Pharmaceuticals Ltd)
23256	LASIX PAED
23380	Catapres 300microgram tablets (Boehringer Ingelheim Ltd)
23427	Bendroflumethiazide 5mg tablets (A A H Pharmaceuticals Ltd)
23456	Hydrochlorothiazide with valsartan 25mg with 160mg Tablet
23459	Hypovase benign prostatic hyperplasia 2mg Tablet (Pfizer Ltd)
23478	Tensopril 50mg tablets (Teva UK Ltd)
23483	HYDROCHLOROTHIAZIDE 12.5MG/K 8.1MMOL S/R
23492	CYCLOPENTHIAZIDE 250MCG/K 8.1MMOL
23505	Adizem xl plus 150mg+12.5mg Modified-release capsule (Napp Pharmaceuticals Ltd)
23683	MINOXIDIL LIQUID
23733	Optil sr 90mg Modified-release capsule (Opus Pharmaceuticals Ltd)
23736	Hypolar XL 30 tablets (Sandoz Ltd)
23746	HYDRALAZINE HCl 10 MG TAB
23761	Methyldopa 250mg/5ml oral suspension
23872	Berkatens 40mg Tablet (Berk Pharmaceuticals Ltd)
24008	Vasetic Tablet (Shire Pharmaceuticals Ltd)
24041	Enalapril 20mg wafer
24189	Neo-bendromax 2.5mg Tablet (Ashbourne Pharmaceuticals Ltd)
24190	Neo-bendromax 5mg Tablet (Ashbourne Pharmaceuticals Ltd)
24196	Dopamet 250mg Tablet (Berk Pharmaceuticals Ltd)
24228	Nimodrel 20mg modified-release tablet (Opus Pharmaceuticals Ltd)
24268	Hydrochlorothiazide with valsartan 12.5mg with 80mg Tablet
24280	Totaretic 100mg+25mg Tablet (C P Pharmaceuticals Ltd)
24359	Diovan 40mg tablets (Novartis Pharmaceuticals UK Ltd)
24365	Cardioplen XL 5mg tablets (Chiesi Ltd)
24366	Cardioplen XL 10mg tablets (Chiesi Ltd)
24482	Captomex 50mg tablets (Actavis UK Ltd)
24484	Hydrochlorothiazide with valsartan 12.5mg with 160mg Tablet
24520	HYDROCHLOROTHIAZIDE /METOPROLOL TARTRATE 25 MG TAB
24557	Dynamin XL25 capsules (Teva UK Ltd)
24632	Hydrochlorothiazide with losartan 25mg with 100mg Tablet

24651	Angitak 1.25mg/dose spray (LPC Medical (UK) Ltd)
24671	Isib 50 xl 50mg Modified-release capsule (Ashbourne Pharmaceuticals Ltd)
24683	Isib 40mg Tablet (Ashbourne Pharmaceuticals Ltd)
24832	Lasipressin Tablet (Hoechst UK Ltd)
24835	Min-i-jet furosemide 10mg/ml Injection (Celltech Pharma Europe Ltd)
24893	Amilospare Tablet (Ashbourne Pharmaceuticals Ltd)
25026	NIFEDIPINE RETARD
25044	NIFEDIPINE RETARD
25047	Hypovase benign prostatic hyperplasia 500microgram Tablet (Pfizer Ltd)
25055	NIFEDIPINE
25059	Berkatens 80mg Tablet (Berk Pharmaceuticals Ltd)
25061	ISOSORBIDE MONONITRATE
25075	FRUSEMIDE 40MG/AMILORIDE HYD 5MG
25086	SPIRONOLACTONE
25100	Modisal LA50 capsules (Sandoz Ltd)
25132	Nifopress MR 20mg tablets (Teva UK Ltd)
25175	Monosorb xl 60mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)
25275	Metalpha 500mg Tablet (Ashbourne Pharmaceuticals Ltd)
25276	Isib 20mg Tablet (Ashbourne Pharmaceuticals Ltd)
25289	Dopamet 500mg Tablet (Berk Pharmaceuticals Ltd)
25334	Furosemide 500mg tablets (A A H Pharmaceuticals Ltd)
25363	Prestim tablets (Meda Pharmaceuticals Ltd)
25382	Co-Diovan 160mg/25mg tablets (Novartis Pharmaceuticals UK Ltd)
25487	Cascor 2mg tablets (Ranbaxy (UK) Ltd)
25494	Diatensec 50mg Tablet (Pharmacia Ltd)
25500	Hypertane 50 Tablet (Schwarz Pharma Ltd)
25505	Spiro-co 50mg+50mg Tablet (IVAX Pharmaceuticals UK Ltd)
25551	Cascor 4mg tablets (Ranbaxy (UK) Ltd)
25572	Felogen XL 5mg tablets (Mylan)
25646	Nivaten retard 20mg Modified-release tablet (Actavis UK Ltd)
25717	Furosemide 40mg tablets (Mylan)
25730	Timolol maleate with amiloride and hydrochlorothiazide Tablet
25777	Dilcardia SR 120mg capsules (Mylan)
25795	Isocard 30mg/dose transdermal spray (LPC Medical (UK) Ltd)
25836	METHYLDOPA 200 MG TAB
25878	Isosorbide mononitrate 60mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)
25919	Nifedipine 20mg modified-release tablets (A A H Pharmaceuticals Ltd)
25965	Co-amilofruse 2.5mg/20mg tablets (Wockhardt UK Ltd)
25998	Captomex 12.5mg tablets (Actavis UK Ltd)
26043	Monosorb XL 60 tablets (Almus Pharmaceuticals Ltd)
26217	Berkamil 5mg Tablet (Berk Pharmaceuticals Ltd)
26219	Zida-co 5mg+50mg Tablet (Opus Pharmaceuticals Ltd)
26220	Delvas Tablet (Berk Pharmaceuticals Ltd)
26221	Angitate 20mg Tablet (Berk Pharmaceuticals Ltd)
26222	Angeze 20 tablets (Opus Pharmaceuticals Ltd)
26237	Alphavase 500microgram Tablet (Ashbourne Pharmaceuticals Ltd)
26238	Alphavase 1 tablets (Ashbourne Pharmaceuticals Ltd)
26246	Angeze 40mg Tablet (Opus Pharmaceuticals Ltd)
26248	Tenchlor 100mg/25mg tablets (Teva UK Ltd)
26251	Dynamin 20mg tablets (Teva UK Ltd)
26252	Berkatens 160mg Tablet (Berk Pharmaceuticals Ltd)

26253	Angeze 10 tablets (Opus Pharmaceuticals Ltd)
26256	Opumide 2.5mg Tablet (Opus Pharmaceuticals Ltd)
26260	Angitate 10mg Tablet (Berk Pharmaceuticals Ltd)
26265	Calanif 5mg Capsule (Berk Pharmaceuticals Ltd)
26266	Monosorb XL 60 tablets (Dexcel-Pharma Ltd)
26267	Optil sr 120mg Modified-release capsule (Opus Pharmaceuticals Ltd)
26269	Optil sr 180mg Modified-release capsule (Opus Pharmaceuticals Ltd)
26270	Optil xl 300mg Modified-release capsule (Opus Pharmaceuticals Ltd)
26271	Angeze sr 60mg Modified-release capsule (Opus Pharmaceuticals Ltd)
26275	Nindaxa 2.5 tablets (Ashbourne Pharmaceuticals Ltd)
26279	Dynamin 10mg tablets (Teva UK Ltd)
26292	Diuresal 40mg Tablet (Lagap)
26309	Optil xl 240mg Modified-release capsule (Opus Pharmaceuticals Ltd)
26328	LASIX (25ML)
26337	Cabren 10mg modified-release tablets (Teva UK Ltd)
26460	Dilcardia xl 240mg Modified-release capsule (Generics (UK) Ltd)
26463	Zemret xl 240mg Capsule (Neo Laboratories Ltd)
26529	Furosemide with penbutolol Tablet
26583	Vascardin 30mg Tablet (Nicholas Laboratories Ltd)
26674	Verapamil 5mg/2ml solution for injection ampoules
26675	XIPAMIDE
26693	Hypovase benign prostatic hyperplasia bd BD Starter pack (Pfizer Ltd)
26741	Totaretic 50mg+12.5mg Tablet (C P Pharmaceuticals Ltd)
26759	Zildil SR 60mg capsules (Healthcare Pharma Ltd)
26774	Nifedipine 10mg/5ml Oral suspension
26853	Monosorb xl 60mg Modified-release tablet (Ratiopharm UK Ltd)
26919	Methyldopa 50mg/ml Injection
26995	Kaplon 25mg tablets (Teva UK Ltd)
27135	Diltiazem sr 90mg Capsule (Hillcross Pharmaceuticals Ltd)
27136	Diltiazem 90mg modified-release tablets (A A H Pharmaceuticals Ltd)
27256	Bendroflumethiazide 2.5mg tablets (Wockhardt UK Ltd)
27295	Securon IV 5mg/2ml solution for injection ampoules (Mylan)
27401	Kenzem SR 90mg capsules (Kent Pharmaceuticals Ltd)
27447	Furosemide 40mg tablets (Wockhardt UK Ltd)
27485	Soni-Slo SR 40mg capsules (Lipha Pharmaceuticals Ltd)
27520	Olmetec Plus 20mg/25mg tablets (Daiichi Sankyo UK Ltd)
27545	ISOSORBIDE MONONITRATE
27685	Diltiazem HCl 300mg Capsule (PLIVA Pharma Ltd)
27689	Bendroflumethiazide 2.5mg tablets (IVAX Pharmaceuticals UK Ltd)
27690	Furosemide 40mg tablets (A A H Pharmaceuticals Ltd)
27696	Furosemide 40mg tablets (Kent Pharmaceuticals Ltd)
27774	ISOSORBIDE MONONITRATE MR
27871	Innovace melt 10mg Wafer (Merck Sharp & Dohme Ltd)
27890	ENALAPRIL MALEATE
27894	CLONIDINE HYDROCHLORIDE
27926	Furosemide 20mg tablets (Mylan)
27946	Nadolol 80mg / Bendroflumethiazide 5mg tablets
27957	Natramid 2.5mg Tablet (Trinity Pharmaceuticals Ltd)
28127	Enalapril 2.5mg tablets (Teva UK Ltd)
28129	Co-amilofruse 5mg/40mg tablets (Teva UK Ltd)
28157	Kalspare ls Tablet (Dominion Pharma)

28177	Hydrochlorothiazide with atenolol and amiloride Capsule
28438	Triapin 2.5mg/2.5mg modified-release tablets (Sanofi)
28486	Captopril 6.25mg/5ml oral suspension
28586	Lopace 5mg capsules (Discovery Pharmaceuticals)
28688	Nifedipine 10mg modified-release tablets (A A H Pharmaceuticals Ltd)
28719	Zemon 40 XL tablets (Kent Pharmaceuticals Ltd)
28721	Neofel XL 5mg tablets (Kent Pharmaceuticals Ltd)
28738	Methyldopa with hydrochlorothiazide Tablet
28820	Captomex 25mg tablets (Actavis UK Ltd)
28843	Verapamil hc 80mg Tablet (Celltech Pharma Europe Ltd)
28844	Berkatens 120mg Tablet (Berk Pharmaceuticals Ltd)
28949	Bi-carzem sr 120mg Modified-release capsule (Tillomed Laboratories Ltd)
29044	Neofel XL 10mg tablets (Kent Pharmaceuticals Ltd)
29072	Cedocard iv 1mg/ml Injection (Pharmacia Ltd)
29145	Felendil xl 2.5mg Modified-release tablet (Ratiopharm UK Ltd)
29397	Spiretic 100mg Tablet (DDSA Pharmaceuticals Ltd)
29427	Hydrochlorothiazide with metoprolol tartrate 12.5mg with 100mg tablet
29529	Hydroflumethiazide with spironolactone 25mg+25mg Tablet
29530	Innovace melt 2.5mg Wafer (Merck Sharp & Dohme Ltd)
29570	Dopamet 125mg Tablet (Berk Pharmaceuticals Ltd)
29627	Lopace 2.5mg capsules (Discovery Pharmaceuticals)
29634	Olmetec Plus 20mg/12.5mg tablets (Daiichi Sankyo UK Ltd)
29637	Verapress MR 240mg tablets (Teva UK Ltd)
29676	Calazem 60mg Modified-release tablet (Berk Pharmaceuticals Ltd)
29694	Inspra 50mg tablets (Upjohn UK Ltd)
29777	Isotard 25 xl 25mg Modified-release capsule (ProStrakan Ltd)
29780	Furosemide 20mg Tablet (C P Pharmaceuticals Ltd)
29991	Centyl 5mg Tablet (Edwin Burgess Ltd)
30034	CHLOROTHIAZIDE / SPIRONOLACTONE 100 MG POW
30035	CHLOROTHIAZIDE 40MG /SPIRONOLACTONE 4MG POW
30039	Tensopril 25mg tablets (Teva UK Ltd)
30129	Abicol Tablet (Knoll Ltd)
30197	Diltiazem 120mg modified-release capsules
30199	Nifedipine 30mg modified-release tablets
30242	Diltiazem 180mg modified-release capsules
30293	Catapres 150micrograms/1ml solution for injection ampoules (Boehringer Ingelheim Ltd)
30365	CHLOROTHIAZIDE/SPIRONOLACTONE/LACTOSE MG POW
30367	CHLOROTHIAZIDE 60MG / SPIRONOLACTONE 6MG POW
30368	CHLOROTHIAZIDE/SPIRONOLACTONE SACHETS 100 MG
30409	Cibral 20 tablets (Ranbaxy (UK) Ltd)
30462	Ethimil MR 240mg tablets (Genus Pharmaceuticals Ltd)
30473	Coroday MR 20mg tablets (Mylan)
30491	DILTIAZEM HYDROCHLORIDE
30519	Amiloride with timolol with hydrochlorothiazide tablets
30557	Felogen XL 10mg tablets (Mylan)
30592	CHLOROTHIAZIDE / SPIRONOLACTONE / GLUCOS 60 MG POW
30625	Furosemide 20mg tablets (A A H Pharmaceuticals Ltd)
30773	Co-amilofruse 5mg+40mg Tablet (Berk Pharmaceuticals Ltd)
30875	Furosemide 250mg/25ml solution for injection ampoules
30913	Betinex 1mg Tablet (Berk Pharmaceuticals Ltd)

30915	Cabren 2.5mg modified-release tablets (Teva UK Ltd)
30921	Lisinopril 2.5mg tablets (Teva UK Ltd)
30991	Cabren 5mg modified-release tablets (Teva UK Ltd)
31072	Amias 32mg tablets (Takeda UK Ltd)
31131	Spiro-co 25mg+25mg Tablet (IVAX Pharmaceuticals UK Ltd)
31150	Co-amilozide 5mg/50mg tablets (IVAX Pharmaceuticals UK Ltd)
31160	IRBESARTAN
31219	Spironolactone 100mg tablets (A A H Pharmaceuticals Ltd)
31220	Hydralazine 25mg tablets (A A H Pharmaceuticals Ltd)
31375	Amilamont 5mg/5ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)
31470	Tenchlor 50mg/12.5mg tablets (Teva UK Ltd)
31475	Jeridin 10mg Tablet (Berk Pharmaceuticals Ltd)
31489	Bi-carzem xl 240mg Capsule (Tillomed Laboratories Ltd)
31490	Zolvera 40mg/5ml oral solution (Rosemont Pharmaceuticals Ltd)
31529	Spironolactone 25mg tablets (Teva UK Ltd)
31548	Furosemide 20mg tablets (Actavis UK Ltd)
31587	Innovace melt 20mg Wafer (Merck Sharp & Dohme Ltd)
31670	Bendroflumethiazide 2.5mg tablets (Teva UK Ltd)
31676	Diltiazem HCl 120mg Modified-release tablet (Actavis UK Ltd)
31708	Co-tenidone 50mg/12.5mg tablets (Actavis UK Ltd)
31711	Verapamil 80mg tablets (A A H Pharmaceuticals Ltd)
31716	Enalapril 20mg tablets (Actavis UK Ltd)
31737	Zildil SR 120mg capsules (Healthcare Pharma Ltd)
31773	Co-amilofruse 5mg/40mg tablets (Wockhardt UK Ltd)
31820	Bendroflumethiazide 5mg tablets (Wockhardt UK Ltd)
31932	Bumetanide 1mg tablets (C P Pharmaceuticals Ltd)
31971	HYDRALAZINE 6.25 MG SYR
32048	Kaplon 50mg tablets (Teva UK Ltd)
32059	Slomon XL 60 tablets (Zurich Pharmaceuticals)
32089	Diltiazem HCl 120mg Modified-release capsule (Hillcross Pharmaceuticals Ltd)
32091	Bumetanide 1mg tablets (A A H Pharmaceuticals Ltd)
32094	Co-tenidone 50mg/12.5mg tablets (A A H Pharmaceuticals Ltd)
32166	Capto-co 25mg+50mg Tablet (IVAX Pharmaceuticals UK Ltd)
32241	Enalapril 10mg tablets (A A H Pharmaceuticals Ltd)
32253	Carmil XL 60mg tablets (Mylan)
32262	Diltiazem HCl 60mg Tablet (C P Pharmaceuticals Ltd)
32277	Furosemide 80mg/8ml solution for injection pre-filled syringes
32442	Isosorbide mononitrate 25mg modified-release capsules (A A H Pharmaceuticals Ltd)
32514	Ecopace 25mg tablets (Advanz Pharma)
32560	Tanatril 20mg tablets (Mitsubishi Tanabe Pharma Europe Ltd)
32590	Verapamil 40mg tablets (Mylan)
32597	Lisinopril 10mg tablets (Sandoz Ltd)
32658	Dilcardia xl 120mg Modified-release capsule (Generics (UK) Ltd)
32666	ISOSORBIDE MONONITRATE MR
32837	Spironolactone 50mg tablets (Teva UK Ltd)
32841	Isosorbide mononitrate 10mg tablets (Dexcel-Pharma Ltd)
32857	Ramipril 1.25mg capsules (Teva UK Ltd)
32870	Diltiazem 60mg modified-release tablets (Sterwin Medicines)
32896	Furosemide 40mg tablets (Ranbaxy (UK) Ltd)
32913	Methyldopa 250mg tablets (Accord Healthcare Ltd)
32918	Furosemide 20mg tablets (Sandoz Ltd)

32922	Felodipine 10mg Modified-release tablet (Sandoz Ltd)
32934	Lopace 10mg capsules (Discovery Pharmaceuticals)
33025	Nimodrel XL 30mg tablets (Zurich Pharmaceuticals)
33057	Ednyt 5mg Tablet (Dominion Pharma)
33078	Enalapril 20mg tablets (A A H Pharmaceuticals Ltd)
33083	Indapamide 2.5mg tablets (Teva UK Ltd)
33091	Felodipine 10mg modified-release tablets (A A H Pharmaceuticals Ltd)
33093	Clonidine 25microgram tablets (Sandoz Ltd)
33094	Doxazosin 2mg tablets (Mylan)
33095	Perindopril erbumine 4mg tablets (A A H Pharmaceuticals Ltd)
33148	Isoket 0.1% solution for infusion 100ml bottles (Schwarz Pharma Ltd)
33322	Moxonidine 200microgram tablets (Sandoz Ltd)
33336	Captopril 5mg/5ml Oral suspension (Eldon Laboratories)
33353	Lisinopril 20mg / Hydrochlorothiazide 12.5mg tablets (Teva UK Ltd)
33354	Cibral 40 tablets (Ranbaxy (UK) Ltd)
33415	Bendroflumethiazide 2.5mg tablets (Mylan)
33471	Verapamil 40mg tablets (Actavis UK Ltd)
33527	Co-amilofruse 5mg/40mg tablets (Mylan)
33646	Captopril 12.5mg Tablet (Generics (UK) Ltd)
33651	Bendroflumethiazide 2.5mg tablets (A A H Pharmaceuticals Ltd)
33658	Co-amilofruse 5mg/40mg tablets (A A H Pharmaceuticals Ltd)
33659	Hydrochlorothiazide with metoprolol tartrate 25mg with 200mg Modified-release tablet
33660	Isosorbide mononitrate 60mg Modified-release tablet (Actavis UK Ltd)
33661	Isosorbide mononitrate 60mg modified-release tablets (A A H Pharmaceuticals Ltd)
33811	Ramipril 2.5mg capsules (Ranbaxy (UK) Ltd)
33837	Amiloride 5mg tablets (A A H Pharmaceuticals Ltd)
33894	Ramipril 10mg capsules (Teva UK Ltd)
33932	Parmid XL 5mg tablets (Sandoz Ltd)
33977	Lisinopril 10mg tablets (Mylan)
33992	Isosorbide mononitrate 10mg tablets (Teva UK Ltd)
34006	Furosemide 40mg tablets (Actavis UK Ltd)
34012	Co-tenidone 100mg/25mg tablets (IVAX Pharmaceuticals UK Ltd)
34034	Co-tenidone 50mg/12.5mg tablets (IVAX Pharmaceuticals UK Ltd)
34059	Bendroflumethiazide 2.5mg tablets (Actavis UK Ltd)
34101	Nifedipine mr 20mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)
34115	Nifedipine 60mg Modified-release tablet
34124	Bendroflumethiazide 5mg tablets (Accord Healthcare Ltd)
34146	Nifedipine mr 10mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)
34187	Nifedipine 10mg Modified-release tablet (Generics (UK) Ltd)
34196	Isosorbide mononitrate 10mg tablets (Actavis UK Ltd)
34247	Nifedipine 10mg Capsule (Berk Pharmaceuticals Ltd)
34280	Co-amilofruse 2.5mg/20mg tablets (Sandoz Ltd)
34296	Spironolactone 25mg tablets (A A H Pharmaceuticals Ltd)
34318	Isosorbide mononitrate 60mg Modified-release tablet (Lagap)
34324	Amiloride 5mg tablets (Teva UK Ltd)
34342	Doxazosin 1mg tablets (Teva UK Ltd)
34347	Spironolactone 25mg tablets (Actavis UK Ltd)
34357	Ramipril 10mg capsules (Genus Pharmaceuticals Ltd)
34367	Co-amilozide 2.5mg/25mg tablets (Wockhardt UK Ltd)
34374	Furosemide 40mg tablets (Teva UK Ltd)

34377	Diltiazem HCl 90mg Modified-release capsule (Hillcross Pharmaceuticals Ltd)
34382	Ramipril 5mg capsules (Zentiva)
34390	Ramipril 5mg capsules (Genus Pharmaceuticals Ltd)
34400	Enalapril 5mg Tablet (Dowelhurst Ltd)
34412	Ramipril 5mg capsules (Teva UK Ltd)
34426	Isosorbide mononitrate 20mg tablets (IVAX Pharmaceuticals UK Ltd)
34429	Ramipril 5mg capsules (Mylan)
34431	Ramipril 2.5mg capsules (Zentiva)
34432	Ramipril 2.5mg capsules (Genus Pharmaceuticals Ltd)
34449	Co-tenidone 50mg/12.5mg tablets (Mylan)
34453	Enalapril 20mg tablets (Mylan)
34471	Lisinopril 5mg tablets (Mylan)
34475	Diltiazem HCl 90mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)
34490	Ramipril 2.5mg capsules (Teva UK Ltd)
34505	Ramipril 2.5mg capsules (Sandoz Ltd)
34522	Nifedipine 5mg capsules (A A H Pharmaceuticals Ltd)
34528	Ramipril 2.5mg capsules (A A H Pharmaceuticals Ltd)
34539	Ramipril 5mg capsules (Sandoz Ltd)
34540	Ramipril 5mg capsules (A A H Pharmaceuticals Ltd)
34544	Captopril 12.5mg Tablet (IVAX Pharmaceuticals UK Ltd)
34547	Isosorbide dinitrate 10mg tablets (Actavis UK Ltd)
34551	Indapamide 2.5mg tablets (Mylan)
34553	Doxazosin 4mg tablets (Mylan)
34557	Furosemide 40mg tablets (IVAX Pharmaceuticals UK Ltd)
34558	Isosorbide mononitrate 10mg tablets (A A H Pharmaceuticals Ltd)
34562	Captopril 25mg Tablet (IVAX Pharmaceuticals UK Ltd)
34567	Ramipril 2.5mg capsules (Mylan)
34581	Diltiazem HCl 60mg Modified-release tablet (Kent Pharmaceuticals Ltd)
34582	Isosorbide mononitrate 20mg tablets (Mylan)
34583	Ramipril 10mg Capsule (Dexcel-Pharma Ltd)
34589	Ramipril 5mg Capsule (Dexcel-Pharma Ltd)
34601	Doxazosin 1mg tablets (Mylan)
34602	Bendroflumethiazide 2.5mg tablets (Sovereign Medical Ltd)
34607	Nifedipine 5mg capsules (IVAX Pharmaceuticals UK Ltd)
34613	Bumetanide 5mg tablets (Teva UK Ltd)
34622	Co-amilofruse 10mg/80mg tablets (Wockhardt UK Ltd)
34625	Doxazosin 2mg tablets (A A H Pharmaceuticals Ltd)
34651	Ramipril 10mg capsules (Mylan)
34652	Ramipril 5mg Capsule (Sovereign Medical Ltd)
34657	Ramipril 10mg capsules (Zentiva)
34696	Lisinopril 20mg tablets (Mylan)
34698	Ramipril 1.25mg capsules (Zentiva)
34710	Ramipril 10mg capsules (Sandoz Ltd)
34712	Enalapril 20mg tablets (Kent Pharmaceuticals Ltd)
34715	Doxazosin 1mg tablets (A A H Pharmaceuticals Ltd)
34719	Captopril 50mg Tablet (Generics (UK) Ltd)
34732	Ramipril 2.5mg Capsule (Dexcel-Pharma Ltd)
34750	Amiloride 5mg tablets (Actavis UK Ltd)
34768	Enalapril 20mg tablets (IVAX Pharmaceuticals UK Ltd)
34798	Enalapril 20mg tablets (Sandoz Ltd)
34799	Lisinopril 20mg tablets (Zentiva)

34803	Bendroflumethiazide 2.5mg Tablet (Regent Laboratories Ltd)
34824	Diltiazem HCl 120mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)
34825	Co-tenidone 50mg/12.5mg tablets (Teva UK Ltd)
34835	Isosorbide dinitrate 10mg/10ml solution for injection ampoules
34877	Ramipril 10mg Capsule (Sovereign Medical Ltd)
34893	Ramipril 10mg Capsule (IVAX Pharmaceuticals UK Ltd)
34899	Co-tenidone 100mg/25mg tablets (A A H Pharmaceuticals Ltd)
34908	Spironolactone 25mg tablets (IVAX Pharmaceuticals UK Ltd)
34934	Bumetanide 1mg tablets (Mylan)
34936	Captopril 25mg Tablet (Lagap)
34937	Captopril 50mg Tablet (IVAX Pharmaceuticals UK Ltd)
34943	Ramipril 10mg capsules (A A H Pharmaceuticals Ltd)
34951	Isosorbide mononitrate 20mg Tablet (Berk Pharmaceuticals Ltd)
34952	Enalapril 10mg tablets (Mylan)
34953	Enalapril 20mg tablets (Zentiva)
34959	Verapamil 40mg tablets (A A H Pharmaceuticals Ltd)
34975	Nifedipine 5mg capsules (Teva UK Ltd)
35007	Ramipril 10mg/5ml oral suspension
35084	Vascalpha 5mg modified-release tablets (Accord Healthcare Ltd)
35096	Exforge 10mg/160mg tablets (Novartis Pharmaceuticals UK Ltd)
35162	Furosemide 20mg/2ml solution for injection ampoules
35173	Valsartan 160mg with amlodipine 5mg tablets
35174	Valsartan 80mg with amlodipine 5mg tablets
35189	Amlodipine 10mg / Valsartan 160mg tablets
35196	CoAprovel 300mg/25mg tablets (Sanofi)
35272	Doxadura XL 4mg tablets (Dexcel-Pharma Ltd)
35302	Captopril 12.5mg/5ml oral suspension
35304	Valsartan 160mg with amlodipine 10mg tablets
35317	Exforge 5mg/80mg tablets (Novartis Pharmaceuticals UK Ltd)
35329	Amlodipine 5mg / Valsartan 80mg tablets
35343	Amlodipine 5mg / Valsartan 160mg tablets
35380	Hydrochlorothiazide with olmesartan medoxomil 12.5mg with 20mg tablet
35481	Irbesartan 300mg / Hydrochlorothiazide 25mg tablets
35592	Cardioplen XL 2.5mg tablets (Chiesi Ltd)
35603	Doxazosin 4mg/5ml oral suspension
35646	Neozipine XL 60mg tablets (Kent Pharmaceuticals Ltd)
35696	Kenzem SR 120mg capsules (Kent Pharmaceuticals Ltd)
35697	Exforge 5mg/160mg tablets (Novartis Pharmaceuticals UK Ltd)
35729	Verapamil 80mg tablets (Teva UK Ltd)
35731	Perindopril erbumine 8mg tablets (A A H Pharmaceuticals Ltd)
35789	Spironolactone 25mg Tablet (Celltech Pharma Europe Ltd)
35794	Enalapril 5mg tablets (A A H Pharmaceuticals Ltd)
36023	Cardozin xl 4mg Tablet (Hillcross Pharmaceuticals Ltd)
36181	Dynamin XL50 capsules (Teva UK Ltd)
36190	Furosemide 5mg/5ml oral solution sugar free
36519	Esidrex -k Tablet (Novartis Pharmaceuticals UK Ltd)
36583	Zemret xl 180mg Capsule (Neo Laboratories Ltd)
36620	Parmid XL 10mg tablets (Sandoz Ltd)
36664	Zemret xl 300mg Capsule (Neo Laboratories Ltd)
36740	Slocinx XL 4mg tablets (Zentiva)
36742	Captopril 2mg/5ml oral suspension

36753	Ednyt 10mg Tablet (Dominion Pharma)
36767	Bumetanide 1mg tablets (IVAX Pharmaceuticals UK Ltd)
36939	Irbesartan 300mg/5ml oral suspension
37025	Nifedipine 20mg modified-release tablets
37028	Isosorbide mononitrate starter pack Tablet
37080	Enalapril 5mg/5ml oral solution
37087	Enalapril 5mg/5ml oral suspension
37184	Valni XL 30mg tablets (Zentiva)
37243	Cardozin xl 4mg Tablet (Teva UK Ltd)
37294	Triamterene with chlortalidone 50mg + 25mg Tablet
37530	Neozipine XL 30mg tablets (Kent Pharmaceuticals Ltd)
37573	Valsartan 320mg tablets
37650	Losartan 100mg / Hydrochlorothiazide 12.5mg tablets
37655	Captopril 25mg tablets (Teva UK Ltd)
37710	Lisinopril 10mg / Hydrochlorothiazide 12.5mg tablets (Teva UK Ltd)
37725	Co-tenidone 100mg/25mg tablets (Mylan)
37726	Nifedipine 100mg/5ml oral suspension
37747	Cozaar-Comp 100mg/12.5mg tablets (Merck Sharp & Dohme Ltd)
37774	Kenzem SR 60mg capsules (Kent Pharmaceuticals Ltd)
37778	Lisinopril 5mg/5ml oral suspension
37897	Felotens XL 2.5mg tablets (Thornton & Ross Ltd)
37908	Coversyl Arginine Plus 5mg/1.25mg tablets (Servier Laboratories Ltd)
37930	Perindopril arginine 5mg tablets
37964	Perindopril arginine 2.5mg tablets
37965	Coversyl Arginine 5mg tablets (Servier Laboratories Ltd)
37971	Perindopril arginine 10mg tablets
37978	Perindopril arginine 5mg / Indapamide 1.25mg tablets
38026	Coversyl Arginine 10mg tablets (Servier Laboratories Ltd)
38034	Coversyl Arginine 2.5mg tablets (Servier Laboratories Ltd)
38066	Diltiazem HCl 60mg Modified-release tablet (Lagap)
38107	Nifedipine sr 30mg Tablet (Hillcross Pharmaceuticals Ltd)
38285	Perindopril erbumine 4mg tablets (Teva UK Ltd)
38308	Ramipril 2.5/5mg/10mg tablet
38367	Hydrochlorothiazide with losartan 12.5mg with 100mg Tablet
38395	Valsartan 80mg tablets
38434	Keloc SR 10mg tablets (Teva UK Ltd)
38459	Telmisartan 80mg / Hydrochlorothiazide 25mg tablets
38461	Cardozin XL 4mg tablets (Arrow Generics Ltd)
38510	Perindopril erbumine 4mg tablets (Apotex UK Ltd)
38545	Tildiem LA 200 capsules (Sanofi)
38632	Adizem-SR 90mg capsules (Napp Pharmaceuticals Ltd)
38634	Adizem-XL 300mg capsules (Napp Pharmaceuticals Ltd)
38818	Adizem-SR 120mg capsules (Napp Pharmaceuticals Ltd)
38831	Adizem-SR 180mg capsules (Napp Pharmaceuticals Ltd)
38854	Quinapril 20mg/5ml oral solution
38855	Adizem-XL 180mg capsules (Napp Pharmaceuticals Ltd)
38865	Adizem-XL 120mg capsules (Napp Pharmaceuticals Ltd)
38876	Tildiem LA 300 capsules (Sanofi)
38882	Adizem-XL 240mg capsules (Napp Pharmaceuticals Ltd)
38883	Elantan LA25 capsules (Forum Health Products Ltd)
38889	MicardisPlus 80mg/25mg tablets (Boehringer Ingelheim Ltd)

38899	Quinil 10mg tablets (Tillomed Laboratories Ltd)
38901	Frumil LS 20mg/2.5mg tablets (Sanofi)
38946	Elantan LA50 capsules (Forum Health Products Ltd)
38964	Adizem-SR 120mg tablets (Napp Pharmaceuticals Ltd)
38995	Zestoretic 20 tablets (AstraZeneca UK Ltd)
39009	Verapamil 40mg tablets (Teva UK Ltd)
39021	Hydrochlorothiazide with olmesartan medoxomil 25mg with 20mg tablet
39035	Elantan 20 tablets (UCB Pharma Ltd)
39052	Cibral XL 60 tablets (Ranbaxy (UK) Ltd)
39130	Ismo 20 tablets (Intrapharm Laboratories Ltd)
39135	Ismo 10 tablets (Intrapharm Laboratories Ltd)
39137	Zestoretic 10 tablets (AstraZeneca UK Ltd)
39147	Carace 20 Plus tablets (Merck Sharp & Dohme Ltd)
39171	Bi-Carzem SR 60mg capsules (Tillomed Laboratories Ltd)
39199	Diovan 320mg tablets (Novartis Pharmaceuticals UK Ltd)
39227	Capozide LS 12.5mg/25mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
39242	Carace 10 Plus tablets (Merck Sharp & Dohme Ltd)
39298	Bi-Carzem SR 90mg capsules (Tillomed Laboratories Ltd)
39355	Tritace 10mg Tablet (Sterwin Medicines)
39357	Neofel XL 2.5mg tablets (Kent Pharmaceuticals Ltd)
39447	Varbim XL 1.5mg tablets (Teva UK Ltd)
39512	Captopril 25mg/5ml oral suspension
39552	Elantan 40 tablets (UCB Pharma Ltd)
39602	Bumetanide 1mg tablets (Actavis UK Ltd)
39786	Olmesartan medoxomil 10mg/5ml oral suspension
39800	Valni XL 60mg tablets (Zentiva)
39807	Frumil 40mg/5mg tablets (Sanofi)
39944	Losartan 12.5mg tablets
39984	Sevikar 20mg/5mg tablets (Daiichi Sankyo UK Ltd)
40074	Nifedipine 20mg Capsule
40149	Bendroflumethiazide 5mg tablets (IVAX Pharmaceuticals UK Ltd)
40190	Torasemide iv 20mg/4ml Intravenous injection
40247	Furosemide 10mg/ml Injection (Martindale Pharmaceuticals Ltd)
40310	Moxonidine 200microgram tablets (Teva UK Ltd)
40316	Olmesartan medoxomil 20mg / Amlodipine 5mg tablets
40355	Quinil 5mg tablets (Tillomed Laboratories Ltd)
40384	Ramipril 10mg tablets (A A H Pharmaceuticals Ltd)
40405	Verapamil 120mg tablets (Teva UK Ltd)
40571	Cozaar 12.5mg tablets (Merck Sharp & Dohme Ltd)
40633	Vascalpha 5mg modified-release tablets (Almus Pharmaceuticals Ltd)
40639	Olmesartan medoxomil 40mg / Amlodipine 5mg tablets
40668	Olmesartan medoxomil 40mg / Amlodipine 10mg tablets
40678	Doxazosin 4mg tablets (Teva UK Ltd)
40711	Losartan 2.5mg/ml oral suspension sugar free
40738	Torem iv 10mg/2ml Intravenous injection (Boehringer Mannheim UK Ltd)
40886	Bendroflumethiazide 2.5mg tablets (Almus Pharmaceuticals Ltd)
40891	Doxazosin 2mg tablets (IVAX Pharmaceuticals UK Ltd)
40898	Torasemide 5mg tablets (A A H Pharmaceuticals Ltd)
40907	Indapamide 2.5mg tablets (Genus Pharmaceuticals Ltd)
41060	Ismo Retard 40mg tablets (Intrapharm Laboratories Ltd)
41074	Spironolactone 25mg tablets (Almus Pharmaceuticals Ltd)

41203	Sevikar 40mg/10mg tablets (Daiichi Sankyo UK Ltd)
41205	Sevikar 40mg/5mg tablets (Daiichi Sankyo UK Ltd)
41232	Cozaar 2.5mg/ml oral suspension (Merck Sharp & Dohme Ltd)
41292	Furosemide 20mg tablets (Wockhardt UK Ltd)
41405	Furosemide 500mg tablets (Teva UK Ltd)
41417	Enalapril 2.5mg tablets (A A H Pharmaceuticals Ltd)
41421	Isosorbide mononitrate xl 40mg Tablet (Hillcross Pharmaceuticals Ltd)
41489	Bi-Carzem SR 120mg capsules (Tillomed Laboratories Ltd)
41517	Bendroflumethiazide 5mg tablets (Teva UK Ltd)
41522	Lisopress 20mg tablets (Teva UK Ltd)
41532	Lisopress 5mg tablets (Teva UK Ltd)
41533	Co-amilofruse 2.5mg/20mg tablets (Teva UK Ltd)
41538	Lisopress 2.5mg tablets (Teva UK Ltd)
41543	Doxazosin 1mg tablets (IVAX Pharmaceuticals UK Ltd)
41556	Co-amilozide 5mg/50mg tablets (Teva UK Ltd)
41572	Co-tenidone 100mg/25mg tablets (Teva UK Ltd)
41573	Lisopress 10mg tablets (Teva UK Ltd)
41586	Verapamil 80mg tablets (Actavis UK Ltd)
41592	Spironolactone 100mg tablets (Actavis UK Ltd)
41617	Captopril 25mg tablets (Actavis UK Ltd)
41630	Amiloride 5mg Tablet (IVAX Pharmaceuticals UK Ltd)
41633	Captopril 12.5mg tablets (Actavis UK Ltd)
41635	Diltiazem 60mg modified-release tablets (IVAX Pharmaceuticals UK Ltd)
41639	Hydralazine 50mg tablets (Actavis UK Ltd)
41651	Prazosin 500microgram Tablet (Approved Prescription Services Ltd)
41652	Prazosin 500microgram tablets (A A H Pharmaceuticals Ltd)
41660	Spironolactone 100mg tablets (Teva UK Ltd)
41661	Methyldopa 250mg Tablet (C P Pharmaceuticals Ltd)
41676	Isosorbide mononitrate 20mg tablets (Actavis UK Ltd)
41679	Verapamil 80mg tablets (IVAX Pharmaceuticals UK Ltd)
41687	Isosorbide mononitrate 20mg tablets (Teva UK Ltd)
41688	Isosorbide mononitrate 20mg tablets (A A H Pharmaceuticals Ltd)
41693	Verapamil 120mg tablets (Mylan)
41694	Enalapril 2.5mg tablets (IVAX Pharmaceuticals UK Ltd)
41706	Spironolactone 50mg tablets (IVAX Pharmaceuticals UK Ltd)
41719	Co-amilofruse 5mg/40mg tablets (Actavis UK Ltd)
41721	Prazosin 1mg tablets (A A H Pharmaceuticals Ltd)
41737	Isosorbide mononitrate 10mg tablets (IVAX Pharmaceuticals UK Ltd)
41743	Captopril 50mg tablets (Teva UK Ltd)
41746	Enalapril 10mg tablets (Sandoz Ltd)
41828	Furosemide 500mg tablets (Accord Healthcare Ltd)
41861	Tensaid XL 1.5mg tablets (Mylan)
41885	Ethibide XL 1.5mg tablets (Genus Pharmaceuticals Ltd)
41889	TRIAMTERENE 50MG HYDROCHLOROTHIAZIDE25MG
41979	Adipine la 30mg Modified-release tablet (Chiesi Ltd)
41993	Isosorbide dinitrate 40mg Tablet
42081	Tritace 1.25mg Tablet (Sterwin Medicines)
42142	Moduretic 5mg/50mg tablets (Merck Sharp & Dohme Ltd)
42285	Quinil 40mg tablets (Tillomed Laboratories Ltd)
42388	Furosemide 40mg/5ml oral solution sugar free (Advanz Pharma)
42488	Furosemide 40mg/5ml oral solution sugar free (A A H Pharmaceuticals Ltd)

42625	Vera-Til SR 120mg tablets (Actavis UK Ltd)
42723	Pralenal 5 tablets (Opus Pharmaceuticals Ltd)
42731	Diltiazem sr 120mg Capsule (Hillcross Pharmaceuticals Ltd)
42804	Diltiazem HCl 180mg Capsule (PLIVA Pharma Ltd)
42819	Diltiazem xl 240mg Capsule (Hillcross Pharmaceuticals Ltd)
42894	Enalapril 10mg tablets (Teva UK Ltd)
42901	Enalapril 5mg tablets (Teva UK Ltd)
42902	Enalapril 20mg tablets (Teva UK Ltd)
42906	Indapamide 2.5mg tablets (Niche Generics Ltd)
42908	Enalapril 5mg tablets (IVAX Pharmaceuticals UK Ltd)
42912	Nifedipine 10mg capsules (Teva UK Ltd)
43012	Perindopril erbumine oral solution
43184	Mapemid XL 1.5mg tablets (Teva UK Ltd)
43222	Valni 20 Retard tablets (Tillomed Laboratories Ltd)
43322	Olmesartan medoxomil 40mg / Hydrochlorothiazide 12.5mg tablets
43394	Pinefeld XL 10mg tablets (Tillomed Laboratories Ltd)
43410	Nifedipine extra 60mg Modified-release tablet
43411	Enalapril 5mg tablets (Sandoz Ltd)
43412	Lisinopril 2.5mg tablets (A A H Pharmaceuticals Ltd)
43413	Lisinopril 20mg tablets (A A H Pharmaceuticals Ltd)
43416	Lisinopril 10mg tablets (A A H Pharmaceuticals Ltd)
43418	Lisinopril 5mg tablets (A A H Pharmaceuticals Ltd)
43421	Isosorbide mononitrate 40mg tablets (IVAX Pharmaceuticals UK Ltd)
43430	Diltiazem 120mg modified-release tablets (A A H Pharmaceuticals Ltd)
43432	Captopril 6.25mg tablets
43500	Hydralazine 25mg tablets (Accord Healthcare Ltd)
43507	Captopril 25mg Tablet (Generics (UK) Ltd)
43508	Co-amilofruse 5mg/40mg tablets (Sandoz Ltd)
43511	Nifedipine 10mg capsules (A A H Pharmaceuticals Ltd)
43512	Felodipine 5mg modified-release tablets (A A H Pharmaceuticals Ltd)
43514	Spironolactone 50mg tablets (A A H Pharmaceuticals Ltd)
43515	Nifedipine 10mg capsules (Actavis UK Ltd)
43516	Indapamide 2.5mg tablets (Actavis UK Ltd)
43523	Amiloride 5mg tablets (Mylan)
43524	Isosorbide dinitrate 10mg tablets (A A H Pharmaceuticals Ltd)
43531	Moxonidine 400microgram tablets (Sandoz Ltd)
43547	Prazosin 500microgram tablets (IVAX Pharmaceuticals UK Ltd)
43563	Enalapril 2.5mg tablets (Zentiva)
43566	Lisinopril 2.5mg tablets (Sandoz Ltd)
43615	Tardisc XL 60 tablets (Dexcel-Pharma Ltd)
43649	Captopril 25mg tablets (A A H Pharmaceuticals Ltd)
43695	Colixil XL 4mg tablets (Sandoz Ltd)
43753	Adalat LA 30mg tablets (Bayer Plc)
43790	Vascalpha 10mg modified-release tablets (Almus Pharmaceuticals Ltd)
43813	Perindopril erbumine 2mg tablets (Actavis UK Ltd)
43818	Adalat LA 60mg tablets (Bayer Plc)
43879	Vera-Til SR 240mg tablets (Actavis UK Ltd)
43915	Olmetec Plus 40mg/12.5mg tablets (Daiichi Sankyo UK Ltd)
43988	Aldomet 250mg tablets (Aspen Pharma Trading Ltd)
43989	Aldomet 500mg tablets (Aspen Pharma Trading Ltd)
44168	Indipam XL 1.5mg tablets (Accord Healthcare Ltd)

44179	Imo LA 50mg capsules (Kent Pharmaceuticals Ltd)
44192	Zemret 240 XL capsules (Tillomed Laboratories Ltd)
44254	Amiloride 5.67mg tablets
44527	Captopril 5mg/ml oral solution sugar free
44657	Ednyt 2.5mg Tablet (Dominion Pharma)
44712	Relosorb XL 60mg tablets (Relonchem Ltd)
44778	Valsartan 160mg tablets
44859	Felodipine sr 5mg Tablet (Approved Prescription Services Ltd)
44887	Bi-carzem xl 300mg Capsule (Tillomed Laboratories Ltd)
45040	Larbex XL 4mg tablets (Teva UK Ltd)
45051	Verapamil hc 240mg Modified-release tablet (Actavis UK Ltd)
45078	Spironolactone 25mg/5ml Oral solution sugar free (Rosemont Pharmaceuticals Ltd)
45217	Enalapril 5mg tablets (Kent Pharmaceuticals Ltd)
45228	Captopril capsules
45264	Ramipril 1.25mg capsules (Actavis UK Ltd)
45265	Doxazosin sr 4mg Tablet (Generics (UK) Ltd)
45292	Nicardipine 30mg capsules (A A H Pharmaceuticals Ltd)
45300	Lisinopril 10mg tablets (Actavis UK Ltd)
45305	Bumetanide 1mg tablets (Teva UK Ltd)
45308	Verapamil 240mg modified-release tablets (Mylan)
45319	Perindopril erbumine 2mg tablets (A A H Pharmaceuticals Ltd)
45324	Lisinopril 20mg tablets (Actavis UK Ltd)
45328	Doxazosin 1mg tablets (Sandoz Ltd)
45337	Lisinopril 5mg tablets (Actavis UK Ltd)
45340	Ramipril 10mg Capsule (Actavis UK Ltd)
45342	Doxazosin 4mg tablets (Sandoz Ltd)
45554	Ramipril 5mg/5ml oral solution
45564	Diltiazem 2% ointment
45578	Clonidine 25microgram tablets (A A H Pharmaceuticals Ltd)
45583	Doxazosin 2mg tablets (Dexcel-Pharma Ltd)
45600	Diovan 160mg Tablet (Novartis Pharmaceuticals UK Ltd)
45685	Adanif XL 30mg tablets (Advanz Pharma)
45759	Diltiazem HCl 240mg Capsule (PLIVA Pharma Ltd)
45816	Lisinopril 5mg tablets (Almus Pharmaceuticals Ltd)
45916	Hydroflumethiazide with spironolactone 50mg+50mg Tablet
45938	Perindopril erbumine 8mg tablets (Teva UK Ltd)
46009	Verapamil 120mg tablets (Kent Pharmaceuticals Ltd)
46066	Cardozin XL 4mg tablets (Almus Pharmaceuticals Ltd)
46116	Furosemide 10mg/ml Injection (Antigen Pharmaceuticals)
46302	Neo-Naclex 2.5mg tablets (Advanz Pharma)
46355	Sevikar HCT 20mg/5mg/12.5mg tablets (Daiichi Sankyo UK Ltd)
46365	Quinil 20mg tablets (Tillomed Laboratories Ltd)
46445	Nifedipine 10mg capsules (IVAX Pharmaceuticals UK Ltd)
46525	Torasemide 5mg tablets (Teva UK Ltd)
46526	Raporsin XL 4mg tablets (Actavis UK Ltd)
46674	Spironolactone 50mg/5ml Oral suspension sugar free (Rosemont Pharmaceuticals Ltd)
46675	Indapamide 1.5mg modified-release tablets (A A H Pharmaceuticals Ltd)
46687	Olmesartan medoxomil with amlodipine and hydrochlorothiazide 20mg + 5mg + 12.5mg Tablet
46699	Furosemide 40mg tablets (Almus Pharmaceuticals Ltd)

46715	Olmesartan medoxomil with amlodipine and hydrochlorothiazide 40mg + 10mg + 12.5mg Tablet
46792	Olmesartan medoxomil with amlodipine and hydrochlorothiazide 40mg + 5mg + 12.5mg Tablet
46798	Isosorbide mononitrate 60mg Modified-release tablet (Sovereign Medical Ltd)
46851	Captopril 5mg/5ml oral solution
46884	Verapamil hc 240mg Modified-release tablet (Sandoz Ltd)
46887	Adanif XL 60mg tablets (Advanz Pharma)
46890	Ramipril 5mg/5ml oral suspension
46910	Isosorbide mononitrate 10mg Tablet (Berk Pharmaceuticals Ltd)
46911	Isosorbide mononitrate 10mg tablets (Kent Pharmaceuticals Ltd)
46916	Co-amilozide 5mg/50mg tablets (A A H Pharmaceuticals Ltd)
46922	Prazosin 1mg tablets (IVAX Pharmaceuticals UK Ltd)
46930	Amiloride 5mg tablets (Wockhardt UK Ltd)
46937	Diltiazem 60mg modified-release tablets (Actavis UK Ltd)
46948	Furosemide 40mg tablets (Arrow Generics Ltd)
46949	Isosorbide mononitrate 60mg Modified-release tablet (Kent Pharmaceuticals Ltd)
46951	Captopril 12.5mg tablets (A A H Pharmaceuticals Ltd)
46952	Co-tenidone 100mg/25mg tablets (Actavis UK Ltd)
46955	Verapamil 80mg tablets (Mylan)
46957	Captopril 12.5mg tablets (Tillomed Laboratories Ltd)
46974	Enalapril 5mg tablets (Mylan)
46975	Lisinopril 5mg tablets (Sandoz Ltd)
46979	Lisinopril 20mg tablets (Sandoz Ltd)
46990	Spironolactone 50mg/5ml oral suspension
47006	Losartan 100mg tablets (Teva UK Ltd)
47018	Spironolactone 25mg/5ml oral suspension
47021	Ramipril 2.5mg/5ml oral solution sugar free
47027	Nifedipine 10mg Modified-release tablet (Kent Pharmaceuticals Ltd)
47159	Lisinopril 10mg tablets (Almus Pharmaceuticals Ltd)
47217	Adipine la 60mg Modified-release tablet (Chiesi Ltd)
47222	Verapamil 120mg modified-release tablets (A A H Pharmaceuticals Ltd)
47230	Verapamil 240mg modified-release tablets (Teva UK Ltd)
47285	Nifedipine xl 60mg Tablet (Hillcross Pharmaceuticals Ltd)
47331	Lercanidipine 10mg tablets (Mylan)
47415	Diltiazem sr 60mg Capsule (Hillcross Pharmaceuticals Ltd)
47467	Olmesartan medoxomil with amlodipine and hydrochlorothiazide 40mg + 5mg + 25mg Tablet
47529	Nifedipine 20mg/ml oral drops
47530	Horizem SR 60mg capsules (Horizon lifecare)
47573	Sevikar HCT 40mg/5mg/12.5mg tablets (Daiichi Sankyo UK Ltd)
47608	Zemret 300 XL capsules (Tillomed Laboratories Ltd)
47614	Nifedipine 30mg modified-release tablets (A A H Pharmaceuticals Ltd)
47616	Sevikar HCT 40mg/10mg/12.5mg tablets (Daiichi Sankyo UK Ltd)
47647	Co-amilofruse oral liquid
47687	Spiretic 25mg Tablet (DDSA Pharmaceuticals Ltd)
47707	Nifedipine Oral solution
47722	Isosorbide dinitrate 10mg/10ml concentrate for solution for injection ampoules (Mercury Pharma Group Ltd)
47724	Bi-Carzem XL 240mg capsules (Tillomed Laboratories Ltd)
47727	Sevikar HCT 40mg/5mg/25mg tablets (Daiichi Sankyo UK Ltd)

47732	Zemret 180 XL capsules (Tillomed Laboratories Ltd)
47803	Isosorbide mononitrate 20mg tablets (Sandoz Ltd)
47804	Co-triamterzide 50mg/25mg tablets (A A H Pharmaceuticals Ltd)
47807	Doxazosin xl 4mg Tablet (Hillcross Pharmaceuticals Ltd)
47810	Isosorbide mononitrate 40mg Tablet (Lagap)
47814	Isosorbide mononitrate Oral solution
47815	Furosemide 20mg Tablet (Celltech Pharma Europe Ltd)
47844	Bendroflumethiazide 2.5mg tablets (Kent Pharmaceuticals Ltd)
47887	Nimodrel XL 60mg tablets (Zurich Pharmaceuticals)
47950	Isosorbide mononitrate 50mg modified-release capsules (A A H Pharmaceuticals Ltd)
47996	Diltiazem 2% gel
47998	Ramipril 2.5mg capsules (Actavis UK Ltd)
48008	Ramipril 5mg capsules (Actavis UK Ltd)
48009	Felodipine 5mg Modified-release tablet (Sandoz Ltd)
48039	Losartan 100mg / Hydrochlorothiazide 12.5mg tablets (Teva UK Ltd)
48049	Perindopril erbumine 2mg tablets (Mylan)
48053	Ramipril 2.5mg capsules (Almus Pharmaceuticals Ltd)
48079	Indapamide 2.5mg tablets (Zentiva)
48098	Perindopril arginine 4mg with Indapamide 1.25mg tablet
48099	Indapamide 2.5mg tablets (A A H Pharmaceuticals Ltd)
48132	Hydrochlorothiazide Capsule
48150	Doxazosin 1mg tablets (Actavis UK Ltd)
48180	Perindopril erbumine 4mg tablets (Sandoz Ltd)
48214	Perindopril erbumine 4mg tablets (Actavis UK Ltd)
48272	Diltiazem 60mg modified-release capsules (Alliance Healthcare (Distribution) Ltd)
48282	Diltiazem 90mg modified-release capsules (A A H Pharmaceuticals Ltd)
48288	Diltiazem 120mg modified-release capsules (A A H Pharmaceuticals Ltd)
48398	Losartan 25mg tablets (Dexcel-Pharma Ltd)
48457	Diltiazem 90mg modified-release capsules (Alliance Healthcare (Distribution) Ltd)
48745	Timolol 10mg / Amiloride 2.5mg / Hydrochlorothiazide 25mg tablets
48870	Adizem-SR 90mg capsules (DE Pharmaceuticals)
49001	Diltiazem 120mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)
49164	Ramipril 10mg capsules (Actavis UK Ltd)
49237	Diltiazem 0.2% cream
49268	Furosemide 50mg/5ml oral suspension
49289	Diltiazem 120mg modified-release capsules (Alliance Healthcare (Distribution) Ltd)
49338	Nifedipine 20mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)
49388	Spironolactone 100mg/5ml oral suspension
49390	Diltiazem 90mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)
49491	Perindopril erbumine 2mg tablets (Consilient Health Ltd)
49492	Losartan 25mg tablets (Mylan)
49500	Diltiazem 2% ointment (Drug Tariff Special Order)
49529	Indapamide 2.5mg tablets (Phoenix Healthcare Distribution Ltd)
49588	Losartan 100mg tablets (A A H Pharmaceuticals Ltd)
49684	Clonidine 100micrograms/24hours transdermal patches
49752	Metolazone 2.5mg/5ml oral solution
49762	Nifedipine 10mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)
50079	Spironolactone 10mg/5ml oral suspension
50185	Candesartan 8mg tablets (Teva UK Ltd)
50334	Enalapril 4mg/5ml oral suspension
50347	Coversyl Arginine 5mg tablets (Waymade Healthcare Plc)

50370	Spironolactone 5mg/5ml oral suspension
50402	Perindopril 2mg Tablet (Servier Laboratories Ltd)
50467	Doxazosin 2mg tablets (Alliance Healthcare (Distribution) Ltd)
50509	Ramipril 10mg/5ml oral solution
50607	Perindopril arginine 2mg with Indapamide 625 micrograms tablet
50780	Enalapril 2mg/5ml oral solution
50863	Enalapril 5mg/5ml oral solution (Drug Tariff Special Order)
50971	Losartan 25mg tablets (A A H Pharmaceuticals Ltd)
51117	Candesartan 8mg tablets (DE Pharmaceuticals)
51186	Losartan 25mg tablets (Arrow Generics Ltd)
51258	Coversyl Arginine Plus 5mg/1.25mg tablets (DE Pharmaceuticals)
51261	Tildiem Retard 120mg tablets (Mawdsley-Brooks & Company Ltd)
51368	Azilsartan medoxomil 80mg tablets
51433	Lisinopril 20mg tablets (Tillomed Laboratories Ltd)
51461	Securon SR 240mg tablets (Waymade Healthcare Plc)
51489	Anoheal 2% cream (S.L.A. Pharma (UK) Ltd)
51519	Candesartan 8mg tablets (A A H Pharmaceuticals Ltd)
51601	Losartan 50mg tablets (Actavis UK Ltd)
51647	Candesartan 4mg tablets (Mawdsley-Brooks & Company Ltd)
51652	Spironolactone 25mg tablets (DE Pharmaceuticals)
51685	Doxazosin 4mg tablets (Actavis UK Ltd)
51701	Ramipril 5mg capsules (Bristol Laboratories Ltd)
51714	Ramipril 2.5mg capsules (Alliance Healthcare (Distribution) Ltd)
51720	Spironolactone 25mg/5ml oral solution
51807	Coversyl Arginine 5mg tablets (DE Pharmaceuticals)
51897	Edarbi 20mg tablets (Takeda UK Ltd)
51917	Adalat LA 60 tablets (Sigma Pharmaceuticals Plc)
51933	Spironolactone 50mg/5ml oral solution
51983	Furosemide 5mg/5ml oral suspension
52010	Enalapril 10mg tablets (Alliance Healthcare (Distribution) Ltd)
52017	Adalat LA 30 tablets (Mawdsley-Brooks & Company Ltd)
52045	Furosemide 250mg/5ml solution for injection vials
52088	Lisinopril 5mg tablets (Phoenix Healthcare Distribution Ltd)
52145	Cyclopenthiazide 0.25mg with oxprenolol 160mg modified-release tablets
52189	Losartan 100mg / Hydrochlorothiazide 25mg tablets (A A H Pharmaceuticals Ltd)
52197	Ramipril 5mg capsules (Sigma Pharmaceuticals Plc)
52208	Candesartan 16mg tablets (A A H Pharmaceuticals Ltd)
52245	Monosorb XL 60 tablets (Kent Pharmaceuticals Ltd)
52276	Adizem-XL 180mg capsules (DE Pharmaceuticals)
52293	Captopril 2mg capsules
52366	Spironolactone 5mg/5ml oral solution
52399	Ramipril 1.25mg capsules (Kent Pharmaceuticals Ltd)
52407	Ramipril 10mg capsules (Kent Pharmaceuticals Ltd)
52427	Cozaar 100mg tablets (Necessity Supplies Ltd)
52499	Captopril 25mg/5ml oral solution
52555	Clonidine 50micrograms/5ml oral solution
52559	Candesartan 8mg tablets (Zentiva)
52658	Losartan 100mg/5ml oral suspension
52659	Losartan 50mg/5ml oral solution
52701	Tildiem LA 200 capsules (Mawdsley-Brooks & Company Ltd)
52728	Beta-Adalat modified-release capsules (Lexon (UK) Ltd)

52858	Co-Diovan 80mg/12.5mg tablets (Sigma Pharmaceuticals Plc)
52882	Enalapril 5mg/5ml oral suspension sugar free
52886	Losartan 12.5mg tablets (A A H Pharmaceuticals Ltd)
52887	Furosemide 20mg/2ml solution for injection ampoules (A A H Pharmaceuticals Ltd)
52900	Furosemide 80mg/8ml solution for injection Minijet pre-filled syringes (UCB Pharma Ltd)
52970	Spironolactone 10mg/5ml oral solution
52972	Irbesartan 300mg tablets (Sigma Pharmaceuticals Plc)
53033	Doxzogen XL 4mg tablets (Mylan)
53058	Perindopril erbumine 8mg tablets (Sandoz Ltd)
53142	Clonidine 50micrograms/5ml oral suspension
53220	Sevikar HCT 40mg/10mg/25mg tablets (Daiichi Sankyo UK Ltd)
53253	Spironolactone 50mg/5ml oral suspension (Drug Tariff Special Order)
53271	Lisinopril 10mg tablets (Alliance Healthcare (Distribution) Ltd)
53278	Adalat LA 30 tablets (Necessity Supplies Ltd)
53322	Doxazosin 4mg tablets (Bristol Laboratories Ltd)
53357	Nifedipine 10mg/5ml oral suspension
53500	Adalat LA 30 tablets (DE Pharmaceuticals)
53508	Spironolactone 5mg/5ml / Chlorothiazide 50mg/5ml oral suspension
53551	Lisinopril 20mg tablets (Phoenix Healthcare Distribution Ltd)
53612	Ramipril 10mg tablets (Alliance Healthcare (Distribution) Ltd)
53621	Ramipril 2.5mg capsules (Bristol Laboratories Ltd)
53629	Adalat retard 20mg tablets (Lexon (UK) Ltd)
53674	Metolazone 2.5mg tablets
53680	Candesartan 16mg tablets (Teva UK Ltd)
53687	Isosorbide mononitrate 25mg modified-release capsules (Alliance Healthcare (Distribution) Ltd)
53719	Enalapril 20mg tablets (Alliance Healthcare (Distribution) Ltd)
53755	Candesartan 4mg tablets (Teva UK Ltd)
53812	Bendroflumethiazide oral solution
53820	Lisinopril 5mg tablets (Arrow Generics Ltd)
53833	Valsartan 160mg capsules (Mylan)
53915	Enalapril 5mg tablets (Dexcel-Pharma Ltd)
53967	Furosemide 20mg tablets (Bristol Laboratories Ltd)
53990	Nifedipine 5mg/5ml oral suspension
54037	Lisinopril 10mg tablets (Relonchem Ltd)
54049	Losartan 50mg tablets (Accord Healthcare Ltd)
54057	Losartan 50mg tablets (Teva UK Ltd)
54120	Spironolactone 4mg/5ml oral suspension
54201	Lisinopril 20mg / Hydrochlorothiazide 12.5mg tablets (Almus Pharmaceuticals Ltd)
54283	Lisinopril 5mg/5ml oral suspension (Special Order)
54288	Lisinopril 10mg tablets (Arrow Generics Ltd)
54298	Ramipril 2.5mg capsules (Arrow Generics Ltd)
54316	Indapamide 2.5mg tablets (Alliance Healthcare (Distribution) Ltd)
54326	Candesartan 32mg tablets (Teva UK Ltd)
54329	Metolazone 5mg/5ml oral suspension
54404	Losartan 100mg tablets (Actavis UK Ltd)
54414	Candesartan 16mg tablets (Consilient Health Ltd)
54467	Clonidine 300micrograms/24hours transdermal patches
54512	Lisinopril Oral solution
54544	Captopril 25mg/5ml oral suspension

54620	Ramipril 2.5mg capsules (Sigma Pharmaceuticals Plc)
54643	Metolazone Oral solution
54726	Valsartan 40mg capsules (Teva UK Ltd)
54733	Perindopril erbumine 8mg tablets (Consilient Health Ltd)
54735	Losartan 50mg tablets (Alliance Healthcare (Distribution) Ltd)
54740	Losartan 25mg tablets (Actavis UK Ltd)
54757	Eumon 40 XL tablets (Tillomed Laboratories Ltd)
54785	Doxazosin 4mg tablets (Medreich Plc)
54799	Tildiem LA 300 capsules (Mawdsley-Brooks & Company Ltd)
54824	Isosorbide mononitrate 10mg tablets (Alliance Healthcare (Distribution) Ltd)
54825	Furosemide 20mg tablets (Sigma Pharmaceuticals Plc)
54843	Losartan 50mg tablets (Dexcel-Pharma Ltd)
54899	Perindopril erbumine 2mg tablets (Teva UK Ltd)
54928	Lisinopril 10mg tablets (Bristol Laboratories Ltd)
54941	Ramipril 5mg capsules (Alliance Healthcare (Distribution) Ltd)
54942	Perindopril erbumine 8mg tablets (Mylan)
54986	Perindopril erbumine 8mg/5ml oral suspension
55002	Lisinopril 20mg tablets (Accord Healthcare Ltd)
55017	Irbesartan 300mg tablets (Accord Healthcare Ltd)
55050	CHLOROTHIAZIDE/SPIRONOLACTONE/LACT SACH 50 MG
55160	Cozaar-Comp 50mg/12.5mg tablets (Sigma Pharmaceuticals Plc)
55187	Valsartan 160mg capsules (Arrow Generics Ltd)
55257	Diltiazem 60mg/5ml oral solution
55259	Indapamide 2.5mg tablets (Kent Pharmaceuticals Ltd)
55296	Losartan 50mg tablets (Mylan)
55299	Ramipril 1.25mg capsules (A A H Pharmaceuticals Ltd)
55306	Folpik XL 5mg tablets (Teva UK Ltd)
55358	Olmesartan medoxomil with amlodipine and hydrochlorothiazide 40mg + 10mg + 25mg Tablet
55399	Lisinopril 20mg / Hydrochlorothiazide 12.5mg tablets (A A H Pharmaceuticals Ltd)
55446	Losartan 100mg tablets (Bristol Laboratories Ltd)
55455	Nifedipine 10mg capsules (Strides Pharma UK Ltd)
55456	Lisinopril 5mg tablets (Alliance Healthcare (Distribution) Ltd)
55548	Bumetanide 1mg tablets (Alliance Healthcare (Distribution) Ltd)
55588	Lisinopril 20mg tablets (Sigma Pharmaceuticals Plc)
55639	Lisinopril 10mg tablets (Accord Healthcare Ltd)
55718	Losartan 25mg tablets (Phoenix Healthcare Distribution Ltd)
55738	Furosemide 50mg/5ml solution for injection ampoules (hameln pharma Ltd)
55740	Neofel XL 2.5mg tablets (Actavis UK Ltd)
55777	Metolazone 5mg/5ml oral solution
55797	Clonidine 25micrograms/5ml oral solution
55798	Ramipril 5mg capsules (Waymade Healthcare Plc)
55821	Valsartan 160mg capsules (Teva UK Ltd)
55824	Nifedipine 20mg Modified-release tablet (Berk Pharmaceuticals Ltd)
55826	Prazosin 5mg tablets (A A H Pharmaceuticals Ltd)
55896	Lisinopril 2.5mg tablets (Actavis UK Ltd)
55903	Enalapril 10mg tablets (Dexcel-Pharma Ltd)
55906	Doxazosin 1mg tablets (Dexcel-Pharma Ltd)
55916	Doxazosin 1mg tablets (Alliance Healthcare (Distribution) Ltd)
56013	Ramipril 2.5mg capsules (Waymade Healthcare Plc)
56038	Ramipril 10mg tablets (Pfizer Ltd)

56051	Furosemide 20mg tablets (Kent Pharmaceuticals Ltd)
56067	Spironolactone 4mg/5ml oral solution
56079	Perindopril tosilate 10mg tablets
56104	Losartan 50mg tablets (A A H Pharmaceuticals Ltd)
56129	Ramipril 5mg capsules (Kent Pharmaceuticals Ltd)
56145	Doxazosin 2mg tablets (Actavis UK Ltd)
56148	Ramipril 1.25mg tablets (Kent Pharmaceuticals Ltd)
56157	Perindopril tosilate 5mg / Indapamide 1.25mg tablets
56162	Perindopril erbumine 4mg tablets (Consilient Health Ltd)
56169	Ramipril 10mg capsules (Arrow Generics Ltd)
56204	Losartan 50mg / Hydrochlorothiazide 12.5mg tablets (Accord Healthcare Ltd)
56244	Lisinopril 20mg / Hydrochlorothiazide 12.5mg tablets (Tillomed Laboratories Ltd)
56271	Diltiazem 0.2% cream (Special Order)
56274	Spironolactone 4.5mg/5ml oral suspension
56279	Lisinopril 2.5mg/5ml oral solution
56296	Indapamide 2.5mg tablets (Boston Healthcare Ltd)
56356	Ramipril 10mg capsules (Alliance Healthcare (Distribution) Ltd)
56375	Furosemide 40mg tablets (Accord Healthcare Ltd)
56416	Imdur 60mg modified-release tablets (DE Pharmaceuticals)
56467	Tildiem 60mg modified-release tablets (DE Pharmaceuticals)
56469	Adalat LA 60 tablets (Necessity Supplies Ltd)
56472	Perindopril erbumine 4mg tablets (Kent Pharmaceuticals Ltd)
56473	Perindopril erbumine 2mg tablets (Sigma Pharmaceuticals Plc)
56505	Zestril 5mg tablets (Lexon (UK) Ltd)
56506	Coversyl 2mg tablets (Dowelhurst Ltd)
56508	Coversyl 4mg tablets (Dowelhurst Ltd)
56509	Capoten 12.5mg tablets (Dowelhurst Ltd)
56510	Zestril 20mg tablets (Sigma Pharmaceuticals Plc)
56516	Perindopril erbumine 2mg tablets (Sandoz Ltd)
56536	Spironolactone 100mg/5ml oral solution
56606	Azilsartan medoxomil 40mg tablets
56704	Ramipril 1.25mg capsules (Alliance Healthcare (Distribution) Ltd)
56758	Diltiazem 90mg modified-release capsules (Cubic Pharmaceuticals Ltd)
56760	Indapamide 2.5mg tablets (Strides Pharma UK Ltd)
56763	Ramipril 10mg capsules (Phoenix Healthcare Distribution Ltd)
56767	Lercanidipine 20mg tablets (Mylan)
56840	Isoket 0.1% solution for injection 10ml ampoules (Forum Health Products Ltd)
56850	Ecopace 12.5mg tablets (Advanz Pharma)
56855	Ramipril 10mg capsules (Sigma Pharmaceuticals Plc)
56933	Modisal XL 40mg tablets (Ennogen Pharma Ltd)
56970	Losartan 100mg tablets (Pfizer Ltd)
56975	Losartan 50mg / Hydrochlorothiazide 12.5mg tablets (A A H Pharmaceuticals Ltd)
57026	Candesartan 8mg tablets (Waymade Healthcare Plc)
57028	Losartan 100mg tablets (Mylan)
57048	Lisinopril 10mg tablets (Zentiva)
57073	Ramipril 1.25mg capsules (Waymade Healthcare Plc)
57074	Doxazosin 2mg tablets (Sigma Pharmaceuticals Plc)
57104	Spironolactone 200mg/5ml oral suspension
57208	Diltiazem 120mg modified-release capsules (Cubic Pharmaceuticals Ltd)
57235	Ramipril 1.25mg tablets (Sandoz Ltd)
57266	Candesartan 2mg tablets (Actavis UK Ltd)

57273	Candesartan 8mg tablets (Actavis UK Ltd)
57333	Perindopril tosilate 5mg tablets
57346	Ramipril 10mg capsules (Waymade Healthcare Plc)
57378	Enalapril 2mg/5ml oral suspension
57444	Lercanidipine 10mg tablets (Aptil Pharma Ltd)
57448	Doxazosin 4mg tablets (A A H Pharmaceuticals Ltd)
57488	Hydrochlorothiazide Oral solution
57531	Adalat LA 60 tablets (Waymade Healthcare Plc)
57539	Zestoretic 10 tablets (Sigma Pharmaceuticals Plc)
57556	Spironolactone 12mg/5ml oral solution
57588	Zestril 2.5mg tablets (Mawdsley-Brooks & Company Ltd)
57594	Tildiem 60mg modified-release tablets (Waymade Healthcare Plc)
57600	Furosemide 20mg/2ml solution for injection ampoules (Alliance Healthcare (Distribution) Ltd)
57610	Furosemide 20mg/5ml oral solution sugar free (Advanz Pharma)
57653	Adalat LA 20mg tablets (Sigma Pharmaceuticals Plc)
57658	Ramipril 1.25mg tablets (A A H Pharmaceuticals Ltd)
57701	Perindopril erbumine 8mg tablets (Actavis UK Ltd)
57784	Doxazosin 2mg/5ml oral suspension
57796	Cozaar-Comp 50mg/12.5mg tablets (DE Pharmaceuticals)
57801	Perindopril erbumine 4mg tablets (Glenmark Pharmaceuticals Europe Ltd)
57859	Diltiazem 90mg modified-release tablets (Cubic Pharmaceuticals Ltd)
57864	Ramipril 5mg tablets (Sigma Pharmaceuticals Plc)
57882	Enalapril 2.5mg/5ml oral suspension
57908	Co-amilofruse 5mg/40mg tablets (Kent Pharmaceuticals Ltd)
57933	Spironolactone 40mg/5ml oral suspension
57944	Perindopril tosilate 2.5mg tablets
57977	Candesartan 16mg tablets (Alliance Healthcare (Distribution) Ltd)
58077	Spironolactone 8mg/5ml oral suspension
58078	Furosemide 8mg/5ml oral solution
58079	Isosorbide mononitrate 20mg/5ml oral solution
58090	Clonidine 75micrograms/5ml oral solution
58108	Irbesartan 150mg tablets (A A H Pharmaceuticals Ltd)
58133	Isosorbide mononitrate 10mg tablets (Sigma Pharmaceuticals Plc)
58195	Captopril 12.5mg/5ml oral solution
58201	Irbesartan 150mg tablets (Actavis UK Ltd)
58224	Furosemide 10mg/5ml oral solution
58225	Spironolactone 2.5mg/5ml oral suspension
58258	Lisinopril 2.5mg/5ml oral suspension
58274	Losartan 25mg tablets (Accord Healthcare Ltd)
58276	Doxazosin 2mg tablets (Medreich Plc)
58294	Lisinopril 5mg tablets (Accord Healthcare Ltd)
58325	Doxazosin 4mg tablets (Phoenix Healthcare Distribution Ltd)
58339	Neofel XL 2.5mg tablets (Almus Pharmaceuticals Ltd)
58386	Isosorbide mononitrate 20mg tablets (Kent Pharmaceuticals Ltd)
58451	Lisinopril 2.5mg tablets (Almus Pharmaceuticals Ltd)
58461	Lisinopril 2.5mg tablets (Kent Pharmaceuticals Ltd)
58529	Clonidine 200micrograms/24hours transdermal patches
58557	Adalat LA 20mg tablets (Necessity Supplies Ltd)
58646	Candesartan 4mg tablets (Actavis UK Ltd)
58649	Losartan 25mg tablets (Bristol Laboratories Ltd)

58669	Valsartan 40mg capsules (Teva UK Ltd)
58682	Lisinopril 2.5mg tablets (Mylan)
58751	Enalapril 1.25mg/5ml oral suspension
58757	Spironolactone 20mg/5ml oral suspension
58843	Perindopril erbumine 2mg tablets (Kent Pharmaceuticals Ltd)
58863	Lisinopril 10mg tablets (Phoenix Healthcare Distribution Ltd)
58871	Lisinopril 10mg tablets (Waymade Healthcare Plc)
58874	Perindopril erbumine 2mg tablets (Somex Pharma)
58910	Valsartan 80mg capsules (Sigma Pharmaceuticals Plc)
58967	Losartan 12.5mg tablets (Alliance Healthcare (Distribution) Ltd)
58990	Nifedipine 10mg modified-release tablets (Cubic Pharmaceuticals Ltd)
59029	Valsartan 3mg/ml oral solution
59030	Furosemide 20mg/5ml oral solution
59086	Losartan 25mg tablets (Wockhardt UK Ltd)
59098	Dilzem XL 180 capsules (Lexon (UK) Ltd)
59109	Lisinopril 5mg tablets (Tillomed Laboratories Ltd)
59111	Lisinopril 20mg tablets (Alliance Healthcare (Distribution) Ltd)
59163	Nifedipine 20mg modified-release tablets (Cubic Pharmaceuticals Ltd)
59209	Doxazosin 1mg tablets (Kent Pharmaceuticals Ltd)
59233	Lercanidipine 20mg tablets (Accord Healthcare Ltd)
59264	Securon SR 240mg tablets (DE Pharmaceuticals)
59271	Losartan 25mg tablets (Sandoz Ltd)
59290	Furosemide 20mg tablets (Alliance Healthcare (Distribution) Ltd)
59340	Losartan 12.5mg tablets (Dexcel-Pharma Ltd)
59351	Losartan 50mg tablets (Pfizer Ltd)
59393	Irbesartan 300mg tablets (Sandoz Ltd)
59412	Co-amilofruse 5mg/40mg tablets (Waymade Healthcare Plc)
59448	Valsartan 80mg capsules (A A H Pharmaceuticals Ltd)
59512	Hydralazine 50mg/5ml oral solution
59557	Ramipril 2.5mg capsules (Kent Pharmaceuticals Ltd)
59585	Uard 120XL capsules (Ennogen Healthcare Ltd)
59603	Ramipril 2.5mg capsules (Phoenix Healthcare Distribution Ltd)
59616	Rawel XL 1.5mg tablets (Consilient Health Ltd)
59690	Candesartan 8mg tablets (Consilient Health Ltd)
59699	Captopril 5mg/5ml oral solution sugar free
59750	Losartan 50mg tablets (Aptil Pharma Ltd)
59770	Perindopril erbumine 4mg tablets (Aurobindo Pharma Ltd)
59788	Ramipril 10mg capsules (Bristol Laboratories Ltd)
59790	Perindopril erbumine 8mg tablets (Accord Healthcare Ltd)
59802	Candesartan 2mg tablets (Teva UK Ltd)
59862	Doxazosin 4mg tablets (Dexcel-Pharma Ltd)
59863	Dilzem XL 240 capsules (Lexon (UK) Ltd)
59884	Furosemide 20mg tablets (Phoenix Healthcare Distribution Ltd)
59903	Losartan 50mg/5ml oral suspension
59911	Furosemide 40mg tablets (Alliance Healthcare (Distribution) Ltd)
59915	Captopril 25mg/5ml oral solution sugar free
59939	Furosemide 20mg/5ml oral suspension
59972	Perindopril erbumine 2mg tablets (Alliance Healthcare (Distribution) Ltd)
59996	Enalapril 20mg tablets (Milpharm Ltd)
60007	Generic Sevikar HCT 40mg/10mg/12.5mg tablets
60010	Lisinopril 10mg tablets (Kent Pharmaceuticals Ltd)

60020	Indapamide 1.5mg modified-release tablets (Waymade Healthcare Plc)
60055	Isosorbide mononitrate 25mg modified-release capsules (Waymade Healthcare Plc)
60065	Perindopril erbumine 4mg tablets (Sigma Pharmaceuticals Plc)
60067	Perindopril erbumine 4mg / Amlodipine 5mg tablets
60076	Valsartan 160mg capsules (Waymade Healthcare Plc)
60089	Clonidine 25microgram tablets (Waymade Healthcare Plc)
60097	Lisinopril 2.5mg tablets (Zentiva)
60136	Clonidine 100micrograms/5ml oral solution
60143	Enalapril 5mg tablets (Medreich Plc)
60149	Amiloride 5mg/5ml oral suspension
60200	Doxazosin 4mg tablets (DE Pharmaceuticals)
60232	Lisinopril 5mg tablets (Zentiva)
60258	Co-amilofruse 2.5mg/20mg tablets (Milpharm Ltd)
60291	Furosemide 40mg tablets (Advanz Pharma)
60309	Lisinopril 5mg tablets (Relonchem Ltd)
60316	Prazosin 1mg Tablet (Approved Prescription Services Ltd)
60319	Doxazosin 1mg tablets (Bristol Laboratories Ltd)
60336	Isosorbide mononitrate 10mg tablets (Waymade Healthcare Plc)
60343	Spironolactone 25mg tablets (Kent Pharmaceuticals Ltd)
60349	Noyada 25mg/5ml oral solution (Martindale Pharmaceuticals Ltd)
60354	Co-amilozide 2.5mg/25mg tablets (Kent Pharmaceuticals Ltd)
60415	Dilzem XL 180 capsules (Sigma Pharmaceuticals Plc)
60465	Furosemide 5mg/5ml oral solution
60506	Losartan 100mg tablets (Dexcel-Pharma Ltd)
60569	Felodipine 2.5mg modified-release tablets (Waymade Healthcare Plc)
60597	Irbesartan 150mg tablets (Teva UK Ltd)
60620	Adizem-XL 240mg capsules (Waymade Healthcare Plc)
60652	Parmid XL 2.5mg tablets (Sandoz Ltd)
60660	Spironolactone 3mg/5ml oral suspension
60684	Perindopril erbumine 4mg / Amlodipine 10mg tablets
60730	Ramipril 5mg capsules (Phoenix Healthcare Distribution Ltd)
60744	Perindopril erbumine 8mg / Amlodipine 5mg tablets
60780	Generic Sevikar HCT 20mg/5mg/12.5mg tablets
60823	Noyada 5mg/5ml oral solution (Martindale Pharmaceuticals Ltd)
60826	Isosorbide mononitrate 10mg/5ml oral solution
60856	Nifedipine 10mg modified-release tablets (Sigma Pharmaceuticals Plc)
60884	Felodipine 2.5mg modified-release tablets (Phoenix Healthcare Distribution Ltd)
60898	Moxonidine 200microgram tablets (Mylan)
60941	Ismo 20 tablets (Waymade Healthcare Plc)
61010	Diltiazem 120mg modified-release tablets (Cubic Pharmaceuticals Ltd)
61025	Spironolactone 20mg/5ml oral solution
61036	Physiotens 300microgram tablets (Actavis UK Ltd)
61053	Losartan 100mg tablets (Alliance Healthcare (Distribution) Ltd)
61066	Doxazosin 2mg tablets (Bristol Laboratories Ltd)
61067	Ramipril 5mg capsules (Almus Pharmaceuticals Ltd)
61116	Hydralazine 50mg/5ml oral suspension
61117	Perindopril erbumine 4mg/5ml oral solution
61123	Doxazosin 4mg/5ml oral solution
61133	Enalapril 10mg tablets (Phoenix Healthcare Distribution Ltd)
61177	Telmisartan 20mg tablets (Sigma Pharmaceuticals Plc)
61191	Eumon 60 XL tablets (Tillomed Laboratories Ltd)

61245	Diltiazem 60mg modified-release capsules (Sigma Pharmaceuticals Plc)
61256	Clonidine 5micrograms/5ml oral suspension
61262	Lisinopril 20mg tablets (Bristol Laboratories Ltd)
61270	Perindopril erbumine 4mg tablets (Accord Healthcare Ltd)
61283	Doxazosin 4mg tablets (Alliance Healthcare (Distribution) Ltd)
61288	Losartan 100mg tablets (Accord Healthcare Ltd)
61292	Quinapril 40mg tablets (Mylan)
61339	Ramipril 10mg capsules (Almus Pharmaceuticals Ltd)
61365	Furosemide 40mg/5ml oral suspension
61442	Valsartan 160mg capsules (Teva UK Ltd)
61475	Furosemide 20mg tablets (DE Pharmaceuticals)
61495	Losartan 25mg tablets (Aptil Pharma Ltd)
61499	Ramipril 2.5mg tablets (Actavis UK Ltd)
61532	Diltiazem 120mg modified-release capsules (Sigma Pharmaceuticals Plc)
61611	Lercanidipine 10mg tablets (DE Pharmaceuticals)
61693	Perindopril erbumine 8mg tablets (Aurobindo Pharma Ltd)
61694	Ramipril 5mg tablets (Zentiva)
61710	Clonidine 25microgram tablets (Teva UK Ltd)
61719	Beta-Adalat modified-release capsules (Waymade Healthcare Plc)
61754	Losartan 25mg/5ml oral suspension
61781	Irbesartan 300mg tablets (Teva UK Ltd)
61846	Zaroxolyn 2.5mg tablets (IDIS)
61985	Ramipril 1.25mg tablets (Teva UK Ltd)
61998	Isosorbide dinitrate 20mg tablets (Waymade Healthcare Plc)
62019	Doxazosin 1mg tablets (Almus Pharmaceuticals Ltd)
62024	Bumetanide 5mg tablets (A A H Pharmaceuticals Ltd)
62035	Candesartan 16mg tablets (Waymade Healthcare Plc)
62036	Ramipril 5mg tablets (Waymade Healthcare Plc)
62039	Ramipril 1.25mg tablets (Zentiva)
62064	Diltiazem 120mg modified-release tablets (Mawdsley-Brooks & Company Ltd)
62065	Diltiazem 90mg modified-release tablets (Colorama Pharmaceuticals Ltd)
62066	Cardide SR 1.5mg tablets (Teva UK Ltd)
62140	Candesartan 4mg tablets (Sandoz Ltd)
62158	Doxazosin 4mg tablets (Almus Pharmaceuticals Ltd)
62207	Adizem-SR 120mg capsules (Waymade Healthcare Plc)
62249	Co-amilozide 5mg/50mg tablets (Alliance Healthcare (Distribution) Ltd)
62337	Irbesartan 300mg / Hydrochlorothiazide 12.5mg tablets (Actavis UK Ltd)
62351	Doxazosin 2mg tablets (Phoenix Healthcare Distribution Ltd)
62376	Actelsar HCT 80mg/12.5mg tablets (Actavis UK Ltd)
62388	Losartan 12.5mg tablets (DE Pharmaceuticals)
62404	Isosorbide mononitrate 10mg tablets (DE Pharmaceuticals)
62415	Irbesartan 300mg tablets (A A H Pharmaceuticals Ltd)
62513	Methyldopa 250mg tablets (Sovereign Medical Ltd)
62516	Hydrochlorothiazide 12.5mg tablets
62537	Co-tenidone 100mg/25mg tablets (DE Pharmaceuticals)
62552	Verapamil 80mg tablets (Alliance Healthcare (Distribution) Ltd)
62564	Lisinopril 10mg/5ml oral solution
62700	Co-amilozide 5mg/50mg tablets (Phoenix Healthcare Distribution Ltd)
62771	Indapamide 1.5mg modified-release tablets (DE Pharmaceuticals)
62853	Moxonidine 200microgram tablets (A A H Pharmaceuticals Ltd)
62860	Enalapril 5mg tablets (DE Pharmaceuticals)

62911	Losartan 50mg / Hydrochlorothiazide 12.5mg tablets (Teva UK Ltd)
62912	Diltiazem 120mg modified-release capsules (AM Distributions (Yorkshire) Ltd)
62918	Ramipril 2.5mg/5ml oral solution
62958	Ramipril 5mg tablets (Teva UK Ltd)
63010	Ramipril 10mg tablets (Phoenix Healthcare Distribution Ltd)
63030	Lisinopril 10mg tablets (DE Pharmaceuticals)
63041	Nifedipine 10mg capsules (Mylan)
63149	Perindopril erbumine 8mg / Amlodipine 10mg tablets
63158	Doxazosin 2mg tablets (Almus Pharmaceuticals Ltd)
63222	Losartan 25mg tablets (Pfizer Ltd)
63237	Furosemide 20mg tablets (Boston Healthcare Ltd)
63246	Nifedipine 10mg modified-release tablets (AM Distributions (Yorkshire) Ltd)
63309	Spironolactone 6mg/5ml oral suspension
63314	Doxazosin 1mg tablets (Sovereign Medical Ltd)
63322	Enalapril 10mg tablets (Almus Pharmaceuticals Ltd)
63331	Folpik XL 2.5mg tablets (Teva UK Ltd)
63337	Eprosartan 600mg tablets (A A H Pharmaceuticals Ltd)
63385	Sabervel 75mg tablets (Aspire Pharma Ltd)
63411	Irbesartan 300mg tablets (Alliance Healthcare (Distribution) Ltd)
63442	Ramipril 2.5mg tablets (Teva UK Ltd)
63555	Bumetanide 1mg tablets (Phoenix Healthcare Distribution Ltd)
63559	Lisinopril 20mg tablets (Kent Pharmaceuticals Ltd)
63652	Hydralazine Tablet
63717	Irbesartan 300mg tablets (DE Pharmaceuticals)
63824	Lisinopril 10mg/5ml oral suspension
63890	MicardisPlus 80mg/12.5mg tablets (Waymade Healthcare Plc)
63917	Lercanidipine 20mg tablets (A A H Pharmaceuticals Ltd)
63918	Losartan 25mg tablets (Teva UK Ltd)
63938	Moxonidine 300microgram tablets (Sandoz Ltd)
63971	Clonidine 25microgram tablets (Sigma Pharmaceuticals Plc)
64055	Ramipril 2.5mg/5ml oral solution sugar free (Waymade Healthcare Plc)
64062	Enalapril 1mg/5ml oral suspension
64066	Indapamide 2.5mg/5ml oral suspension
64227	Lercanidipine 10mg tablets (Accord Healthcare Ltd)
64233	Doxazosin 1mg tablets (Waymade Healthcare Plc)
64253	Hydralazine 5mg/5ml oral suspension
64255	Furosemide 2mg/5ml oral solution
64284	Dixarit 25microgram tablets (Lexon (UK) Ltd)
64359	Candesartan 4mg tablets (DE Pharmaceuticals)
64424	Lercanidipine 20mg tablets (Zentiva)
64474	Felodipine 2.5mg modified-release tablets (A A H Pharmaceuticals Ltd)
64504	Plendil 5mg modified-release tablets (Necessity Supplies Ltd)
64602	Perindopril erbumine 2mg tablets (Waymade Healthcare Plc)
64624	Diltiazem 4% cream
64677	Furosemide 40mg tablets (DE Pharmaceuticals)
64719	Felodipine 2.5mg modified-release tablets (Sigma Pharmaceuticals Plc)
64739	Captopril 25mg/5ml oral solution (Special Order)
64745	Furosemide 8mg/5ml oral suspension
64760	Felodipine 10mg modified-release tablets (Phoenix Healthcare Distribution Ltd)
64877	Enalapril 2.5mg tablets (Dexcel-Pharma Ltd)
64888	Losartan 12.5mg tablets (Sigma Pharmaceuticals Plc)

64890	Diltiazem cream
64902	Lisinopril 5mg/5ml oral solution sugar free
64907	Bendroflumethiazide 5mg tablets (Almus Pharmaceuticals Ltd)
64917	Felodipine 10mg modified-release tablets (Waymade Healthcare Plc)
65065	Irbesartan 75mg tablets (A A H Pharmaceuticals Ltd)
65094	Losartan 50mg tablets (Sandoz Ltd)
65102	Lisinopril 10mg tablets (Sigma Pharmaceuticals Plc)
65159	Doxazosin 4mg tablets (Waymade Healthcare Plc)
65228	Candesartan 16mg tablets (Mawdsley-Brooks & Company Ltd)
65273	Perindopril erbumine 4mg tablets (Mylan)
65274	Telmisartan 40mg tablets (Actavis UK Ltd)
65349	Folpik XL 10mg tablets (Teva UK Ltd)
65416	Lisinopril 5mg tablets (Lupin Healthcare (UK) Ltd)
65443	Ramipril 1.25mg Tablet (Sovereign Medical Ltd)
65479	Candesartan 2mg tablets (A A H Pharmaceuticals Ltd)
65504	Adizem-SR 180mg capsules (Lexon (UK) Ltd)
65536	Lisinopril 2.5mg tablets (Alliance Healthcare (Distribution) Ltd)
65582	Spironolactone 3mg/5ml oral solution
65583	Furosemide 3mg/5ml oral solution
65599	Ramipril 5mg tablets (A A H Pharmaceuticals Ltd)
65602	Adizem-XL 120mg capsules (Waymade Healthcare Plc)
65636	Adizem-XL 120mg capsules (Lexon (UK) Ltd)
65659	Lercanidipine 20mg tablets (Teva UK Ltd)
65695	Isosorbide mononitrate 25mg modified-release capsules (DE Pharmaceuticals)
65741	Imdur 60mg modified-release tablets (Lexon (UK) Ltd)
65749	Ramipril 5mg capsules (Ennogen Pharma Ltd)
65822	Spironolactone 12.5mg/5ml oral suspension
65853	Doxazosin 1mg tablets (Mawdsley-Brooks & Company Ltd)
65936	Ramipril 5mg capsules (DE Pharmaceuticals)
65970	Nifedipine 2% ointment
65983	Lisinopril 2.5mg tablets (Lupin Healthcare (UK) Ltd)
65985	Lisinopril 2.5mg tablets (DE Pharmaceuticals)
66011	Eplerenone 50mg tablets (A A H Pharmaceuticals Ltd)
66017	Furosemide 20mg tablets (Almus Pharmaceuticals Ltd)
66048	Tildiem Retard 120mg tablets (DE Pharmaceuticals)
66060	Perindopril erbumine 2mg tablets (DE Pharmaceuticals)
66065	Doxazosin 2mg tablets (Kent Pharmaceuticals Ltd)
66095	Felodipine 5mg modified-release tablets (Mawdsley-Brooks & Company Ltd)
66114	Losartan 12.5mg tablets (Mawdsley-Brooks & Company Ltd)
66149	Furosemide 4.5mg/5ml oral solution
66162	Ramipril 10mg tablets (Teva UK Ltd)
66172	Uard 180XL capsules (Ennogen Healthcare Ltd)
66191	Adalat retard 20mg tablets (DE Pharmaceuticals)
66195	Bumetanide 1mg tablets (Almus Pharmaceuticals Ltd)
66197	Sacubitril 49mg / Valsartan 51mg tablets
66205	Entresto 49mg/51mg tablets (Novartis Pharmaceuticals UK Ltd)
66236	Nifedipine 20mg Modified-release tablet (Kent Pharmaceuticals Ltd)
66261	Entresto 24mg/26mg tablets (Novartis Pharmaceuticals UK Ltd)
66329	Ramipril oral solution
66517	Bendroflumethiazide 1.25mg/5ml oral suspension
66551	Losartan 50mg tablets (Bristol Laboratories Ltd)

66558	Lisinopril 5mg tablets (DE Pharmaceuticals)
66597	Captopril 10mg/5ml oral suspension
66598	Losartan 50mg / Hydrochlorothiazide 12.5mg tablets (Lupin Healthcare (UK) Ltd)
66622	Lisinopril 20mg tablets (DE Pharmaceuticals)
66624	Candesartan 16mg tablets (Sandoz Ltd)
66635	Dilzem XL 180 capsules (DE Pharmaceuticals)
66669	Ramipril 10mg capsules (DE Pharmaceuticals)
66701	Diltiazem 240mg modified-release capsules (DE Pharmaceuticals)
66702	Sacubitril 24mg / Valsartan 26mg tablets
66772	Lisinopril 2.5mg tablets (Waymade Healthcare Plc)
66790	Isosorbide mononitrate 40mg modified-release capsules (CST Pharma Ltd)
66829	Entresto 97mg/103mg tablets (Novartis Pharmaceuticals UK Ltd)
66834	Uard 240XL capsules (Ennogen Healthcare Ltd)
66850	Diltiazem 240mg modified-release capsules (Icarus Pharmaceuticals Ltd)
66895	Enalapril 10mg/5ml oral suspension
66910	Felodipine 2.5mg modified-release tablets (DE Pharmaceuticals)
66931	Sacubitril 97mg / Valsartan 103mg tablets
66958	Candesartan 8mg tablets (Sandoz Ltd)
66997	MicardisPlus 40mg/12.5mg tablets (Waymade Healthcare Plc)
67074	Adalat 10mg capsules (DE Pharmaceuticals)
67075	Lisinopril 2.5mg tablets (Mawdsley-Brooks & Company Ltd)
67194	Lisinopril 2.5mg tablets (Bristol Laboratories Ltd)
67200	Clonidine 10micrograms/5ml oral solution
67257	Elantan LA50 capsules (Dowelhurst Ltd)
67269	Coversyl 2mg tablets (Waymade Healthcare Plc)
67284	Ismo Retard 40mg tablets (Dowelhurst Ltd)
67293	Half Securon SR 120mg tablets (Mawdsley-Brooks & Company Ltd)
67307	Staril 20mg tablets (Dowelhurst Ltd)
67317	Dilzem XL 120 capsules (Mawdsley-Brooks & Company Ltd)
67321	Elantan 10 tablets (Waymade Healthcare Plc)
67335	Elantan 20 tablets (Waymade Healthcare Plc)
67344	Diltiazem 300mg modified-release capsules (Ennogen Pharma Ltd)
67486	Isosorbide mononitrate 10mg/5ml oral suspension
67663	Valsartan 160mg capsules (Dexcel-Pharma Ltd)
67664	Valsartan 160mg / Hydrochlorothiazide 12.5mg tablets (Teva UK Ltd)
67665	Moxonidine 400microgram tablets (Actavis UK Ltd)
67719	Ramipril 5mg capsules (Mawdsley-Brooks & Company Ltd)
67737	Bendroflumethiazide 2.5mg tablets (Dr Reddy's Laboratories (UK) Ltd)
67738	Bendroflumethiazide 5mg tablets (Dr Reddy's Laboratories (UK) Ltd)
67741	Ramipril 1.25mg capsules (Almus Pharmaceuticals Ltd)
67767	Lisinopril 10mg / Hydrochlorothiazide 12.5mg tablets (Almus Pharmaceuticals Ltd)
67780	Bendroflumethiazide 5mg tablets (DE Pharmaceuticals)
67789	Perindopril erbumine 2mg tablets (Accord Healthcare Ltd)
67795	Lisinopril 20mg tablets (Almus Pharmaceuticals Ltd)
67801	Dyazide 50mg/25mg tablets (Lexon (UK) Ltd)
67808	Physiotens 200microgram tablets (Actavis UK Ltd)
67810	Imdur 60mg modified-release tablets (Waymade Healthcare Plc)
67890	Uard 300XL capsules (Ennogen Healthcare Ltd)
67902	Losartan 100mg tablets (Sandoz Ltd)
67910	Furosemide 40mg/5ml oral solution
67913	Spironolactone 50mg tablets (Kent Pharmaceuticals Ltd)

67929	Candesartan 16mg tablets (Tillomed Laboratories Ltd)
67934	Isosorbide mononitrate 20mg tablets (Waymade Healthcare Plc)
68020	Beta-Adalat modified-release capsules (Sigma Pharmaceuticals Plc)
68021	Perindopril erbumine 4mg tablets (Alliance Healthcare (Distribution) Ltd)
68022	Doxazosin 4mg tablets (Sovereign Medical Ltd)
68054	Diltiazem 60mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)
68068	Furosemide 4mg/5ml oral solution
68094	Lisinopril 5mg tablets (Sigma Pharmaceuticals Plc)
68161	Doxazosin 4mg tablets (Mawdsley-Brooks & Company Ltd)
68181	Felodipine 5mg modified-release tablets (Sigma Pharmaceuticals Plc)
68192	Ramipril 5mg capsules (Brown & Burk UK Ltd)
68247	Lisinopril 5mg tablets (Bristol Laboratories Ltd)
68340	Losartan 12.5mg tablets (Consilient Health Ltd)
68372	Ramipril 5mg tablets (Actavis UK Ltd)
68381	Perindopril erbumine 4mg tablets (Mawdsley-Brooks & Company Ltd)
68384	Elantan LA50 capsules (Mawdsley-Brooks & Company Ltd)
68429	Diltiazem 120mg modified-release capsules (Ethigen Ltd)
68432	Metolazone 2.5mg/5ml oral suspension
68480	Ramipril 10mg capsules (Mawdsley-Brooks & Company Ltd)
68496	Enalapril 10mg tablets (Kent Pharmaceuticals Ltd)
68499	Felodipine sr 10mg Tablet (Approved Prescription Services Ltd)
68531	Verapamil 40mg/5ml oral suspension
68603	Losartan 50mg tablets (Wockhardt UK Ltd)
68647	Candesartan 8mg tablets (Genesis Pharmaceuticals Ltd)
68718	Candesartan 4mg tablets (A A H Pharmaceuticals Ltd)
68751	Candesartan 16mg tablets (Genesis Pharmaceuticals Ltd)
68759	Perindopril erbumine 2mg tablets (Aurobindo Pharma Ltd)
68828	Felodipine 5mg modified-release tablets (DE Pharmaceuticals)
68948	Valsartan 160mg capsules (Actavis UK Ltd)
69009	Zaroxolyn 5mg tablets (Imported (Canada))
69016	Perindopril erbumine 8mg tablets (DE Pharmaceuticals)
69028	Diltiazem 60mg modified-release capsules (DE Pharmaceuticals)
69074	Lisinopril 20mg tablets (Relonchem Ltd)
69108	Adizem-XL 300mg capsules (Lexon (UK) Ltd)
69116	Diltiazem 60mg modified-release tablets (DE Pharmaceuticals)
69126	Isosorbide mononitrate 20mg/5ml oral suspension
69127	Isosorbide mononitrate 30mg/5ml oral suspension
69192	Captopril oral solution
69202	Nifedipine 2mg/5ml oral suspension
69206	Felodipine 2.5mg/5ml oral solution
69239	Lercanidipine 10mg tablets (A A H Pharmaceuticals Ltd)
69269	Lisinopril 20mg tablets (Waymade Healthcare Plc)
69277	Adizem-XL 240mg capsules (Lexon (UK) Ltd)
69288	Ramipril 10mg capsules (Brown & Burk UK Ltd)
69319	Doxazosin 2mg tablets (DE Pharmaceuticals)
69334	Bendroflumethiazide 5mg with Nadolol 80mg tablets
69338	Furosemide 40mg/5ml sugar free Oral solution (Rosemont Pharmaceuticals Ltd)
69445	Furosemide 40mg/5ml oral solution sugar free (Sigma Pharmaceuticals Plc)
69473	Spironolactone 3.5mg/5ml oral suspension
69521	Isosorbide dinitrate 20mg tablets (Accord Healthcare Ltd)
69599	Captopril 500micrograms/5ml oral suspension

69600	Captopril 1mg/5ml oral suspension
69667	Losartan 100mg/5ml oral solution
69668	Nifedipine 30mg/5ml oral suspension
69757	Doxazosin 8mg/5ml oral suspension
69763	Isosorbide dinitrate 50mg/50ml concentrate for solution for infusion vials (Torbay Pharmaceuticals)
69802	Candesartan 4mg tablets (Mylan)
69818	Diltiazem 0.5% ointment
69858	Losartan 25mg tablets (Alliance Healthcare (Distribution) Ltd)
70072	Ramipril 1.25mg capsules (Mawdsley-Brooks & Company Ltd)
70251	Telmisartan 20mg tablets (Teva UK Ltd)
70306	Diltiazem 180mg modified-release capsules (Mawdsley-Brooks & Company Ltd)
70325	Losartan 50mg tablets (Almus Pharmaceuticals Ltd)
70370	Eplerenone 25mg tablets (Actavis UK Ltd)
70431	Irbesartan 150mg tablets (Lupin Healthcare (UK) Ltd)
70455	Candesartan 4mg/5ml oral suspension
70509	Indapamide 2.5mg tablets (DE Pharmaceuticals)
70543	Eplerenone 50mg tablets (Actavis UK Ltd)
70628	Diovan 3mg/1ml oral solution (Novartis Pharmaceuticals UK Ltd)
70650	Furosemide 50mg/5ml solution for injection ampoules (Peckforton Pharmaceuticals Ltd)
70655	Hydralazine 25mg/5ml oral suspension
70667	Lisinopril 5mg tablets (Mawdsley-Brooks & Company Ltd)
70709	Ramipril 10mg tablets (Actavis UK Ltd)
70732	Lercanidipine 20mg tablets (Alliance Healthcare (Distribution) Ltd)
70754	Losartan 50mg / Hydrochlorothiazide 12.5mg tablets (Ranbaxy (UK) Ltd)
70765	Losartan 100mg tablets (Almus Pharmaceuticals Ltd)
70805	Candesartan 8mg tablets (Crescent Pharma Ltd)
70827	Lercanidipine 10mg tablets (Teva UK Ltd)
70916	Perindopril erbumine 8mg tablets (Glenmark Pharmaceuticals Europe Ltd)
70917	Perindopril erbumine 2mg tablets (Glenmark Pharmaceuticals Europe Ltd)
70918	Eplerenone 25mg tablets (Alliance Healthcare (Distribution) Ltd)
70922	Losartan 100mg / Hydrochlorothiazide 12.5mg tablets (Phoenix Healthcare Distribution Ltd)
70955	Irbesartan 300mg/5ml Oral suspension (Martindale Pharmaceuticals Ltd)
70961	Tildiem Retard 90mg tablets (DE Pharmaceuticals)
70989	Bendroflumethiazide 2.5mg tablets (Genesis Pharmaceuticals Ltd)
70994	Captopril 12.5mg tablets (Sandoz Ltd)
70995	Isosorbide mononitrate 10mg tablets (Almus Pharmaceuticals Ltd)
71004	Perindopril erbumine 8mg tablets (Accord Healthcare Ltd)
71009	Verapamil 40mg tablets (Kent Pharmaceuticals Ltd)
71010	Spironolactone 25mg tablets (Genesis Pharmaceuticals Ltd)
71018	Lercanidipine 10mg tablets (Arrow Generics Ltd)
71019	Irbesartan 75mg tablets (Dr Reddy's Laboratories (UK) Ltd)
71025	Ramipril 1.25mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)
71028	Valsartan 80mg capsules (Arrow Generics Ltd)
71030	Lercanidipine 20mg tablets (Arrow Generics Ltd)
71040	Ramipril 5mg tablets (Pfizer Ltd)
71068	Ramipril 2.5mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)
71080	Candesartan 4mg tablets (Zentiva)
71096	Irbesartan 150mg tablets (Dr Reddy's Laboratories (UK) Ltd)

71097	Hydralazine 50mg tablets (Almus Pharmaceuticals Ltd)
71110	Aldomet 500mg tablets (Sigma Pharmaceuticals Plc)
71115	Zestoretic 10 tablets (Waymade Healthcare Plc)
71215	Irbesartan 75mg tablets (Actavis UK Ltd)
71256	Hydralazine 20mg powder for concentrate for solution for injection ampoules (Advanz Pharma)
71277	Captopril 7.5mg/5ml oral suspension
71339	Adalat LA 30 tablets (Dowelhurst Ltd)
71342	Dilzem XL 240 capsules (Waymade Healthcare Plc)
71348	Frumil 40mg/5mg tablets (Waymade Healthcare Plc)
71377	Frumil LS 20mg/2.5mg tablets (Waymade Healthcare Plc)
71385	Aldomet 250mg tablets (Sigma Pharmaceuticals Plc)
71398	Spironolactone 12.5mg/5ml oral solution
71405	Cardura XL 4mg tablets (DE Pharmaceuticals)
71406	Furosemide 1mg/5ml oral solution
71413	Diltiazem 120mg modified-release capsules (A A H Pharmaceuticals Ltd)
71491	Ramipril 2.5mg capsules (Ennogen Pharma Ltd)

Codes to identify Statin medication (CPRD GOLD)

prodcode	productname
25	simvastatin 20mg tablets
28	atorvastatin 10mg tablets
42	simvastatin 10mg tablets
51	simvastatin 40mg tablets
75	atorvastatin 20mg tablets
379	fluvastatin 20mg capsules
490	pravastatin 10mg tablets
713	rosuvastatin 10mg tablets
730	pravastatin 20mg tablets
745	atorvastatin 40mg tablets
802	simvador 40mg tablets (discovery pharmaceuticals)
818	simvastatin 20mg/5ml oral solution sugar free
1219	pravastatin 40mg tablets
1221	lipostat 10mg tablets (bristol-myers squibb pharmaceuticals ltd)
1223	lipostat 40mg tablets (bristol-myers squibb pharmaceuticals ltd)
2137	fluvastatin 40mg capsules
2718	zocor 10mg tablets (merck sharp & dohme ltd)
2955	lipitor 40mg tablets (pfizer ltd)
3411	lipitor 10mg tablets (pfizer ltd)
3690	lipostat 20mg tablets (bristol-myers squibb pharmaceuticals ltd)
5148	simvastatin 80mg tablets
5775	atorvastatin 80mg tablets
5985	lescol xl 80mg tablets (novartis pharmaceuticals uk ltd)
6168	zocor 40mg tablets (merck sharp & dohme ltd)
6213	rosuvastatin 20mg tablets
7196	zocor 20mg tablets (merck sharp & dohme ltd)
7347	crestor 10mg tablets (astrazeneca uk ltd)
7374	lipitor 20mg tablets (pfizer ltd)
7552	simvastatin 20mg / ezetimibe 10mg tablets
7554	rosuvastatin 5mg tablets
8380	lescol 20mg capsules (novartis pharmaceuticals uk ltd)
9153	lescol 40mg capsules (novartis pharmaceuticals uk ltd)
9897	rosuvastatin 40mg tablets
9920	simvador 20mg tablets (discovery pharmaceuticals)
9930	crestor 40mg tablets (astrazeneca uk ltd)
10172	simvastatin 40mg / ezetimibe 10mg tablets
10183	simvastatin 40mg with ezetimibe 10mg tablet
10206	simvastatin 80mg with ezetimibe 10mg tablet
11627	fluvastatin 80mg modified-release tablets
11815	simvastatin 20mg with ezetimibe 10mg tablet
13041	simvador 10mg tablets (discovery pharmaceuticals)
14219	simvastatin 80mg / ezetimibe 10mg tablets
15252	crestor 20mg tablets (astrazeneca uk ltd)

16186	inegy 10mg/80mg tablets (merck sharp & dohme ltd)
17059	inegy 10mg/40mg tablets (merck sharp & dohme ltd)
17683	lipitor 80mg tablets (pfizer ltd)
17688	crestor 5mg tablets (astrazeneca uk ltd)
21020	inegy 10mg/20mg tablets (merck sharp & dohme ltd)
22579	zocor 80mg tablets (merck sharp & dohme ltd)
24509	simvastatin
29438	simvastatin
31930	zocor heart-pro 10mg tablet (mcneil products ltd)
32909	simvastatin 80mg tablets (a a h pharmaceuticals ltd)
32921	pravastatin 10mg tablet (dr reddy's laboratories (uk) ltd)
33082	simvastatin 20mg tablets (a a h pharmaceuticals ltd)
34312	simvastatin 20mg tablets (mylan)
34316	simvastatin 20mg tablets (teva uk ltd)
34353	simvastatin 40mg tablets (mylan)
34366	simvastatin 20mg tablets (ivax pharmaceuticals uk ltd)
34376	simvastatin 40mg tablets (teva uk ltd)
34381	simvastatin 40mg tablets (ivax pharmaceuticals uk ltd)
34476	simvastatin 20mg tablet (ratiopharm uk ltd)
34481	simvastatin 10mg tablets (ivax pharmaceuticals uk ltd)
34502	simvastatin 40mg tablets (a a h pharmaceuticals ltd)
34535	simvastatin 10mg tablets (mylan)
34545	simvastatin 40mg tablet (ratiopharm uk ltd)
34560	simvastatin 10mg tablet (ratiopharm uk ltd)
34746	simvastatin 20mg tablet (niche generics ltd)
34814	simvastatin 20mg tablets (wockhardt uk ltd)
34820	pravastatin 40mg tablets (a a h pharmaceuticals ltd)
34879	simvastatin 40mg tablet (niche generics ltd)
34891	simvastatin 20mg tablets (kent pharmaceuticals ltd)
34907	simvastatin 40mg tablets (wockhardt uk ltd)
34955	simvastatin 10mg tablets (a a h pharmaceuticals ltd)
34969	simvastatin 40mg tablets (actavis uk ltd)
36377	pravastatin 20mg tablets (teva uk ltd)
37434	simvastatin 40mg tablets (sandoz ltd)
39060	simvastatin 20mg tablets (dexcel-pharma ltd)
39652	simvastatin 40mg/5ml oral solution sugar free
39675	simvastatin 20mg/5ml oral suspension (martindale pharmaceuticals ltd)
39870	simvador 80mg tablets (discovery pharmaceuticals)
40340	simvastatin 10mg tablets (teva uk ltd)
40382	pravastatin 20mg tablets (a a h pharmaceuticals ltd)
40601	simvastatin 20mg tablets (ranbaxy (uk) ltd)
41657	simvastatin 80mg tablets (teva uk ltd)
43218	pravastatin 10mg tablets (teva uk ltd)
44528	simvastatin 20mg/5ml oral suspension sugar free (rosemont pharmaceuticals ltd)

44650	simvastatin 40mg tablets (dexcel-pharma ltd)
44878	ranzolont 10mg tablets (ranbaxy (uk) ltd)
45219	simvastatin 40mg tablets (kent pharmaceuticals ltd)
45235	simvastatin 20mg tablets (sandoz ltd)
45245	simvastatin 20mg tablets (actavis uk ltd)
45346	simvastatin 40mg tablets (arrow generics ltd)
46878	simvastatin 40mg tablets (almus pharmaceuticals ltd)
46956	simvastatin 80mg tablets (arrow generics ltd)
47065	atorvastatin 20mg chewable tablets sugar free
47090	atorvastatin 10mg chewable tablets sugar free
47630	lipitor 20mg chewable tablets (pfizer ltd)
47721	lipitor 10mg chewable tablets (pfizer ltd)
47774	simvastatin 10mg tablets (arrow generics ltd)
47948	simvastatin 10mg tablets (tillomed laboratories ltd)
47988	pravastatin 40mg tablets (mylan)
48018	simvastatin 20mg tablets (arrow generics ltd)
48051	simvastatin 10mg tablets (kent pharmaceuticals ltd)
48058	simvastatin 10mg tablets (ranbaxy (uk) ltd)
48078	simvastatin 10mg tablets (actavis uk ltd)
48097	pravastatin 40mg tablets (teva uk ltd)
48221	simvastatin 20mg/5ml oral suspension sugar free
48346	atorvastatin 60mg tablets
48431	simvastatin 40mg/5ml oral suspension sugar free
48518	atorvastatin 10mg/5ml oral solution
48867	simvastatin 40mg tablets (alliance healthcare (distribution) ltd)
48973	atorvastatin 30mg tablets
49061	simvastatin 40mg tablets (bristol laboratories ltd)
49062	simvastatin 20mg tablets (alliance healthcare (distribution) ltd)
49558	atorvastatin 20mg tablets (a a h pharmaceuticals ltd)
49587	simvastatin 80mg tablets (almus pharmaceuticals ltd)
49751	atorvastatin 40mg tablets (alliance healthcare (distribution) ltd)
50236	atorvastatin 10mg tablets (zentiva)
50272	atorvastatin 40mg tablets (pfizer ltd)
50483	simvastatin 40mg tablets (relonchem ltd)
50564	simvastatin 20mg tablets (relonchem ltd)
50670	simvastatin 40mg tablets (aurobindo pharma ltd)
50703	simvastatin 40mg tablets (accord healthcare ltd)
50754	simvastatin 20mg tablets (medreich plc)
50788	atorvastatin 20mg tablets (pfizer ltd)
50790	atorvastatin 20mg tablets (dexcel-pharma ltd)
50882	simvastatin 40mg tablets (somex pharma)
50925	pravastatin 10mg tablets (sigma pharmaceuticals plc)
50963	atorvastatin 40mg tablets (teva uk ltd)
51085	simvastatin 10mg tablets (medreich plc)
51134	atorvastatin 10mg tablets (a a h pharmaceuticals ltd)
51166	simvastatin 40mg tablets (medreich plc)

51200	atorvastatin 40mg tablets (arrow generics ltd)
51233	simvastatin 10mg tablets (alliance healthcare (distribution) ltd)
51359	atorvastatin 20mg tablets (arrow generics ltd)
51483	simvastatin 20mg tablets (aurobindo pharma ltd)
51622	atorvastatin 20mg tablets (consilient health ltd)
51676	pravastatin 40mg tablets (medreich plc)
51715	simvastatin 10mg tablets (sigma pharmaceuticals plc)
51876	atorvastatin 40mg tablets (consilient health ltd)
51890	pravastatin 20mg tablets (medreich plc)
52097	atorvastatin 40mg tablets (wockhardt uk ltd)
52098	simvastatin 40mg tablets (ranbaxy (uk) ltd)
52168	atorvastatin 20mg tablets (aspire pharma ltd)
52211	atorvastatin 20mg tablets (actavis uk ltd)
52257	simvastatin 20mg tablets (accord healthcare ltd)
52397	atorvastatin 40mg tablets (dr reddy's laboratories (uk) ltd)
52398	atorvastatin 40mg tablets (a a h pharmaceuticals ltd)
52459	atorvastatin 80mg tablets (actavis uk ltd)
52460	atorvastatin 40mg tablets (aspire pharma ltd)
52625	simvastatin 10mg tablets (wockhardt uk ltd)
52676	simvastatin 10mg/5ml oral suspension
52755	pravastatin 20mg tablets (alliance healthcare (distribution) ltd)
52812	simvastatin 20mg tablets (sigma pharmaceuticals plc)
52821	atorvastatin 80mg tablets (dr reddy's laboratories (uk) ltd)
52953	simvastatin 20mg tablets (bristol laboratories ltd)
52962	simvastatin 80mg tablets (medreich plc)
53087	simvastatin 20mg tablets (somex pharma)
53340	zocor 40mg tablets (lexon (uk) ltd)
53415	simvastatin 10mg tablets (aurobindo pharma ltd)
53460	crestor 10mg tablets (de pharmaceuticals)
53594	lipitor 80mg tablets (mawdsley-brooks & company ltd)
53676	simvastatin 20mg tablets (tillomed laboratories ltd)
53770	fluvastatin 40mg capsules (a a h pharmaceuticals ltd)
53772	atorvastatin 80mg tablets (alliance healthcare (distribution) ltd)
53822	simvastatin 10mg tablets (bristol laboratories ltd)
53887	atorvastatin 40mg tablets (actavis uk ltd)
53890	atorvastatin 80mg tablets (pfizer ltd)
53908	simvastatin 10mg tablets (dexcel-pharma ltd)
53966	simvastatin 40mg tablets (phoenix healthcare distribution ltd)
54240	simvastatin 40mg tablets (sigma pharmaceuticals plc)
54266	simvastatin 20mg/5ml oral suspension
54435	pravastatin 40mg tablets (almus pharmaceuticals ltd)
54493	simvastatin 10mg tablets (relonchem ltd)
54535	atorvastatin 10mg tablets (pfizer ltd)
54606	simvastatin 20mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
54607	pravastatin 20mg tablets (almus pharmaceuticals ltd)

54655	simvastatin 10mg tablets (accord healthcare ltd)
54819	simvastatin 40mg/5ml oral suspension sugar free (rosemont pharmaceuticals ltd)
54947	simvastatin 20mg tablets (almus pharmaceuticals ltd)
54976	simvastatin 10mg tablets (somex pharma)
54985	simvastatin 40mg/5ml oral suspension
54992	atorvastatin 10mg/5ml oral suspension
55032	atorvastatin 10mg tablets (dexcel-pharma ltd)
55034	atorvastatin 40mg/5ml oral suspension
55444	atorvastatin 40mg tablets (zentiva)
55452	simvastatin 20mg tablets (phoenix healthcare distribution ltd)
55727	atorvastatin 10mg tablets (actavis uk ltd)
55912	pravastatin 40mg tablets (alliance healthcare (distribution) ltd)
56016	lipitor 20mg chewable tablets (pfizer ltd)
56065	simvastatin 20mg/5ml oral suspension sugar free (waymade healthcare plc)
56097	atorvastatin 10mg chewable tablets sugar free
56146	pravastatin 10mg tablets (waymade healthcare plc)
56165	atorvastatin 20mg chewable tablets sugar free
56182	atorvastatin 80mg tablets (zentiva)
56248	atorvastatin 20mg tablets (sigma pharmaceuticals plc)
56481	zocor 10mg tablets (sigma pharmaceuticals plc)
56494	zocor 20mg tablets (sigma pharmaceuticals plc)
56564	atorvastatin 20mg tablets (almus pharmaceuticals ltd)
56607	pravastatin 20mg tablets (waymade healthcare plc)
56735	pravastatin 20mg tablets (mylan)
56841	atorvastatin 40mg tablets (dexcel-pharma ltd)
56893	pravastatin 40mg tablets (accord healthcare ltd)
56916	pravastatin 40mg tablets (pliva pharma ltd)
57108	pravastatin 40mg tablets (waymade healthcare plc)
57117	atorvastatin 80mg tablets (waymade healthcare plc)
57137	pravastatin 10mg tablets (almus pharmaceuticals ltd)
57296	pravastatin 20mg tablets (phoenix healthcare distribution ltd)
57329	simvastatin 25mg/5ml oral suspension
57348	atorvastatin 10mg tablets (consilient health ltd)
57397	pravastatin 10mg tablets (accord healthcare ltd)
57568	zocor 10mg tablets (lexon (uk) ltd)
57763	rosuvastatin 10mg tablets (waymade healthcare plc)
57834	atorvastatin 40mg tablets (de pharmaceuticals)
57836	atorvastatin 80mg tablets (teva uk ltd)
57999	crestor 40mg tablets (lexon (uk) ltd)
58041	atorvastatin 20mg tablets (teva uk ltd)
58110	atorvastatin 20mg tablets (zentiva)
58315	simvastatin 20mg tablets (waymade healthcare plc)
58394	atorvastatin 20mg tablets (alliance healthcare (distribution) ltd)
58418	atorvastatin 80mg tablets (a a h pharmaceuticals ltd)

58617	rosuvastatin 20mg/5ml oral suspension
58742	atorvastatin 80mg tablets (arrow generics ltd)
58755	simvastatin 10mg tablets (phoenix healthcare distribution ltd)
58834	atorvastatin 10mg tablets (de pharmaceuticals)
58868	atorvastatin 10mg tablets (sigma pharmaceuticals plc)
59272	atorvastatin 20mg tablets (waymade healthcare plc)
59278	fluvastatin 20mg capsules (zentiva)
59331	lipitor 10mg tablets (de pharmaceuticals)
59357	atorvastatin 10mg tablets (ranbaxy (uk) ltd)
59446	atorvastatin 40mg tablets (almus pharmaceuticals ltd)
59447	crestor 20mg tablets (waymade healthcare plc)
59452	rosuvastatin 5mg tablets (waymade healthcare plc)
59508	pravastatin 20mg tablets (accord healthcare ltd)
59776	atorvastatin 80mg tablets (aspire pharma ltd)
59859	atorvastatin 10mg tablets (teva uk ltd)
60160	rosuvastatin 5mg tablets (mawdsley-brooks & company ltd)
60251	pravastatin 10mg tablets (sandoz ltd)
60464	atorvastatin 20mg/5ml oral suspension
60511	atorvastatin 40mg tablets (ranbaxy (uk) ltd)
60607	atorvastatin 80mg tablets (de pharmaceuticals)
60989	atorvastatin 80mg tablets (phoenix healthcare distribution ltd)
61134	pravastatin 20mg tablets (sigma pharmaceuticals plc)
61149	atorvastatin 10mg tablets (waymade healthcare plc)
61155	simvastatin 40mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
61321	simvastatin 10mg tablets (sandoz ltd)
61360	simvastatin 10mg tablets (almus pharmaceuticals ltd)
61665	simvastatin 10mg tablets (waymade healthcare plc)
62137	simvastatin 40mg tablets (waymade healthcare plc)
62148	fluvastatin 20mg capsules (actavis uk ltd)
62219	atorvastatin 20mg tablets (de pharmaceuticals)
62429	atorvastatin 20mg tablets (de pharmaceuticals)
62476	atorvastatin 80mg tablets (almus pharmaceuticals ltd)
62979	pravastatin 40mg tablets (kent pharmaceuticals ltd)
63074	pravastatin 20mg tablets (pliva pharma ltd)
63140	atorvastatin 10mg tablets (alliance healthcare (distribution) ltd)
63249	atorvastatin 80mg tablets (consilient health ltd)
63469	atorvastatin 30mg tablets (consilient health ltd)
63787	pravastatin 10mg tablets (tillomed laboratories ltd)
64067	atorvastatin 20mg/5ml oral solution
64104	simvastatin 20mg tablets (crescent pharma ltd)
64180	simvastatin 10mg tablets (crescent pharma ltd)
64307	simvastatin 40mg tablets (crescent pharma ltd)
64702	atorvastatin 30mg tablets (a a h pharmaceuticals ltd)
64810	atorvastatin 40mg tablets (phoenix healthcare distribution ltd)
64825	atorvastatin 10mg tablets (phoenix healthcare distribution ltd)

64868	atorvastatin 40mg tablets (sigma pharmaceuticals plc)
64968	simvastatin 10mg tablets (de pharmaceuticals)
65181	simvastatin 40mg tablets (de pharmaceuticals)
65193	atorvastatin 20mg tablets (ranbaxy (uk) ltd)
65679	simvastatin 20mg tablets (de pharmaceuticals)
65901	simvastatin 40mg tablets (zentiva)
65925	simvastatin 20mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
66505	fenofibrate 145mg / simvastatin 40mg tablets
66780	fenofibrate 145mg / simvastatin 20mg tablets
66963	atorvastatin 80mg tablets (sigma pharmaceuticals plc)
67098	simvastatin 10mg tablets (brown & burk uk ltd)
67328	lescol xl 80mg tablets (mawdsley-brooks & company ltd)
67402	atorvastatin 40mg tablets (kent pharmaceuticals ltd)
67573	atorvastatin 10mg tablets (de pharmaceuticals)
67660	atorvastatin 80mg tablets (ranbaxy (uk) ltd)
67745	simvastatin 10mg tablets (zentiva)
67773	simvastatin 20mg tablets (zentiva)
67829	pravastatin 20mg tablets (sandoz ltd)
67846	atorvastatin 10mg tablets (almus pharmaceuticals ltd)
68023	atorvastatin 10mg tablets (aspire pharma ltd)
68048	atorvastatin 20mg tablets (phoenix healthcare distribution ltd)
68156	pravastatin 10mg tablets (a a h pharmaceuticals ltd)
68467	atorvastatin 20mg tablets (kent pharmaceuticals ltd)
68563	simvastatin 40mg tablets (brown & burk uk ltd)
68686	simvastatin 20mg tablets (genesis pharmaceuticals ltd)
68785	atorvastatin 10mg tablets (mylan)
68827	atorvastatin 20mg tablets (mylan)
69093	atorvastatin 80mg tablets (wockhardt uk ltd)
69413	simvastatin 20mg tablets (brown & burk uk ltd)
69427	atorvastatin 40mg tablets (mylan)
69528	cholib 145mg/20mg tablets (mylan)
70308	crestor 20mg tablets (sigma pharmaceuticals plc)
70486	cholib 145mg/40mg tablets (mylan)
70693	atorvastatin 10mg tablets (sigma pharmaceuticals plc)
70987	atorvastatin 10mg tablets (dr reddy's laboratories (uk) ltd)
71014	rosuvastatin 20mg tablets (waymade healthcare plc)
71015	pravastatin 10mg tablets (medreich plc)
71017	atorvastatin 20mg tablets (dr reddy's laboratories (uk) ltd)
71029	fluvastatin 40mg capsules (sandoz ltd)

Codes to identify BMI (CPRD Aurum)

Medcodeid	Term
8286991000006119	baseline bmi (body mass index)
8286961000006110	baseline bmi (body mass index) centile
2196071000000116	baseline body mass index
2196031000000118	baseline body mass index centile
6831331000006118	bmi (body mass index) 20-24 - normal
6763401000006111	bmi (body mass index) 40+ - severely obese
7332961000006118	bmi (body mass index) centile
3484801000006114	bmi - body mass index
4553721000006113	bmi 25-29 - overweight
4553741000006118	bmi 30+ - obesity
1728141000006115	bmi centile
5998281000006119	bmi less than 20
100716012	body mass index
1808071000006119	body mass index 18.5-24.9
4553701000006115	body mass index 25-29 - overweight
253848011	body mass index 30+ - obesity
6763391000006114	body mass index 40+ - morbidly obese
2160062010	body mass index 40+ - severely obese
1551651000000111	body mass index centile
253845014	body mass index high k/m2
253847018	body mass index index 25-29 - overweight
1808061000006114	body mass index less than 18.5
453856012	body mass index less than 20
253846010	body mass index low k/m2
253844013	body mass index normal k/m2
2603621000006111	decreased bmi (body mass index)
8334011000006117	down's syndrome bmi (body mass index) centile
1922491000006113	down's syndrome body mass index centile
3284711000006119	increased bmi (body mass index)
857321000006113	moderately obese
3070611000006119	normal bmi (body mass index)
253687013	o/e - underweight
2350241000000116	obese class i (body mass index 30.0 - 34.9)
2350261000000115	obese class ii (body mass index 35.0 - 39.9)
1900331000006113	obese class iii (bmi equal to or greater than 40.0)
4551891000006115	on examination - underweight
356960015	overweight
5117851000006111	patient overweight
857911000006118	very obese
923861000006112	body mass index
3484781000006110	body mass index

Codes to identify asthma (CPRD GOLD)

medcode	readterm
78	asthma
81	asthma monitoring
185	acute exacerbation of asthma
232	asthma attack
233	severe asthma attack
1555	bronchial asthma
2290	allergic asthma
3018	mild asthma
3366	severe asthma
3458	occasional asthma
3665	late onset asthma
4442	asthma unspecified
4606	exercise induced asthma
4892	status asthmaticus nos
5267	intrinsic asthma
5627	hay fever with asthma
5798	chronic asthmatic bronchitis
5867	exercise induced asthma
6707	extrinsic asthma with asthma attack
7058	emergency admission, asthma
7146	extrinsic (atopic) asthma
7191	asthma limiting activities
7378	asthma management plan given
7416	asthma disturbing sleep
7731	pollen asthma
8335	asthma attack nos
8355	asthma monitored
9018	number of asthma exacerbations in past year
9552	change in asthma management plan
9663	step up change in asthma management plan
10043	asthma annual review
10274	asthma medication review
10487	asthma - currently active
11370	asthma confirmed
12987	late-onset asthma
13064	asthma severity
13065	moderate asthma
13175	asthma disturbs sleep frequently
13176	asthma follow-up
14777	extrinsic asthma without status asthmaticus
15248	hay fever with asthma
16070	asthma nos
16667	asthma control step 2

16785	asthma control step 1
18223	step down change in asthma management plan
18224	asthma control step 3
18323	intrinsic asthma with asthma attack
19167	asthma monitoring by nurse
19519	asthma treatment compliance unsatisfactory
19520	asthma treatment compliance satisfactory
19539	asthma monitoring check done
20860	asthma control step 5
20886	asthma control step 4
21232	allergic asthma nec
22752	occupational asthma
24479	emergency asthma admission since last appointment
24506	further asthma - drug prevent.
24884	asthma causes daytime symptoms 1 to 2 times per week
25181	asthma restricts exercise
25791	asthma clinical management plan
26501	asthma never causes daytime symptoms
26503	asthma causes daytime symptoms most days
26504	asthma never restricts exercise
26506	asthma severely restricts exercise
26861	asthma sometimes restricts exercise
27926	extrinsic asthma with status asthmaticus
29325	intrinsic asthma without status asthmaticus
30458	asthma monitoring by doctor
30815	asthma causing night waking
31167	asthma night-time symptoms
31225	asthma causes daytime symptoms 1 to 2 times per month
38143	asthma never disturbs sleep
38144	asthma limits walking up hills or stairs
38145	asthma limits walking on the flat
38146	asthma disturbs sleep weekly
39478	wood asthma
39570	asthma causes night symptoms 1 to 2 times per month
40823	brittle asthma
41017	aspirin induced asthma
41020	absent from work or school due to asthma
42824	asthma daytime symptoms
45073	intrinsic asthma nos
45782	extrinsic asthma nos
46529	attends asthma monitoring
47337	asthma accident and emergency attendance since last visit
47684	detergent asthma
58196	intrinsic asthma with status asthmaticus
73522	work aggravated asthma
93353	sequoiosis (red-cedar asthma)

93736	royal college of physicians asthma assessment
98185	asthma control test
99793	patient has a written asthma personal action plan
100107	health education - asthma self management
100397	asthma control questionnaire
100509	under care of asthma specialist nurse
100740	health education - structured asthma discussion
102170	asthma review using roy colleg of physicians three questions
102209	mini asthma quality of life questionnaire
102301	asthma trigger - seasonal
102341	asthma trigger - pollen
102395	asthma causes symptoms most nights
102400	asthma causes night time symptoms 1 to 2 times per week
102449	asthma trigger - respiratory infection
102713	asthma limits activities 1 to 2 times per month
102871	asthma trigger - exercise
102888	asthma limits activities 1 to 2 times per week
102952	asthma trigger - warm air
103318	health education - structured patient focused asthma discuss
103321	asthma trigger - animals
103612	asthma never causes night symptoms
103631	royal college physician asthma assessment 3 question score
103813	asthma trigger - cold air
103944	asthma trigger - airborne dust
103945	asthma trigger - damp
103952	asthma trigger - emotion
103955	asthma trigger - tobacco smoke
103998	asthma limits activities most days
105420	asthma self-management plan review
105674	asthma self-management plan agreed
106805	chronic asthma with fixed airflow obstruction
107167	number days absent from school due to asthma in past 6 month

Codes to identify asthma (CPRD Aurum)

medcodeid	readterm
78	asthma
81	asthma monitoring
185	acute exacerbation of asthma
232	asthma attack
233	severe asthma attack
1555	bronchial asthma
2290	allergic asthma
3018	mild asthma
3366	severe asthma
3458	occasional asthma
3665	late onset asthma
4442	asthma unspecified
4606	exercise induced asthma
4892	status asthmaticus nos
5267	intrinsic asthma
5627	hay fever with asthma
5798	chronic asthmatic bronchitis
5867	exercise induced asthma
6707	extrinsic asthma with asthma attack
7058	emergency admission, asthma
7146	extrinsic (atopic) asthma
7191	asthma limiting activities
7378	asthma management plan given
7416	asthma disturbing sleep
7731	pollen asthma
8335	asthma attack nos
8355	asthma monitored
9018	number of asthma exacerbations in past year
9552	change in asthma management plan
9663	step up change in asthma management plan
10043	asthma annual review
10274	asthma medication review
10487	asthma - currently active
11370	asthma confirmed
12987	late-onset asthma
13064	asthma severity
13065	moderate asthma
13175	asthma disturbs sleep frequently
13176	asthma follow-up
14777	extrinsic asthma without status asthmaticus
15248	hay fever with asthma
16070	asthma nos
16667	asthma control step 2

16785	asthma control step 1
18223	step down change in asthma management plan
18224	asthma control step 3
18323	intrinsic asthma with asthma attack
19167	asthma monitoring by nurse
19519	asthma treatment compliance unsatisfactory
19520	asthma treatment compliance satisfactory
19539	asthma monitoring check done
20860	asthma control step 5
20886	asthma control step 4
21232	allergic asthma nec
22752	occupational asthma
24479	emergency asthma admission since last appointment
24506	further asthma - drug prevent.
24884	asthma causes daytime symptoms 1 to 2 times per week
25181	asthma restricts exercise
25791	asthma clinical management plan
26501	asthma never causes daytime symptoms
26503	asthma causes daytime symptoms most days
26504	asthma never restricts exercise
26506	asthma severely restricts exercise
26861	asthma sometimes restricts exercise
27926	extrinsic asthma with status asthmaticus
29325	intrinsic asthma without status asthmaticus
30458	asthma monitoring by doctor
30815	asthma causing night waking
31167	asthma night-time symptoms
31225	asthma causes daytime symptoms 1 to 2 times per month
38143	asthma never disturbs sleep
38144	asthma limits walking up hills or stairs
38145	asthma limits walking on the flat
38146	asthma disturbs sleep weekly
39478	wood asthma
39570	asthma causes night symptoms 1 to 2 times per month
40823	brittle asthma
41017	aspirin induced asthma
41020	absent from work or school due to asthma
42824	asthma daytime symptoms
45073	intrinsic asthma nos
45782	extrinsic asthma nos
46529	attends asthma monitoring
47337	asthma accident and emergency attendance since last visit
47684	detergent asthma
58196	intrinsic asthma with status asthmaticus
73522	work aggravated asthma
93353	sequoiosis (red-cedar asthma)

93736	royal college of physicians asthma assessment
98185	asthma control test
99793	patient has a written asthma personal action plan
100107	health education - asthma self management
100397	asthma control questionnaire
100509	under care of asthma specialist nurse
100740	health education - structured asthma discussion
102170	asthma review using roy colleg of physicians three questions
102209	mini asthma quality of life questionnaire
102301	asthma trigger - seasonal
102341	asthma trigger - pollen
102395	asthma causes symptoms most nights
102400	asthma causes night time symptoms 1 to 2 times per week
102449	asthma trigger - respiratory infection
102713	asthma limits activities 1 to 2 times per month
102871	asthma trigger - exercise
102888	asthma limits activities 1 to 2 times per week
102952	asthma trigger - warm air
103318	health education - structured patient focused asthma discuss
103321	asthma trigger - animals
103612	asthma never causes night symptoms
103631	royal college physician asthma assessment 3 question score
103813	asthma trigger - cold air
103944	asthma trigger - airborne dust
103945	asthma trigger - damp
103952	asthma trigger - emotion
103955	asthma trigger - tobacco smoke
103998	asthma limits activities most days
105420	asthma self-management plan review
105674	asthma self-management plan agreed
106805	chronic asthma with fixed airflow obstruction
107167	number days absent from school due to asthma in past 6 month

Codes to identify arrythmia (CPRD Aurum)

Medcodeid	Terms
19216010	sinus tachycardia
20728011	bouveret-hoffmann syndrome
42864016	ventricular tachycardia
74409013	persistent sinus bradycardia
81702012	severe sinus bradycardia
82343012	atrial fibrillation
111643014	paroxysmal supraventricular tachycardia
119481012	ventricular fibrillation
254026011	o/e - pulse rate tachycardia
256478018	ecg: atrial fibrillation
256479014	ecg: atrial flutter
256484015	ecg: ventricular tachycardia
300130013	atrial fibrillation and flutter
300133010	ventricular fibrillation and flutter
300166014	bigeminal pulse
350465014	non-rheumatic atrial fibrillation
371119011	pulse missed beats
419130013	arrhythmogenic right ventricular cardiomyopathy
2576883015	brugada syndrome
2674238014	tachycardia-induced cardiomyopathy
2674487014	external ventricular defibrillation
2675253013	chronic atrial fibrillation
2692063011	history of atrial flutter
294601000000110	atrial fibrillation resolved
303131000000116	history of supraventricular tachycardia
406861000000119	atrial fibrillation annual review
636701000000115	persistent atrial fibrillation
636721000000112	permanent atrial fibrillation
991651000006115	cardiac dysrhythmias nos
1656521000006113	arrhythmogenic right ventricular cardiomyopathy
1662471000006119	brugada syndrome
1855501000006118	atrial fibrillation monitoring in primary care
1855511000006115	atrial fibrillation monitoring in secondary care
1856431000006118	atrial fibrillation follow-up
2197581000000114	atrial fibrillation care pathway
2608211000000115	typical atrial flutter
300126010	paroxysmal tachycardia unspecified
300134016	ventricular fibrillation and flutter nos
453227015	[d]sinus bradycardia
289521000006112	o/e - bradycardia
291991000006116	[d] bradycardia, unspecified
537191000006113	cardiac arrest-ventricular fibrillation
783761000006118	implant intravenous pacemaker for atrial fibrillation
1587601000006117	perc translum ablat pulmon vein to lft atrium conduct system
371151012	heart beats irregular
5590611000006118	atrial tachycardia
3309351000006110	multifocal atrial tachycardia
4586741000006117	ekg: ventricular tachycardia

3909141000006115	tachycardia - pulse
3400781000006115	syndrome of short p-r interval, normal qrs complexes and supraventricular tachycardias
4586781000006111	ekg: ventricular fibrillation
7803631000006115	atrial flutter type i
7055121000006117	electrocardiogram: sinus bradycardia
6016401000006115	history of atrial fibrillation
4777381000006118	pat - paroxysmal atrial tachycardia
2691431000006114	pt - paroxysmal tachycardia
3179871000006110	bradycardia - pulse
4777451000006119	nodal paroxysmal tachycardia
4777351000006114	atrial paroxysmal tachycardia
2908961000006115	vt - ventricular tachycardia
5669601000006117	paf - paroxysmal atrial fibrillation
5669591000006113	af - paroxysmal atrial fibrillation
4555741000006119	on examination - pulse rate - bradycardia
4777431000006114	junctional paroxysmal tachycardia
4586771000006113	electrocardiographic ventricular fibrillation
4777411000006115	atrioventricular paroxysmal tachycardia
4586631000006118	electrocardiographic atrial flutter
4586661000006110	electrocardiogram: paroxysmal atrial tachycardia
4586611000006112	electrocardiographic atrial fibrillation
12725201000006118	cardiac dysrhythmia nos
884401000006112	cardiac dysrhythmias nos
884391000006110	cardiac dysrhythmias nos
317997017	[x]bradycardia, unspecified
2675306013	paroxysmal atrial flutter
254022013	o/e - pulse rate - bradycardia
9988012	atrial flutter
20729015	essential paroxysmal tachycardia
119266015	nodal rhythm disorder
7046521000006117	inappropriate sinus tachycardia
1755871000000117	referral to atrial fibrillation clinic
4777401000006118	av paroxysmal tachycardia
4586751000006115	electrocardiographic ventricular tachycardia
4555821000006119	on examination - pulse rate tachycardia
4586671000006115	ecg: paroxysmal atrial tachycardia
7068741000006111	electrocardiogram: sinus tachycardia
9868941000006116	atrial flutter type 2
12727421000006117	other cardiac dysrhythmias
9868951000006119	atrial flutter type ii
274941000006115	o/e - tachycardia
300129015	paroxysmal tachycardia nos
300163018	sinoatrial node dysfunction nos
300167017	supraventricular tachycardia nos
421235014	paroxysmal atrial fibrillation
300110014	paroxysmal atrioventricular tachycardia
300111013	paroxysmal junctional tachycardia
256485019	ecg: ventricular fibrillation

60214017	sick sinus syndrome
71437017	pulsus alternans
556551000000115	[d]postural orthostatic tachycardia syndrome (pots)
2602941000006117	svt - supraventricular tachycardia
4540631000006113	history of ventricular fibrillation
3299911000006116	af - atrial fibrillation
395771010	other cardiac dysrhythmias
300119010	paroxysmal supraventricular tachycardia nos
300132017	atrial fibrillation and flutter nos
1932021000006117	3d study - problems with atrial fibrillation management
1823951000006111	atrial fibrillation confirmed
303101000000110	history of ventricular tachycardia
2920703018	atrial standstill
110733013	paroxysmal ventricular tachycardia
178509016	ventricular flutter
256481011	ecg: supraventric. arryth. nos
5669611000006119	intermittent atrial fibrillation
5057281000006117	nraf - non-rheumatic atrial fibrillation
4586641000006111	ekg: atrial flutter
300106011	paroxysmal atrial tachycardia
300169019	other cardiac dysrhythmia nos
300170018	cardiac dysrhythmia nos
317327019	[d]tachycardia, unspecified
2676301014	ecg: sinus bradycardia
2676303012	ecg: sinus tachycardia
371120017	skipped beat
7803641000006113	atrial flutter type 1
300114017	paroxysmal nodal tachycardia
216183015	atrial fibrillation monitoring
884361000006119	parox. supravent. tachycardia
1587611000006119	perc transluminal ablation of atrial wall for atrial flutter
1587631000006113	perc translum ablat conduct sys heart for atrial flutter nec
194271000006110	pulsus alternans
2608251000000116	atypical atrial flutter
1230146013	cardiac dysrhythmias
3669671000006119	vf - ventricular fibrillation

Appendix 4: Supplementary material for chapter 8

Relationship between accelerated FEV_1 decline and risk of heart failure.

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	1.01 (0.89 – 1.15)	0.99 (0.83 – 1.20)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.09 (0.93 – 1.27)	0.97 (0.78 – 1.22)
2 moderate, 0 severe	1.12 (0.93 – 1.34)	1.22 (0.95 – 1.57)
≥3 moderate, 0 severe	1.47 (1.26 – 1.72)**	1.46 (1.17 – 1.82)*
1 severe, any moderate	2.72 (2.18 – 3.40)**	2.22 (1.62 – 3.02)**
≥2 severe, any moderate	2.54 (1.60 – 4.02)**	1.60 (0.81 – 3.16)
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.18 (1.00 – 1.39)*	1.21 (0.97 – 1.52)
30-50%	1.74 (1.48 – 2.06)**	1.55 (1.21 – 1.98)*
<30%	2.07 (1.64 – 2.62)**	1.91 (1.34 – 2.70)**
Age	1.06 (1.05 – 1.07)**	1.10 (1.05 – 1.07)**
Men	1.23 (1.10 – 1.38)**	1.61 (1.36 – 1.91)**
Current smokers	0.79 (0.70 – 0.88)**	1.15 (0.97 – 1.36)
BMI		
Normal	Ref	Ref
Underweight	1.27 (0.94 – 1.70)	1.19 (0.80 – 1.78)
Overweight	1.02 (0.87 – 1.18)	0.89 (0.72 – 1.09)
Obese	1.35 (1.16 – 1.56)**	1.31 (1.07 – 1.62)*
mMRC		
0	Ref	Ref
1	1.39 (1.08 – 1.78)*	1.19 (0.91 – 1.55)
2	2.27 (1.73 – 2.87)**	1.60 (1.22 – 2.11)*
3	3.23 (2.47 – 4.23)**	1.94 (1.44 – 2.63)**
4	4.49 (2.91 – 6.93)**	2.10 (1.30 – 3.40)*
Asthma	0.85 (0.76 – 0.95)*	0.88 (0.74 – 1.04)
Hypertension	2.30 (2.05 – 2.58)**	1.70 (1.42 – 2.03)**
Diabetes	1.78 (1.54 – 2.07)**	1.25 (1.00-1.56)*
Statin use	1.43 (1.27 – 1.60)**	0.97 (0.81 – 1.16)

***Note:** *p value <0.05; **p value<0.0001*

Relationship between accelerated FEV_1 decline and risk of myocardial infarction.

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	1.02 (0.87 – 1.19)	0.89 (0.70 – 1.12)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.07 (0.89 – 1.29)	1.21 (0.94 – 1.56)
2 moderate, 0 severe	1.10 (0.88 – 1.37)	1.13 (0.83 – 1.55)
≥3 moderate, 0 severe	1.44 (1.20- 1.74)**	1.38 (1.04 – 1.81)*
1 severe, any moderate	2.19 (1.63 – 2.94)**	1.57 (1.01 – 2.45)*
≥2 severe, any moderate	3.49 (2.16 – 5.62)**	2.58 (1.29 – 5.16)*
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.01 (0.84 – 1.21)	1.08 (0.83 – 1.40)
30-50%	1.30 (1.08 – 1.58)*	1.18 (0.88 – 1.59)
<30%	1.31 (0.97 – 1.78)	1.08 (0.68 – 1.72)
Age	1.04(1.03 – 1.04)**	0.14 (2.03 -1.05)**
Men	1.50 (1.31 -1.72)**	1.44(1.17 – 1.77)*
Current smokers	1.09(0.95 – 1.26)	1.45 (1.17 – 1.81)*
BMI		
Normal	Ref	Ref
Underweight	1.36 (0.98 – 1.88)	1.43 (0.94 – 2.17)
Overweight	0.97 (0.82 – 1.16)	0.87 (0.69 – 1.10)
Obese	0.76 (0.63 – 0.93)*	0.69 (0.53- 0.91)*
mMRC		
0	Ref	Ref
1	1.23 (0.92- 1.63)	1.14 (0.85 – 1.54)
2	1.65 (1.23-2.21)*	1.45 (1.06 – 1.99)*
3	2.50 (1.82 – 3.44)**	2.11(1.48 – 2.99)**
4	2.85 (1.60 -5.06)**	2.07 (1.11 – 3.7)*
Asthma	0.90 (0.79 – 1.03)	1.07 (0.88 – 1.31)
Hypertension	1.21 (1.06 – 1.39)*	1.08 (0.88 – 1.34)
Diabetes	1.30 (1.06 – 1.60)*	1.03(1.11 – 3.87)*
Statin use	1.01 (0.87 – 1.17)	1.16 (0.93 -1.44)

***Note**: *p value <0.05; **p value<0.0001*

Relationship between accelerated FEV_1 decline and risk of stroke.

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	0.99 (0.86- 1.14)	1.01(0.82- 1.23)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	0.97 (0.82 – 1.14)	1.01 (0.81- 1.27)
2 moderate, 0 severe	1.23 (1.03 – 1.47)*	1.06 (0.81- 1.39)
≥3 moderate, 0 severe	1.00 (0.84 – 1.20)	1.14 (0.88 – 1.46)
1 severe, any moderate	1.58 (1.19 -2.11)*	1.54 (1.04 – 2.29)*
≥2 severe, any moderate	2.50 (1.56 – 4.01)**	1.22 (0.50 – 3.01)
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.16 (0.99 – 1.36)	1.20 (0.95 – 1.50)
30-50%	1.07 (0.90 – 1.28)	1.03 (0.79 – 1.36)
<30%	1.28 (0.97 – 1.68)	1.26 (0.83-1.91)
Age	1.06 (1.05 – 1.06)**	1.05 (1.04 – 1.06)**
Men	1.24 (1.10 – 1.40)*	1.29 (1.07 – 1.55)*
Current smokers	0.87 (0.77 – 0.98)*	1.24 (1.03 – 1.50)*
BMI		
Normal	Ref	Ref
Underweight	0.83 (0.59 – 1.17)	0.85 (0.54 – 1.35)
Overweight	0.97 (0.83-1.12)	0.97 (0.80 – 1.18)
Obese	0.63 (0.53 – 0.76)**	0.65 (0.51-0.84)*
mMRC		
0	Ref	Ref
1	1.09 (0.87 – 1.36)	0.96 (0.76 – 1.22)
2	1.17 (0.91 – 1.49)	0.94 (0.72 – 1.24)
3	1.62 (1.23 -2.14)*	1.31 (0.96 – 1.78)
4	2.27 (1.38 – 3.74)*	1.56 (0.89 – 2.75)
Asthma	0.77 (0.68 – 0.87)**	0.82(0.68 – 0.99)*
Hypertension	1.37 (1.22 – 1.55)**	1.00 (0.83 – 1.21)
Diabetes	1.23 (1.03 – 1.48)*	1.23 (0.94-1.61)
Statin use	2.30 (1.14 – 1.47)**	0.97 (0.80 – 1.19)

Note: **p value <0.05; **p value<0.0001*

Relationship between accelerated FEV_1 decline and risk of atrial fibrillation.

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	0.92(0.82-1.04)	0.97 (0.81 -1.15)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.14 (0.99 – 1.30)	1.06 (0.87 – 1.28)
2 moderate, 0 severe	1.12 (0.95 – 1.32)	1.06 (0.83- 1.34)
≥3 moderate, 0 severe	1.27 (1.10-1.47)*	1.31 (1.07 – 1.61)*
1 severe, any moderate	1.57 (1.22 – 2.03)*	1.53 (1.07 – 2.17)*
≥2 severe, any moderate	2.56 (1.68- 3.88)**	2.64 (1.49 – 4.66)*
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.11 (0.97 – 1.28)	1.06 (0.88 – 1.28)
30-50%	1.26 (1.09-1.46)*	1.09(0.87 – 1.36)
<30%	1.20(0.94 – 1.53)	1.09 (0.75 -1.60)
Age	1.07 (1.06 – 1.07)**	1.07 (1.06 – 1.-8)**
Men	1.39 (1.25 – 1.54)**	1.44 (1.23- 1.68)**
Current smokers	0.61 (0.55 – 0.68)**	0.91 (0.78 – 1.06)
BMI		
Normal	Ref	Ref
Underweight	0.95 (0.69 -1.32)	1.28 (0.84 – 1.93)
Overweight	1.29 (1.12-1.48)**	1.26 (1.05- 1.52)*
Obese	1.37 (1.18 – 1.58)**	1.50 (1.23 – 1.83)**
mMRC		
0	Ref	Ref
1	1.11 (0.91 -1.34)	0.98 (0.79 – 1.20)
2	1.36 (1.11 – 1.66)*	1.06(0.85 – 1.33)
3	1.43 (1.12 – 1.82)*	1.03 (0.78 – 1.37)
4	1.75 (1.09 – 2.82)*	1.16 (0.69 – 1.93)
Asthma	0.01 (0.82-1.01)	1.09 (0.94-1.27)
Hypertension	1.82 (1.64 – 2.12)**	1.42 (1.21- 1.67)**
Diabetes	1.25 (1.07 -1.46)*	1.09 (0.88 – 1.35)
Statin use	1.25 (1.12- 1.40)**	0.99 (0.84-1.16)

***Note**: *p value <0.05; **p value<0.0001*

Relationship between accelerated FEV_1 decline and risk of coronary artery disease excluding myocardial infarction.

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	1.03(0.93-1.15)	1.02(0.87 – 1.19)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	0.98 (0.87 – 1.12)	1.11 (0.93 – 1.32)
2 moderate, 0 severe	1.09 (0.94- 1.26)	1.18 (0.96 – 1.44)
≥3 moderate, 0 severe	1.14 (1.00 – 1.31)*	1.20 (0.99 – 1.45)
1 severe, any moderate	1.64 (1.32 -2.04)**	1.86 (1.39 – 2.50)**
≥2 severe, any moderate	2.17 (1.46 - 3.21)**	2.69 (1.61 – 4.49)**
FEV1 % predicted		
>80%	Ref	Ref
50-80%	0.90 (0.80 – 1.01)	0.91 (0.77 – 1.07)
30-50%	0.77 (0.68 – 0.89)**	0.68 (0.56 – 0.84)**
<30%	0.82 (0.66 – 1.03)	0.70 (0.50- 0.99)*
Age	1.02 (1.02 -1.02)**	1.02 (0.87 – 1.19)
Men	1.28 (1.25 -1.52)**	1.33 (1.15 – 1.53)*
Current smokers	0.97 (0.88- 1.07)	1.31 (1.04 -1.39)*
BMI		
Normal	Ref	Ref
Underweight	0.94 (0.71 -1.25)	0.74 (0.47 – 1.16)
Overweight	1.17 (1.03-1.33)*	1.02 (0.87 – 1.20)
Obese	1.27 (1.12- 1.45)**	1.13 (0.95 – 1.35)
mMRC		Ref
0	Ref	1.05 (0.87 – 1.27)
1	1.14 (0.95 – 1.37)	1.30 (1.06 -1.60)*
2	1.43 (1.18 – 1.73)**	1.59 (1.26 – 2.01)**
3	1.77 (1.43 – 2.20)**	1.04 (0.60 – 1.79)
4	1.26 (0.75 – 2.10)	
Asthma	1.07 (0.97 – 1.18)	1.17(1.03 -1.34)*
Hypertension	1.61 (1.46 – 1.77)**	1.32 (1.14 – 1.53)**
Diabetes	1.42 (1.24 – 1.63)**	0.94 (0.78 – 1.15)
Statin use	1.80 (1.64 – 1.99)**	1.60 (1.39 – 1.85)**

***Note**: *p value <0.05; **p value<0.0001*

Relationship between accelerated FEV_1 decline and risk of CVD death.

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	0.96 (0.79-1.17)	0.94 (0.71-1.25)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.12 (0.90-1.39)	1.19 (0.89-1.61)
2 moderate, 0 severe	1.06 (0.90-1.38)	1.13 (0.78-1.63)
≥3 moderate, 0 severe	1.03 (0.81-1.31)	0.73 (0.50-1.09)
1 severe, any moderate	2.61 (0.80-1.61)**	1.94 (1.24-3.05)*
≥2 severe, any moderate	2.13 (1.90-4.34)*	0.91 (0.29-2.92)
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.23 (0.97-1.57)	1.12 (0.81-1.54)
30-50%	1.87 (1.46-2.40)**	1.23 (0.86-1.77)
<30%	2.18 (1.53-3.09)**	1.40 (0.83-2.38)
Age	1.06 (1.05-1.08)**	1.06 (1.04-1.07)**
Men	1.50 (1.26-1.78)**	1.80 (1.40-2.32)**
Current smokers	1.08 (0.91-1.29)	1.62 (1.24-2.10)**
BMI		
Normal	Ref	Ref
Underweight	1.28 (0.87-1.89)	1.03 (0.59-1.81)
Overweight	0.73 (0.59-0.92)*	0.63 (0.47-0.86)*
Obese	0.84 (0.67-1.06)	0.94 (0.70-1.27)
mMRC		
0	Ref	Ref
1	1.08 (0.75-1.55)	0.94 (0.64-1.39)
2	2.02 (1.41-2.89)	1.57 (1.06-2.32)*
3	3.16 (2.16-4.63)	2.52 (1.66-3.83)**
4	5.15 (2.90-9.16)	2.94 (1.52-5.69)*
Asthma	0.78 (0.66-0.93)*	0.80 (0.62-1.03)
Hypertension	1.83 (1.55-2.16)**	1.49 (1.15-1.93)*
Diabetes	1.62 (1.29-2.04)**	0.90 (0.63-1.29)
Statin use	1.27 (1.-7-1.51)*	1.17 (0.90-1.52)

***Note**: *p value <0.05; **p value<0.0001*

Appendix 5: Publications Associated with this Thesis

Peer- Reviewed Articles

Whittaker HR, Pimenta JM, Jarvis D, Kiddle SJ, Quint JK. (2020). Characteristics Associated with Accelerated Lung Function Decline in a Primary Care Population with Chronic Obstructive Pulmonary Disease. *International Journal of COPD*. https://www.dovepress.com/characteristics-associated-with-accelerated-lung-function-decline-in-a-peer-reviewed-article-COPD. [**Chapter 5].**

Whittaker HR, Bloom C, Morgan A, Jarvis D, Kiddle SJ, Quint JK. (2020). Accelerated FEV_1 decline and risk of cardiovascular disease and mortality in a primary care population of COPD patients. *ERJ.* https://erj.ersjournals.com/content/early/2020/09/09/13993003.00918-2020. [**Chapter 8]**.

Whittaker HR, Jarvis D, Sheikh MR, Kiddle SJ, Quint JK. (2019). BMC Respiratory Medicine. https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-019-1249-x. [**Chapter 2**].

Whittaker HR, Mullerova H, Jarvis D, Barnes NC, Jones PW, Compton CH, Kiddle SJ, Quint JK. (2019). Inhaled corticosteroids, blood eosinophils, and FEV1 decline in patients with COPD in a large UK primary health care setting. International Journal of COPD. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6536812/pdf/copd-14-1063.pdf. [**Chapter 6**].

Abstracts

Whittaker HR, Morgan A, Jarvis D, Kiddle SJ, Quint JK. (2020). Accelerated Lung Function Decline and Rate of Cardiovascular Disease in a Primary Care Population of Chronic Obstructive Pulmonary Disease Patients in England. *AJRCCM*. https://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A7151. [**Chapter 8]**.

Whittaker HR, Mullerova H, Jarvis D, Barnes NC, Jones PW, Compton CH, Kiddle SJ, Quint JK. (2018) Late breaking abstract- Inhaled corticosteroids, blood eosinophils, and FEV1 decline in patients with COPD in a large UK primary health care setting. *European Respiratory Journal.* 52: PA1163; DOI: 10.1183/13993003.congress-2018.PA1163. https://erj.ersjournals.com/content/52/suppl_62/PA1163. [**Chapter 6**].

Whittaker HR, Mullerova H, Jarvis D Kiddle SJ, Quint JK. (2018). Rate of FEV1 decline in a primary care UK chronic obstructive pulmonary disease (COPD) population. Thorax. 73(Suppl 4):A164-A165. https://thorax.bmj.com/content/73/Suppl_4/A164. [**Chapter 5**].

Presentations

(Cancelled due to COVID-19) Whittaker HR, Morgan A, Jarvis D, Kiddle SJ, Quint JK. (2020). Accelerated Lung Function Decline and Rate of Cardiovascular Disease in a Primary Care Population of Chronic Obstructive Pulmonary Disease Patients in England. American Thoracic Society Conference, Philadelphia, Pennsylvania. [Poster]. [**Chapter 8**].

Whittaker HR. (2019). Rate of lung function decline in a primary care UK Chronic Obstructive Pulmonary Disease (COPD) population. NHLI Postgraduate Research Day. Imperial College London, London, England. [Poster]. 2nd Prize for best Clinical poster. **[Chapter 5].**

Whittaker HR, Mullerova H, Jarvis D Kiddle SJ, Quint JK. (2018). Rate of FEV1 decline in a primary care UK chronic obstructive pulmonary disease (COPD) population. British Thoracic Society Winter Meeting. London, England. [Poster Discussion]. **[Chapter 5].**

Whittaker HR, Mullerova H, Jarvis D, Barnes NC, Jones PW, Compton CH, Kiddle SJ, Quint JK. (2018) Inhaled corticosteroids, blood eosinophils, and FEV1 decline in patients with COPD in a large UK primary health care setting. European Respiratory Society. Paris, France. [Poster]. [**Chapter 6].**

Whittaker HR, Mullerova H, Jarvis D, Barnes NC, Jones PW, Compton CH, Kiddle SJ, Quint JK. (2018) Inhaled corticosteroids, blood eosinophils, and FEV1 decline in patients with COPD in a large UK primary health care setting. HES Day. Imperial College London, London, England. [Oral presentation]. [**Chapter 6**].