In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

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- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
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TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Final Study Report
Control: Non-Interventional

Title:	WWE117397: Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting
Phase:	IV
Compound Number:	GSK573719+GW642444
Effective Date:	10-DEC-2019

Description

This is the final report of a descriptive Category 3 Post-Authorisation Study fulfilling a voluntary commitment made in the European Union – Risk Management Plan (EU-RMP) for UMEC/VI and UMEC to examine the utilisation among new users (including possible off-label prescribing) of these medications in a real-world, post-approval setting.

Subject:

Drug Utilisation Study, Post-Authorization Safety Study (PASS), Chronic Obstructive Pulmonary Disease, Electronic Medical Records, Long-Acting Muscarinic Antagonists, Long-Acting Beta-2-Agonists

Author(s): Clinical Practice Research Datalink: PPD
GlaxoSmithKline: PPD

Indication Studied: Chronic Obstructive Pulmonary Disease

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved

PASS INFORMATION

Title	Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting
Version identifier of the report	1.0
Date of last version of the report.	February 2 2018
EU PAS register number	ENCEPP/SDPP/7761
Active substance	Umeclidinium bromide/Vilanterol trifenatate (UMEC/VI) ATC R03AL03: Adrenergics in combination with anticholinergics Umeclidinium bromide (UMEC) ATC R03BB07: Anticholinergics
Medicinal product	UMEC (Incruse Ellipta™ /Rolufta Ellipta™), UMEC/VI (Anoro Ellipta™/Laventair Ellipta™) OTHER long-acting bronchodilators will be included in the study analysis, provided they will be available to prescribers, inclusive but not limited to medications containing: Tiotropium Glycopyrronium Glycopyrronium/Indacaterol Aclidinium Indacaterol Formoterol Salmeterol Olodaterol
Product reference	The EU Marketing Authorisation numbers are: Anoro Ellipta EU/1/14/898/001 EU/1/14/898/002

	EU/1/14/898/003 Laventair Ellipta: EU/1/14/899/001 EU/1/14/899/002 EU/1/14/899/003 Incruse Ellipta: EU/1/14/922/001 EU/1/14/922/002 EU/1/14/922/003 Rolufta Ellipta: EU/1/17/1174/001 EU/1/17/1174/002 EU/1/17/1174/003
Procedure number	Incruse Ellipta: EMEA/H/C/002809/0000 Rolufta Ellipta: EMEA/H/C/004654/0000 Anoro Ellipta: EMEA/H/C/002751/0000 Laventair Ellipta: EMEA/H/C/003754
Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford Middlesex, TW8 9GS UK
Joint PASS	No
Research question and objectives	In the initial post-approval period of up to 24 months from the start of UMEC/VI and UMEC availability in the United Kingdom (UK), we identified patients newly prescribed long-acting bronchodilators (LABD) from the Clinical Practice Research Datalink GOLD database (referred to hereafter as CPRD-GOLD) and from The Health Information Network (THIN) database. We conducted a drug utilisation review focusing on the following aims: *Objective 1:* In new users of UMEC/VI, UMEC, or Other LABD report the proportion of patients with a possible off-label use and characterize them, using

	information available up to the time of censoring, in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use. *Objective 2:* In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality and pneumonia, and rates of exacerbations of COPD during follow-up. *Objective 3:* In new users of UMEC/VI or UMEC with 12 or more months of follow-up after initiation, describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up.
Country(-ies) of study	United Kingdom
Author	PPD Clinical Practice Research Datalink (CPRD) MHRA, 151 Buckingham Palace Road London SW1W 9SZ UK Telephone: PPD Email: PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Ltd 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland
MAH contact person	PPD Regulatory Project Manager, Respiratory Therapeutic Group Global Regulatory Affairs GlaxoSmithKline Research & Development Ltd

SPONSOR SIGNATORY SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study WWE117397.

PPD

Name of Project Officer: Gema Requena

Title of Project Officer: Manager, Respiratory Epidemiology

PPD

Signature: _____

Date: 9th December 2019

PPD

Name of Therapy Area Head: Melissa Van Dyke

Title of Therapy Area Head: Senior Director and Therapy Area Head, Respiratory Epidemiology

PPD

Signature: _____

Date: 9-DEC-2019

PPD

Name of SERM Head: John Finkle

Title of SERM Head: Vice President, SERM, Safety and Medical Governance

PPD

Signature: _____

PPD

Date: 10 Dec 2019

INVESTIGATOR SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge Study WWE117397 was carried out as described in this GlaxoSmithKline Report

Name of Investigator: Daniel Dedman

Affiliation: Clinical Practice Research Datalink (CPRD)

Signature of Investigator: PPD

Date: 20 Nov 2019.

PPD

TABLE OF CONTENTS

PAGE

1 LIST OF ABBREVIATIONS

AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
BMI	Body Mass Index
CAG	Confidentiality Advisory Group
CHF	Congestive Heart Failure
CI	95% Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CPRD-GOLD	CPRD primary care electronic health record database derived from Vision GP software
EHR	Electronic Health Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU-RMP	European Union – Risk Management Plan
FEV1	Forced Expiratory Volume (in one second)
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GORD	Gastro-oesophageal reflux disease
GP	General Practitioner
GSK	GlaxoSmithKline
HES	Hospital Episodes Statistics
HRA	Health Research Authority
ICS	Inhaled Corticosteroids
ICD-10	International Classification of Diseases, Tenth Revision
IQR	InterQuartile Range
ISAC	Independent Scientific Advisory Committee
LABA	Long-Acting Beta2-Agonists
LABD	Long-Acting Bronchodilators
LAMA	Long-Acting Muscarinic Antagonists
LSOA	Lower Super Output Area
MAH	Marketing Authorization Holder
MI	Myocardial Infarction
MITT	Multiple inhaler triple therapy
MPR	Medication possession ratio
MRC	Medical Research Council
MREC	NHS Multi-centre Research Ethics Committee
ONS	Office for National Statistics
OPCS-4	OPCS Classification of Interventions and Procedures version 4
PASS	Post Authorisation Safety Study
PDC	Proportion of days covered
QOF	NHS Quality and Outcomes Framework
SABA	Short-Acting Beta2-Agonists
SABD	Short-Acting Bronchodilators
SAMA	Short-Acting Muscarinic Antagonists

SD	Standard Deviation
SRC	Scientific Review Committee
TIA	Transient ischaemic attack
THIN	The Health Information Network primary care electronic health record database derived from Vision GP software
UK	United Kingdom
UMEC	Umeclidinium bromide
VI	Vilanterol trifenatate

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Striverdi
Ultibro

2 RESPONSIBLE PARTIES

Sponsor

The Marketing Authorization Holder (MAH) has served as the sponsor of this study. It was the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

Role/Title: Respiratory Project Manager, Respiratory Therapeutic Group, Global Regulatory Affairs

Name: PPD

Address: GlaxoSmithKline Research & Development Ltd.

Study Coordination

The MAH contracted with Clinical Practice Research Datalink (CPRD), a research organisation specialising in observational studies and a managing body of the CPRD database, as a partner to provide scientific leadership and to conduct the study. The CPRD conducted the study with review and input from the MAH. A Scientific Committee provided expert medical and epidemiological input and advice, reviewed the interim and final reports and monitored the overall study progress through regular teleconferences and meetings. The responsibilities of the Scientific Committee are further described below.

CPRD:
10 South Colonnade,
Canary Wharf,
London
E14 4PU

STUDY ADVISORY COMMITTEE

The Scientific Committee consisted of epidemiologists and clinicians with expertise in designing observational studies in electronic medical record databases. It consisted of three external members with relevant clinical and epidemiologic experience, as well as two GSK employees, and two representatives from the CPRD. This group assisted with protocol development, developed and review the statistical analysis plan, provided technical input during study development, and assisted with interpretation and dissemination of study results.

The Scientific Committee were convened on a regular basis in association with important study milestones: protocol development, statistical plan approval, annual interim analysis and final study report.

External Members

Prof PPD (Professor, Head of the Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine).

Prof PPD (Professor, Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, The Netherlands)

Dr PPD (Consultant in Chest Medicine and Clinical Senior Lecturer in Respiratory Epidemiology, Imperial College)

CPRD Members

PPD (Senior Researcher, CPRD)

Dr PPD (Observational Research Manager, CPRD)

GSK Members

Dr PPD (Senior Director and Respiratory Therapy Area Lead, GSK)

Dr PPD (Director, Respiratory Epidemiology, GSK)

3 ABSTRACT

Title

Final Study Report: Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting

Keywords

Chronic Obstructive Pulmonary Disease, Electronic Medical Records, Long-acting Beta-2-Agonists, Long-acting Muscarinic Antagonists

Rationale and background

This post authorization safety study primarily aimed to collect data reflecting the 'real-world' experience with umeclidinium/vilanterol (UMEC/VI) and umeclidinium (UMEC) in the post-approval setting. UMEC/VI and UMEC as well as other medications containing only long-acting bronchodilators (LABD) are indicated for the treatment of Chronic Obstructive Pulmonary Disease (COPD). The study fulfils a voluntary commitment made in the European Union – Risk Management Plans (EU-RMP) for UMEC/VI and UMEC to examine the utilisation (including possible off-label prescribing) of these medications in a real-world, post-approval setting.

Additionally, the study aimed to provide descriptive incidence estimates for several potential safety related outcomes among new users of UMEC/VI and UMEC, describe treatment patterns, and estimate adherence to these therapies.

Research questions and objectives

In the initial post-approval period of up to 24 months from the start of UMEC/VI and UMEC availability in the United Kingdom (UK), we identified patients newly prescribed long-acting bronchodilators (LABD) from the Clinical Practice Research Datalink GOLD database (referred to hereafter as CPRD-GOLD) and from The Health Information Network (THIN) database. We conducted a drug utilisation review focusing, on the following objectives:

Objective 1: In new users of UMEC/VI, UMEC, or Other LABD report the proportion of patients with a possible off-label use and characterize them, using information available up to the time of censoring, in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Objective 2: In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality and pneumonia, and rates of exacerbations of COPD during follow-up.

Objective 3: In new users of UMEC/VI or UMEC with 12 or more months of follow-up following initiation, describe treatment patterns and adherence including Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) during follow-up.

Study design

This was a retrospective longitudinal non-interventional observational study of new users of UMEC/VI, UMEC, or Other LABD between July 1, 2014 to June 30, 2016 and followed-up from their index prescription date until censoring at death, leaving practice, or end of follow up on June 30, 2017. New use was defined as never having had a prescription for the same specific active substance ever recorded in the past. Prior or concomitant use of respiratory medications containing a different specific active substance (or combination) than the new substance (or combination) being initiated was allowed. A minimum registration period of at least 12 months prior to index prescription date was required for all new users to allow for a standardised period of history to describe selected patient demographics, disease burden, and previous respiratory medication use. A patient could have contributed information on more than one index new LABD if they met the "new user" definition for more than one medication during the inclusion period of July 1, 2014 to June 30, 2016.

Setting

UK primary care: Clinical Practice Research Datalink (CPRD) GOLD and The Health Information Network (THIN) primary care electronic health record (EHR) databases.

UK secondary care: Linked administrative data on hospital admissions [the Hospital Episode Statistics (HES) Admitted Patient Care (APC) dataset], and death registration information [from the UK Office of National Statistics (ONS)], was available for CPRD GOLD patients registered with a subset of English general practices which participated in the linkage scheme.

Subjects and study size

In CPRD-GOLD, 24,815 unique patients and in THIN, 9,701 unique patients were included. This gave a combined CPRD GOLD +THIN primary care cohort of 34,516 patients, but as patients could qualify for cohort entry for multiple new use index medications, a total of 38,908 new medication starts were recorded (3,875 UMEC, 2,224 UMEC/VI and 32,809 Other LABD).

In the linked primary and secondary care CPRD GOLD-HES ONS cohort there were 10,646 patients. Among these patients, there were 547 new starters of UMEC, 512 of UMEC/VI and 10,590 of Other LABD.

Variables

For Objective 1, study variables included patient characteristics (demographics, disease burden, comorbidities, prior and concomitant respiratory medication use) and possible off-label prescribing, defined as use of UMEC/VI, UMEC or Other LABD in a patient not classified as having COPD.

For Objective 2, potential safety related outcomes included major cardiovascular outcomes [myocardial infarction (MI), stroke and newly diagnosed congestive heart failure (CHF)], respiratory outcomes (pneumonia, COPD exacerbations) and mortality.

These outcomes were identified from primary care records, and where applicable from linked hospitalisation (HES) data. Primary care data, and where applicable links to death registration data (ONS) were used to ascertain deaths from all causes, and from cardiovascular causes. No formal comparison of incidence of these potential safety related outcomes were conducted between the UMEC/VI and UMEC users.

For Objective 3, treatment patterns and adherence to therapy were estimated using primary care prescribing records.

Results

In the combined CPRD GOLD + THIN primary care cohort there were 3,875 new users of UMEC, 2,224 new users of UMEC/VI, and 32,809 new users of Other LABD.

In the linked CPRD GOLD-HES-ONS cohort there were 547 new users of UMEC, 512 new users of UMEC/VI, and 10,590 new users of Other LABD.

Objective 1: Possible off-label use was similar for UMEC (7.0%) and UMEC/VI (8.8%), and higher in new users of Other LABD (18%).

Objective 2: Incidence rates (IR) per 1000 person-years (p-y) of cardiovascular outcomes (MI, stroke and newly diagnosed CHF) in the combined CPRD GOLD+THIN primary care cohort were similar for UMEC and UMEC/VI users: IR of MI was 6.9 (4.4 to 10.2) for UMEC and 6.8 (3.5 to 11.9) for UMEC/VI; IR of Stroke was 30.9 (25.3 to 37.4) for UMEC and 30.5 (22.8 to 39.8) for UMEC/VI; and IR of CHF was 14.8 (10.9 to 19.6) for UMEC and 11.0 (6.5 to 17.4) for UMEC/VI. Rates of pneumonia and acute exacerbations of COPD (AECOPD) were slightly higher among UMEC users compared to UMEC/VI: IR of pneumonia per 1000 p-y was 6.9 (4.4 to 10.2) for UMEC and 3.4 (1.2 to 7.4) for UMEC/VI; the rate of AECOPD per p-y was 0.98 (0.93 to 1.03) for UMEC and 0.75 (0.69 to 0.81) for UMEC/VI. This was consistent with the observed channelling of UMEC + ICS/LABA (inhaled corticosteroids /long-acting beta2-Agonists) to patients with more severe COPD. AECOPD rates tended to be higher among patients taking concomitant ICS at index date, again consistent with this group having more severe disease.

Objective 3: Analysis of treatment patterns during the first 12 months after initiating treatment with UMEC or UMEC/VI suggest that both medications were acceptable and tolerated by the majority of patients. Approximately 20% of patients in both treatment groups switched the index medication for another therapy, and about 12% permanently discontinued the medication.

Adherence was estimated with two different methods. Using the medication possession ratio (MPR) up to the first discontinuation of the drug during the 12 months of follow-up (365 days), an estimated of 64% of UMEC users and 64% UMEC/VI users were classified as adherent (MPR ≥80%). Using the proportion of days covered (PDC) during the 12 months of follow-up (365 days), an estimated of 41% of UMEC users and 33% UMEC/VI users were classified as adherent (MPR ≥80%).

Discussion

There were some differences between the CPRD GOLD and THIN databases in terms of regional distribution of practices, however the characteristics of new LABD users in each database were very similar, meaning they could be combined into a single cohort which provided a large and broadly representative cohort of COPD patients from UK primary care.

Patients characteristics in the three different treatment groups were similar, although compared to new users of UMEC/VI or Other LABD, new UMEC users had more severe respiratory disease and were taking more concomitant respiratory medications, mainly ICS/LABA at index date.

Potential off-label use was low and similar in UMEC and UMEC/VI, and the majority of new users with asthma were taking a concomitant ICS, in line with the clinical guidelines. In contrast, most of the users categorised as without COPD or asthma were not taking an ICS at index date. It is likely that some patients in this group had COPD or asthma, but their diagnosis may have been recorded in free text (which is not available for researchers) rather than diagnosis codes. In others, the diagnosis may be uncertain, and a small number may have been excluded from the COPD because they were aged less than 35 years.

The incidence of cardiovascular outcomes (MI, stroke and newly diagnosed CHF) were similar for UMEC and UMEC/VI users and similar for main and secondary analyses. Rates of pneumonia and COPD exacerbations (AECOPD) were slightly higher among UMEC users compared with UMEC/VI, which is consistent with the observed channelling of UMEC + ICS/LABA to patients with more severe COPD. The use of ICS at index date was not associated with the incidence of pneumonia, but those who used ICS at index had higher rates of AECOPD in both treatments groups, again indicating channelling by severity. Mortality rates were similar among study groups, and they were not associated with the use of ICS at index date.

Despite comparability across cohorts, the rates of pneumonia, exacerbations and mortality were higher in the linked (primary and secondary care) CPRD-GOLD-HES-ONS cohort compared to the combined primary care cohort. Differences in the composition of these cohorts may explain some of these variations. In addition, severe pneumonia and severe AECOPD are more likely to be captured in a hospital setting than in a primary care record, as they are normally treated at hospital level which may not be communicated to the GP. Similarly, mortality is likely to be recorded in the linked ONS death registrations more accurately than in primary care records. However, the concordance of death records between CPRD GOLD and linked ONS death registrations was expected to be high according the literature. One possible explanation for why this was not seen in this study may again be the composition of the cohorts as mortality rates varied substantially between THIN and CPRD databases.

Treatment patterns during the first 12 months after initiating treatment with UMEC or UMEC/VI suggested that both medications were acceptable and tolerated by new users. A third of patients switched or permanently discontinued the medication. At the time of the index prescription, around 65% of UMEC users were taking an ICS/LABA

medication, with the addition of UMEC probably representing a step up in treatment for patients with more severe disease. Around half of patients (52%) continued to take both treatments for at least 12 months, although almost a quarter discontinued UMEC after a single prescription. In contrast, only 22% of UMEC/VI users were receiving concomitant treatment at the index date. Among UMEC/VI users who were not taking concomitant medication, 45% continued to take UMEC/VI for at least 12 months, and a further 25% resumed UMEC/VI after a break of more than 90 days.

Medication adherence in COPD is an important issue for both patients and health care systems. Poor adherence is common and is associated with significant negative impact on morbidity, health care costs, quality of life and mortality. In this study, we used two complementary measures for adherence (MPR and PDC), which can be interpreted differently. Using the MPR-based measure, which considered only patients receiving two or more prescriptions and only the first period of continuous treatment (i.e. ignoring time after discontinuation and any subsequent treatment periods, if applicable), almost two thirds of UMEC and UMEC users had acceptable levels of adherence, as measured by MPR≥80%. The PDC-based measure included all patients with at least one prescription, and it considered the whole 12-month follow up, irrespective of whether patients discontinued treatment during that time. The PDC based estimate suggested that 41% of UMEC users and 33% of UMEC/VI users had medication supply during at least 80% of days in the year after initiating this therapy. Neither measure could account for primary non-adherence because it was not possible to identify prescriptions that were issued but not dispensed.

Conclusions

The combined dataset from CPRD and THIN databases provided a large cohort of COPD patients from UK primary care. Despite differences in the composition of cohorts and between primary and secondary care records, the study population had similar characteristics and was comparable across treatments arms and data sources, although new users of UMEC tended to have more severe COPD. The low levels of possible off-label use for both UMEC and UMEC/VI demonstrate that physicians were prescribing according to the authorised indications for these therapies.

This combined cohort provided reliable estimates for incidence of cardiovascular outcomes, which could be used for planning future comparative studies in similar patient populations. Differences were seen in the rates of pneumonia and AECOPD when ascertained using primary care only, compared with using primary and secondary care, which highlights the need for careful definition of these outcomes in future studies.

We observed that around two thirds of patients starting UMEC were effectively multiple inhaler triple therapy (MITT) users, and this should be taken into account when interpreting the study results and comparing these results to other studies. A significant proportion of UMEC and UMEC/VI users only received one prescription, and further research would be needed to understand these patterns.

In summary, we have provided an assessment of both risks and benefit of UMEC and UMEC/VI in the same study allowing any risks to be placed into context of patients' broader experience with the medicines including healthcare utilisation. This study has illustrated low off-label prescribing rates of UMEC and UMEC/VI compared to other LABD in a primary care UK setting. The incidence of CV events and respiratory outcomes was as expected for these drugs classes, and no new safety signals were observed. As such, the benefit/risk balance of these medications continues to be favourable. Finally, two-thirds of new users of UMEC were adding UMEC as a step-up to MITT, revealing important considerations regarding the study of new users of long-acting muscarinic antagonists (LAMAs) in a real-world setting.

4 AMENDMENTS AND UPDATES

Amendments are described in Section 4 of the protocol (Annex 2).

5 MILESTONES

Milestone	Planned date
Start of data collection	March, 2015
Last day of follow up	June 30, 2017
Registration in the EU PAS register	October, 2014
Interim report 1 of study results (Characteristics of the exposure cohorts, possible off-label prescribing) utilizing data up to index date only	February, 2018
Final report of study results (All objectives)	December, 2019

6 RATIONALE AND BACKGROUND

6.1 Background

Long acting bronchodilators (LABD) including monotherapy long-acting antimuscarinics (LAMA), monotherapy long-acting beta2-agonists (LABA), and combination LAMA/LABA dual therapies including fixed dose-combinations are available for treatment of COPD patients experiencing breathlessness and are most often given to prevent or reduce symptoms [GOLD, 2017]. LAMA and LABA monotherapies demonstrate benefits of improved lung function and health status and have been shown to reduce dyspnoea and COPD exacerbations, with LAMAs having a greater effect on exacerbation reduction than LABA [GOLD, 2017]. LAMA/LABA fixed-dose combinations are a recommended treatment for patients with persistent dyspnoea when treated with monotherapy and as a starting therapy for GOLD group D COPD patients. The combination provides greater benefit on lung function and symptom control then either monotherapy alone.

Prior to 2014, several medications containing LAMA only (glycopyrronium, tiotropium, and aclidinium) and LABA only (salmeterol, formoterol, indacaterol, olodaterol) were approved for COPD treatment in the United Kingdom (UK) along with one fixed dose LAMA/LABA (glycopyrronium/indacaterol). Newer entrants to the market in the LABD class include umeclidinium bromide/vilanterol trifenatate (UMEC/VI) fixed dose LAMA/LABA and umeclidinium bromide (UMEC) LAMA monotherapy which were approved by the European Commission for the treatment of COPD in May 2014 and April 2014, respectively.

The safety and efficacy of mono component LABA and LAMA medications in COPD have been studied extensively; however, with fewer approved fixed dose LAMA/LABA therapies, less is known about their risk/benefit profile in COPD.

There is a potential for off-label prescribing of LABDs alone as a controller medication in asthma, however, this would not be consistent with established guidance by the Global Initiative for Asthma [GINA, 2017]. LABAs are not recommended as monotherapy in asthma, as they do not influence airway inflammation and are potentially associated with a risk of asthma-related deaths [Bateman, 2008; Sears, 2009]. LABAs are most effective in asthma when combined with ICS, and this combination is the preferred treatment when ICS monotherapy fails to control asthma. Only one LAMA, tiotropium, is currently approved as an add on-treatment for asthma for patients who are currently treated with the maintenance combination of ICS and a LABA and who experienced one or more severe exacerbations in the previous year.

6.2 Rationale

In the early post-approval period for UMEC/VI and UMEC, this study aimed to collect data reflecting the 'real-world' experience of new users of LABD in a UK primary care setting. We focused on cohorts of new users of UMEC/VI and UMEC aiming to place the analysis output into context of experience of new users of other LABD. This study fulfils a voluntary commitment made in the European Union – Risk Management Plans (EU-RMP) for UMEC/VI and UMEC to examine the utilisation (including possible off-label prescribing) of these medications in a real-world, post-approval setting.

7 RESEARCH QUESTION AND OBJECTIVES

In the initial post-approval period of up to 24 months from the start of UMEC/VI and UMEC availability in the UK, we identified patients newly prescribed long-acting bronchodilators (LABD) from the Clinical Practice Research Datalink GOLD database (referred to hereafter as CPRD-GOLD) and from The Health Information Network (THIN) database. We conducted a drug utilisation review with the following objectives:

Objective 1: In new users of UMEC/VI, UMEC, or Other LABD report the proportion of patients with a possible off-label use and characterize them, using information available up to the time of censoring, in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Objective 2: In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality and pneumonia, and rates of exacerbations of COPD during follow-up. No formal comparison of incidence of these potential safety related outcomes was conducted between the UMEC/VI and UMEC users.

Objective 3: In new users of UMEC/VI or UMEC with 12 or more months of follow-up following initiation, describe treatment patterns and adherence including Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) during follow-up.

The analyses undertaken were purely descriptive. No formal comparisons of specific groups were undertaken and no inferential statistics were estimated.

8 RESEARCH METHODS

8.1 Study design

This study took a naturalistic approach, capturing routine medical care using a retrospective longitudinal non-interventional observational design. All patients with a record of a new prescription for UMEC/VI, UMEC or Other LABD during the identification period of July 1, 2014 to June 30, 2016 (corresponding with a period up to 24 months of UMEC/VI or UMEC availability to prescribers in the UK) were identified and assessed for eligibility to be included in the study. The index date was the date of new use of UMEC/VI, UMEC or Other LABD prescription that occurred during the inclusion period. The end date of the study was June 30, 2017 (end of inclusion period on June 30, 2016 plus 12 months), thus allowing all patients the potential to contribute at least 12 months of follow-up time.

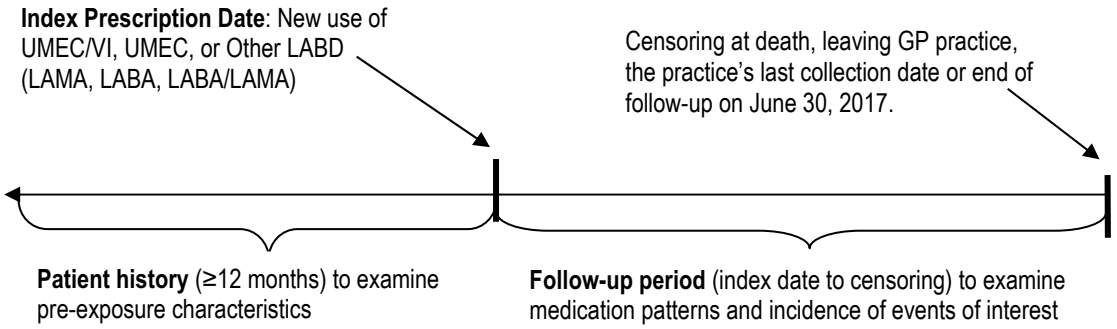
Each patient was followed-up from their index prescription date until their censoring date which was the earliest of the following events:

- death
- leaving general practitioner (GP) practice
- the practice's last collection date
- end of follow-up on June 30, 2017

A minimum period of at least 12 months prior to index prescription date, defined as being registered with the practice for at least one year, was required for all new users to allow for a standardised period of history to describe selected patient demographics, disease burden, and previous respiratory medication use.

The study schematic is provided in Figure 1.

Figure 1 Study Schematic: Individual patient history assessment



A patient could contribute information on more than one index new LABD if they met the "new user" definition for more than one medication during the inclusion period, for example, a patient who was newly prescribed one 'Other LABD' (i.e. glycopyrronium /indacaterol) and then UMEC/VI during the inclusion period contributed information to both the 'Other LABD' and then UMEC/VI cohorts. The Study Protocol contains a full description of the study design, including more detailed information on patient follow-up time through censoring Protocol [**Annex 2**].

8.2 Study population and setting

8.2.1 Main study population

The main study population consisted of new users of UMEC/VI, UMEC or Other LABD with 'acceptable' data quality in the CPRD-GOLD and THIN databases. Patients were labelled as 'acceptable' if they had continuous follow up and did not meet criteria for poor data recording.

Inclusion criteria:

- A record for a new prescription of UMEC/VI, UMEC, or Other LABD between July 1, 2014 and June 30, 2016 (inclusive).
- At least 12 months of registration at a practice with 'up to standard data' recording prior to index prescription date to allow characterization of patient's status, demographics and clinical characteristics. Data were considered 'up to standard' when the GP practice had continuous high-quality data fit for use in research.

Exclusion criteria:

- A prescription for the same specific inclusion medication (or combination) of LABD ever recorded in the past. Prior or concomitant use of respiratory medications containing a different specific active substance (or combination) than the new substance initiated was allowed.

8.2.2 Study cohorts

From the main study populations, four study cohorts were identified:

Cohort 1: CPRD GOLD cohort: all patients in the CPRD GOLD database who were included in the main study population

Cohort 2: THIN cohort: all patients in the THIN database who were included in the main study population.

Cohort 3: Combined CPRD-GOLD and THIN cohort: all patients in Cohort 1 and 2 above. In combining the datasets, the aim was to provide a larger and more representative sample of new users. Analysis conducted for the interim report [GlaxoSmithKline Document Number 2018N357592_00] showed that the two databases were sufficiently comparable to justify combining, and this decision was ratified by the Study Scientific Committee. All main results for study Objectives 1-3 are therefore reported for this combined cohort and not separately for Cohorts 1 and 2.

Cohort 4: Linked CPRD GOLD-HES-ONS cohort: a subset of patients from Cohort 1 above, who were additionally eligible for linkage to both HES and Office of National Statistics (ONS) data. Patients were considered eligible for linkage (irrespective of whether linkage is actually successful) to HES and ONS mortality data if they were registered in practices contributing to the linkage scheme, had a valid NHS number when their identifiers were sent to CPRD's trusted third party (NHS Digital) for linkage; and had not dissented from data transfer to NHS Digital.

Inclusion of linked HES data allowed more complete ascertainment of outcomes which are diagnosed and/or treated in a hospital inpatient setting. Although it is usual practice for general practitioners to receive copies of hospital discharge letters for their patients, these may not always result in a coded entry in the primary care record, and some outcomes may therefore be missing from the primary care data source. Linked ONS mortality data was included to allow ascertainment of all-cause mortality and cardiovascular disease mortality only; it was not used for the ascertainment of other events.

8.2.3 Diagnosis group classification

Patients meeting criteria for entry were classified into diagnosis groups sequentially, based on evidence of a recorded diagnosis of: (a) COPD, (b) Asthma, (c) 'Other' (i.e. neither COPD nor asthma), as described below.

These definitions were applied in a stepwise manner, with the definition of COPD applied first. For those who did not meet the COPD definition, we looked to see if they fulfilled the case definition of asthma. Lastly, patients who met neither the COPD nor asthma definition were captured in the third category of 'Other'.

In the interim analysis submitted in February 2018, the assessment of diagnosis group classification only included data captured in a patient's history up to and including the initiation date of UMEC/VI, UMEC or Other LABD. In this final report, the assessment

of diagnosis group classification included both the time prior to medication initiation and also data captured in the patient record up to the end of the study period.

a) **COPD:** Patients were considered to have COPD if they had a COPD diagnosis recorded any time in their primary care record history up to and including the censoring date and were age 35 years or older at the time of their first COPD medical code.

b) **Asthma:** Patients who did not fulfil the case definition of COPD as described above were considered to have asthma if they had at least one medical code for asthma recorded any time in their primary care record history up to and including the censoring date.

c) **Neither COPD nor asthma ('Other'):** Patients were classified into this category if they did not meet either the definition of COPD or asthma above.

8.2.4 Exposure definitions

8.2.4.1 New users (UMEC/VI, UMEC or Other LABD)

We identified all new users of UMEC/VI, UMEC or Other LABD during the period of July 1, 2014 and June 30, 2016 inclusive. New use was defined as never having had a prescription for the same specific active substance ever recorded in the past. The first day of the first qualifying new use prescriptions was the index date. Prior or concomitant use of respiratory medications containing a different specific active substance (or combination) than the new substance (or combination) being initiated was allowed. A single patient could contribute more than one qualifying index medication during the study if they met the definition of new use for multiple LABD medications.

Other LABD included - but was not limited to - medications containing: tiotropium, glycopyrronium, glycopyrronium/indacaterol, aclidinium, indacaterol, salmeterol, olodaterol, and formoterol, according to the availability. The Other LABD group was stratified as LAMA, LABA, and LAMA/LABA. No drugs in the Other LABD group were analysed individually. The new use of ICS/LABA combinations in a single device was not considered as new Other LABD unless it was accompanied with a new prescription for LAMA. New users of LAMA/LABA were included in the other LABD group if they received a prescription for either a fixed dose combination therapy, or an open combination, defined as a prescription for both LAMA and a LABA on the same date.

All individual prescriptions of UMEC/VI, UMEC or Other LABD were assigned a default length of 30 days per container prescribed irrespective of whether they had a recorded value for script length.

Note: GP prescriptions were used as proxy for pharmacy dispensing, for which records were not available. It is known that for a variety of reasons a proportion of prescriptions are not dispensed [Gadkari, 2010].

8.2.4.2 Concomitant use of other respiratory maintenance medications at index date and during follow up

Given the naturalistic nature of the study design, some patients could have initiated UMEC/VI, UMEC or Other LABD while on other respiratory medications. In some instances, these patients may have been transitioning from the old medication to the new one with a small overlap. In other cases, they may have continued to take both medications for a longer period of time.

We searched the patient record and flagged instances when the patients were receiving concomitant respiratory maintenance therapy at the time of the index prescription. Concomitant therapy was defined as at least two continuous prescriptions for the other respiratory therapy which started either before, or up to 30 days after the index date, and overlapped for at least 30 days with the index treatment.

8.2.5 Follow up period and person-time

For Objective 2, new users of UMEC/VI and UMEC were followed from their index date until their censoring date for disease outcomes. Person-time during follow-up was classified in several exposure categories, described below:

8.2.5.1 Current exposure to UMEC/VI or UMEC:

Current exposure was defined as person-time starting from the index date and continuing until the earliest of the censoring date or discontinuation date. Discontinuation was considered to have occurred if there was either:

- A break of at least 91 days between prescriptions. The discontinuation date was set at 30 days after the prescription before the break.

  or

- Complete cessation in prescribing of the index medication. The discontinuation date was set at 30 days after the final prescription.

Using this definition, it was not possible to determine whether a patient discontinues UMEC or UMEC/VI if they were censored between 31 and 90 days after their last prescription. In such cases a conservative approach was taken, and current exposure was assumed to end 30 days after their last prescription.

If a patient discontinued the index medication but resumed taking that medication at a later date, the second exposure period was considered within the "currently exposed" person-time.

8.2.5.2 Follow up time while not currently exposed to UMEC/VI or UMEC:

Among new users of UMEC/VI and UMEC who discontinued the index medication, all person-time from the discontinuation date up to the censoring date, or up to the date of

resumption of the index medication (if applicable), was classified as not currently exposed.

8.2.5.3 Concurrent treatment with other respiratory maintenance medications while currently exposed to UMEC/VI or UMEC

Among new users of UMEC/VI or UMEC only, we identified periods of concurrent treatment with other respiratory maintenance treatment, while the patient was currently exposed to the index medication. Concurrent treatment periods were defined as two or more continuous prescriptions (i.e. separated by no more than 90 days) which overlapped with the period during which the patient was currently exposed to index medication.

Respiratory maintenance treatments included in the concurrent use category were inhaled therapies used for COPD and/or asthma, and containing one or more of ICS, LABA, LAMA, or theophylline.

8.2.6 Outcome definitions

All codes and detailed algorithms were reviewed by a clinician, agreed with the study Scientific Committee, and summarised in the detailed statistical analysis plan. The COPD code list [**Annex 4.1**] was based on a validated list of medcodes published by a UK-based consultant in chest medicine, Dr. Jennifer Quint [Quint, 2014]. The asthma codelist [**Annex 4.2**] was developed as part of an asthma validation study [Nissen, 2017].

8.2.6.1 Objective 1

In new users of UMEC/VI, UMEC, or Other LABD report the proportion of patients with possible off-label use and characterize them, using information available up to the time of censoring, in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Possible off-label prescribing

UMEC/VI and UMEC as well as other medications containing only long-acting bronchodilators (LABD) (i.e. without an ICS) are indicated for the treatment of COPD only. Therefore, the primary off-label prescribing definition was defined as prescribing of UMEC, UMEC/VI or Other LABD (excluding specific treatment combinations specified below in definitions 2 and 3) in patients without evidence of COPD in their primary care record (i.e. a relevant diagnosis code). A secondary definition, applied to the Other LAMA subgroup only, was used to account for the authorisation in September 2014 of tiotropium as an add on therapy to ICS/LABA for the treatment of asthma in patients with asthma exacerbations. A third definition was employed for new users of other LABD only to account for the fact that LABA plus an ICS in two devices (i.e. open combination) might be an option utilized to treat asthma.

- **Off-label prescribing definition 1**: prescribing in patients without evidence of COPD in their primary care record, at any time up to and including their censoring date;
- **Off-label prescribing definition 2 (only for the Other LAMA subgroup):** prescribing in patients without evidence of COPD in their primary care record but

excluding patients with evidence of asthma who entered the study on or after 13/09/2014 with an index prescription for 2.5mcg tiotropium AND a concurrent prescription for ICS/LABA.

- **Off-label prescribing definition 3 (only for the Other LABA subgroup):** prescribing in patients without evidence of COPD in their primary care record but excluding patients with evidence of asthma who entered the study with an index prescription for other LABA AND were receiving concomitant ICS at index date. This definition was added following analyses conducted for the interim report and approved by the Study Scientific Committee.

Description of new users

The following variables were defined to describe characteristics of new users of UMEC/VI, UMEC and Other LABD separately.

Demographic variables

- Age at index prescription
- Gender
- Smoking status (current, ex-smoker, no/never smoker, missing)
- Body mass index (BMI, kg/m^2)
- Area based deprivation: based on quintiles of Townsend score, calculated at lower super output area (LSOA) level using data from the 2001 Census. This information was only available for the linked primary and secondary care CPRD GOLD-HES-ONS cohort.

Disease burden variables

- Acute exacerbations of COPD (AECOPD) in the 12 months prior to the index date were identified and presented as a count, with categories (0,1, 2+), and as a rate per person-year) with 95% confidence intervals (CI). In all cohorts, 'moderate COPD exacerbations' were identified using primary care data only. In the linked primary and secondary care CPRD GOLD-HES-ONS cohort only, a second variable ('moderate and severe COPD exacerbations') was generated using primary care records and the linked secondary care (HES) data to identify additional, severe exacerbations which resulted in hospitalisation. AECOPD counts were estimated for all patients irrespective of whether they had a COPD diagnosis.
- Dyspnoea was identified based on medical codes for Medical Research Council (MRC) Dyspnoea Scale grades 1-5. The number and proportion (%) of patients in each group, or with a missing value, and the mean and standard deviation (SD) MRC grade was reported, based on the nearest value taken prior to index date.

- COPD severity was also characterised on the basis of airflow limitation as measured by lung function test (spirometry), taking the most recent available result in the 24 months prior to index date. Two lung function parameters were used:

  1. The forced expiratory volume in one second (FEV_1) was estimated and expressed as percent of predicted was reported as mean (SD), and in categories defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of airflow limitation [GOLD, 2017] using cut points of:

     - FEV_1 ≥80% predicted for mild Grade 1
     - ≥50% to <80% FEV_1 predicted for moderate Grade 2
     - ≥30% to <50% FEV_1 predicted for severe Grade 3
     - <30% FEV_1 predicted for very severe Grade 4 or missing.

     The count and percent of patients in each category was reported. The nearest FEV_1 measurement value taken prior to index date was used.

  2. FEV_1 as a proportion of Forced Vital Capacity (FEV_1/FVC) was expressed as mean percentage (with SD), and as a binary categorical variable based on a threshold of 70%.

Comorbidity variables

History of key comorbid conditions from diagnosis records were based on the presence of specific codes in the patients' history at any time prior to the index date. Conditions identified were:

- cardio-and cerebrovascular diseases
- beta blocker prescribing (in the year prior to the index date only)
- pneumonia
- gastroesophageal reflux disease
- diabetes
- renal disease (acute and chronic)
- cancer

Prior use of COPD or asthma medication variables

- Prior use was defined as receiving one or more prescriptions for other respiratory therapies (classified according to categories in Table 1) within the 12 months prior to index date.

Table 1 Categories of COPD and asthma medications

Category	Description
SABD	Short-Acting Beta2-Agonist (SABA), Short-Acting Anticholinergic (SAMA), Fixed Combinations of SABA/Cromoglycate, Fixed Combinations of SABA/SAMA
ICS and ICS/SABA*	Inhaled Corticosteroids OR Fixed Combination of Short-Acting Beta2-Agonist and Inhaled Corticosteroid
LABA*	Long-Acting Beta2-Agonists
ICS/LABA*	Fixed Combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist OR Open combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist in two devices (LABA script overlaps with ICS by at least one day)
LAMA*	Long-Acting Anticholinergics
LAMA/LABA*	Fixed Combination of Long-Acting Beta2-Agonist along with a Long-Acting Anticholinergic OR Open combination of Long-Acting Beta2-Agonist and Long-Acting Anticholinergic in two devices (LABA script overlaps with LAMA by at least one day)
Theophylline*	Theophylline and its derivates
Oral corticosteroids	Only "chronic use" defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days.

*Medications explored also as concomitant maintenance medications (See Section 8.2.4.2 for definition of concomitant maintenance therapy use)

8.2.6.2 Objective 2

In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality and pneumonia, and rates of exacerbations of COPD during follow-up.

For the enumeration of counts and incidence of potential adverse events among, the following outcomes were defined for new users of UMEC/VI and UMEC:

Cardiovascular Outcomes

Myocardial infarction (MI): a new occurrence of a diagnosis code for MI in the primary care record or linked HES data (where applicable) after the index date, including those with prior history of MI. All MI event records within seven days of each other were considered to be part of the same episode. For incidence calculations, only the first MI event after index date was considered; however, for total event counts first and all subsequent events were considered.

Stroke: a new occurrence of a diagnosis or administrative code for stroke (including transient ischaemic attack [TIA]) in the primary care record or linked HES data (where applicable) after the index date, including those with prior history of stroke. All stroke event records occurring within seven days of each other were considered to be part of the same episode. For incidence calculations, only the first stroke event after index date was considered. For total event counts, first and all subsequent events were considered.

Congestive heart failure (CHF): a **first** occurrence of a diagnosis code for CHF in the primary care record or linked HES data (where applicable), occurring after the index date, among patients with no prior history of CHF. For analyses using linked CPRD data, the earliest record of CHF in either source was selected. Patients with prior history of CHF at index date were excluded from the denominator due to the high potential to misclassify acute worsening of heart failure with an acute exacerbation of COPD in an EMR database [Valk, 2015]. Note: for MI and stroke calculations, those with prior history were included in the calculations.

Respiratory outcomes

Pneumonia: a new occurrence of a diagnosis code for pneumonia in the primary care record or linked HES data (where applicable). All pneumonia event records occurring within 28 days of each other were considered to be part of the same episode. For incidence calculations, only the first pneumonia event after index date was considered. For total event counts, first and all subsequent events were considered

Acute exacerbation of COPD (AECOPD): AECOPD episodes were identified using a validated algorithm [Rothnie, 2016a and Rothnie, 2016b]. As well as specific AECOPD diagnosis codes, the algorithm uses information on lower respiratory tract infections (LRTI) and related respiratory symptoms, and prescriptions for antibiotics (ATB) and/or oral corticosteroids (OCS) occurring around the same time. For the linked primary and secondary care CPRD GOLD-HES-ONS cohort, the algorithm also used linked HES data. AECOPD event records occurring within 14 days of each other were considered to be part of the same episode. First and all subsequent AECOPD episodes were considered in event rate calculations and event counts. AECOPD event rates with 95% confidence intervals, rates were calculated as total (i.e. first and all subsequent) exacerbation events divided by the relevant person-time. AECOPD events were ascertained for all patients irrespective of whether they had a COPD diagnosis. Cautious interpretation of AECOPD event rates is recommended for patients without a COPD diagnosis; however, the significance of such events in these patients is not clear.

Mortality

Deaths from any cause: deaths from any cause were identified in the primary care record, and additionally using death registration data in the linked primary and secondary care CPRD-HES-ONS cohort only.

Cardiovascular deaths: deaths from cardiovascular disease can only be reliably identified from death registration information and were therefore only considered in the linked CPRD-HES-ONS cohort.

8.2.6.3 Objective 3

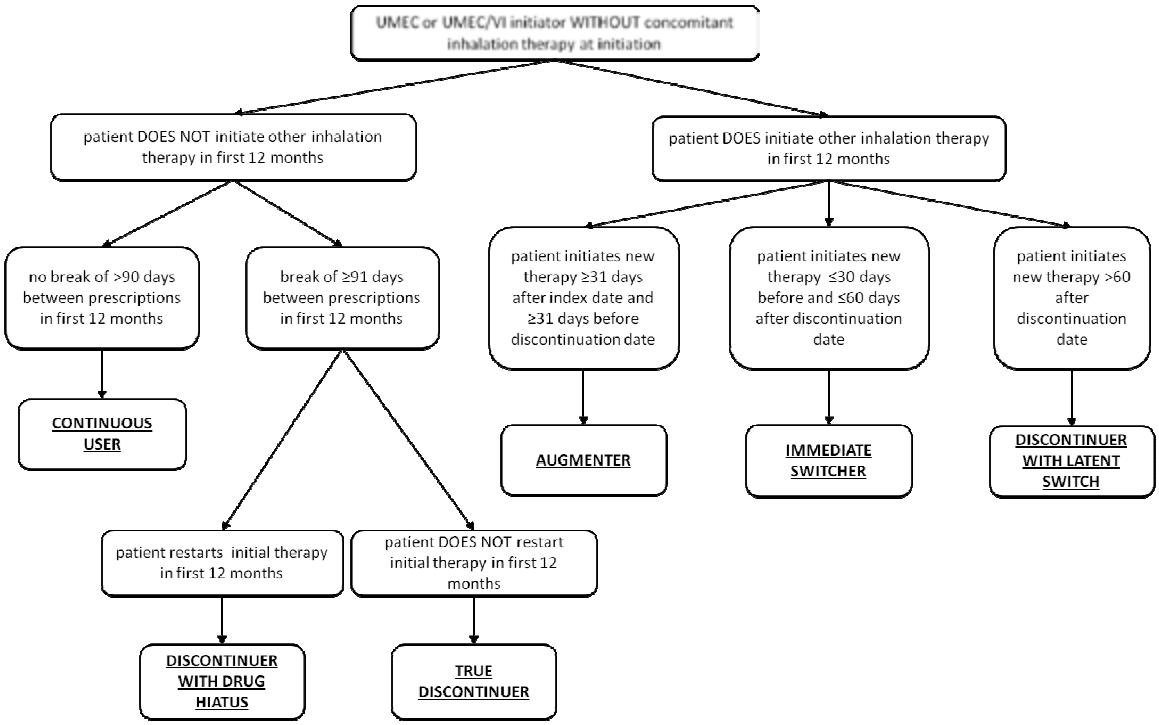
In new users of UMEC/VI or UMEC with at least 12 months of follow-up following initiation, describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered within the first 12 months of follow-up.

Treatment patterns during follow-up:

New users of UMEC and UMEC/VI were classified into mutually exclusive treatment pattern groups based on prescription records. Only the first change during the 12-month follow-up period following the index prescription date was considered. Treatment patterns were not considered in patients who were censored between 31 and 90 days after their last prescription as it was not possible to determine whether these patients discontinued their index treatment.

For patients who were not taking a concomitant COPD (inhalation) maintenance therapy at the index date, six mutually exclusive patterns were defined (shown in Figure 2):

Figure 2 Algorithm for identifying mutually exclusive treatment patterns in patients not taking a concomitant COPD maintenance therapy at index date



Treatment pattern 1: Continuous User: Patient DID NOT start taking another inhaled COPD maintenance therapy and continued to use index treatment throughout the 12 months after the index date.

Treatment pattern 2: Augmenter: Patient started taking another inhaled COPD maintenance therapy (1 or more prescriptions) at least 31 days after the index date and at least 31 days before the discontinuation date for the index treatment or end of 12 months following the index date. The augmentation date was defined as the date of first prescription for the new COPD maintenance therapy. Note: for patients who qualified for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication was considered to be a switch and not an augmentation. This was in line with the decision to allow patients to enter the study separately for UMEC and UMEC/VI (i.e. they are considered as separate products).

Treatment pattern 3: Immediate Switcher: Patient started taking another inhaled COPD maintenance therapy (1 or more prescriptions) within 12 months of the index date, and the new treatment started between 30 days before and 60 days after the discontinuation date for the index treatment. The switching date was defined as the date of first prescription for the new COPD maintenance therapy. Note: for patients who qualified for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication was considered a switch as described above.

Discontinuer: Patient meets the definition of discontinuation as defined in Section 8.2.5.1 prior to 12 months after the index date and does not meet the definitions for continuous use, immediate switching and augmentation above. The discontinuation date was as defined in Section 8.2.5.1.

In addition, patients who discontinued the index medication were further followed until 12 months after the index date, and an additional sub-classification was applied:

Treatment pattern 4: 'True discontinuer': patient discontinued and did do not restart the index medication and did not start a new inhaled COPD maintenance treatment.

Treatment pattern 5: 'Discontinuer with drug hiatus': patient discontinued by resumes treatment with the index medication after a gap of at least 61 days from the discontinuation date.

Treatment pattern 6: 'Discontinuer with latent switch': patient discontinued and started a new inhaled COPD maintenance treatment more than 60 days after discontinuation of the index medication. Note: for patients who qualify for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication will be considered a latent switch based on the rationale described earlier.

For patients who were taking a concomitant COPD (inhalation) maintenance therapy at index date, the following patterns were defined:

Treatment pattern 1: Continuous use of both drugs: Patient continued to use both medications for 12 months from the date of index treatment until censoring.

Treatment pattern 2: Discontinuation of index drug only: Patient discontinued the index drug within 12 months of the index date but continued to use the concomitant therapy. The discontinuation date (see Section 8.2.5.1) was therefore the date the index drug stopped.

Treatment pattern 3: Discontinuation of concomitant drug only: Patient discontinued the concomitant therapy within 12 months of the index date but continued to use the index drug. The discontinuation date (see Section 8.2.5.1) was therefore the date the concomitant drug stopped.

Treatment pattern 4: Discontinuation of both drugs: Patient discontinued both drugs *on the same day* and within 12 months from the index. Discontinuation date (Section 8.2.5.1) was therefore the date that both treatments were discontinued.
Further details on Treatment pattern definitions are included in **Annex 3**.

Adherence to index medication

Treatment adherence was assessed during the first 12 months following the index UMEC/VI or UMEC prescription. Patients with less than 12 months of follow up were excluded. Two complementary measures of adherence - medication possession ratio (MPR), and proportion of days covered (PDC) - were calculated. Key differences in the two measures are summarised in Table 2.

Medication possession ratio (MPR), estimates how much medication was available to a patient *during the first period of continuous use of the medication*, defined by the date of the first and last prescriptions during the first period of continuous use.

MPR was calculated for patients with at least 12 complete months of follow-up and *at least two prescriptions* for the index medication during the first period of continuous use, as follows:

$$MPR = \frac{\text{(Number of days' supply between index and last prescription)}}{\text{(Total number of days between index date and last prescription date)}}$$

Where number of days' supply was calculated by multiplying the number of prescriptions issued in the period (not including the last prescription) by the assumed duration of 30 days and using the date of last prescription issued before end of follow-up or first discontinuation date (where applicable).

The MPR was expressed as a percentage, with nonadherence defined as MPR <80% and adherence defined as MPR ≥80%. Note that patients could receive a medication supply which exceeded the amount of available follow up, and the MPR could therefore exceed 100%.

Proportion of days covered (PDC), estimates the proportion of days in year after the index date in which the patient was 'covered' i.e. had medication available.

PDC was calculated for patients with at least 365 days of follow-up from the index date, as follows:

$$PDC = \frac{\textit{(Number of days 'covered' between index and end of follow up)}}{\textit{(365 days)}}$$

Where number of days 'covered' by prescriptions was calculated by multiplying the number of prescriptions (at any dose) in the period - *including* the last prescription - by the assumed duration of 30 days. All prescriptions issued during fixed coverage period (365 days) were included, but the total number of days covered was capped at 365, (because each day in the period can only be covered or not covered). Patients with a single prescription of the index medication were included in the PDC calculation.

PDC was expressed as a percentage. The minimum possible value for PDC was 8% (i.e. one index prescription lasting 30 days), and the maximum was 100% (i.e. medication available every day for the 365 day follow up period). PDC was also dichotomised, with nonadherence defined as PDC <80% and adherence defined as PDC ≥80%.

Table 2 summary and comparison of methods for calculating medication possession ratio (MPR), and proportion of days covered (PDC).

	Medication possession ratio (MPR)	Proportion of days covered (PDC)
Patient inclusion criteria	At least 12 m of follow up. *At least two* prescriptions.	At least 12 m of follow up. *At least one* prescription.
Observation period	Variable: *first* period of continuous use only.	Fixed: 12 m from index date
Prescription inclusion criteria	*Last prescription* during the observation period is *excluded*	*All prescriptions* during observation period are *included*
Prescription duration	Fixed: 30 days	Fixed: 30 days
Numerator definition	Number of prescriptions x duration	Number of prescriptions x duration
Denominator definition	Variable: number of days from first to last prescription during the first period of continuous use.	Fixed: 365 days
Capped at 100%	No	Yes

8.2.7 Confounders and effect modifiers

The confounders and effect modifiers variables have been described above in Section 8.2.6. As this was a descriptive study, no adjustment for confounding was made.

8.3 Data sources

Primary care data

CPRD GOLD serves as the main primary care database for development and benchmarking of analyses. It contains data extracted from Vision Patient Record Management software and includes anonymised longitudinal electronic health records (EHR) of patients registered with contributing primary care practices across the UK. As of August 2018, there were 740 GP practices and 15.5 million acceptable (research quality) patients in GOLD, of which 4.3 million were currently registered at the start of the study accrual period on 01 July 2014. Data has been collected from GP practices since 1987. Further detail on CPRD GOLD is provided in the Study Protocol [**Annex 2, Document 1**].

The Health Improvement Network (THIN) database is a collaboration between two companies: In Practice Systems (INPS) - who developed Vision software used by general practitioners (GPs) in the UK to manage patient data; and IQVIA who then provide access to the data for use in medical research. THIN data currently contains the electronic medical records of 11.1 million patients collected from 562 general practices in the UK, covering 6.2% of the UK population. All data are fully anonymised, processed and validated by CSD Medical Research UK (THIN, 2017). Some general practices had contributed data to both the CPRD GOLD and THIN databases. All data from these practices were maintained in CPRD GOLD and excluded from the THIN data extract to avoid double counting.

Linked Hospital Episodes Statistics Admitted Patient Care (referred to as HES)

HES contains details of episodes of care delivered by (or on behalf of) the NHS, to patients admitted to hospitals in England. A wide range of information is recorded including clinical information about diagnoses (up to 20 per episode, coded using International Classification of Diseases, Tenth Revision (ICD-10), and operations or procedures (up to 24 per episode, coded using OPCS Classification of Interventions and Procedures version 4 (OPCS-4); patient information (age group, gender and ethnicity); and administrative information, including dates and methods of admission and discharge. Data included in for this study covered admissions between 01 April 1997 and 31 December 2017.

Linked Death Registrations from ONS

The linked death registrations include information derived from death certificates of all deaths registered in England, including date of death, and underlying and contributory causes of death (coded using ICD-10). Data included in this study covered deaths registered between 02 January 1998 and 13 February 2018.

Linkage mechanism

HES and ONS death registrations data were linked to CPRD GOLD primary care records of patients from 411 English general practices using a multistep deterministic algorithm, based on an exact match of NHS number plus at least one or more of gender, postcode of residence, date of birth (full or partial). The linkage was undertaken by NHS Digital which acted as a 'trusted third party' for CPRD and held the linkage identifiers for all three datasets.

Description of validated diagnoses

All code lists [**Annex 4.1** and **Annex 4.2**] for this report were agreed with GSK and CPRD, reviewed with the Scientific Committee, and are summarised in the detailed statistical analysis plan. Where possible previously validated and published code lists were used, including: COPD diagnosis [Quint, 2014]; COPD exacerbations [Rothnie, 2016a and Rothnie, 2016b]; asthma diagnosis [Nissen, 2017]. Further detail on data sources used are provided in the Study Protocol [**Annex 2, Document 1**].

8.4 Study size

The three objectives of this study are descriptive in nature. Hence, we did not propose a formal hypothesis-driven specification of sample size.

Assuming 5% of patients used UMEC or UMEC/VI off-label, we needed a sample size of 1,000 new users in each group to produce a 95% confidence interval equal to the sample proportion plus or minus 1.3% (Confidence interval of a proportion).

In CPRD-GOLD, 24,815 unique patients were included in the final analysis, but as patients could qualify for cohort entry for multiple new use index medications, a total of 27,956 new medication starts were recorded (2,486 UMEC, 1,645 UMEC/VI and 23,825 Other LABD).

In THIN, 9,701 unique patients were included in the final analysis, but as patients could qualify for cohort entry for multiple medications, a total of 10,952 new medication starts were recorded (1,389 UMEC, 579 UMEC/VI and 8,984 Other LABD).

8.5 Data management

8.5.1 Data transformation (data handling conventions)

Data was collected retrospectively from CPRD GOLD and THIN. All programming was performed using Stata (StataCorp. College Station, TX).

8.5.2 Resourcing needs

GSK outsourced this study to CPRD. GSK have closely collaborated and monitored the deliverables including finalization of the study protocol, statistical analysis plan and the study report.

8.6 Data analyses

The analysis of exposure cohorts (Section 8.6.1.2) was repeated for all four cohorts i.e. CPRD GOLD; THIN; combined CPRD GOLD + THIN primary care cohort; and linked primary and secondary care CPRD GOLD-HES-ONS cohort. This allowed an assessment of the similarity of the CPRD GOLD and THIN data with respect to patient characteristics prior to conducting analysis on the pooled dataset (CPRD GOLD+THIN).

All other analyses were conducted using the combined CPRD GOLD + THIN primary care; and linked primary and secondary care CPRD GOLD-HES-ONS cohorts.

GSK obtained from CPRD a class exemption for the masking of cells with less than 5 events for this regulatory submission report (Jan 2019).

This version of the report cannot be disseminated beyond the GSK internal reviewers and external regulatory reviewers. Small cell counts (<5) must be suppressed (with secondary suppression as necessary to protect small cell counts) if the GSK or regulators wish to publish or disseminate results in the interest of transparency.

8.6.1 Describing the participants

8.6.1.1 Diagnosis groups

Patients in each defined exposure category (UMEC/VI, UMEC, or Other LABD) were split into the three pre-defined disease categories of 1) COPD, 2) asthma, and 3) "Other" (neither COPD nor asthma) (see Section 8.2.3 for definitions) and frequencies tabulated.

8.6.1.2 Exposure cohorts

The number (%) of new users in the UMEC, UMEC/VI and Other LABD exposure cohorts was described separately with the Other LABD group further characterized as LABA, LAMA, or LAMA/LABA.

The number (%) of patients contributing more than one index drug was described, and for these patients, mean (SD) time in days between the discontinuation date of the first index medication and the index date of the subsequent medication (in cases where the two index medications do not overlap) or the mean (SD) time during which the two index medications overlap (in cases where the medication do overlap).

The number (%) of UMEC and UMEC/VI users taking concomitant maintenance therapy at the index date (See Section 8.2.4.2 for definition) was calculated and the type of concomitant drug described.

Other baseline characteristics of the exposure cohorts including respiratory disease burden, co-morbidity and previous use of COPD and asthma medication (see Section 8.2.6.1), were summarised using counts and proportions for categorical variables and mean (SD) for continuous variables.

8.6.2 Essential analyses

8.6.2.1 Objective 1

In new users of UMEC/VI, UMEC, or Other LABD report the proportion of patients with possible off-label use and characterize them, using information available up to the time of censoring in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Ascertainment of possible off-label prescribing

Off-label prescribing of UMEC, UMEC/VI or Other LABD using definition 1 was calculated as follows (expressed as a percentage):

- % Off-label prescribing (UMEC) =

$$\frac{\text{\# of new UMEC users with Asthma or 'other' indication}}{\text{\# UMEC new users}}$$

- % Off-label prescribing (UMEC/VI) =

$$\frac{\text{\# of new UMEC/VI users with Asthma or 'other' indication}}{\text{\# UMEC/VI new users}}$$

- % Off-label prescribing (Other LABD excluding LAMA or LABA) =

$$\frac{\text{\# of new Other LABD users with Asthma or 'other' indication}}{\text{\# Other LABD new users}}$$

[Calculated separately for LAMA, LABA or LAMA/LABA]

- % Off-label prescribing definition 2 (Other LAMA only) =

$$\frac{\text{\# of new Other LAMA users with Asthma or 'other' indication minus \# with asthma indication taking tiotropium after 13/09/2014 along with a concomitant ICS/LABA}}{\text{\# Other LAMA users}}$$

- % Off-label prescribing definition 3 (Other LABA only) =

$$\frac{\text{\# of new Other LABA users with Asthma or 'other' indication minus \# with asthma indication taking concomitant ICS}}{\text{\# Other LAMA users}}$$

New user demographic and clinical characteristics

Demographic characteristics of the UMEC, UMEC/VI and Other LABD cohorts at baseline were presented using the variables described in Section 8.2.6.1. Characteristics were summarised as mean (SD) and median (interquartile range [IQR]) for quantitative variables and number and proportion (%) for categorical variables. The numbers and proportion of patients with missing observations for each variable were reported where applicable.

The COPD disease burden of the UMEC, UMEC/VI and Other LABD cohorts at baseline were presented according to the variables described in Section 8.2.6.1. The number of COPD exacerbations during the year prior to the index date was summarised as a mean rate (per person-year) with 95% confidence interval, and as the number and proportion of patients with 0, 1 or 2+ exacerbations.

The history of comorbidities (see Section 8.2.6.1) recorded in primary care, by index LABD group was described with count and percentage.

Lastly, respiratory medications (see Section 8.2.6.1) ever used in year prior to index date was described with count and percentage.

8.6.2.2 Objective 2

In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality and pneumonia, and rates of exacerbations of COPD during follow-up.

Primary and secondary analyses were repeated in the combined CPRD GOLD + THIN primary care cohort, and in the linked primary and secondary care CPRD GOLD-HES-ONS cohort. Cardiovascular death outcomes were only considered in the linked cohort.

All analyses were conducted separately among new users of UMEC/VI and UMEC.

Primary analyses

In the patients' available history prior to the index prescription. For incidence rates with exact Poisson 95% confidence intervals (CI), only the first occurrence after index date was considered, with follow up censored at this point.

For congestive heart failure (CHF), outcomes were only evaluated among patients with no history of CHF prior to index date.

For cardiovascular outcomes (MI, stroke, CHF), analyses were stratified according to concomitant use of beta blockers at index date.

For COPD exacerbations, incidence was based on total (i.e. first and subsequent) events and used all available person time. Incidence and 95% confidence intervals were calculated using negative binomial regression to account for additional inter-individual variation in baseline risk.

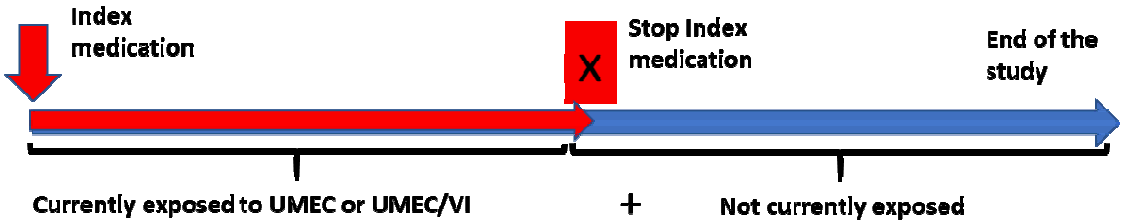
For all outcomes, time to first occurrence was visualised using Kaplan-Meier plots.

Secondary analyses

Two secondary analyses were undertaken:

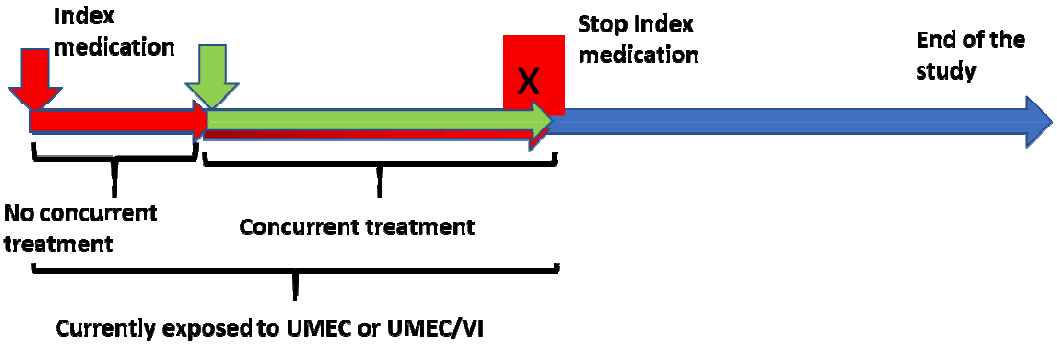
1. All primary analysis was repeated but including all outcome events and person-time during follow-up classified as *currently **AND** not currently exposed to UMEC or UMEC/VI* (see Section 8.2.5.2 and Figure 3).

Figure 3 Follow-up time of currently AND not currently exposed to UMEC or UMEC/VI (*Intention to treat analysis*)



2. Primary analysis was repeated but with further stratification of person-time during follow-up classified as currently exposed to *UMEC or UMEC/VI, according to concurrent exposure to other COPD maintenance therapy* (see Figure 4). For these analyses, stratification by concomitant ICS containing medication at index date was not undertaken.

Figure 4 Follow-up time of currently exposed to UMEC or UMEC/VI *with* other concurrent treatment



8.6.2.3 Objective 3

In new users of UMEC/VI or UMEC with at least 12 months of follow-up following initiation, describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered within the first 12 months of follow-up.

Primary analyses

All analyses were conducted in the combined CPRD GOLD + THIN primary care cohort. The number and proportion of patients in each treatment pattern group was presented, along with the mean and standard deviation of the time (in days) from the index date to

the first change, if observed. Analyses were conducted separately in new users of UMEC and UMEC/VI, and with and without concomitant use of another inhaled maintenance therapy at index date. Time to first treatment change was visualised in each of the four groups using Kaplan-Meier plots.

The mean and standard deviation of the MPR and PDC was estimated, as well as the number and proportion of patients classified as adherent, based on MPR and PDC thresholds of ≥80%. Baseline characteristics of patients classified as adherent and non-adherent were summarised using means (SD) and proportions.

8.6.3 Exploratory Analyses

8.6.3.1 Objective 1

Not applicable

8.6.3.2 Objective 2

Using the combined primary care CPRD GOLD + THIN primary care cohort, and the linked primary and secondary care CPRD GOLD-HES-ONS cohort, all analyses set out in Section 8.6.2 except the stratification by concomitant ICS prescribing at baseline were repeated with a further stratification according to on-label or possible off-label use of UMEC and UMEC/VI.

8.6.3.3 Objective 3

Using the combined CPRD GOLD + THIN primary care cohort, analysis of treatment patterns, and adherence was repeated separately for patients with on-label and possible off-label use of UMEC and UMEC/VI.

8.6.4 General considerations for data analyses

All analyses were descriptive in nature, using summary statistics where applicable. No formal comparisons between specific groups, for example between new users of UMEC and UMEC/VI were undertaken and no inferential statistics such as p-values or effect estimates are presented.

Where data were missing, the numbers of patients with missing data were reported.

For rate calculations, 95% confidence intervals were calculated throughout, corresponding to a significance level of 0.05.

8.6.5 Amendments to the statistical analysis plan

The following amendments to the statistical analysis plan were made:

- Measures of area level deprivation (Townsend 2001 quintiles) were not available in the THIN data provided for the final report.

- **Off-label prescribing definition 3 (for the Other LABA subgroup only): see Section 8.2.6.1.** The decision to add this definition was taken following analyses carried out for the interim report and ratified at a meeting of the Study Scientific Committee.
- **Calculation of proportion of days covered (PDC): Section 8.2.6.3**. For the PDC numerator definition of number of days 'covered' by prescriptions, the last prescription during the 12-month follow up was *included* in the calculation. This corrected an error in the Protocol and Statistical Analysis Plan [**Annex 2, Document 1 and 2, p49**] which specified that the last prescription should be *excluded* from the calculation.

8.7 Quality control and quality assurance

CPRD-GOLD has been used previously for descriptive drug utilisation studies for prescription medications in respiratory diseases [Dedman, 2019; DiSantostefano, 2014; Ashworth, 2004].

The standard operating procedures of CPRD include internal quality audits; following rules for secure storage and backup of confidential data and study documentation; quality control procedures for programming, and requirements for senior scientific review. All patients are required to have data of acceptable research quality according to CPRD standards.

The QC of analysis has been performed in accordance with GSK Standard Operating Procedures (SOPs) and Guidance Documents, specifically the SOP_52213 (4.0): Conducting Quality Control Review of Worldwide Epidemiology Study Results. The common data model allowed the use of one set of programming following creation of a standardised structure. All statistical programming was independently reviewed by a second analyst. Key study documents, such as the protocol for obtaining study approval from the Independent Scientific Advisory Committee ('ISAC Protocol'), statistical analysis plan, and study reports underwent quality-control checks and were reviewed by the Study Scientific Committee.

9 PROTECTION OF HUMAN SUBJECTS

9.1 Ethical approval and subject consent

CPRD and THIN are databases of pseudonymised patient electronic health records (EHR). Our approach to the study was naturalistic; we did not conduct further diagnostic tests, alter disease management strategies, or collect data in addition to or above routine medical care.

CPRD's processes have been reviewed by the Confidentiality Advisory Group (CAG) and approved by the Health Research Authority (HRA) and Secretary of State in the UK to process patient identifiable information without consent under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002. This effectively removes the obligation to obtain patient consent for the use of confidential patient information for conducting purely observational research using CPRD databases and

associated linked datasets. This approval is conditional on approval of a study protocol by the CPRD Independent Scientific Advisory Committee (ISAC). ISAC approval for this study was obtained in March 2017, ISAC protocol number 17_023.

THIN data approval is conditional on approval of a study protocol to the Scientific Review Committee (SRC). The SRC has been approved by NHS Multi-centre Research Ethics Committee (MREC) for studies using the THIN Database. SRC approval for this study was obtained in March 2017, THIN protocol number 17THIN018.

9.2 Subject confidentiality

CPRD and THIN contain only fully de-identified patient data. No patient identifiable information was available to the study team, or to GSK. All data held and processed by CPRD and any other partners in the distributed network was done in compliance with the relevant legal obligations including the Data Protection Act 1998.

All data were held on a secure computer network, with access restricted to authorised users.

10 RESULTS

10.1 Study cohorts

[Full results for this section are in the following files in **Annex 1**:
Annex 1: Exposure Cohort Results
Annex 1: Baseline Tables T1]

Basic demographic and related characteristics of the four study cohorts i.e. CPRD GOLD, THIN, combined CPRD GOLD + THIN primary care cohort, and linked primary and secondary care CPRD GOLD-HES-ONS cohort (see **Section 8.2.2**) are summarised in Table 3. Other characteristics relating to study entry, follow up, and exit are summarised for the same cohorts in Table 4. **CPRD GOLD primary care cohort**

There were 24,815 unique patients in the CPRD cohort. Around 11% of patients entered the study for more than one index medication, which gave a total of 27,956 new 'medication starts' (Table 3). Of these, 2,486 (8.9%) started UMEC, 1,645 (5.9%) UMEC/VI, and 23,825 (85.2%) started one or more Other LABD. Mean age at entry was 66 years, 50.5% were female, and 84.9% were classified as current or ex-smokers. Area based deprivation data was only available for a subset of patients registered with the 411 English practices which participated in the linkage scheme. Of these patients in Townsend quintiles 3 and 4 (middle and second most deprived) were slightly over-represented relative to the other quintiles.

The number new users entering the study each quarter increased slightly during the recruitment period, from 3,108 in July-September 2014, to 3,810 in April-June 2016 (Table 4). The median follow-up time was 529 days (IQR 373-753 days). Around 13.1% of new users exited the study because they died or transferred out of the practice, and

26.2% were lost to follow up because the practice stopped contributing data before the end of the study. Just over half (51.6%) of new users were registered with practices in England.

During the study period (01 July 2014 to 30 June 2017) 227 practices stopped contributing to the CPRD GOLD database, of which 213 (94%) were in England. In many cases this occurred because practices switched to using other GP software systems during the re-organisation of primary care services which took place in England (but not in the devolved administrations).

THIN primary care cohort

The THIN cohort comprised 9,701 unique patients, from which a total of 10,952 new 'medication starts' were recorded (Table 3). Compared with the CPRD GOLD cohort, there were relatively more new users of UMEC (12.7% [1,389 new users]), slightly fewer UMEC/VI (5.3%) and fewer new users of other LABD (82.0%). These modest differences were likely due to variation in the regional distributions of general practices in the CPRD GOLD and THIN cohorts – for example 51.6% of new users in the CPRD GOLD cohort were from England, compared with 31.4% in THIN (Table 4). The THIN cohort was very similar to the CPRD GOLD cohort in other characteristics such as age, gender, BMI and smoking status.

Compared to CPRD GOLD, patients in the THIN cohort had a slightly longer median follow up (603 days [IQR 436-805 days]), and there were fewer losses to follow up as a result of practices stopping contributing (10.6% in THIN compared with 26.2% in CPRD GOLD), partly because THIN was less impacted by the loss of English practices which switched to a different software provider during the study period.

Combined CPRD GOLD + THIN primary care cohort

Given their similar characteristics, the CPRD GOLD and THIN cohorts were pooled for the main analyses and treated as a single dataset of 34,516 patients. There were 38,908 new 'medication starts' during the study period, of which 10.0% were UMEC, 5.7% were UMEC/VI and 84.3% were for other LABD (Table 3).

Linked primary and secondary care CPRD GOLD-HES-ONS cohort

The linked cohort comprised 10,646 patients and, unlike the other three study cohorts, patients were restricted to English practices only. Regional variations in uptake of the newly launched therapies may have contributed to the slightly lower proportions of new users of UMEC (4.7%) and UMEC/VI (4.4%) in this cohort, compared to the cohorts which included practices from Northern Ireland, Scotland, and Wales (Table 3 **and** Table 4).

Table 3 Study cohorts: basic patient characteristics at index date

	Study Cohort							
	CPRD GOLD (primary care)		THIN (primary care)		Combined CPRD GOLD + THIN (primary care)		Linked CPRD GOLD-HES-ONS (primary + secondary)	
	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Patients[1]	24,815		9,701		34,516		10,646	
New Users[1]								
All LABD	27,956	100	10,952	100	38,908	100	11,649	100
UMEC	2,486	8.9	1,389	12.7	3,875	10.0	547	4.7
UMEC/VI	1,645	5.9	579	5.3	2,224	5.7	512	4.4
Other LABD	23,825	85.2	8,984	82.0	32,809	84.3	10,590	90.9
Age (in years) at index date								
mean (SD)	66.28	14.5	65.94	14.1	66.18	14.4	66.09	15.5
<18 years	449	1.6	160	1.5	609	1.6	242	2.1
18-34 years	447	1.6	175	1.6	622	1.6	238	2.0
35-64 years	9,873	35.3	3,913	35.7	13,786	35.4	3,953	33.9
≥65 years	17,187	61.5	6,704	61.2	23,891	61.4	7,216	61.9
Gender								
female	14,130	50.5	5,632	51.4	19,762	50.8	5,755	49.4
male	13,826	49.5	5,320	48.6	19,146	49.2	5,894	50.6
Smoking status								
current smoker	11,121	39.8	4,525	41.3	15,646	40.2	4,205	36.1
ex-smoker	12,621	45.1	4,852	44.3	17,473	44.9	5,354	46.0
no/never smoker	3,978	14.2	1,489	13.6	5,467	14.1	1,959	16.8
Missing[3]	236	0.8	86	0.8	322	0.8	131	1.1
Body Mass Index (kg/m^2)								
mean (SD)	28.03	6.7	27.99	6.6	28.02	6.7	28.00	6.6
underweight <18.5	1,193	4.3	445	4.1	1,638	4.2	481	4.1
normal 18.5-24.9	8,225	29.4	3,232	29.5	11,457	29.4	3,442	29.5
overweight 25.0-29.9	8,604	30.8	3,343	30.5	11,947	30.7	3,611	31.0
obese ≥30	8,872	31.7	3,468	31.7	12,340	31.7	3,621	31.1
Missing[3]	1,062	3.8	464	4.2	1,526	3.9	494	4.2
Area based deprivation quintile[4]								
Q1 (least deprived)	2,099	7.5	--	--	--	--	2,098	18.0
Q2	2,184	7.8	--	--	--	--	2,184	18.7
Q3	2,601	9.3	--	--	--	--	2,601	22.3
Q4	2,797	10.0	--	--	--	--	2,797	24.0
Q5 (most deprived)	1,963	7.0	--	--	--	--	1,962	16.8
missing[3]	16,312	58.3	--	--	--	--	7	0.1

[1]Individuals can enter study as new users more than once, which is reflected in the higher number of new users relative to patients
[2]Unless otherwise specified
[3]Percentages were calculated separately for those with missing and without missing data
[4]Area based deprivation is measured using patient-level Townsend (2001) quintile; data are available for practices within England for CPRD only
Source tables: Annex 1, Tables: Baseline - T1.1; T1.2; T1.3; T1.4

Table 4 Study cohorts: enrolment and follow-up summary

	Study Cohort							
	CPRD GOLD (primary care)		THIN (primary care)		Combined CPRD GOLD + THIN (primary care)		Linked CPRD GOLD-HES-ONS (primary + secondary)	
	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
New users (all LABD)[3]	27,956	100.0	10,952	100.0	38,908	100.0	11,649	100.0
Time period of study entry								
July - September 2014	3,108	11.1	946	8.6	4,054	10.4	1,509	13.0
October - December 2014	3,134	11.2	1,214	11.1	4,348	11.2	1,549	13.3
January - March 2015	3,777	13.5	1,350	12.3	5,127	13.2	1,788	15.3
April - June 2015	3,327	11.9	1,267	11.6	4,594	11.8	1,493	12.8
July - September 2015	3,285	11.8	1,407	12.8	4,692	12.1	1,288	11.1
October - December 2015	3,581	12.8	1,428	13.0	5,009	12.9	1,329	11.4
January - March 2016	3,934	14.1	1,616	14.8	5,550	14.3	1,414	12.1
April - June 2016	3,810	13.6	1,724	15.7	5,534	14.2	1,279	11.0
Follow-up time in days[4]								
mean (SD)	546.69	273.8	612.61	248.7	565.25	268.6	493.31	286.1
median (IQR)	529	373 - 753	603	436 - 805	554	392 - 771	473	259 - 711
Reason for censoring								
Death	2,432	8.7	765	7.0	3,197	8.2	879	7.5
left GP practice	1,237	4.4	784	7.2	2,021	5.2	562	4.8
last collection from practice	7,328	26.2	1,165	10.6	8,493	21.8	5,164	44.3
end of study	16,959	60.7	8,238	75.2	25,197	64.8	5,044	43.3
Patients with multiple index dates[1]								
gap between index dates	1,505	5.4	581	5.3	2,086	5.4	471	4.0
mean (SD) gap in days	138.11	146.1	151.04	155.4	141.71	148.8	137.15	141.3
median (IQR)	79	20 - 227	87	23 - 251	81	21 - 233	89	19 - 222
overlap between index dates	1,609	5.8	658	6.0	2,267	5.8	524	4.5
mean (SD) overlap in days	105.80	199.6	101.39	190.1	104.52	196.9	102.79	191.1
median (IQR)	21	9 - 74	20	9 - 57	21	9 - 70	22	9 - 93
Practice country								
England	14,426	51.6	3,441	31.4	17,867	45.9	11,649	100.0
Northern Ireland	1,500	5.4	1,245	11.4	2,745	7.1	0	0.0
Scotland	6,540	23.4	4,435	40.5	10,975	28.2	0	0.0
Wales	5,490	19.6	1,831	16.7	7,321	18.8	0	0.0

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] Unless otherwise specified.

[3] All LABD includes UMEC, UMEC/VI, Other LAMA, Other LABA, and Other LABA/LAMA

[4] Follow-up time from index date until censoring or study end (inclusive)

Source tables: Annex 1. Table: Exposure Cohorts - T1.1; T1.2; T1.3; T1.4

10.2 Exposure cohorts

[Full results for this section are in the following files in **Annex 1**:
Annex 1: Exposure Cohort Results
Annex 1: Baseline Tables T1
Annex 1: Baseline Tables T2
Annex 1: Baseline Tables T3
Annex 1: Baseline Tables T4]

10.2.1 Patient demographics and comorbidity

Demographic characteristics of new users of UMEC, UMEC/VI and Other LABD in the combined CPRD GOLD + THIN primary care cohort are summarised in Table 5, along with information on comorbidities recorded on or prior to the index date.

Among 3,875 new users of UMEC and 2,224 new UMEC/VI users, the mean age was similar at around 69 years, and very few patients were aged under 35 (0.4% UMEC, 0.3% UMEC/VI). Just over half (51.2%) of UMEC users, and just under half (47.4%) of UMEC/VI users were female. Just over 90% of UMEC and UMEC/VI users were current or ex-smokers. Around a third of patients were obese (32.1% UMEC; 34.6% UMEC/VI)

Around 65% of UMEC and UMEC/VI users had a history of cardiovascular disease, with around 20% treated with beta-blockers in the 12 months prior to index date. Around 7% had a history of pneumonia.

New users of other LABD treatments were generally similar to new users of UMEC and UMEC/VI, though they were more likely to be aged under 35 years (3.7%), slightly less likely to be current or ex-smokers (83.9%), and less likely to have pre-existing cardiovascular disease (60.1%).

Table 5 Demographic characteristics and comorbidities at baseline, by index LABD group: Combined CPRD GOLD+THIN primary care cohort

	Cohort of Patients (N=34,516)[1]					
	UMEC		UMEC/VI		Other LABD	
	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
New users	3,875		2,224		32,809	
Age (in years) at index date						
mean (SD)	68.75	10.8	69.02	10.7	65.69	14.9
<18 years	0	0.0	0	0.0	609	1.9
18-34 years	16	0.4	6	0.3	600	1.8
35-64 years	1,237	31.9	686	30.8	11,863	36.2
≥65 years	2,622	67.7	1,532	68.9	19,737	60.2
Gender						
female	1,984	51.2	1,055	47.4	16,723	51.0
male	1,891	48.8	1,169	52.6	16,086	49.0
Smoking status						
current smoker	1,656	42.7	883	39.7	13,107	39.9
ex-smoker	1,886	48.7	1,152	51.8	14,435	44.0
no/never smoker	332	8.6	188	8.5	4,947	15.1
missing[3]	1	0.0	1	0.0	320	1.0
Body Mass Index (kg/m^2)						
mean (SD)	27.87	6.5	28.35	6.4	28.01	6.7
underweight <18.5	189	4.9	82	3.7	1,367	4.2
normal 18.5-24.9	1,162	30.0	615	27.7	9,680	29.5
overweight 25.0-29.9	1,228	31.7	732	32.9	9,987	30.4
obese ≥30	1,244	32.1	770	34.6	10,326	31.5
missing[3]	52	1.3	25	1.1	1,449	4.4
Comorbidities						
Cardio and cerebrovascular disease (ever)	2,510	64.8	1,453	65.3	19,711	60.1
Beta-blocker prescribing (past 12m)	707	18.2	485	21.8	6,391	19.5
Pneumonia (ever)	284	7.3	160	7.2	2,312	7.0
GORD[4] (ever)	890	23.0	525	23.6	7,440	22.7
Diabetes (ever)	753	19.4	410	18.4	5,863	17.9
Kidney disease (ever)	826	21.3	438	19.7	5,883	17.9
Cancer (ever)	564	14.6	313	14.1	4,287	13.1

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
[2] Unless otherwise specified
[3] Percentages were calculated separately for those with missing and without missing data
[4] Gastroesophageal disease
Source tables: Annex 1, Tables: Baseline - T1.1, Baseline - T2

10.2.2 COPD disease severity

Indicators of COPD disease severity at baseline are shown for new users of UMEC, UMEC/VI and Other LABD in the combined CPRD GOLD + THIN primary care cohort in Table 6.

Among new users of UMEC, the rate of moderate COPD exacerbations identified in the primary care record in the year prior to index date was 1.09 per person year (95% CI 1.06 to 1.12), which was significantly higher than in new users of UMEC/VI (rate 0.77, CI 0.73 to 0.81), and new users of other LABD (rate 0.83, CI 0.82 to 0.84).

UMEC, UMEC/VI and other LABD patients were generally similar in terms of other markers of severity (MRC dyspnoea score, FEV_1 % predicted and FEV_1/FVC), though new users of UMEC tended towards worse scores for dyspnoea (24% of UMEC *vs* 18.9% of UMEC/VI users were MRC Grade 4 or 5). UMEC users also had slightly lower mean scores for FEV_1 % predicted and FEV_1/FVC ratio compared to UMEC/VI users, while new users of other LABD had less severe scores.

Table 6 COPD disease burden at baseline, by index LABD group: Combined CPRD GOLD+THIN primary care cohort

	Cohort of Patients (N=34,516)[1]					
	UMEC		UMEC/VI		Other LABD	
	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
New users[1]	3,875		2,224		32,809	
'Moderate' COPD exacerbations (from primary care record)						
Rate per person year (95% CI)	1.09	(1.06, 1.12)	0.77	(0.73, 0.81)	0.83	(0.82, 0.84)
0 events	1,826	47.1	1,257	56.5	17,629	53.7
1 event	984	25.4	563	25.3	8,535	26.0
2+ events	1,065	27.5	404	18.2	6,645	20.3
Dyspnoea (MRC Grade)						
mean (SD)	2.8	1.0	2.7	0.9	2.6	1.0
MRC Grade 1	196	6.5	100	5.9	1,643	9.2
MRC Grade 2	1,070	35.5	680	40.4	7,091	39.8
MRC Grade 3	1,018	33.7	585	34.8	5,586	31.4
MRC Grade 4	629	20.8	278	16.5	2,935	16.5
MRC Grade 5	105	3.5	40	2.4	545	3.1
missing[3]	857	22.1	541	24.3	15,009	45.7
FEV_1 percent predicted						
mean (SD)	58.1	19.2	60.0	19.0	59.8	19.4
mild, Grade 1 (≥80%)	329	12.2	226	13.9	2,882	14.0
moderate, Grade 2 (≥50% to <80%)	1,427	53.1	915	56.3	11,312	54.9
severe, Grade 3 (≥30% to <50%)	768	28.6	401	24.7	5,266	25.6
very severe, Grade 4 (<30%)	165	6.1	83	5.1	1,149	5.6
missing[3]	1,186	30.6	599	26.9	12,200	37.2
FEV_1/FVC ratio						
mean (SD)	58.9	15.9	60.4	14.1	62.1	15.6
<70%	1,752	79.1	1,130	77.8	12,866	72.1
≥70%	464	20.9	323	22.2	4,975	27.9
missing[4]	1,659	42.8	771	34.7	14,968	45.6

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
[2] Unless otherwise specified
[3] Percentages were calculated separately for those with missing and without missing data
Source tables: Annex 1, Table: Baseline – T4.1

10.2.3 Previous and concomitant use of respiratory medication at index date

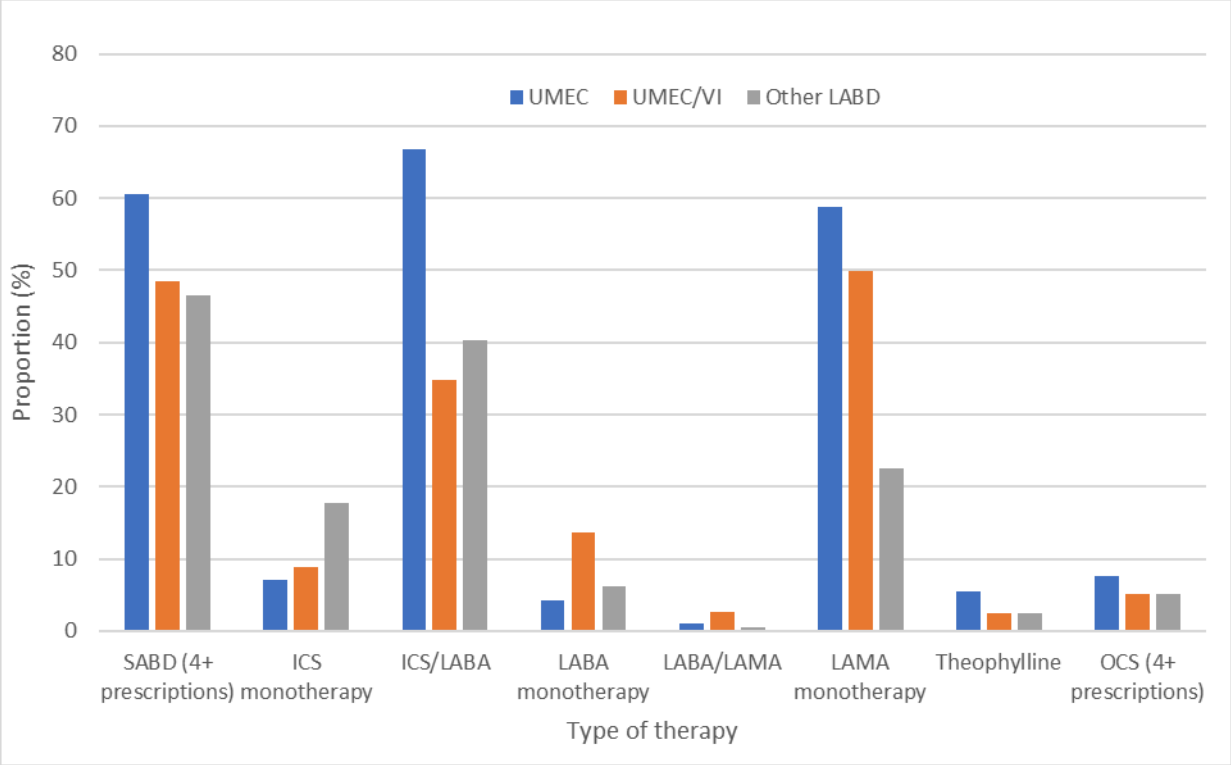
Previous use of respiratory medication at index date is shown for new users of UMEC, UMEC/VI and Other LABD in the combined CPRD GOLD + THIN primary care cohort in Figure 5 and concomitant use of other therapies at index date in the same cohort is shown in Figure 6 and Table 7**,** Table 8 **and** Table 9**.**

Previous use

Overall use of other respiratory medications was common in the 12 months prior to index date. For example, 80% of all patients had at least one prescription for SABD, while 48% received at least four prescriptions (see **Annex 1, Table: Baseline – T3 and** Figure 5). Around 55% had received an ICS-containing medication, either as monotherapy (16%) or more commonly as a fixed dose combination of ICS+LABA (43%). Around 48% had received LABA-containing medication (mostly fixed combination with ICS); and 28% had received LAMA containing medication – mostly as monotherapy. Use of theophyllines (2.8%) or chronic oral corticosteroid use (5.4%) was uncommon, and fewer than five patients were recorded as receiving roflumilast (see **Annex 1, Table: Baseline – T3**).

New users of UMEC were most likely to have been previously treated with SABD (four or more prescriptions) or ICS+LABA compared to users of UMEC/VI and other LABD. (Figure 5). Compared to both UMEC and UMEC/VI users, new users of other LABD were more likely to have received ICS monotherapy, but less likely to have received LAMA containing medication (Figure 5).

Figure 5 Previous use[1] of other inhaled COPD therapy at index date in new users of UMEC, UMEC/VI, and other LABD: CPRD GOLD + THIN primary care cohort



[1] Prior use defined as at least 1 prescription (unless stated otherwise) in the year prior to, and not including the index date

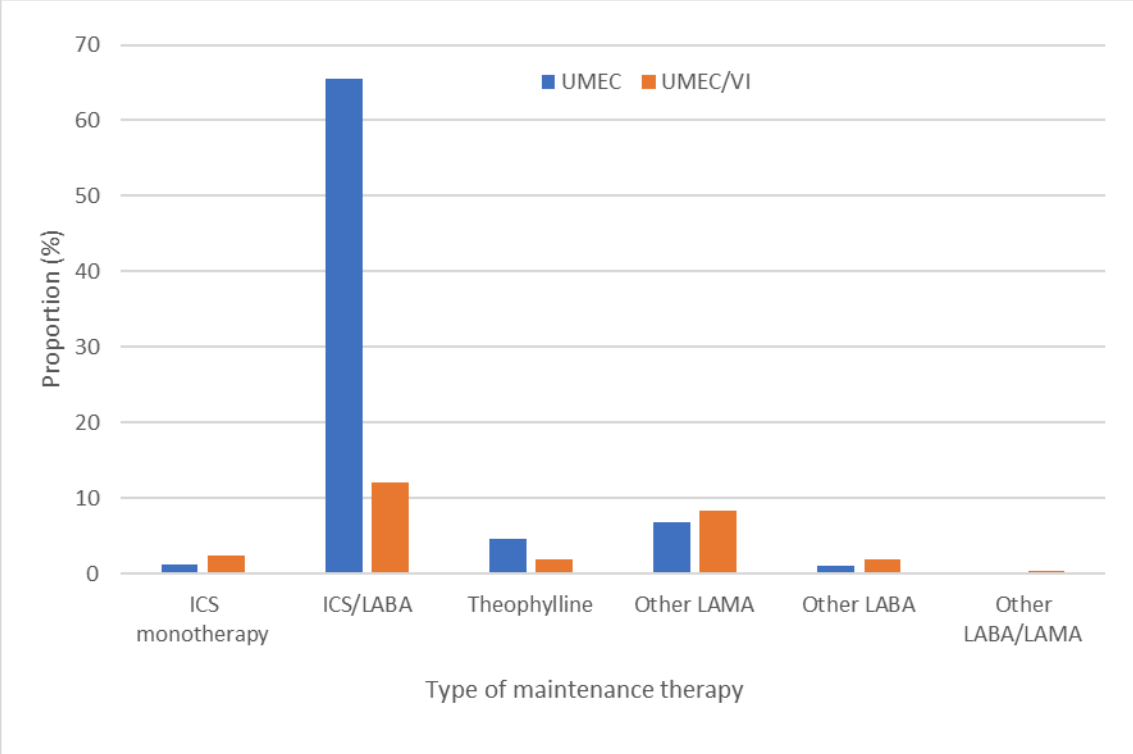
Source tables: Annex 1, Table: Baseline - T3

Concomitant use

Concomitant use of ICS+LABA was reported for over 65% of new users of UMEC (Figure 6). Such use would be consistent with NICE guidelines for addition of LAMA as step-up treatment for patients whose COPD is not well controlled using ICS+LABA alone.

Overall, around 68% of new users of UMEC had concomitant treatment at baseline, and their characteristics are compared with users without concomitant treatment in Table 7. Patients with and without concomitant treatment were broadly similar in terms of age, gender, smoking status and BMI. However concomitant treatment - the great majority of which was ICS+LABA - was associated with greater COPD disease burden at baseline. Most notably, incidence of moderate COPD exacerbations in the 12 months prior to index date was more than twice as high in the concomitant treatment group (1.34 per person year, 95% CI 1.28 to 1.38) compared to the non-concomitant group (0.56, 95% CI 0.52 to 0.60). The concomitant treatment group also fared worse in terms of dyspnoea (29.2% vs 12.6% with MRC Grade 4 or 5), and FEV_1 (41.2% vs 19.9% with severe or very severe obstruction). (Table 7).

Figure 6 **Concomitant use[1] of other inhaled COPD therapy at index date in new users of UMEC and UMEC/VI: CPRD GOLD + THIN primary care cohort**



[1] Concomitant use defined as at least two continuous prescriptions starting either before, or up to 30 days after the index medication, and overlapping for at least 30 days with the index treatment.

Source tables: Annex 1, Table: ExposureCohorts - T1.1

Table 7 Demographic characteristics and COPD burden at baseline: new users of UMEC with and without concomitant[1] maintenance therapy at index date: CPRD GOLD + THIN primary care cohort

Characteristics of new users of UMEC		Use of concomitant maintenance therapy at index date			
		WITH concomitant therapy		NO concomitant therapy	
		No.[2]	(%)[2]	No.[2]	(%)[2]
New users		2,648	68.3	1,227	31.7
Age (y)	mean (SD)	68.68	10.8	68.92	10.9
Female		1,377	52.0	607	49.5
Smoking status	current smoker	1,085	41.0	571	46.5
	ex-smoker	1,340	50.6	546	44.5
	no/never smoker	223	8.4	109	8.9
	missing[3]	0	0.0	1	0.1
BMI	mean (SD)	27.91	6.6	27.79	6.4
'Moderate' COPD exacerbations (from primary care record)	Rate per person year (95% CI)	1.34	(1.29, 1.38)	0.56	(0.52, 0.60)
	0 events	1,040	39.3	786	64.1
	1 event	701	26.5	283	23.1
	2+ events	907	34.3	158	12.9
Dyspnoea (MRC Grade)	mean (SD)	3.0	0.9	2.4	0.9
	MRC Grade 1	89	4.2	107	12.0
	MRC Grade 2	638	30.0	432	48.5
	MRC Grade 3	778	36.6	240	26.9
	MRC Grade 4	534	25.1	95	10.7
	MRC Grade 5	88	4.1	17	1.9
	missing[3]	521	19.7	336	27.4
FEV_1 percent predicted	mean (SD)	55.4	19.3	64.4	17.6
	mild, Grade 1 (≥80%)	184	9.8	145	17.7
	moderate, Grade 2 (≥50% to <80%)	915	49.0	512	62.4
	severe, Grade 3 (≥30% to <50%)	622	33.3	146	17.8
	very severe, Grade 4 (<30%)	148	7.9	17	2.1
	missing[3]	779	29.4	407	33.2
FEV_1/FVC ratio	mean (SD)	57.6	16.4	61.8	14.2
	<70%	1,227	80.6	525	75.8
	≥70%	296	19.4	168	24.2
	missing[3]	1,125	42.5	534	43.5

[1] Concomitant use defined as at least two continuous prescriptions starting either before, or up to 30 days after the index medication, and overlapping for at least 30 days with the index treatment.
[2] Unless otherwise specified
[3] Percentages were calculated separately for those with missing and without missing data
Source tables: Annex 1. Tables: Baseline - T1.1(a)/(b); Baseline - T2; Baseline - T4.1(a)/(b)

Among new users of UMEC/VI, 21.8% were receiving concomitant treatment at baseline, a substantially lower proportion compared to UMEC users (Table 8). Patients with and without concomitant treatment were broadly similar in terms of age, gender, smoking status and BMI. Similar to UMEC users, UMEC/VI patients receiving concomitant treatment had substantially higher rates of moderate COPD exacerbations in the 12 months prior to index date (1.25 per person year, 95% CI 1.16 to 1.36) relative to the non-concomitant group (0.63, 95% CI 0.60 to 0.67). The concomitant treatment group were also more severe in terms of dyspnoea (27.2% vs 16.5% with MRC Grade 4 or 5), and FEV1 (40.5% vs 26.6% with severe or very severe obstruction) (Table 8).

A similar pattern was seen for new users of other LABD. Around 83% of these patients were receiving concomitant treatment at index date, and this group had higher rates of moderate COPD exacerbations in the 12 months prior to index date (0.88 per person year, 95% CI 0.87 to 0.89) relative to the non-concomitant group (0.57, 95% CI 0.55 to 0.59), and both dyspnoea scores, and spirometric measures were more severe (Table 9).

Table 8 Demographic characteristics and COPD burden at baseline: new users of UMEC/VI with and without concomitant[1] maintenance therapy at index date: CPRD GOLD + THIN primary care cohort

Characteristics of new users of UMEC/VI		Use of concomitant maintenance therapy at index date			
		WITH concomitant therapy		NO concomitant therapy	
		No.[2]	(%)[2]	No.[2]	(%)[2]
New users		485	21.8	1,739	78.2
Age (y)	mean (SD)	68.64	11.0	69.12	10.6
Female		251	51.8	804	46.2
Smoking status	current smoker	169	34.8	714	41.1
	ex-smoker	270	55.7	882	50.7
	no/never smoker	46	9.5	142	8.2
	missing[3]	0	0.0	1	0.1
BMI	mean (SD)	28.82	6.9	28.21	6.2
'Moderate' COPD exacerbations (from primary care record)	Rate per person year (95% CI)	1.25	(1.16, 1.36)	0.63	(0.60, 0.67)
	0 events	210	43.3	1,047	60.2
	1 event	123	25.4	440	25.3
	2+ events	152	31.3	252	14.5
Dyspnoea (MRC Grade):	mean (SD)	2.9	0.9	2.6	0.9
	MRC Grade 1	17	4.4	83	6.4
	MRC Grade 2	126	32.6	554	42.7
	MRC Grade 3	138	35.8	447	34.5
	MRC Grade 4	93	24.1	185	14.3
	MRC Grade 5	12	3.1	28	2.2
	missing[3]	99	20.4	442	25.4
FEV_1 percent predicted:	mean (SD)	55.9	20.0	61.2	18.5
	mild, Grade 1 (≥80%)	45	12.0	181	14.5
	moderate, Grade 2 (≥50% to <80%)	178	47.5	737	59.0
	severe, Grade 3 (≥30% to <50%)	114	30.4	287	23.0
	very severe, Grade 4 (<30%)	38	10.1	45	3.6
	missing[3]	110	22.7	489	28.1
FEV_1/FVC ratio	mean (SD)	58.5	16.3	60.9	13.4
	<70%	260	79.5	870	77.3
	≥70%	67	20.5	256	22.7
	missing[3]	158	32.6	613	35.3

[1] Concomitant use defined as at least two continuous prescriptions starting either before, or up to 30 days after the index medication, and overlapping for at least 30 days with the index treatment.
[2] Unless otherwise specified
[3] Percentages were calculated separately for those with missing and without missing data
Source tables: Annex 1. Tables: Baseline - T1.1(a)/(b); Baseline - T2; Baseline - T4.1(a)/(b)

Table 9 Demographic characteristics and COPD burden at baseline: new users of other LABD with and without concomitant[1] maintenance therapy at index date: CPRD GOLD + THIN primary care cohort

Characteristics of new users of other LABD		Use of concomitant maintenance therapy at index date			
		WITH concomitant therapy		NO concomitant therapy	
		No.[2]	(%)[2]	No.[2]	(%)[2]
New users		27,313	83.2	5,496	16.8
Age (y) at index date: mean (SD)		66.27	14.1	62.81	18.2
Female		13,965	51.1	2,758	50.2
Smoking status	current smoker	10,866	39.8	2,241	40.8
	ex-smoker	12,370	45.3	2,065	37.6
	no/never smoker	3,867	14.2	1,080	19.7
BMI	mean (SD)	28.09	6.8	27.59	6.3
'Moderate' COPD exacerbations (from primary care record)	Rate per person year (95% CI)	0.88	(0.87, 0.89)	0.57	(0.55, 0.59)
	0 events	14,157	51.8	3,472	63.2
	1 event	7,210	26.4	1,325	24.1
	2+ events	5,946	21.8	699	12.7
Dyspnoea (MRC Grade)	mean (SD)	2.7	1.0	2.5	1.0
	MRC Grade 1	1,350	8.8	293	12.3
	MRC Grade 2	6,040	39.2	1,051	44.0
	MRC Grade 3	4,921	31.9	665	27.9
	MRC Grade 4	2,631	17.1	304	12.7
	MRC Grade 5	471	3.1	74	3.1
	missing[3]	11,900	43.6	3,109	56.6
FEV_1 percent predicted	mean (SD)	59.0	19.2	64.6	19.4
	mild, Grade 1 (≥80%)	2,311	13.1	571	19.6
	moderate, Grade 2 (≥50% to <80%)	9,604	54.3	1,708	58.6
	severe, Grade 3 (≥30% to <50%)	4,723	26.7	543	18.6
	very severe, Grade 4 (<30%)	1,057	6.0	92	3.2
	missing[3]	9,618	35.2	2,582	47.0
FEV_1/FVC ratio	mean (SD)	61.6	15.9	65.0	13.7
	<70%	11,175	73.2	1,691	65.5
	≥70%	4,086	26.8	889	34.5
	missing[3]	12,052	44.1	2,916	53.1

[1] Concomitant use defined as at least two continuous prescriptions starting either before, or up to 30 days after the index medication, and overlapping for at least 30 days with the index treatment.
[2] Unless otherwise specified
[3] Percentages were calculated separately for those with missing and without missing data
Source tables: Annex 1. Tables: Baseline - T1.1(a)/(b); Baseline - T2; Baseline - T4.1(a)/(b)

10.3 Objective 1

In new users of UMEC/VI, UMEC, or Other LABD report the proportion of patients with possible off-label use and characterize them, using information available up to the time of censoring, in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

[Full results for this section are in the following files in **Annex 1**:
Annex 1: Objective 1 Results]

As shown in Table 10, overall, 16.4% of new users of LABD treatments in the CPRD GOLD + THIN primary care cohort were considered to have received treatment which was possibly off-label (using a combination of all three definitions); either because they did not have evidence of a COPD diagnosis, or because they evidence of asthma diagnosis but the respiratory treatment combination was not appropriate (see Section 8.2.6.1 for full definitions of possible off-label treatment).

Possible off-label prescribing was much lower for new users of UMEC (7.0%) and UMEC/VI (8.8%), compared with Other LABD (18.0%).

Figure 7 compares the timing of COPD and asthma diagnoses relative to the index medication prescription, for the three exposure groups. The pattern was similar for all groups; in 91%-97% of new users, a diagnosis was recorded on or before the index prescription, and in most cases six months or more before. COPD diagnoses were more likely to be recorded in the three months up to and including the index date, compared with asthma diagnosis, and this was true for all exposure groups.

The prevalence of concomitant prescribing of ICS containing medications varied between diagnosis groups. Concomitant ICS treatment was highest in the asthma diagnosis group, and substantially lower in the group with no evidence of COPD/asthma (Table 11), and this was seen in new users of UMEC, UMEC/VI and other LABD. Among the 2,224 new users of UMEC/VI there were 39 (1.8%) with an asthma diagnosis who were not taking concomitant ICS at initiation. Among the 3,875 new users of UMEC there were 34 (0.9%) with an asthma diagnosis who were not taking concomitant ICS at initiation.

Table 10 Diagnosis groups and possible off-label prescribing in new users of UMEC, UMEC/VI, and other LABD: CPRD GOLD + THIN primary care cohort

	Cohort of Patients (N=34,516)[1]									
	Diagnosis group									
	All new users	COPD		Asthma		Other (not COPD or asthma)		Possible off-label group		Off-label definition[2]
Index therapy		No.	(%)	No.	(%)	No.	(%)	No.	(%)	
All	38,908[1]	31,000[1]	79.7	4,876[1]	12.5	3,032[1]	7.8	6,385[1]	16.4	1,2,3
UMEC	3,875	3,604	93.0	130	3.4	141	3.6	271	7.0	1
UMEC/VI	2,224	2,029	91.2	69	3.1	126	5.7	195	8.8	1
Other LABD	32,809	25,367	77.3	4,677	14.3	2,765	8.4	5,919	18.0	1,2,3
Other LAMA	24,125	19,655	81.5	2,327	9.6	2,143	8.9	3,980	16.5	2
Other LABA	6,218	3,458	55.6	2,278	36.6	482	7.8	1,727	27.8	3
Other LABA/LAMA	2,466	2,254	91.4	72	2.9	140	5.7	212	8.6	1

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] Definitions of off-label varied according to type of index medication, as follows:

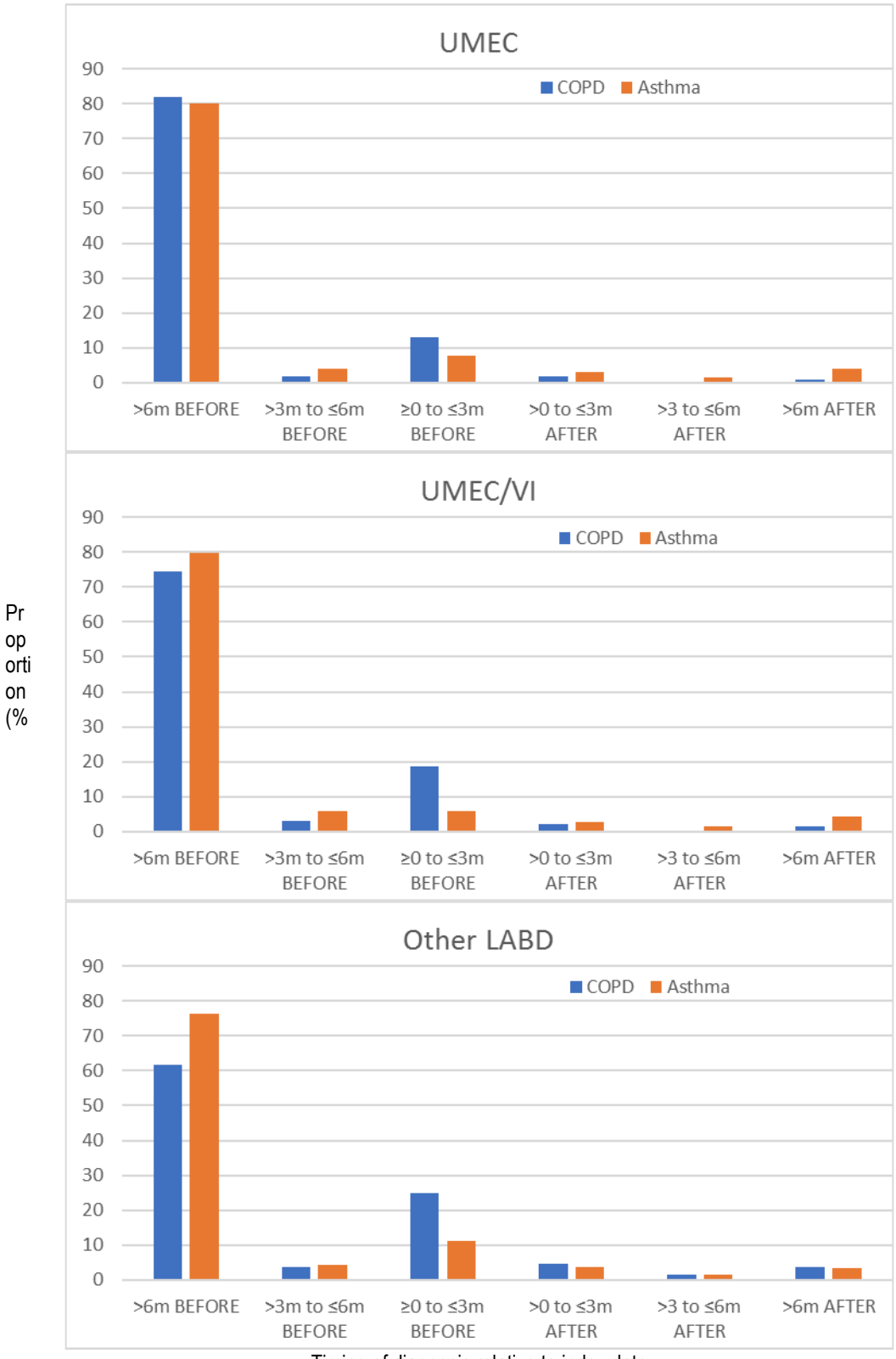
Definition 1 (Primary): Patients without evidence of COPD.

Definition 2: Prescribing of LAMA without evidence of COPD unless they: 1) had an index prescription for 2.5 mg tiotropium on or after 13/09/2014, and 2) were in the asthma category, and 3) had concomitant ICS+LABA

Definition 3: Prescribing of LABA without evidence of COPD unless they: 1) were in the asthma category, and 2) had concomitant ICS

Source table: Annex 1. Table: Obj.1 – T2

Figure 7 Timing of COPD or asthma diagnosis relative to index date in new users of UMEC, UMEC/VI and other LABD: CPRD GOLD +THIN cohort.



Source table: Annex 1. **Table: Obj.1 – T1**

Table 11 Diagnosis groups and concomitant use[1] of ICS in new users of UMEC, UMEC/VI, and other LABD: CPRD GOLD + THIN primary care cohort

		Cohort of Patients (N=34,516)[2]					
		Diagnosis group					
		COPD N= 31,000		Asthma N= 4,876		Other (no COPD/asthma) N= 3,032	
Index medication	Subgroup	No.	(%)	No.	(%)	No.	(%)
UMEC							
	with concomitant ICS	2,437	67.6	96	73.8	43	30.5
	without concomitant ICS	1,167	32.4	34	26.2	98	69.5
UMEC/VI							
	with concomitant ICS	284	14.0	30	43.5	6	4.8
	without concomitant ICS	1,745	86.0	39	56.5	120	95.2
Other LABD[3]							
	with concomitant ICS	9,509	37.5	2,848	60.9	482	17.4
	without concomitant ICS	15,858	62.5	1,829	39.1	2,283	82.6
Other LAMA							
	with concomitant ICS	8,751	44.5	1,708	73.4	420	19.6
	without concomitant ICS	10,904	55.5	619	26.6	1,723	80.4
Other LABA							
	with concomitant ICS	413	11.9	1,108	48.6	59	12.2
	without concomitant ICS	3,045	88.1	1,170	51.4	423	87.8
Other LAMA/LABA							
	with concomitant ICS	345	15.3	32	44.4	3	2.1
	without concomitant ICS	1,909	84.7	40	55.6	137	97.9

[1] Concomitant use defined as at least two continuous prescriptions for ICS starting either before, or up to 30 days after the index medication, and overlapping for at least 30 days with the index treatment.
[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of new users relative to patients
[3] The Other LABD group includes Other LAMA, Other LABA, and Other LABA/LAMA
Source table: Annex 1. Table: Obj.1 - T1

Other characteristics of patients in each diagnosis group are shown for new users of UMEC and UMEC/VI in Table 12-Table 13, and Figure 8-Figure 9**.** For both UMEC and UMEC/VI users, patients with COPD tended to be older, were less likely to be female, and tended to have poorer lung function based on spirometry parameters, compared to those with an asthma diagnosis.

Again, for both UMEC and UMEC/VI users, patients with asthma were slightly less likely to have a history of cardiovascular disease or to have received beta blockers in the year prior to index date (Figure 8), but otherwise patterns of comorbidity were similar across diagnosis groups.

Patients without a diagnosis of COPD or asthma were much less likely to have received other respiratory treatments in the previous year, compared to patients with a diagnosis (Figure 9). Among UMEC/VI users, those with an asthma diagnosis were much more likely to have received an ICS containing medication in the previous year.

Table 12 Demographic characteristics and COPD burden at baseline, by diagnosis group in new users of UMEC: CPRD GOLD + THIN primary care cohort

		Cohort of Patients (N=3,875)					
		COPD		Asthma		Other (not COPD/asthma)	
		N=	3,604	N=	130	N=	141
		No.	(%)	No.	(%)	No.	(%)
Age at index date (y)	mean (SD)	69.0	10.3	60.2	15.9	69.8	13.8
Gender	female	1,829	50.8	75	57.7	80	56.7
Smoking status	current smoker	1,555	43.2	42	32.3	59	42.1
	ex-smoker	1,788	49.6	44	33.9	54	38.6
	no/never smoker	261	7.2	44	33.9	27	19.3
	missing[1]	0	0.0	0	0.0	1	0.7
BMI	mean (SD)	27.8	6.4	30.9	7.9	27.6	7.1
'Moderate' COPD exacerbations (from primary care record)	Rate per person year (95% CI)	1.12	(1.08, 1.15)	n/a		n/a	
	0 events	1,687	46.8				
	1 event	904	25.1				
	2+ events	1,013	28.1				
Dyspnoea (MRC Grade)	mean (SD)	2.79	1.0	2.71	1.0	3.38	0.9
	MRC Grade 1	195	6.5	1	7.1	0	0.0
	MRC Grade 2	1,062	35.5	6	42.9	2	15.4
	MRC Grade 3	1,010	33.8	3	21.4	5	38.5
	MRC Grade 4	620	20.7	4	28.6	5	38.5
	MRC Grade 5	104	3.5	0	0.0	1	7.7
	missing[1]	613	17.0	116	89.2	128	90.8
FEV_1 percent predicted	mean (SD)	57.9	19.2	67.9	18.8	64.1	21.2
	mild, Grade 1 (≥80%)	312	11.9	9	24.3	8	22.2
	moderate, Grade 2 (≥50% to <80%)	1,387	53.0	21	56.8	19	52.8
	severe, Grade 3 (≥30% to <50%)	755	28.9	6	16.2	7	19.4
	very severe, Grade 4 (<30%)	162	6.2	1	2.7	2	5.6
	missing[1]	988	27.4	93	71.5	105	74.5
FEV_1/FVC ratio	mean (SD)	58.6	15.9	70.3	11.8	68.6	13.1
	<70%	1,722	79.9	16	48.5	14	50.0
	≥70%	433	20.1	17	51.5	14	50.0
	missing[1]	1,449	40.2	97	74.6	113	80.1

[1] Percentages were calculated separately for those with missing and without missing data
Source tables: Annex 1. Table: Obj.1 - T3(a)

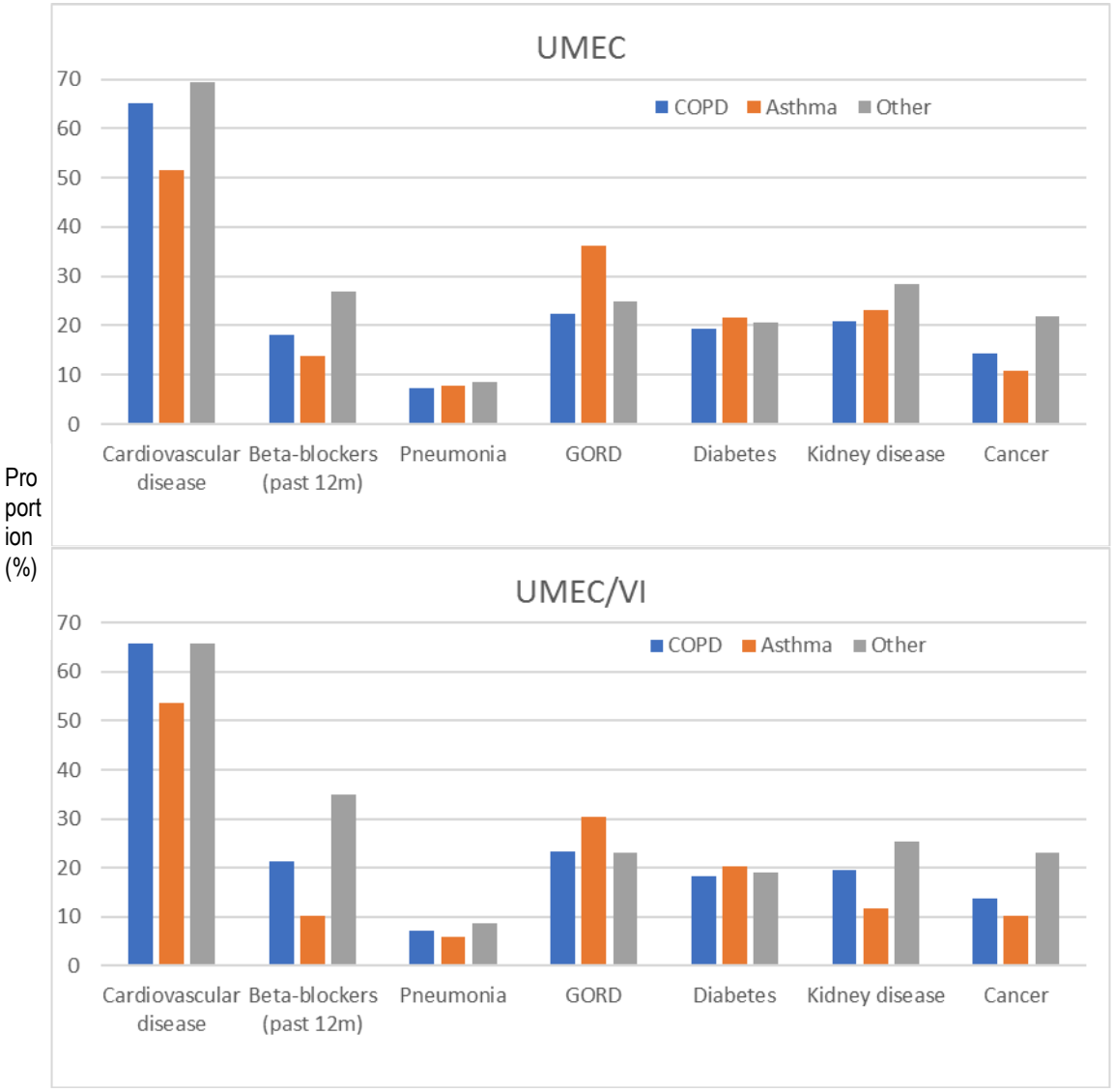
Table 13 Demographic characteristics and COPD burden at baseline, by diagnosis group in new users of UMEC/VI: CPRD GOLD + THIN primary care cohort

		Cohort of Patients (N=2,224)					
		COPD N= 2,029		Asthma N= 69		Other (not COPD/asthma) N= 126	
		No.	(%)	No.	(%)	No.	(%)
Age at index date (y)	mean (SD)	69.3	10.2	62.3	15.0	68.4	14.3
Gender	female	947	46.7	47	68.1	61	48.4
Smoking status	current smoker	819	40.4	16	23.2	48	38.1
	ex-smoker	1,080	53.3	26	37.7	46	36.5
	no/never smoker	129	6.4	27	39.1	32	25.4
	missing[1]	1	0.1	0	0.0	0	0.0
BMI	mean (SD)	28.3	6.3	30.3	6.7	28.8	6.8
'Moderate' COPD exacerbations (identified in primary care record)	Rate per person year (95% CI)	0.79	(0.75, 0.83)	n/a		n/a	
	0 events	1,136	56.0				
	1 event	513	25.3				
	2+ events	380	18.7				
Dyspnoea (MRC Grade)	mean (SD)	2.7	0.9	2.7	0.8	2.6	0.7
	MRC Grade 1	100	6.0	0	0.0	0	0.0
	MRC Grade 2	667	40.2	3	50.0	10	55.6
	MRC Grade 3	577	34.8	2	33.3	6	33.3
	MRC Grade 4	275	16.6	1	16.7	2	11.1
	MRC Grade 5	40	2.4	0	0.0	0	0.0
	missing[1]	370	18.2	63	91.3	108	85.7
FEV_1 percent predicted	mean (SD)	59.6	18.7	76.6	21.7	70.1	22.2
	mild, Grade 1 (≥80%)	210	13.4	6	37.5	10	27.8
	moderate, Grade 2 (≥50% to <80%)	886	56.3	9	56.3	20	55.6
	severe, Grade 3 (≥30% to <50%)	395	25.1	1	6.3	5	13.9
	very severe, Grade 4 (<30%)	82	5.2	0	0.0	1	2.8
	missing[1]	456	22.5	53	76.8	90	71.4
FEV_1/FVC ratio	mean (SD)	60.0	14.0	73.7	12.5	73.0	15.0
	<70%	1,112	79.1	4	30.8	14	41.2
	≥70%	294	20.9	9	69.2	20	58.8
	missing[1]	623	30.7	56	81.2	92	73.0

[1] Percentages were calculated separately for those with missing and without missing data

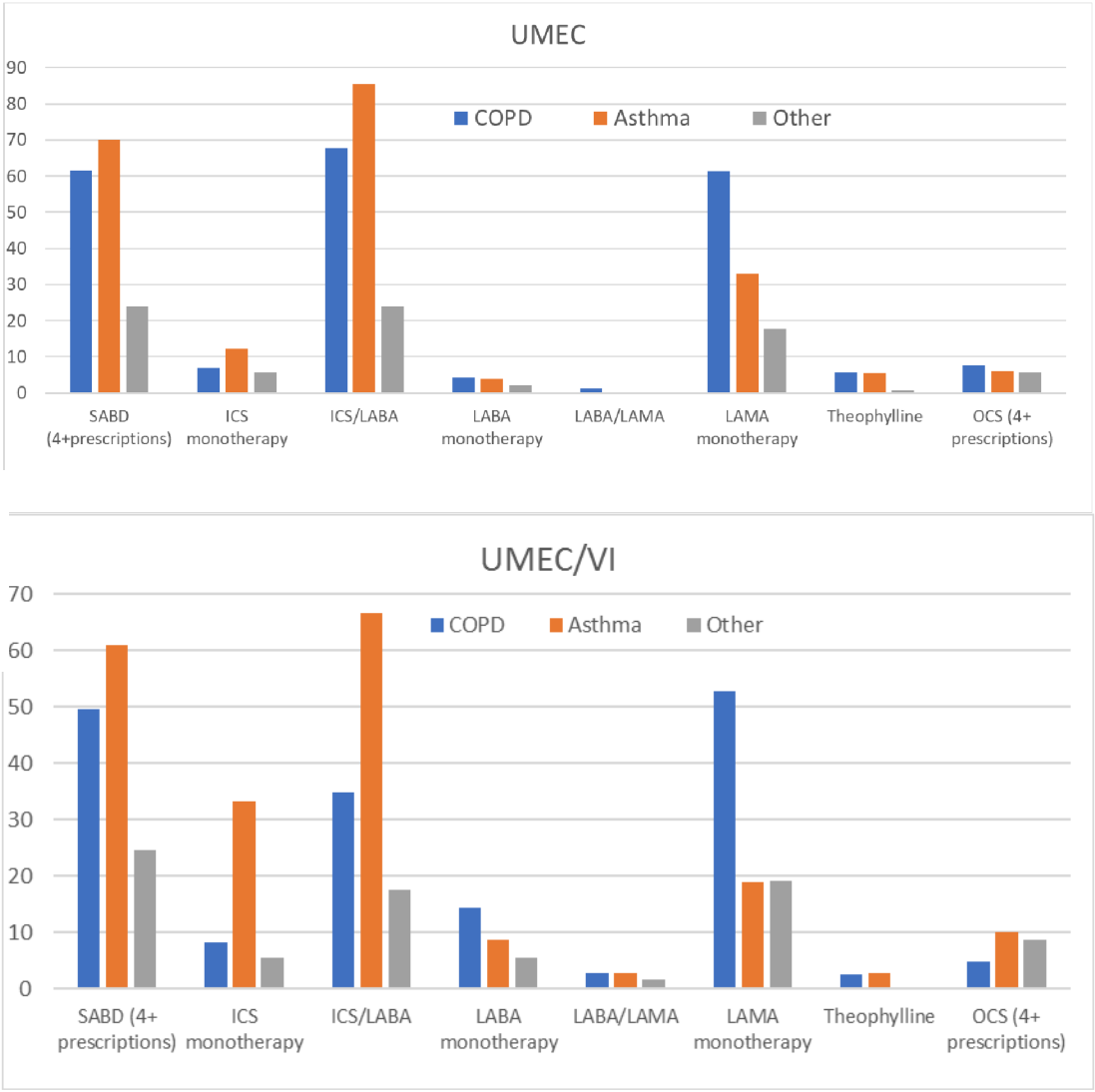
Source tables: Annex 1. Table: Obj.1 - T3(b)

Figure 8 Comorbidity at index date, by diagnosis group in new users of UMEC and UMEC/VI: CPRD GOLD + THIN primary care cohort



Source tables: Annex 1. Tables: Obj.1 - T3(a)/(b)

Figure 9 **Respiratory medication use in year prior to index date, by diagnosis group in new users of UMEC and UMEC/VI: CPRD GOLD + THIN primary care cohort**



Source tables: Annex 1. Tables: Obj.1 - T3(a)/(b)

10.4 Objective 2

In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality and pneumonia, and rates of exacerbations of COPD during follow-up.

[Full results for this section are in the following files in **Annex 1**:
Annex 1: Objective 2 Results]

Summary results and key findings are presented below. Incidence rates are expressed per 1000 person years except for AECOPD events rates which are expressed per person year.

In the combined CPRD GOLD + THIN primary care cohort, there were 3,875 new users of UMEC and 2,224 new users of UMEC/VI. Table 13**,** Table 14 **and** Table 15 summarise incidence respectively for cardiovascular, respiratory and mortality outcomes in this cohort during follow-up while currently exposed to the index medication.

In the smaller linked primary and secondary care CPRD GOLD-HES-ONS cohort, there were 547 new users of UMEC and 512 new users of UMEC/VI. Table 16**,** Table 17 **and** Table 18 summarise incidence respectively for cardiovascular, respiratory and mortality outcomes in the linked cohort during follow-up while currently exposed to the index medication.

10.4.1 Cardiovascular outcomes during current exposure to index medication: combined CPRD GOLD + THIN primary-care cohort

Myocardial infarction (MI): there were 27 events in total among UMEC users, and 13 among UMEC/VI users. Incidence was similar in each group: 6.9 [95% CI 4.4 to 10.2] per 1000 person years for UMEC, and 6.8 [95% CI 3.5 to 11.9] per 1000 person years for UMEC/VI (Table 14).

Among UMEC users, incidence was higher in patients with a previous MI compared to those with no such history (20.4 [95% CI 7.5 to 44.3] vs 5.6 [95% CI 3.3 to 8.9], respectively). Incidence was higher among UMEC users receiving beta-blockers in the 12 months up to and including the index date compared to those who were not (16.7 [95% CI 8.0 to 30.7] *vs* 4.8 [95% CI 2.6 to 8.1], respectively). Concomitant treatment with ICS at index date was not associated with incidence of MI.

Among UMEC/VI users, incidence of MI was not associated with prior history or with beta-blocker use at index date. Very few UMEC/VI patients were receiving concomitant ICS at baseline and there were no MIs recorded in this group.

Stroke: stroke incidence was very similar for users of UMEC (171 events in total, incidence 30.9 [95% CI 25.3 to 37.4]) and UMEC/VI (84 events, with an incidence of 30.5 [95% CI 22.8 to 39.8]). Incidence was substantially higher in patients with a stroke history compared to those without a prior history of stroke, for users of both UMEC (278.4 [95% CI 219.7 to 347.9] vs 9.2 [95% CI 6.2 to 13.2]) and UMEC/VI (250.0 [95%

CI 173.1 to 349.3] vs 11.8 [95% CI 7.1 to 18.5]); 81.9% and 67.9% of UMEC and UMEC/VI patients were reported as having a prior history of stroke. Incidence was not associated with prior use of beta-blockers or concomitant use of ICS at index date for both UMEC and UMEC/VI users.

Newly diagnosed congestive heart failure (CHF): among UMEC users, there were 48 patients with newly diagnosed CHF, for an incidence of 14.8 [95% CI 10.9 to 19.6]. Overall there were 18 patients with newly diagnosed CHF among UMEC/VI users and the incidence was similar at 11.0 [95% CI 6.5 to 17.4]). Incidence was higher among UMEC users receiving beta-blockers at index date compared to those who were not (40.8 [95% CI 24.9 to 63.0] *vs* 10.2 [95% CI 6.8 to 14.7], respectively) but not for UMEC/VI users. There was no apparent association with ICS use at index date among either UMEC or UMEC/VI users.

Table 14 Cardiovascular outcomes in new users of UMEC and UMEC/VI during current exposure to the index medication. Combined CPRD GOLD + THIN primary care cohort.

Outcome (identified in primary care record)	Index medication			
	UMEC (n=3875)		UMEC/VI (n=2224)	
Subgroup	Total Events[1]	Incidence (95% CI)[2]	Total Events[1]	Incidence (95% CI)[2]
Myocardial infarction (MI) (per 1000 PY)				
All patients	27	6.9 (4.4 to 10.2)	13	6.8 (3.5 to 11.9)
With prior history of outcome	6	20.4 (7.5 to 44.3)	1	7.3 (0.2 to 40.7)
No prior history of outcome	21	5.6 (3.3 to 8.9)	12	6.8 (3.4 to 12.1)
With beta-blocker use at index date	11	16.7 (8.0 to 30.7)	3	8.1 (1.7 to 23.6)
No beta-blocker use at index date	16	4.8 (2.6 to 8.1)	10	6.5 (3.0 to 12.3)
With ICS use at index date	19	6.7 (3.9 to 10.7)	0	0.0 (0.0 to 21.6)
No ICS use at index date	8	7.4 (3.0 to 15.3)	13	7.5 (3.9 to 13.2)
Stroke (per 1000 PY)				
All patients	171	30.9 (25.3 to 37.4)	84	30.5 (22.8 to 39.8)
With prior history of outcome	140	278.4 (219.7 to 347.9)	57	250.0 (173.1 to 349.3)
No prior history of outcome	31	9.2 (6.2 to 13.2)	27	11.8 (7.1 to 18.5)
With beta-blocker use at index date	29	32.0 (19.3 to 50.0)	21	43.5 (24.9 to 70.7)
No beta-blocker use at index date	142	30.7 (24.6 to 37.8)	63	27.0 (19.0 to 37.2)
With ICS use at index date	113	26.7 (20.7 to 33.9)	7	23.7 (6.5 to 60.7)
No ICS use at index date	58	42.3 (30.1 to 57.9)	77	31.2 (23.1 to 41.2)
Newly diagnosed congestive heart failure (CHF)[3] (per 1000 PY)				
All patients	48	14.8 (10.9 to 19.6)	18	11.0 (6.5 to 17.4)
With beta-blocker use at index date	20	40.8 (24.9 to 63.0)	8	27.8 (12.0 to 54.8)
No beta-blocker use at index date	28	10.2 (6.8 to 14.7)	10	7.4 (3.6 to 13.7)
With ICS use at index date	35	14.9 (10.4 to 20.7)	0	0.0 (0.0 to 23.8)
No ICS use at index date	13	14.5 (7.7 to 24.8)	18	12.2 (7.2 to 19.2)

[1] Includes first and subsequent events
[2] Incidence based on first event only
[3] Newly diagnosed cases only; patients with prior history of CHF were excluded
Source table: Annex 1. Tables: Obj. 2 - T1.1(a)/(b)

10.4.2 Respiratory outcomes during current exposure to index medication: combined CPRD GOLD + THIN primary care cohort

Pneumonia: based on primary care records alone, 25 events in total were identified among UMEC users, for an incidence of 6.9 [95% CI 4.4 to 10.2] per 1000 person years. Among UMEC/VI users, there were six pneumonia events, for an incidence of 3.4 [95% CI 1.2 to 7.4] (Table 15).

Incidence tended to be higher in patients with a history of pneumonia prior to index date compared to those with no prior history for both UMEC and UMEC/VI users. There was no evidence that incidence of pneumonia was different among patients with and without ICS use at index date, though number of events was small.

'Moderate' COPD exacerbations (AECOPD) identified in the primary care record:
'Moderate' exacerbations were relatively common. The incidence of AECOPD in new users of UMEC was 0.98 [95% CI 0.93 to 1.03] per person year. The rate was more than twice as high among UMEC users taking concomitant ICS at index date, compared to those were not (1.16 [95% CI 1.10 to 1.22] vs 0.53 [95% CI 0.47 to 0.61]).

Compared with UMEC users, incidence of AECOPD was significantly lower among new users of UMEC/VI (0.75 [95% CI 0.69 to 0.81] per person year). Similar to UMEC users, incidence was higher in patients taking ICS at index date compared with those who were not (1.34 [95% CI 1.10 to 1.63] vs 0.67 [95% CI 0.62 to 0.74]).

Table 15 Respiratory outcomes in new users of UMEC and UMEC/VI during current exposure to the index medication. Combined CPRD GOLD + THIN primary care cohort.

Outcome (identified in primary care record)	Index medication			
	UMEC	(n=3875)	UMEC/VI	(n=2224)
Subgroup	Total Events[1]	Incidence (95% CI)[2]	Total Events[1]	Incidence (95% CI)[2]
Primary care Pneumonia (per 1000 PY)				
All patients	25	6.9 (4.4 to 10.2)	6	3.4 (1.2 to 7.4)
With prior history of outcome	5	16.0 (4.4 to 41.0)	1	7.6 (0.2 to 42.6)
No prior history of outcome	20	6.2 (3.8 to 9.5)	5	3.1 (1.0 to 7.1)
With ICS use at index date	21	7.8 (4.8 to 12.1)	2	11.7 (1.4 to 42.4)
No ICS use at index date	4	4.2 (1.2 to 10.9)	4	2.5 (0.7 to 6.4)
'Moderate' COPD exacerbations (per PY)				
All patients	3409	0.98 (0.93 to 1.03)	1275	0.75 (0.69 to 0.81)
With ICS use at index date	2919	1.16 (1.10 to 1.22)	231	1.34 (1.10 to 1.63)
No ICS use at index date	490	0.53 (0.47 to 0.61)	1044	0.67 (0.62 to 0.74)

[1] Includes first and subsequent events
[2] Incidence of pneumonia based on first event only. Incidence of AECOPD used all events
Source table: Annex 1. Tables: Obj. 2 - T1.1(a)/(b)

10.4.3 Mortality outcomes during current exposure to index medication: combined CPRD GOLD + THIN primary care cohort

Among new users of UMEC, 105 (2.7%) died for an all-cause mortality rate of 29.9 [95% CI 24.5 to 36.2] per 1000 person years (Table 16). There were 62 deaths among new users of UMEC/VI (2.8%) giving a similar mortality rate of 35.1 [95% CI 26.9 to 44.9]. Rates were similar in patients who were or were not taking concomitant ICS at index date for both UMEC and UMEC/VI.

Table 16 Mortality from all causes in new users of UMEC and UMEC/VI during current exposure to the index medication. Combined CPRD GOLD + THIN primary care cohort.

Outcome (identified in primary care record)	Index medication			
	UMEC	(n=3875)	UMEC/VI	(n=2224)
Subgroup	Events	Incidence (95% CI)	Events	Incidence (95% CI)
Death (all causes) (per 1000 PY)				
All patients	105	29.9 (24.5 to 36.2)	62	35.1 (26.9 to 44.9)
With ICS use at index date	77	30.1 (23.7 to 37.6)	5	29.3 (9.5 to 68.3)
No ICS use at index date	28	29.6 (19.7 to 42.8)	57	35.7 (27.0 to 46.2)

Source table: **Annex 1**. **Tables: Obj. 2 - T1.1(a)/(b)**

Kaplan Meier analysis was carried out comparing cumulative survival in new users of UMEC and UMEC/VI for all outcomes other than COPD exacerbations (see **Annex 1. Obj. 2 – F1-F5**). No differences between the groups were observed in the cumulative survival functions.

10.4.4 Cardiovascular outcomes during current exposure to index medication: linked primary and secondary care CPRD GOLD-HES-ONS cohort

The linked primary and secondary care CPRD GOLD-HES-ONS cohort was substantially smaller than the combined CPRD GOLD + THIN primary care cohort, having only 547 users of UMEC and 512 UMEC/VI users. There were therefore relatively few events for some outcomes, making it difficult to reliably discern or interpret patterns.

Myocardial infarction (MI): there were five events in total among UMEC users, and only two among UMEC/VI users. Incidence was similar in each group: 8.0 [95% CI 1.7 to 23.4] per 1000 person years for UMEC, and 5.5 [95% CI 0.7 to 19.9] per 1000 person years for UMEC/VI (Table 17). Overall incidence of MI during follow-up was therefore very similar to that seen in the combined CPRD GOLD + THIN primary care cohort.

Small numbers of events limited interpretation of stratified analyses. For both UMEC and UMEC/VI users, results were generally consistent with those seen for the combined CPRD GOLD + THIN primary care cohort in terms of the directions and magnitude of differences in the point estimates, although confidence intervals were wide.

Stroke: there were 19 events among UMEC users, and 13 among UMEC/VI users. Stroke incidence was 35.4 [95% CI 18.9 to 60.6] per 1000 person years for UMEC and 16.5 [95% CI 6.1 to 36.0]) per 1000 person years for UMEC/VI (Table 17). Incidence was substantially higher in patients with a stroke history compared to those without a stoke history in both groups, e.g. for UMEC users was (345.3 [95% CI 157.9 to 655.4]) vs (11.7 [95% CI 3.2 to 30.1]); the majority of patients had a prior report of stroke (78.9% and 61.5% of UMEC and UMEC/VI users respectively). There was no evidence that incidence of stroke differed according to use of beta blockers or ICS at index date.

Congestive heart failure (CHF): among UMEC users, there were 5 cases of newly diagnosed CHF, for an incidence of 14.6 [CI 4.7 to 34.0] per 1000 person years. There were 7 patients with newly diagnosed CHF among UMEC/VI users and the point estimate of incidence was a little higher at 20.5 [CI 8.3 to 42.3] per 1000 person years. There was no evidence that incidence of CHF differed according to use of beta blockers or ICS at index date (Table 17).

Table 17 Cardiovascular outcomes in new users of UMEC and UMEC/VI during current exposure to the index medication. Linked primary and secondary care CPRD GOLD-HES-ONS cohort.

Outcome (identified in primary and secondary care record)	Index medication			
	UMEC (n=547)		UMEC/VI (n=512)	
Subgroup	Total Events[1]	Incidence (95% CI)[2]	Total Events[1]	Incidence (95% CI)[2]
Myocardial infarction (MI) (per 1000 PY)				
All patients	5	8.0 (1.7 to 23.4)	2	5.5 (0.7 to 19.9)
With prior history of outcome	2	40.2 (1.0 to 224.1)	0	0.0 (0.0 to 139.8)
No prior history of outcome	3	5.7 (0.7 to 20.7)	2	5.9 (0.7 to 21.5)
With beta-blocker use at index date	2	17.9 (0.5 to 99.8)	1	15.6 (0.4 to 87.1)
No beta-blocker use at index date	3	6.3 (0.8 to 22.7)	1	3.3 (0.1 to 18.6)
With ICS use at index date	4	7.6 (0.9 to 27.5)	0	0.0 (0.0 to 71.8)
No ICS use at index date	1	9.0 (0.2 to 49.9)	2	6.4 (0.8 to 23.2)
Stroke (per 1000 PY)				
All patients	19	35.4 (18.9 to 60.6)	13	16.5 (6.1 to 36.0)
With prior history of outcome	15	345.3 (157.9 to 655.4)	8	136.7 (28.2 to 399.5)
No prior history of outcome	4	11.7 (3.2 to 30.1)	5	8.8 (1.8 to 25.7)
With beta-blocker use at index date	2	36.1 (4.4 to 130.4)	4	47.0 (9.7 to 137.3)
No beta-blocker use at index date	17	35.3 (17.6 to 63.2)	9	10.0 (2.1 to 29.3)
With ICS use at index date	14	31.1 (13.4 to 61.4)	1	19.5 (0.5 to 108.8)
No ICS use at index date	5	45.5 (14.8 to 106.3)	12	16.0 (5.2 to 37.4)
Newly diagnosed Congestive heart failure (CHF)[3] (per 1000 PY)				
All patients	5	14.6 (4.7 to 34.0)	7	20.5 (8.3 to 42.3)
With beta-blocker use at index date	0	0.0 (0.0 to 88.5)	4	79.2 (21.6 to 202.9)
No beta-blocker use at index date	5	16.6 (5.4 to 38.7)	3	10.3 (2.1 to 30.2)
With ICS use at index date	5	21.0 (6.8 to 49.0)	1	20.2 (0.5 to 112.5)
No ICS use at index date	0	0.0 (0.0 to 35.2)	6	20.6 (7.6 to 44.8)

[1] Includes first and subsequent events
[2] Incidence based on first event only.
[3] Newly diagnosed cases only; patients with prior history of CHF were excluded

Source table: Annex 1. Tables: Obj. 2 - T1.2(a)/(b)

10.4.5 Respiratory outcomes during current exposure to index medication: linked primary and secondary care CPRD GOLD-HES-ONS cohort

Pneumonia recorded in primary and secondary care: there were 25 events among UMEC users, for an incidence of 66.0 [95% CI 42.3 to 98.2] per 1000 person years. Among UMEC/VI users, there were 18 events, giving an overall incidence of 47.3 [CI 27.5 to 75.7] (Table 18). Incidence in both groups was therefore substantially higher than in the combined CPRD GOLD + THIN primary care cohort, where incidence was 6.9 and 3.4 per 1000 person years for UMEC and UMEC/VI respectively (Table 15). Pneumonia frequently results in hospitalisation, especially in patients with chronic lung conditions. Such episodes are likely to be captured in the HES data, and relatively less likely to be captured as a coded diagnosis in the primary care record.

Incidence was higher in patients with a history of pneumonia prior to index date compared to those without prior pneumonia. Among both UMEC and UMEC/VI users, there was no evidence that pneumonia incidence differed according to use ICS at index date.

COPD exacerbations (AECOPD):

Moderate and severe COPD exacerbations were common. The AECOPD event rate in new users of UMEC was 1.48 [CI 1.33 to 1.66] per person year. Rates were slightly lower among new users of UMEC/VI at 1.17 [CI 1.01 to 1.35] per person year. In both groups, incidence was highest in patients who were taking concomitant ICS at index date.

Rates of AECOPD were roughly 50% higher in the linked primary and secondary care CPRD GOLD-HES-ONS cohort than in the combined CPRD GOLD + THIN primary care cohort.

Table 18 Respiratory outcomes in new users of UMEC and UMEC/VI during current exposure to the index medication. Linked primary and secondary care CPRD GOLD-HES-ONS cohort.

Outcome (identified in primary and secondary care record)	Index medication			
	UMEC (n=547)		UMEC/ VI (n=512)	
Subgroup	Total Events [1]	Incidence (95% CI)[2]	Total Events[1]	Incidence (95% CI)[2]
Primary+ secondary care pneumonia (per 1000 PY)				
All patients	25	66.0 (42.3 to 98.2)	18	47.3 (27.5 to 75.7)
With prior history of outcome	9	203.1 (92.9 to 385.6)	10	161.0 (73.6 to 305.7)
No prior history of outcome	16	47.0 (26.3 to 77.5)	8	26.3 (11.4 to 51.9)
With ICS use at index date	21	78.6 (48.0 to 121.3)	1	19.5 (0.5 to 108.8)
No ICS use at index date	4	36.7 (10.0 to 94.0)	17	51.9 (29.6 to 84.2)
'Moderate and severe' COPD exacerbation (per PY)				
All patients	554	1.48 (1.33 to 1.66)	421	1.17 (1.01 to 1.35)
With ICS use at index date	437	1.66 (1.47 to 1.87)	103	1.93 (1.43 to 2.62)
No ICS use at index date	117	1.09 (0.83 to 1.43)	318	1.03 (0.88 to 1.20)

[1] Includes first and subsequent events
[2] Incidence of pneumonia based on first event only. Incidence of AECOPD used all events
Source table: Annex 1. Tables: Obj. 2 - T1.2(a)/(b)

10.4.6 Mortality outcomes during current exposure to index medication: linked primary and secondary care CPRD GOLD-HES-ONS cohort

Among new users of UMEC, 18 (3.3%) died, for an overall mortality rate of 48.0 [95% CI 28.5 to 75.9] per 1000 person years (Table 19). There were 19 deaths among new users of UMEC/VI (giving a similar overall mortality rate of 52.0 [95% CI 31.3 to 81.2]. The inclusion of linked ONS death registration data in this cohort allowed the ascertainment of some deaths that might have been missed using the primary care record alone. As a result, mortality in the linked cohort was slightly higher than in the combined primary-care only CPRD GOLD + THIN cohort. Mortality rates when stratified by ICS use were broadly comparable for both medications.

There were 4 deaths from cardiovascular causes in the UMEC group, giving a cardiovascular mortality rate of 10.7 [95% CI 2.9 to 27.3] per 1000 person years, and 6 in the UMEC/VI, for a mortality rate of 16.4 [95% CI 6.0 to 35.7] per 1000 person years. There was no evidence to suggest cardiovascular mortality differed according to concomitant ICS use.

Table 19 Mortality outcomes in new users of UMEC and UMEC/VI during current exposure to the index medication. Linked primary and secondary care CPRD GOLD-HES-ONS cohort.

Outcome (identified in primary care and death registration record)	Index medication			
	UMEC	(n=547)	UMEC/VI	(n=512)
Subgroup	Events	Incidence (95% CI)	Events	Incidence (95% CI)
Death (all causes) (per 1000 PY)				
All patients	18	48.0 (28.5 to 75.9)	19	52.0 (31.3 to 81.2)
With ICS use at index date	12	45.6 (23.6 to 79.7)	3	58.4 (12.0 to 170.7)
No ICS use at index date	6	53.8 (19.7 to 117.0)	16	50.9 (29.1 to 82.7)
Cardiovascular deaths (per 1000 PY)				
All patients	4	10.7 (2.9 to 27.3)	6	16.4 (6.0 to 35.7)
With ICS use at index date	2	7.6 (0.9 to 27.5)	0	0.0 (0.0 to 71.8)
No ICS use at index date	2	17.9 (2.2 to 64.7)	6	19.1 (7.0 to 41.6)

Source table: Annex 1. Tables: Obj. 2 - T1.2(a)/(b)

10.4.7 Secondary analyses:

10.4.7.1 Outcomes during all available follow up including time while not currently exposed to index medication: combined CPRD GOLD + THIN primary care cohort

This analysis used all available follow up, *including* any time between discontinuation of the index medication and censoring or restarting of index medication (see Section 8.2.5.2 for 'not currently exposed' to index medication and Section 8.6.2.2 for 'intention to treat' diagram, Figure 3).

Including all available follow up increased the total amount of person time by around 41% in the UMEC group (from 3508.7 to 4962.6 person years), and by 71% in UMEC/VI users (from 1768.3 to 3019.6 person years). The number of outcome events increased accordingly (Table 20). The incidence of all cardiovascular outcomes was very similar to that seen in the primary analysis of follow up time while currently exposed to index medication (see Table 14). Similar trends were also seen in the stratified analyses: for both MI and stroke, rates were higher among patients with a previous history of the outcome, and this was especially the case for stroke. Patients treated with beta-blockers tended to have higher rates of CHF, and UMEC users treated with beta-blockers also tended to have higher rates of MI.

Incidence of respiratory outcomes during all available follow-up time (i.e. including that while not currently exposed to the index medication) was very similar to that seen in the primary analysis. Incidence of pneumonia (as recorded in primary care) was higher in patients with prior history of the disease, and moderate AECOPD rates were higher among patients treated with ICS at the index date (Table 21).

All-cause mortality during all available follow-up time was higher than observed during current exposure to the index medication. Around 7% of patients died during study, for a rate of 54.6 [95% CI 48.3 to 61.5] vs main analysis 29.9 [95% CI 24.5 to 36.2] in UMEC users, and 58.3 [95% CI 50.0 to 67.6] vs main analysis 35.1 [95% CI 26.9 to 44.9] in UMEC/VI users (Table 22 **compared to** Table 16). For both UMEC and UMEC/VI, there was no difference in all-cause mortality when stratified by ICS use, similar to the primary analyses.

Table 20 Cardiovascular outcomes in new users of UMEC and UMEC/VI during all available follow up, *including time while not currently exposed* to index medication. Combined CPRD GOLD + THIN primary care cohort.

Outcome (identified in primary care record)	Index medication			
	UMEC	(n=3875)	UMEC/VI	(n=2224)
Subgroup	Total Events[1]	Incidence (95% CI)[2]	Total Events[1]	Incidence (95% CI)[2]
Myocardial infarction (MI) (per 1000 PY)				
All patients	36	6.5 (4.4 to 9.1)	23	7.3 (4.6 to 11.1)
With prior history of outcome	8	18.6 (8.0 to 36.7)	5	20.5 (6.6 to 47.7)
No prior history of outcome	28	5.3 (3.4 to 7.9)	18	6.2 (3.6 to 9.9)
With beta-blocker use at index date	13	13.6 (7.1 to 23.8)	6	9.5 (3.5 to 20.7)
No beta-blocker use at index date	23	4.9 (3.0 to 7.6)	17	6.7 (3.9 to 10.9)
With ICS use at index date	23	6.0 (3.7 to 9.3)	1	2.1 (0.1 to 11.7)
No ICS use at index date	13	7.4 (3.8 to 12.9)	22	8.3 (5.1 to 12.7)
Stroke (per 1000 PY)				
All patients	245	32.0 (27.2 to 37.5)	142	30.4 (24.5 to 37.4)
With prior history of outcome	190	269.2 (221.2 to 324.4)	102	263.3 (200.5 to 339.7)
No prior history of outcome	55	10.2 (7.4 to 13.6)	40	11.3 (7.7 to 16.1)
With beta-blocker use at index date	48	39.5 (27.4 to 55.2)	36	42.1 (27.5 to 61.6)
No beta-blocker use at index date	197	30.4 (25.2 to 36.3)	106	27.4 (21.1 to 34.9)
With ICS use at index date	144	27.0 (21.6 to 33.2)	13	17.0 (7.3 to 33.4)
No ICS use at index date	101	42.4 (32.9 to 53.9)	129	33.0 (26.2 to 40.9)
Newly diagnosed congestive heart failure (CHF)[3] (per 1000 PY)				
All patients	60	13.1 (10.0 to 16.8)	36	13.0 (9.1 to 17.9)
With beta-blocker use at index date	22	30.5 (19.1 to 46.2)	14	28.3 (15.5 to 47.5)
No beta-blocker use at index date	38	9.8 (7.0 to 13.5)	22	9.6 (6.0 to 14.6)
With ICS use at index date	41	13.4 (9.6 to 18.2)	3	6.8 (1.4 to 20.0)
No ICS use at index date	19	12.4 (7.5 to 19.4)	33	14.1 (9.7 to 19.8)

[1] Includes first and subsequent events
[2] Incidence based on first event only.
[3] Newly diagnosed cases only; patients with prior history of CHF were excluded
Source table: Annex 1. Tables: Obj. 2 – T2.1(a)/(b)

Table 21 Respiratory outcomes in new users of UMEC and UMEC/VI during all available follow up, *including time while not currently exposed* to index medication. Combined CPRD GOLD + THIN primary care cohort.

Outcome (identified in primary care record)	Index medication			
	UMEC	(n=3875)	UMEC/VI	(n=2224)
Subgroup	Total Events[1]	Incidence (95% CI)[2]	Total Events[1]	Incidence (95% CI)[2]
Primary care Pneumonia (per 1000 PY)				
All patients	46	8.9 (6.5 to 12.0)	18	5.3 (3.0 to 8.6)
With prior history of outcome	10	26.3 (12.0 to 49.9)	4	18.9 (5.2 to 48.5)
No prior history of outcome	36	7.6 (5.3 to 10.6)	14	4.3 (2.2 to 7.5)
With ICS use at index date	34	9.7 (6.6 to 13.6)	5	8.4 (2.3 to 21.5)
No ICS use at index date	12	7.4 (3.8 to 12.9)	13	4.7 (2.4 to 8.3)
'Moderate' COPD exacerbations (per PY)				
All patients	4663	0.94 (0.90 to 0.98)	2241	0.74 (0.69 to 0.79)
With ICS use at index date	3848	1.16 (1.10 to 1.21)	567	1.21 (1.06 to 1.38)
No ICS use at index date	815	0.50 (0.45 to 0.56)	1674	0.65 (0.61 to 0.71)

[1] Includes first and subsequent events
[2] Incidence based on first event only.
Source table: Annex 1. Tables: Obj. 2 – T2.1(a)/(b)

Table 22 All-cause mortality in new users of UMEC and UMEC/VI during all available follow up, *including time while not currently exposed* to index medication. Combined CPRD GOLD + THIN primary care cohort.

Outcome (identified in primary care record)	Index medication			
	UMEC	(n=3875)	UMEC/VI	(n=2224)
Subgroup	Events	Incidence (95% CI)	Events	Incidence (95% CI)
Death (all causes) (per 1000 PY)				
All patients	271	54.6 (48.3 to 61.5)	176	58.3 (50.0 to 67.6)
With ICS use at index date	181	54.3 (46.7 to 62.9)	24	50.2 (32.2 to 74.7)
No ICS use at index date	90	55.2 (44.4 to 67.8)	152	59.8 (50.7 to 70.1)

Source table: Annex 1. Tables: Obj. 2 – T2.1(a)/(b)

The secondary analysis of outcomes during all available follow-up time was repeated in the linked primary and secondary care CPRD GOLD-HES-ONS cohort (see **Annex 1, Obj. 2 – T2.2[a/b]**). Including time after discontinuation of the index medication increased the total amount of follow up from 374.9 to 549.0 person years in UMEC users, and from 365.6 to 649.9 person years in UMEC/VI users. For outcomes other than all-cause mortality, incidence was very similar to that seen during currently exposed follow up. For all-cause mortality, a trend towards modestly increased rates during all follow up (relative to currently exposed follow up) was apparent for UMEC users (67.5 [95% CI

47.5 to 93.0] *vs.* 48.0 [95% CI 28.5 to 75.9]) and UMEC/VI users (70.8 [95% CI 51.8 to 94.4] *vs.* 52.0 [95% CI 31.3 to 81.2]).

10.4.7.2 Outcomes during current exposure to index medication with and without concurrent treatment with other respiratory maintenance therapy: combined CPRD GOLD + THIN primary care cohort

Concurrent treatment with the index medication and other respiratory maintenance therapy (i.e. inhaled treatments for COPD or asthma, containing one or more of ICS, LABA, LAMA or theophyllines) was relatively common among new users of UMEC: 81% (3151/3875) had a least 1 day of follow up with concurrent treatment, and 78% of person time was classified as on concurrent treatment (Table 23). This was substantially lower among UMEC/VI users; around 56% (1252/2224) of new users of UMEC/VI had at least one day of concurrent treatment, and overall only 16% of follow up time was classified as concurrent treatment (Table 23).

The concurrent treatment analysis was not stratified by medication type, but it is likely that a large part of concurrent treatment was with ICS containing medications, since a high proportion of patients (especially UMEC users) were taking ICS-containing medications at the index date (Figure 6). It was therefore expected that patterns of incidence stratified by concurrent treatment would resemble those seen for the stratification by concomitant use of ICS undertaken as part of the primary analysis (Table 7-Table 9), especially among UMEC users.

For cardiovascular outcomes, incidence rates were similar during follow up with and without concurrent treatment, for both UMEC and UMEC/VI users (Table 24).

Among UMEC users, rates of moderate AECOPD were more than twice as high during concurrent treatment periods compared with non-concurrent periods (1.14 [95% CI 1.09 to 1.20] vs. 0.51 [95% CI 0.44 to 0.58] per person year), and a similar pattern was seen for UMEC/VI (1.11 [95% CI 0.96 to 1.29] vs. 0.66 [95% CI 0.60 to 0.73]). This pattern is expected since patients with more severe airway obstruction and/or at high risk of exacerbations are more likely to receive more intensive treatment - especially with ICS-containing medications.

Higher incidence of primary-care diagnosed pneumonia during concurrent treatment was seen for UMEC/VI users, but not UMEC users.

Among UMEC and UMEC/VI users, all-cause mortality was similar among patients who were or were not receiving with other respiratory therapies concurrently (Table 24).

Table 23 Patients and person time with and without concurrent treatment with index medication and other COPD maintenance therapy. Combined primary care CPRD GOLD + THIN cohort.

	UMEC Users (n=3,875)				UMEC/VI users (n=2,224)			
Concurrent treatment	Patients	(%)	Person years	(%)	Patients	(%)	Person years	(%)
With concurrent treatment	3151	(81.3%)	2647.3	(77.8%)	1252	(56.3%)	271.3	(15.6%)
No concurrent treatment	1337	(34.5%)	755.1	(22.2%)	1807	(81.3%)	1465.6	(84.4%)

Table 24 Outcomes in new users of UMEC and UMEC/VI with and without concurrent treatment with index medication and other COPD maintenance therapy. Combined CPRD GOLD + THIN primary care cohort.

Outcome (identified in primary care record)	Index medication			
	UMEC	(n=3875)	UMEC/VI	(n=2224)
Subgroup	Total Events[1]	Incidence (95% CI)[2]	Total Events[1]	Incidence (95% CI)[2]
Myocardial infarction (MI) (per 1000 PY)				
All follow up	27	6.9 (4.4 to 10.2)	13	6.8 (3.5 to 11.9)
With concurrent treatment	19	6.4 (3.7 to 10.2)	3	11.7 (2.4 to 34.1)
No concurrent treatment	8	8.4 (3.4 to 17.4)	10	6.0 (2.7 to 11.4)
Stroke (per 1000 PY)				
All follow up	171	30.9 (25.3 to 37.4)	84	30.5 (22.8 to 39.8)
With concurrent treatment	124	28.6 (22.5 to 35.9)	10	27.2 (11.0 to 56.1)
No concurrent treatment	47	38.2 (25.9 to 54.2)	74	31.0 (22.7 to 41.4)
Newly diagnosed congestive heart failure (CHF)[3] (per 1000 PY)				
All follow up	48	14.8 (10.9 to 19.6)	18	11.0 (6.5 to 17.4)
With concurrent treatment	36	14.6 (10.3 to 20.3)	1	4.2 (0.1 to 23.5)
No concurrent treatment	12	15.3 (7.9 to 26.7)	17	12.2 (7.1 to 19.5)
Pneumonia recorded in primary care (per 1000 PY)				
All follow up	25	6.9 (4.4 to 10.2)	6	3.4 (1.2 to 7.4)
With concurrent treatment	22	7.9 (4.9 to 12.0)	2	7.7 (0.9 to 27.9)
No concurrent treatment	3	3.6 (0.7 to 10.5)	4	2.7 (0.7 to 6.8)
Moderate COPD Exacerbation (per PY)				
All follow up	3409	0.98 (0.93 to 1.03)	1275	0.75 (0.69 to 0.81)
With concurrent treatment	3025	1.14 (1.09 to 1.20)	302	1.11 (0.96 to 1.29)
No concurrent treatment	384	0.51 (0.44 to 0.58)	973	0.66 (0.60 to 0.73)

Outcome (identified in primary care record)	Index medication			
	UMEC	(n=3875)	UMEC/ VI	(n=2224)
Death (all causes) (per 1000 PY)				
All follow up	105	29.9 (24.5 to 36.2)	62	35.1 (26.9 to 44.9)
With concurrent treatment	77	28.8 (22.7 to 36.0)	9	34.8 (15.9 to 66.0)
No concurrent treatment	28	33.6 (22.3 to 48.5)	53	35.1 (26.3 to 45.9)

[1] Includes first and subsequent events
[2] Incidence based on first event only, except for COPD exacerbation which was based on all events.
[3] Newly diagnosed cases only; patients with prior history of CHF were excluded
Source table: Annex 1. Tables: Obj. 2 – T3.1(a)/(b)

10.4.8 Exploratory analysis: outcomes during possible "off-label" current exposure to index medication: combined CPRD GOLD + THIN primary care cohort

Patients prescribed UMEC or UMEC/VI potentially "off-label" (i.e. without a recorded COPD diagnosis) comprised a small proportion of the total: around 7.0% of new UMEC users (n=271), and 8.8% of UMEC/VI users (n=195) (Table 10). Consequently, the number of outcome events in this group tended to be small (Table 25).

There was no evidence to suggest that incidence of cardiovascular outcomes or pneumonia differed with off-label use (Table 25).

Rates of moderate AECOPD were significantly lower among both UMEC and UMEC/VI users classified as potentially off-label, compared to the on-label population with a COPD diagnosis. However, this can in large part be explained by the definition of "off-label" used, since it excludes patients with a specific record for COPD exacerbation. Moreover, the algorithm used to ascertain COPD exacerbations was developed specifically for use among patients with COPD, and the clinical significance of such events may be different in patients who do not have COPD.

Among new users of UMEC/VI, mortality was higher in patients with potential off-label use (122.9 [95% CI 65.4 to 210.1]) compared with on-label users (29.5 [95% CI 21.8 to 39.0]). A more modest increase was also noted for potentially off-label UMEC users although the numbers were small and the confidence intervals wide.

The exploratory analysis of outcomes in the potentially "off-label" population was also repeated in the linked primary and secondary care CPRD GOLD-HES-ONS cohort. For most outcomes there were too few events among possible off-label users to allow meaningful interpretation of rates (see **Annex 1,** Obj.2 T4.2). Mortality from all causes and from cardiovascular causes are shown in Table 26. Among UMEC users, all cause mortality in the possible "off-label" group was 185.3 [95% CI 60.2 to 432.4] – somewhat higher than that seen in UMEC users with a COPD diagnosis (37.4 [95% CI 19.9 to 63.9]). In UMEC/VI users, all-cause mortality was relatively high at 109.6 (95% CI 22.6 to 320.2) among the possible off-label group - though this was based on only three events

– compared to 47.3 (95% CI 27.0 to 76.8) among UMEC/VI users with a COPD diagnosis (Table 26).

Table 25 Outcomes in new users of UMEC and UMEC/VI with and without possible off-label use. Combined CPRD GOLD + THIN primary care cohort.

Outcome (identified in primary care record)	Index medication			
	UMEC	(n=3875)	UMEC/VI	(n=2224)
Subgroup	Total Events[1]	Incidence (95% CI)[2]	Total Events[1]	Incidence (95% CI)[2]
Myocardial infarction (MI) (per 1000 PY)				
All patients	27	6.9 (4.4 to 10.2)	13	6.8 (3.5 to 11.9)
"On-label"	25	7.0 (4.4 to 10.4)	13	7.3 (3.7 to 12.7)
Possible "off-label"	2	5.3 (0.1 to 29.3)	0	0.0 (0.0 to 34.9)
Stroke (per 1000 PY)				
All patients	171	30.9 (25.3 to 37.4)	84	30.5 (22.8 to 39.8)
"On-label"	166	31.1 (25.4 to 37.8)	80	30.0 (22.2 to 39.6)
Possible "off-label"	5	26.5 (8.6 to 61.9)	4	38.0 (10.4 to 97.4)
Newly diagnosed congestive heart failure (CHF)[3] (per 1000 PY)				
All patients	48	14.8 (10.9 to 19.6)	18	11.0 (6.5 to 17.4)
"On-label"	47	15.3 (11.2 to 20.3)	16	10.4 (6.0 to 16.9)
Possible "off-label"	1	5.9 (0.1 to 32.7)	2	20.8 (2.5 to 75.0)
Primary-care pneumonia (per 1000 PY)				
All patients	25	6.9 (4.4 to 10.2)	6	3.4 (1.2 to 7.4)
"On-label"	22	6.4 (3.9 to 9.7)	6	3.6 (1.3 to 7.9)
Possible "off-label"	3	15.8 (3.3 to 46.2)	0	0.0 (0.0 to 34.9)
'Moderate' COPD exacerbation (per PY)				
All patients	3409	0.98 (0.93 to 1.03)	1275	0.75 (0.69 to 0.81)
"On-label"	3297	1.00 (0.95 to 1.05)	1229	0.77 (0.71 to 0.84)
Possible "off-label"	112	0.60 (0.46 to 0.79)	46	0.41 (0.29 to 0.58)
Death (all causes) (per 1000 PY)				
All patients	105	29.9 (24.5 to 36.2)	62	35.1 (26.9 to 44.9)
"On-label"	96	28.9 (23.4 to 35.3)	49	29.5 (21.8 to 39.0)
Possible "off-label"	9	47.4 (21.7 to 89.9)	13	122.9 (65.4 to 210.1)

[1] Includes first and subsequent events
[2] Incidence based on first event only, except for COPD exacerbation which was based on all events.
[3] Newly diagnosed cases only; patients with prior history of CHF were excluded
Source table: Annex 1. Tables: Obj. 2 – T4.1)

Table 26 Mortality outcomes in new users of UMEC and UMEC/VI with and without possible off-label use. Linked primary and secondary care CPRD GOLD-HES-ONS cohort.

Outcome (identified in primary and secondary care record)	Index medication			
	UMEC	(n=547)	UMEC/VI	(n=512)
Subgroup	Events	Incidence (95% CI)	Events	Incidence (95% CI)
Death (all causes) (per 1000 PY)				
All patients	18	48.0 (28.5 to 75.9)	19	52.0 (31.3 to 81.2)
"On-label"	13	37.4 (19.9 to 63.9)	16	47.3 (27.0 to 76.8)
Possible "off-label"	5	185.3 (60.2 to 432.4)	3	109.6 (22.6 to 320.2)
Cardiovascular deaths (per 1000 PY)				
All patients	4	10.7 (2.9 to 27.3)	6	16.4 (6.0 to 35.7)
"On-label"	3	8.6 (1.8 to 25.2)	5	14.8 (4.8 to 34.5)
Possible "off-label"	1	37.0 (0.9 to 206.3)	1	36.5 (0.9 to 203.5)

Source table: **Annex 1**. Tables: Obj. 2 – T4.2

10.5 Objective 3

In new users of UMEC/VI or UMEC with 12 or more months of follow up, treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up are described in the combined CPRD GOLD +THIN primary-care cohort.

[Full results for this section are in the following files in **Annex 1**:
Annex 1: Objective 3 Results]

10.5.1 Treatment patterns

*New users of UMEC with **no concomitant treatment** with other inhaled COPD maintenance therapy at initiation (32.3% of all UMEC users)*: There were 3,240 new users of UMEC with at least 12 months of follow up, of which 1,047 (32.3%) were not receiving concomitant treatment at the time of initiation. Just over a third (35.4%) of these patients continued to receive UMEC for at least 12 months **(**Table 27**)**. More than half (50.6%) discontinued during the follow up period, defined as a gap in prescribing of at least 91 days. The Kaplan Meier analysis (Figure 10**a**) shows that around 41% of discontinuers (215 patients) did so at 30 days, i.e. after a single prescription, but thereafter discontinuations occurred relatively steadily over the remaining 11 months.

More than half of patients who discontinued (279/530) did resume the index medication during the 12-month follow up period, after a hiatus of at least 90 days (Table 27). A gap of 91+ days between UMEC prescriptions could be the result of an extended hospital stay (with medication use there not captured in the electronic record), or could indicate low adherence, or a failure to identify prescriptions for multiple inhaler devices intended to cover a period longer than 90 days. Three quarters of patients who switched, did so within 120 days (Figure 10**a**).

Treatment patterns were generally similar for UMEC users grouped according to on-label and potential off-label use. The most notable difference was that the proportion of true discontinuers was higher in the potential off-label group (60.8% of all patients who discontinued), compared to the on-label group (38.6% of all discontinuers) (see **Annex 1. Table: Obj3 T4**).

*New users of UMEC with **concomitant treatment** with other inhaled COPD maintenance therapy (67.7% of all UMEC users)*: There were 2,193 new users of UMEC with at least 12 months of follow up, and who were receiving concomitant treatment at the time of initiation. More than half of these patients (50.9%) continued both UMEC and concomitant treatments throughout the first 12 months. Around a quarter of patients (25.2%) discontinued UMEC only, and 7% discontinued both treatments. Discontinuation of UMEC and/or the concomitant medication frequently occurred at 30 days, i.e. after a single prescription (296 patients, 27.4%), after which time the discontinuation rate was relatively steady (Figure 10**b**).

Treatment patterns were broadly similar irrespective of on-label or potential off-label use. (**Annex 1. Table: Obj3 T4**)

*New users of UMEC/VI with **no concomitant treatment** with other inhaled COPD maintenance therapy at initiation (81.1% of UMEC/VI users)*: There were 1,822 new users of UMEC/VI with at least 12 months of follow up. In contrast to UMEC users, the majority (1,478, 81.1%) were not receiving concomitant treatment at the time of initiation. Of these, 44.3% of new users of UMEC/VI continued with their index medication for the full 12 months of follow up (Table 27). Discontinuation occurred in 36.7% of patients, but two thirds of these patients resumed taking UMEC/VI after a gap of 91 days or more. Around 1 in 6 patients (16.8%) immediately switched to another therapy. The Kaplan Meier plot (Figure 10**c**) shows that discontinuation after a single prescription (30 days) was relatively common, occurring in 35.2% of discontinuers (191/542 patients). After 30 days discontinuations occurred relatively steadily during the remaining follow up.

Treatment patterns were generally similar for UMEC/VI users grouped according to on-label and potential off-label use, but a higher proportion of potential off-label users discontinued UMEC/VI (48.7%, of which the majority were true discontinuations) compared to the on-label group (35.7% discontinued but the majority of these resumed after a gap of more than 90 days) (see **Annex 1. Table: Obj3 T4**).

*New users of UMEC/VI with **concomitant treatment** with other inhaled COPD maintenance therapy (18.9% of all UMEC/VI users)*: There were 344 new users of UMEC/VI with at least 12 months of follow up, who were receiving concomitant treatment at the time of initiation. Only 22 patients (6.4%) continued to receive both UMEC/VI and a concomitant treatment (Table 27). This is expected because the majority of concomitant treatments contained LABA, LAMA or even both. The most common pattern was for the concomitant treatment to be discontinued (43.0%), and in almost half of instances (72/148) this occurred after 30 days, consistent with a switch from the concomitant medication to UMEC/VI. A third of patients discontinued UMEC/VI – and in almost half of cases (51/115) this occurred after a single prescription (Figure 10**d**).

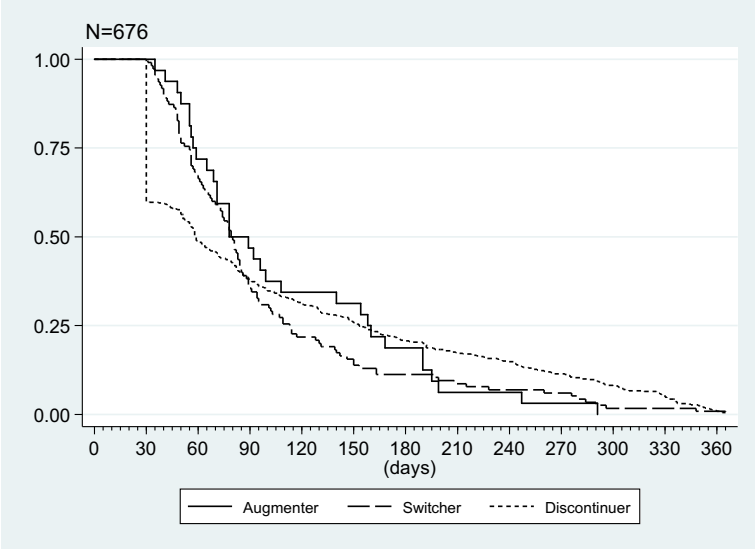
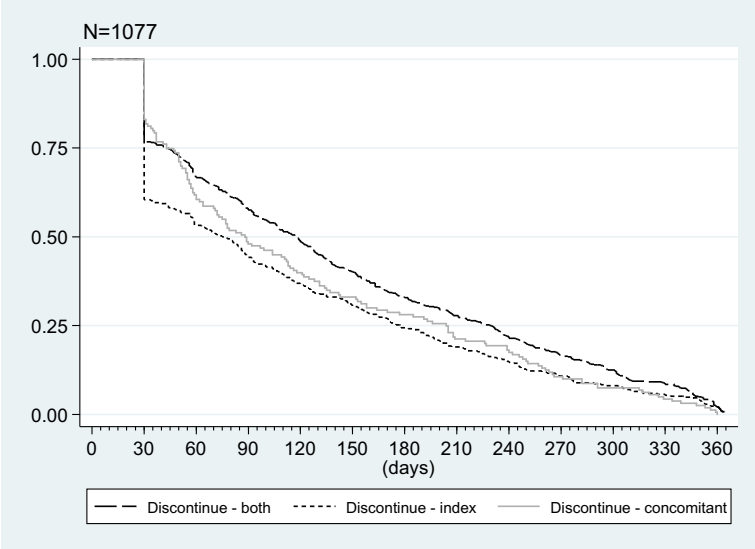
Treatment patterns were similar in patients with a COPD diagnosis, and those with possible off-label use, although there were only 25 patients in the latter group (see **Annex 1. Table: Obj3 T4**).

Table 27 Treatment patterns of inhaled COPD maintenance therapies in the first 12 months[1] following initiation of UMEC and UMEC/VI. Combined CPRD GOLD +THIN primary care cohort

	UMEC (n=3,240)[1]			UMEC/VI (n=1,822)[1]		
Treatment pattern	No.	(%)	Days to first change Mean (SD)	No.	(%)	Days to first change Mean (SD)
No concomitant COPD maintenance therapy						
All patients	1047	(32.3)		1478	(81.1)	
Continuous user	371	(35.4)	n/a	655	(44.3)	n/a
Augmenter	32	(3.1)	110.69 (65.64)	32	(2.2)	118.19 (72.01)
Immediate switcher	114	(10.9)	96.17 (66.68)	249	(16.8)	120.67 (88.81)
Discontinuer	530	(50.6)	106.52 (98.52)	542	(36.7)	111.34 (95.92)
True discontinuer	216	(40.8)	96.15 (98.22)	177	(32.7)	84.42 (89.74)
Discontinuer with drug hiatus	279	(52.6)	121.26 (100.72)	359	(66.2)	125.54 (96.54)
Discontinuer with latent switch	35	(6.6)	53.11 (40.95)	6	(1.1)	55.83 (31.49)
With concomitant COPD maintenance therapy						
All patients	2193	(67.7)		344	(18.9)	
Continuous use of both drugs	1116	(50.9)	n/a	22	(6.4)	n/a
Discontinuation of index drug only	553	(25.2)	143.24 (105.92)	115	(33.4)	87.25 (81.83)
Discontinuation of concomitant drug only	364	(16.6)	114.74 (99.37)	148	(43.0)	68.39 (70.39)
Discontinuation of both drugs	160	(7.3)	125.36 (97.76)	59	(17.2)	87.27 (69.57)

[1] Treatment patterns were only classified in patients with at least 12 months follow-up after initiation.
Source table: Annex 1. Tables: Obj.3 – T1

Figure 10 Kaplan Meier plots of time (in days) to first treatment change, by type of treatment change, for new users of UMEC and UMEC/VI with and without concomitant inhaled COPD maintenance therapy at index date. Combined CPRD GOLD + THIN primary care cohort[1]

<table>
<tr><td>UMEC users: no concomitant maintenance therapy at index date</td><td>UMEC users: with concomitant maintenance therapy at index date</td></tr>
<tr><td> 
</td><td> 
</td></tr>
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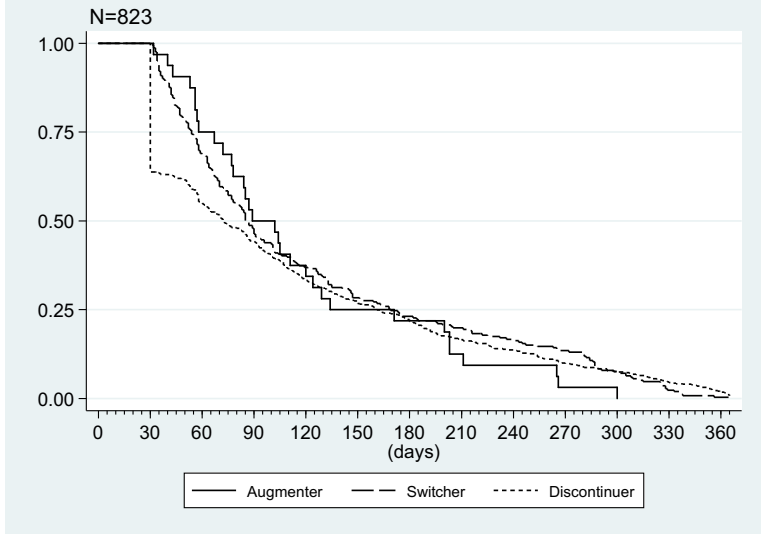

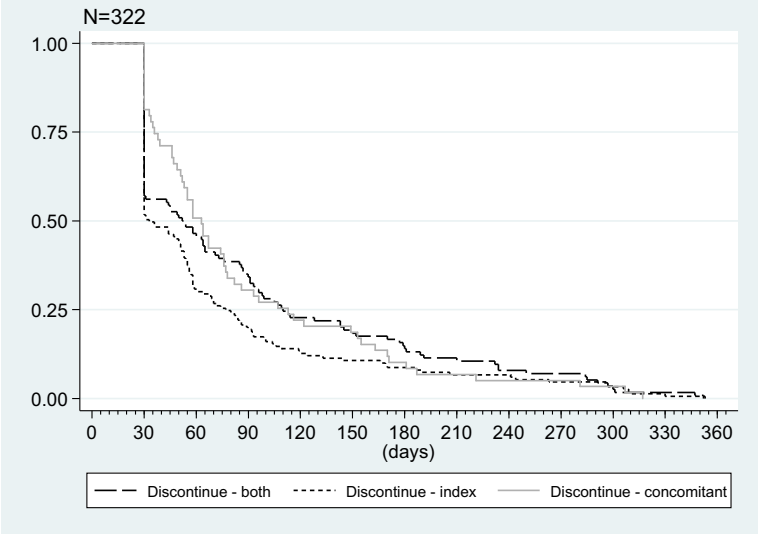

Source Figure Obj. 3 F1. F2, F3 and F4

[1] Treatment patterns were only classified in patients with at least 12 months follow-up after initiation.

10.5.2 Treatment adherence

Using a medication possession ratio (MPR) threshold of ≥80% to classify adherence to medication, 64% of UMEC users, and 64% of UMEC/VI users were classified as adherent over 12 months. The mean MPR was 92% (SD 75%) among UMEC users and 100% (SD 147%) for UMEC/VI users (see **Annex 1. Table: Ob3. T2**).

Using the MPR definition, baseline characteristics were very similar among patients who were adherent or not adherent, (see **Annex 1. Table: Ob3. T3**). Adherence was very similar among patients with and without a COPD diagnosis, and this was the case for both UMEC and UMEC/VI users **(**Table 28**)**.

Using a more conservative definition of adherence based on a proportion of days covered (PDC) ≥80%, 41% of UMEC users, and 33% of UMEC/VI users were classified as adherent. Compared to MPR, the mean PDC was also lower, at 63% (SD 33%) among UMEC users and 55% (SD 34%) for UMEC/VI users (see **Annex 1. Table: Ob3. T2**). The difference is due in part to the methodology used e.g. the use of a fixed denominator of 365 days for the PDC calculation, irrespective of whether a patient discontinued the medication before that time, while the denominator for the MPR calculation only considers the time during the first continuous treatment period, which in some cases may be much less than 365 days (see Table 2, **Section 8.2.6.3**). In addition, the PDC calculation includes patients who only received a single prescription, whereas these patients are excluded in the MPR calculation.

No substantial differences were observed in the baseline characteristics of patients who were adherent (PDC ≥80%) or not adherent (see **Annex 1. Table: Ob3. T3**). Adherence defined as PDC ≥80% tended to be lower in patients without a COPD diagnosis (i.e. the possible off-label group) compared to those with a COPD diagnosis (Table 28), and this was the case for both UMEC (adherence 34% in off-label users vs 42% for on-label users) and UMEC/VI (adherence 22% for off-label users vs 34% for on-label users).

Table 28 Adherence to UMEC and UMEC/VI therapy in the first 12 months[1] after index date. Combined CPRD GOLD + THIN primary care cohort.

		Patients with a recorded COPD diagnosis "on label"				Patients without a recorded COPD diagnosis "possible off-label"			
		UMEC		UMEC/VI		UMEC		UMEC/VI	
		No.[2]	Proportion[2]	No.[2]	Proportion[2]	No.[2]	Proportion[2]	No.[2]	Proportion[2]
Medication Possession Ratio (MPR)	Total patients[1]	2,563		1,349		153		83	
	Mean % (SD)	92%	76%	100%	147%	97%	52%	90%	32%
	≥80%	1,635	63.8	866	64.2	99	64.7	55	66.3
	<80%	928	36.2	483	35.8	54	35.3	28	33.7
Proportion Days Covered (PDC)	Total patients[1]	3,047		1,684		193		138	
	mean % (SD)	63%	33%	56%	34%	57%	34%	41%	34%
	≥80%	1,267	41.6	568	33.7	65	33.7	31	22.5
	<80%	1,780	58.4	1,116	66.3	128	66.3	107	77.5

1 Adherence was only calculated in patients with at least 12 months of follow up
[2] Unless otherwise specified.
Source table: Annex 1. Tables: Obj.3 -T5

11 DISCUSSION

This large, retrospective study combined data from two primary care databases (CPRD GOLD and THIN) to identify and characterise a substantive number of new users of UMEC (3,875 patients), UMEC/VI (2,224 patients), and Other LABD (32,809 patients). The study design has a number of notable strengths. The study utilised rich data sources which included clinical characteristics of COPD patients (e,g. spirometry, dyspnoea scores) not typically available in other large linked healthcare databases. The study allowed more complete ascertainment of events including deaths in both primary and secondary care via linkage to HES (hospital admission) and ONS (death registration) data. The non-interventional design increased the likelihood that GPs and patients' routine healthcare behaviours were observed with less opportunity to bias observed associations between newly prescribed medication and recording of outcomes of interest. Furthermore, restriction of the population of interest to new-users minimised the potential for survivor bias.

Within the CPRD GOLD + THIN, the mean age of patients was 66 years. Fifty one percent were female, and 85% were current or ex-smokers. The number of new users of UMEC and UMEC/VI substantially exceeded the notional target of 1,000 patients for each group required to allow acceptable precision on the estimates of potential off-label use.

There were some differences between the CPRD GOLD and THIN databases in terms of regional distribution of practices. This meant that the loss of contributing English practices during the study period disproportionately affected the CPRD GOLD database, resulting in a slightly shorter median follow up in patients from CPRD GOLD. However,

baseline analyses demonstrated that the characteristics of new LABD users in each database were very similar, meaning data could be combined into a single cohort.

A linked cohort of patients from a subset of English practices from the CPRD GOLD database with linked HES and ONS was also used to provide additional information on outcomes recorded in secondary care, and on cause of death. The overall characteristics of the two cohorts were very similar.

New UMEC users had more severe respiratory disease compared to new users of UMEC/VI or Other LABD. The UMEC group had the highest rates of COPD exacerbation events, more severe MRC dyspnoea scores, and greatest airflow limitation (as measured by spirometry). UMEC users were also much more likely to have received other respiratory therapies in the 12 months prior to their index prescription. Around two thirds of new UMEC users were already receiving treatment with ICS/LABA and were therefore either stepping up to triple therapy (i.e. LABA + LAMA + ICS; multiple inhaler triple therapy or MITT) or were already receiving triple therapy but switching to UMEC from a different LAMA. MITT is recommended for the most severe COPD patients such as those in GOLD group D [GOLD 2017], which appears to be aligned with characteristics of UMEC users.

Objective 1: possible off-label use.
Possible off-label use was low and similar in UMEC and UMEC/VI: 7.0% of new users of UMEC and 8.8% of new users of UMEC/VI had no coded diagnosis of COPD. This compared with 18% of new users of Other LABD without a COPD diagnosis.

There were 130 new users of UMEC (3.4%) with an asthma diagnosis, but only 34 of these patients (0.9% of all UMEC patients) were not taking concomitant ICS at the index date. Similarly, there were 69 new users of UMEC/VI (3.1%) with an asthma diagnosis, and 39 patients of these patients (1.8% of all UMEC/VI users) were not taking concomitant ICS at the index date. This suggests that the majority of GPs follow clinical guidelines which specifically contraindicate LABA for treatment of asthma except in combination with ICS.

In contrast, the majority of UMEC or UMEC/VI users with neither COPD nor asthma diagnosis were not taking concomitant ICS at index date. This group with neither COPD nor asthma may be comprised of a number of different patient types:

- Patients with COPD or asthma who do not (yet) have a coded diagnosis recorded. In some cases, results of further investigations may be pending before a final firm diagnosis was recorded. In other cases, a working diagnosis may have been recorded as free text. It is also possible that Quality and Outcomes Framework (QOF) targets for managing COPD or asthma created perverse incentives for practices to not include on the COPD or asthma register patients who may for a variety of reasons be difficult to manage.
- Patients with COPD but who were younger than 35 years old.

- Patients with some other undiagnosed condition (not COPD or asthma) but with no firm diagnosis who may be prescribed UMEC or UMEC/VI as a therapeutic trial for symptomatic relief.

Objective 2

The study provides incidence estimates for potential safety-related outcomes in patients using UMEC and UMEC/VI. These estimates will be useful for planning future studies which may include more formal comparative safety evaluations.

The incidence of cardiovascular outcomes (MI, stroke and newly diagnosed CHF) in the combined CPRD GOLD+THIN primary care cohort were similar for UMEC and UMEC/VI users. Other primary care EMR database studies using the same data sources THIN [Jara, 2012]; CPRD, [Suissa, 2017a, Suissa, 2017b] have reported IRs of cardiovascular events in new users of LAMA, LABA or LAMA + LABA. In those studies, reported incidence of MI ranged between 10-13 per 1000 PY compared to 6.8-6.9 per 1000 PY in our study, and incidence of HF ranged between 29-46 per 1000 PY compared to 11-14.8 per 1000 PY in our study. The higher incidence reported in earlier studies may be explained by a number of factors. A key difference was that both earlier studies were restricted to patients aged over 55 years at index date, whereas no age restriction was imposed in the current study. The earlier studies examined incidence between 2003-2013, compared with 2014-2016 in the current study, so temporal trends in MI incidence may also be important. Finally, differences in the code lists and algorithms used to identify cases may also contribute to differences.

The [Jara, 2012] and [Suissa, 2017a, Suissa, 2017b] studies also reported incidence of stroke which ranged from 7-16 per 1,000 PY, which was somewhat lower than the rates in the current study (30.5-30.9 per 1,000 PY). The inclusion of codes for TIA in the case identification algorithm may have contributed to the higher rates seen in the current study. Inclusion of some administrative codes may also have resulted in case management of patients with a previous stroke being misclassified as a new stroke event. This is supported by the observation that a very high proportion of 'incident' stroke events occurred in patients with a prior stroke history. In UMEC and UMEC/VI users with no prior history in the current study rates of stroke ranged from 9.2-11.8 per 1,000 PY, which was much more consistent with rates from earlier studies.

In the combined CPRD GOLD+THIN primary care cohort, rates of pneumonia and COPD exacerbations (AECOPD) were slightly higher among UMEC users compared with UMEC/VI, which is consistent with the channelling of UMEC to patients with more severe COPD. Similarly, in both UMEC and UMEC/VI users, AECOPD tended to be higher among patients taking concomitant ICS at index date, who were also likely to have more severe disease. Rates of pneumonia did not vary with ICS use at index date.

For some outcomes, event rates in the CPRD GOLD + THIN primary care cohort were lower when compared to the same outcome ascertained using both primary care and

linked HES data in the CPRD GOLD-HES-ONS cohort. In particular, incidence of pneumonia was much higher in the CPRD GOLD-HES-ONS for both UMEC and UMEC/VI. There are a number of possible reasons for this. For pneumonia especially – but also to some extent for other outcomes – the linked HES data effectively identifies severe cases which result in hospital admission. Although hospital diagnoses are normally communicated to the GP after discharge, they do not always result in a specific diagnosis code being entered in the primary care record. Instead they may be captured as a non-specific record indicating a hospital admission, perhaps linked to a scanned copy of a discharge letter, or to a free text note. Less severe cases of pneumonia treated in primary care - often without X-ray confirmation - may be recorded using non-specific codes such as lower respiratory tract infection. Therefore, to ascertain the cases of severe pneumonia which are of particular relevance when investigating potential safety issues, it is essential to use a data source such as HES which captures these efficiently. To contextualise the rates reported here, [Suissa, 2019] reported similar rates of hospitalised pneumonia among COPD patients on LAMA/LABA using the same data source (51 per 1000 PY) and in another study (53 per 1000 PY) among patients on LAMA [Suissa, 2017a]. [Pate, 2018] also utilised CPRD GOLD-HES linked data and reported higher rates (107 per 1000 PY); however, users were exposed to all inhaled maintenance therapy (including ICS, LAMA, LAMA/LABA and ICS/LAMA/LABA), where the inclusion of ICS-exposed patients likely accounted for the increased rate seen.

Differences in regional composition of the two cohorts may contribute to minor variations in incidence rates: the linked GOLD-HES-ONS cohort is a subset of the combined GOLD + THIN cohort and comprised of English general practices only. By contrast, English practices contribute only 20% of the UMEC users, and 33% of UMEC/VI users in the combined GOLD + THIN cohort, meaning that the overall incidence is substantially influenced mainly by non-English UK regions. Finally, the use of two different data sources increases the risk of double counting of outcome events which would inflate the rate in the linked CPRD GOLD-HES-ONS cohort relative to the CPRD GOLD + THIN primary care cohort. For example, the occurrence of myocardial infarction (for example) may be captured in both the primary care record and in HES sources however, the identification algorithm attempts to account for this by treating events occurring within a specified time window as part of the same episode. Nevertheless, this automated approach is likely to result in some misclassification, especially if there are reporting delays or inaccuracies in recording occurrence dates in one or other data source. For comparative safety evaluations involving such outcomes, a more thorough outcome adjudication method would be essential.

Similar considerations may account for the increased rates of COPD exacerbations in the linked CPRD GOLD-HES-ONS cohort, which were 51-56% higher than in the CPRD GOLD + THIN primary care cohort. This reflects in part the ascertainment of additional severe exacerbations (i.e. those resulting in hospitalisation) which is captured relatively well in the HES data, but not in the primary care record. This difference was much less pronounced than seen for pneumonia, possibly because a smaller proportion of AECOPD events result in a hospital admission. Differences in the composition of the two cohorts

may also explain part of the difference in AECOPD rates: analysis of AECOPD rates in the year prior to index date were estimated in the linked CPRD GOLD-HES-ONS cohort using the primary care data alone (described as 'moderate' AECOPD) as well as using primary care and linked HES data ('moderate and severe' AECOPD) – [**Annex 1, Table: Baseline T4.2**] – and in this analysis the addition of HES data only increased the overall AECOPD rate by 15-20%.

In both cohorts and for both treatments, the rate of moderate AECOPD was higher among users taking concomitant ICS at index date, compared to those were not. This pattern is not unexpected, since international guidelines recommend addition of ICS to regular long acting bronchodilator treatment in patients with severe/very severe airway obstruction, and/or at high risk of further exacerbations [GOLD, 2017].

All-cause mortality was 48-61% higher in the linked CPRD GOLD-HES-ONS cohort compared to the combined CPRD GOLD + THIN primary care cohort. This difference was slightly unexpected, since the overall concordance of fact and date of death between CPRD GOLD and linked ONS death registrations was expected to be high, especially in recent years: [Gallagher, 2019] found that 97% of ONS death registrations were also recorded in CPRD GOLD with a date within 30 days of the registered death date. Further investigation confirmed that of 83 death registrations identified in the linked CPRD GOLD-HES-ONS cohort, 79 (95%) were also identified in the primary care record (data not shown). The discrepancies in mortality is largely explained by the low mortality seen in the THIN cohort, which was substantially lower than in the CPRD GOLD cohort for both (data not shown). Differences in the method used for estimating date of death may explain some of the discrepancy in deaths rates between CPRD GOLD and THIN. In particular, in some circumstance the THIN algorithm can result in an estimated date of death which is *after* the transfer out date, even if the reason for transfer is stated as death. These patients were therefore considered to be censored prior to death (and the death is therefore excluded). By contrast, in CPRD GOLD where the transfer out reason is death, the algorithm uses the earlier of the transfer out date and the date estimated using other data items, and these patients would be considered to have died. Mortality rates reported in this study (using linked CPRD-HES-ONS) data are comparable to those reported by [Rebordosa, 2019] using the same dataset for other LAMAs (aclidinium [32.91, 95% CI 26.75-40.07], tiotropium [45.10, 42.24-48.11), other LAMA (glycopyrronium/umeclidinium; 39.26, 33.04-46.30) and other LABAs [39.93, 33.78-46.88] [Rebordosa, 2019].

Mortality rates were lower during current exposure to UMEC or UMEC/VI compared to those when all follow up time was considered, suggesting that mortality increases substantially after patients discontinue their medication. Because the additional follow up time came later in the course of a progressive disease, some increase in mortality would be expected, though not enough to explain the size of the increase observed. Other factors may contribute – for example some patients may be switched to UMEC or UMEC/VI when they experience worsening symptoms, but this treatment is discontinued quickly if their condition continues to deteriorate with attendant high mortality. Discontinuation of therapy may itself be a marker for deterioration; for example it may occur when a patient

is admitted to hospital, or their management is taken over by specialist services or palliative care.

The reasons for the high mortality among potential off-label users of UMEC/VI (122.9 [CI 65.4 to 210.1]) relative to on-label users (29.5 [CI 21.8 to 39.0]) are not clear. One possible explanation for this finding is that the potential "off-label" group included patients who presented with severe pulmonary symptoms and were treated but died before a COPD diagnosis was established.

Objective 3

The results provide an overview of treatment patterns during the first 12 months after initiating treatment with UMEC or UMEC/VI and suggest that both medications were acceptable and tolerated by the majority of patients, with approximately 1 in 3 patients likely to have switched or permanently discontinued the medication.

At the time of the index prescription, around 65% of UMEC users were taking an ICS/LABA medication, with the addition of UMEC probably representing a step up to triple therapy (LABA + LAMA + ICS) in patients with more severe or poorly controlled disease, and around half of patients (52%) continued to take both treatments for at least 12 months, although almost a quarter discontinued UMEC after a single prescription.

Only 22% of UMEC/VI users were receiving concomitant treatment at the index date – generally either ICS/LABA or LAMA. As expected, the majority of these patients discontinued either the index medication, or the concomitant medication. Among UMEC/VI users who were not taking concomitant medication, 45% continued to take it for at least 12 months, and a further 25% resumed taking it after a break of more than 90 days.

Medication adherence in COPD is an important issue for both patients and health care systems. Non-adherence is very common, and is associated with significant negative impact on morbidity, health care costs, quality of life and mortality [Bourbeau, 2008; Mäkelä, 2013]. The two measures adopted in this study provide insight into complementary aspects of medication adherence.

MPR provides an estimate of patients' medication supply *during the first period of continuous treatment*. It is a less conservative measure of adherence: it excludes patients who received only one prescription, and it ignores all person time after the patient stops taking the medication. The measure may also overestimate true adherence in patients who routinely pick up their medication early, and in some situations, it may exceed 100%. In this study, the 64% of both UMEC and UMEC/VI users were classified as adherent, based on MPR ≥80%, whereas adherence estimated from PDC ≥80% was 41% for UMEC and 33% for UMEC/VI.

The starting assumption for the PDC calculation is that *all* patients will continue taking the index medication throughout the 1 year follow period. It then estimates the proportion

of days during that period when medication supply is available. The PDC calculation therefore combines the distinct issues of adherence and discontinuation.

Both MPR and PDC could underestimate adherence if the patient received medications through some route other than via GP prescribing – for example during a hospital stay. Both measures also rely on correctly estimating the expected duration of each prescription. Both UMEC and UMEC/VI are available only as inhaler devices delivering 30 fixed daily doses, and exploratory analyses confirmed that in CPRD GOLD over 98% of prescriptions were for a single device (data not shown). Therefore, the assumed 30-day duration for each prescription was expected to be sufficiently accurate. Neither MPR nor PDC can account for primary non-adherence whereby prescriptions are issued but not fulfilled.

11.1 Limitations of the research methods

- Generalizability of the UK data to the other EU countries is a potential study limitation. GSK proposed this study in the UK environment because of the presence of robust data and possibility to use a distributed design within one health-care system ensuring fast delivery.
- Analysis of respiratory diagnoses and other co-morbidities include only diagnosed diseases that are recorded using coded data in EMR by the GP. Patients with COPD and asthma may have been wrongly placed into the 'not COPD or asthma' diagnosis group because their medical record did not contain a coded diagnosis (i.e. the diagnosis was written in free text or in letters from specialists) or because they were in the process of receiving a diagnosis. Additionally, the COPD group may include patients with a COPD diagnoses code but whose diagnosis was not confirmed with spirometry.
- There is the potential to misdiagnose COPD as asthma (or vice versa), particularly in patients 40 years of age and older [Tinkelman, 2006]. Some patients may indeed have both COPD and active, concurrent asthma. We accept limitations of our disease algorithms, particularly for mixed disease, and note the potential for some misclassification as would be expected in electronic medical records.
- Data on new exposure to UMEC/VI, UMEC, or Other LABD are based on records of prescribed medications by the general practitioner and information on prescriptions initiated in hospitals or secondary care are not accessible for analysis. This meant we were not able to ascertain exposure start accurately in situations where UMEC/VI, UMEC, or Other LABD may have been initially prescribed by a chest specialist, in hospital or at hospital. This may lead to an underestimation of UMEC and UMEC/VI prescribing, off-label use and adherence.
- Medication use is based on prescribed medications recorded by the general practitioner, which might not have been dispensed at the pharmacy or ultimately utilized by the patient. As such, this study is only able to assess off-label prescribing and cannot make strong inferences about off-label use. Where medicines have been prescribed but not dispensed, we will over estimate off-label use. Similarly, we would overestimate adherence to prescribed medications, particularly using the PDC

measure that does not require a second prescription (a recognised sign of compliance with the first prescription).

- An assumption was made that each prescribed medication provides treatment for 30 days, which may introduce a bias, albeit one of a systematic nature, impacting on all medications.
- A strength of the study is that it uses two databases (CPRD-GOLD and THIN) to increase the sample size; however, it may also be viewed as a limitation in that it increases the complexity of data analysis arising from differences in coding procedures and classification across the databases. To overcome challenges with combinations of data, a maximally integrated model was selected, with each separate database extract processed and converted at CPRD into an analysis dataset conforming to a standard specification. Analyses were then performed using a single set of programs which could be run against either a pooled analysis dataset, or where necessary on each dataset separately. This provided the greatest control over standardisation and quality assurance of the analyses.

12 CONCLUSIONS

The combined dataset from two electronic healthcare records databases, CPRD GOLD and THIN, provided a large and broadly representative cohort of COPD patients from UK primary care, and allowed detailed characterisation of new users of UMEC and UMEC/VI. Patients characteristics in the three different treatment groups were similar, although compared to new users of UMEC/VI or Other LABD, new UMEC users had more severe respiratory disease and were taking more concomitant respiratory medications at index date. Two-thirds of UMEC users were stepping up to MITT, which appears to be appropriate, given their increased disease severity.

With this drug utilisation study, we provide a benefit/risk assessment of UMEC and UMEC/VI allowing any risks to be placed into context of patients' broader experience with the medicines and conclude the following:

Objective 1: The proportion of patients with possible off-label use in both UMEC and UMEC/VI was low compared with users of other LABD. This demonstrates that physicians were prescribing according to the authorised indications for these therapies, in a UK primary care setting.

Objective 2: Among new users of UMEC/VI or UMEC, we found reliable incidence estimates for cardiovascular and cerebrovascular outcomes, although the total number of MI events was relatively modest (21 in UMEC and 11 in UMEC/VI groups). Differences were seen in the rates of pneumonia and AECOPD when ascertained using primary care only compared with using primary and secondary care, and this highlights the need for careful definition of these outcomes in future comparative studies. The incidence of CV events and respiratory outcomes was as expected for these drugs classes, and no new safety signals were observed. As such, the benefit/risk balance of these medications continues to be favourable.

Objective 3: Concerning treatment patterns, around two-thirds of new users of UMEC were adding UMEC as a step-up to MITT revealing important considerations regarding the study of new users of LAMAs in a real-world setting. This pattern of use may partly explain why UMEC users were observed to have more severe COPD compared to UMEC/VI users and should be taken into account when comparing these results to those from other studies.

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APPENDICES

ANNEX 1. Full Results Tables

File ID	Title
1	Exposure Cohort Results
2	Baseline Tables T1
3	Baseline Tables T2
4	Baseline Tables T3
5	Baseline Tables T4
6	Objective 1 Results
7	Objective 2 Results
8	Objective 3 Results

Descriptive statistics of cohort, overall and by index LABD group[1]
CPRD-GOLD+THIN Cohort

		Cohort of Patients (N=34,516)1													
		UMEC		UMEC/VI		Other LABD[2]		Other LAMA		Other LABA		Other LABA/LAMA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		3,875	9.96	2,224	5.72	32,809	84.32	24,125	62.01	6,218	15.98	2,466	6.34	38,908	100.00
Time period of initiation	July - September 2014	0	0.00	24	1.08	4,030	12.28	3,061	12.69	927	14.91	42	1.70	4,054	10.42
	October - December 2014	11	0.28	97	4.36	4,240	12.92	3,223	13.36	964	15.50	53	2.15	4,348	11.18
	January - March 2015	175	4.52	185	8.32	4,767	14.53	3,664	15.19	983	15.81	120	4.87	5,127	13.18
	April - June 2015	257	6.63	192	8.63	4,145	12.63	3,057	12.67	835	13.43	253	10.26	4,594	11.81
	July - September 2015	458	11.82	324	14.57	3,910	11.92	2,917	12.09	676	10.87	317	12.85	4,692	12.06
	October - December 2015	709	18.30	348	15.65	3,952	12.05	2,841	11.78	650	10.45	461	18.69	5,009	12.87
	January - March 2016	1,012	26.12	452	20.32	4,086	12.45	2,867	11.88	664	10.68	555	22.51	5,550	14.26
	April - June 2016	1,253	32.34	602	27.07	3,679	11.21	2,495	10.34	519	8.35	665	26.97	5,534	14.22
Follow-up time in days[4]	mean (SD)	467.76	175.48	495.92	212.55	581.46	277.78	585.41	278.81	603.75	291.35	486.65	204.42	565.25	268.62
	median (IQR)	470	387 - 581	487	387 - 638	577	394 - 806	585	395 - 812	609	399 - 851	479	381 - 618	554	392 - 771
Reason for censoring	death	272	7.02	176	7.91	2,749	8.38	2,166	8.98	333	5.36	250	10.14	3,197	8.22
	left GP practice	155	4.00	85	3.82	1,781	5.43	1,289	5.34	384	6.18	108	4.38	2,021	5.19
	last collection from GP practice	433	11.17	328	14.75	7,732	23.57	5,737	23.78	1,638	26.34	357	14.48	8,493	21.83
	end of follow-up on 30 June 2017	3,015	77.81	1,635	73.52	20,547	62.63	14,933	61.90	3,863	62.13	1,751	71.01	25,197	64.76
Total length of current exposure in days[5]	mean (SD)	330.81	215.66	290.41	236.16										
	median (IQR)	371	120 - 489	248	60 - 457										
Patients contributing to multiple index medication groups	gap between index medications	87	2.25	121	5.44	1,878	5.72							2,086	5.36
	mean (SD) gap in days	69.55	90.04	78.55	113.85	149.12	151.15							141.71	148.82
	median (IQR)	38	11 - 84	25	8 - 122	91	23 - 247							81	21 - 233
	overlap between index medications	147	3.79	173	7.78	1,947	5.93							2,267	5.83
	mean (SD) overlap in days	44.53	107.81	55.13	122.58	113.44	205.82							104.52	196.87
	median (IQR)	15	7 - 24	16	7 - 27	22	9 - 90							21	9 - 70
Concomitant maintenance therapy at index date	Any	2,648	68.34	485	21.81										
	ICS any	2,576	66.48	320	14.39										
	ICS monotherapy	47	1.21	55	2.47										
	ICS/LABA	2,538	65.50	270	12.14										
	Theophylline	176	4.54	43	1.93										
	Other LAMA	263	6.79	187	8.41										
	Other LABA	37	0.95	41	1.84										
	Other LABA/LAMA	6	0.15	9	0.40										
Strategic Health Authority for practice	England	761	19.64	743	33.41	16,363	49.87	12,191	50.53	3,249	52.25	923	37.43	17,867	45.92
	Northern Ireland	557	14.37	365	16.41	1,823	5.56	1,450	6.01	164	2.64	209	8.48	2,745	7.06
	Scotland	1,784	46.04	692	31.12	8,499	25.90	5,885	24.39	1,815	29.19	799	32.40	10,975	28.21
	Wales	773	19.95	424	19.06	6,124	18.67	4,599	19.06	990	15.92	535	21.70	7,321	18.82

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] The Other LABD group includes Other LAMA, Other LABA, and Other LABA/LAMA

[3] Unless otherwise specified.

[4] Follow-up time from index date until censoring or study end (inclusive) .

[5] Where discontinuation is considered after a break of 91 days. Current exposure for patients censored between 31 and 90 days after their last prescription will end 30 days after the last prescription.

Notes: Text in grey is optional and dependent on sufficient sample size

Descriptive statistics of cohort, overall and by index LABD group[1]
CPRD-GOLD Cohort

		Cohort of Patients (N=24,815)1													
		UMEC		UMEC/VI		Other LABD[2]		Other LAMA		Other LABA		Other LABA/LAMA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		2,486	8.89	1,645	5.88	23,825	85.22	17,521	62.67	4,512	16.14	1,792	6.41	27,956	100.00
Time period of initiation	July - September 2014	0	0.00	21	1.28	3,087	12.96	2,359	13.46	694	15.38	34	1.90	3,108	11.12
	October - December 2014	11	0.44	77	4.68	3,046	12.78	2,345	13.38	662	14.67	39	2.18	3,134	11.21
	January - March 2015	112	4.51	135	8.21	3,530	14.82	2,708	15.46	737	16.33	85	4.74	3,777	13.51
	April - June 2015	151	6.07	141	8.57	3,035	12.74	2,214	12.64	636	14.10	185	10.32	3,327	11.90
	July - September 2015	256	10.30	232	14.10	2,797	11.74	2,106	12.02	476	10.55	215	12.00	3,285	11.75
	October - December 2015	496	19.95	257	15.62	2,828	11.87	2,027	11.57	471	10.44	330	18.42	3,581	12.81
	January - March 2016	707	28.44	338	20.55	2,889	12.13	2,027	11.57	445	9.86	417	23.27	3,934	14.07
	April - June 2016	753	30.29	444	26.99	2,613	10.97	1,735	9.90	391	8.67	487	27.18	3,810	13.63
Follow-up time in days[4]	mean (SD)	450.71	176.18	480.56	213.34	561.28	283.06	566.57	284.37	575.04	297.68	474.89	208.15	546.69	273.81
	median (IQR)	465	380 - 563	473	380 - 619	555	372 - 787	563	373 - 798	570	363.5 - 82	470	374.5 - 60	529	373 - 753
Reason for censoring	death	203	8.17	148	9.00	2,081	8.73	1,638	9.35	249	5.52	194	10.83	2,432	8.70
	left GP practice	79	3.18	58	3.53	1,100	4.62	790	4.51	242	5.36	68	3.79	1,237	4.42
	last collection from GP practice	361	14.52	283	17.20	6,684	28.05	4,960	28.31	1,442	31.96	282	15.74	7,328	26.21
	end of follow-up on 30 June 2017	1,843	74.14	1,156	70.27	13,960	58.59	10,133	57.83	2,579	57.16	1,248	69.64	16,959	60.66
Total length of current exposure in days[5]	mean (SD)	314.03	210.77	285.72	236.77										
	median (IQR)	356	95 - 478	235	58 - 456										
Patients contributing to multiple index medication groups	gap between index medications	60	2.41	85	5.17	1,360	5.71							1,505	5.38
	mean (SD) gap in days	76.15	95.47	97.59	127.71	143.38	148.02							138.11	146.07
	median (IQR)	44	12.5 - 104	34	12 - 150	86	21 - 239							79	20 - 227
	overlap between index medications	101	4.06	129	7.84	1,379	5.79							1,609	5.76
	mean (SD) overlap in days	33.52	78.25	54.82	116.69	115.86	209.90							105.80	199.61
	median (IQR)	12	4 - 22	16	7 - 27	23	9 - 99							21	9 - 74
Concomitant maintenance therapy at index date	Any	1,689	67.94	370	22.49										
	ICS any	1,642	66.05	247	15.02										
	ICS monotherapy	29	1.17	40	2.43										
	ICS/LABA	1,618	65.08	211	12.83										
	Theophylline	97	3.90	27	1.64										
	Other LAMA	176	7.08	141	8.57										
	Other LABA	26	1.05	33	2.01										
	Other LABA/LAMA	6	0.24	8	0.49										
Strategic Health Authority for practice	North East	0	0.00	0	0.00	188	0.79	145	0.83	32	0.71	11	0.61	188	0.67
	North West	71	2.86	101	6.14	2,128	8.93	1,591	9.08	419	9.29	118	6.58	2,300	8.23
	Yorkshire & The Humber	0	0.00	26	1.58	277	1.16	225	1.28	39	0.86	13	0.73	303	1.08
	East Midlands	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	West Midlands	143	5.75	76	4.62	1,532	6.43	1,162	6.63	276	6.12	94	5.25	1,751	6.26
	East of England	3	0.12	11	0.67	932	3.91	676	3.86	241	5.34	15	0.84	946	3.38
	South West	93	3.74	119	7.23	1,499	6.29	1,115	6.36	339	7.51	45	2.51	1,711	6.12
	South Central	162	6.52	95	5.78	2,029	8.52	1,363	7.78	561	12.43	105	5.86	2,286	8.18
	London	11	0.44	37	2.25	2,066	8.67	1,536	8.77	402	8.91	128	7.14	2,114	7.56
	South East Coast	151	6.07	167	10.15	2,509	10.53	2,025	11.56	330	7.31	154	8.59	2,827	10.11
	England	634	25.50	632	38.42	13,160	55.24	9,838	56.15	2,639	58.49	683	38.11	14,426	51.60
	Northern Ireland	273	10.98	214	13.01	1,013	4.25	841	4.80	66	1.46	106	5.92	1,500	5.37
	Scotland	971	39.06	439	26.69	5,130	21.53	3,447	19.67	1,085	24.05	598	33.37	6,540	23.39
	Wales	608	24.46	360	21.88	4,522	18.98	3,395	19.38	722	16.00	405	22.60	5,490	19.64

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] The Other LABD group includes Other LAMA, Other LABA, and Other LABA/LAMA

[3] Unless otherwise specified.

[4] Follow-up time from index date until censoring or study end (inclusive) .

[5] Where discontinuation is considered after a break of 91 days. Current exposure for patients censored between 31 and 90 days after their last prescription will end 30 days after the last prescription.

NB. Text in grey is optional and dependent on sufficient sample size.

Descriptive statistics of cohort, overall and by index LABD group[1]
THIN Cohort

		Cohort of Patients (N=9,701)1													
		UMEC		UMEC/VI		Other LABD[2]		Other LAMA		Other LABA		Other LABA/LAMA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		1,389	12.68	579	5.29	8,984	82.03	6,604	60.30	1,706	15.58	674	6.15	10,952	100.00
Time period of initiation	July - September 2014	0	0.00	3	0.52	943	10.50	702	10.63	233	13.66	8	1.19	946	8.64
	October - December 2014	0	0.00	20	3.45	1,194	13.29	878	13.29	302	17.70	14	2.08	1,214	11.08
	January - March 2015	63	4.54	50	8.64	1,237	13.77	956	14.48	246	14.42	35	5.19	1,350	12.33
	April - June 2015	106	7.63	51	8.81	1,110	12.36	843	12.76	199	11.66	68	10.09	1,267	11.57
	July - September 2015	202	14.54	92	15.89	1,113	12.39	811	12.28	200	11.72	102	15.13	1,407	12.85
	October - December 2015	213	15.33	91	15.72	1,124	12.51	814	12.33	179	10.49	131	19.44	1,428	13.04
	January - March 2016	305	21.96	114	19.69	1,197	13.32	840	12.72	219	12.84	138	20.47	1,616	14.76
	April - June 2016	500	36.00	158	27.29	1,066	11.87	760	11.51	128	7.50	178	26.41	1,724	15.74
Follow-up time in days[4]	mean (SD)	498.28	170.08	539.54	204.29	634.99	255.71	635.39	256.89	679.70	259.10	517.92	190.81	612.61	248.71
	median (IQR)	477	395 - 615	519	415 - 676	635	457 - 840	640	456 - 842	683	497 - 899	511	400 - 647	603	436 - 805
Reason for censoring	death	69	4.97	28	4.84	668	7.44	528	8.00	84	4.92	56	8.31	765	6.99
	left GP practice	76	5.47	27	4.66	681	7.58	499	7.56	142	8.32	40	5.93	784	7.16
	last collection from GP practice	72	5.18	45	7.77	1,048	11.67	777	11.77	196	11.49	75	11.13	1,165	10.64
	end of follow-up on 30 June 2017	1,172	84.38	479	82.73	6,587	73.32	4,800	72.68	1,284	75.26	503	74.63	8,238	75.22
Total length of current exposure in days[5]	mean (SD)	360.83	221.07	303.74	234.12										
	median (IQR)	381	164 - 509	298	72 - 459										
Patients contributing to multiple index medication groups	gap between index medications	27	1.94	36	6.22	518	5.77							581	5.30
	mean (SD) gap in days	54.89	76.24	33.58	48.38	164.21	158.24							151.04	155.44
	median (IQR)	34	5 - 57	14	5.5 - 26	108	28 - 278							87	23 - 251
	overlap between index medications	46	3.31	44	7.60	568	6.32							658	6.01
	mean (SD) overlap in days	68.70	152.43	56.05	139.87	107.55	195.61							101.39	190.11
	median (IQR)	20	11 - 29	15	7.5 - 26.5	21	9 - 74.5							20	9 - 57
Concomitant maintenance therapy at index date	Any	959	69.04	115	19.86										
	ICS any	934	67.24	73	12.61										
	ICS monotherapy	18	1.30	15	2.59										
	ICS/LABA	920	66.23	59	10.19										
	Theophylline	79	5.69	16	2.76										
	Other LAMA	87	6.26	46	7.94										
	Other LABA	11	0.79	8	1.38										
	Other LABA/LAMA	0	0.00	1	0.17										
Strategic Health Authority for practice	England	127	9.14	111	19.17	3,203	35.65	2,353	35.63	610	35.76	240	35.61	3,441	31.42
	Northern Ireland	284	20.45	151	26.08	810	9.02	609	9.22	98	5.74	103	15.28	1,245	11.37
	Scotland	813	58.53	253	43.70	3,369	37.50	2,438	36.92	730	42.79	201	29.82	4,435	40.49
	Wales	165	11.88	64	11.05	1,602	17.83	1,204	18.23	268	15.71	130	19.29	1,831	16.72

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] The Other LABD group includes Other LAMA, Other LABA, and Other LABA/LAMA

[3] Unless otherwise specified.

[4] Follow-up time from index date until censoring or study end (inclusive) .

[5] Where discontinuation is considered after a break of 91 days. Current exposure for patients censored between 31 and 90 days after their last prescription will end 30 days after the last prescription.

NB. Text in grey is optional and dependent on sufficient sample size.

Descriptive statistics of cohort, overall and by index LABD group[1]
CPRD-GOLD+HES+ONS Cohort

		Cohort of Patients (N=10,646)1													
		UMEC		UMEC/VI		Other LABD[2]		Other LAMA		Other LABA		Other LABA/LAMA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		547	4.70	512	4.40	10,590	90.91	7,882	67.66	2,175	18.67	533	4.58	11,649	100.00
Time period of initiation	July - September 2014	0	0.00	18	3.52	1,491	14.08	1,132	14.36	348	16.00	11	2.06	1,509	12.95
	October - December 2014	8	1.46	54	10.55	1,487	14.04	1,139	14.45	332	15.26	16	3.00	1,549	13.30
	January - March 2015	70	12.80	85	16.60	1,633	15.42	1,246	15.81	355	16.32	32	6.00	1,788	15.35
	April - June 2015	68	12.43	60	11.72	1,365	12.89	1,000	12.69	321	14.76	44	8.26	1,493	12.82
	July - September 2015	61	11.15	62	12.11	1,165	11.00	885	11.23	218	10.02	62	11.63	1,288	11.06
	October - December 2015	86	15.72	67	13.09	1,176	11.10	862	10.94	207	9.52	107	20.08	1,329	11.41
	January - March 2016	112	20.48	74	14.45	1,228	11.60	896	11.37	218	10.02	114	21.39	1,414	12.14
	April - June 2016	142	25.96	92	17.97	1,045	9.87	722	9.16	176	8.09	147	27.58	1,279	10.98
Follow-up time in days[4]	mean (SD)	366.59	208.99	463.64	262.04	501.29	289.00	506.98	288.18	506.02	301.66	397.75	221.37	493.31	286.08
	median (IQR)	385	169 - 507	457	247.5 - 65	480	264 - 726	491	275 - 731	479	254 - 757	399	221 - 541	473	259 - 711
Reason for censoring	death	34	6.22	47	9.18	798	7.54	676	8.58	81	3.72	41	7.69	879	7.55
	left GP practice	13	2.38	23	4.49	526	4.97	385	4.88	113	5.20	28	5.25	562	4.82
	last collection from GP practice	256	46.80	190	37.11	4,718	44.55	3,412	43.29	1,085	49.89	221	41.46	5,164	44.33
	end of follow-up on 30 June 2017	244	44.61	252	49.22	4,548	42.95	3,409	43.25	896	41.20	243	45.59	5,044	43.30
Total length of current exposure in days[5]	mean (SD)	250.32	208.84	260.82	255.52										
	median (IQR)	187	56 - 408	154	30 - 426										
Patients contributing to multiple index medication groups	gap between index medications	14	2.56	30	5.86	427	4.03							471	4.04
	mean (SD) gap in days	66.86	63.96	135.67	157.14	139.56	141.65							137.15	141.34
	median (IQR)	47	11 - 126	51	9 - 263	91	21 - 227							89	19 - 222
	overlap between index medications	21	3.84	38	7.42	465	4.39							524	4.50
	mean (SD) overlap in days	42.81	97.23	62.87	128.51	108.76	197.78							102.79	191.12
	median (IQR)	13	9 - 23	16	8 - 27	23	9 - 104							22	9 - 93
Concomitant maintenance therapy at index date	Any	364	66.54	136	26.56										
	ICS any	351	64.17	95	18.55										
	ICS monotherapy	9	1.65	19	3.71										
	ICS/LABA	344	62.89	78	15.23										
	Theophylline	18	3.29	7	1.37										
	Other LAMA	46	8.41	56	10.94										
	Other LABA	6	1.10	9	1.76										
	Other LABA/LAMA	2	0.37	2	0.39										
Strategic Health Authority for practice	North East	0	0.00	0	0.00	187	1.77	145	1.84	32	1.47	10	1.88	187	1.61
	North West	59	10.79	91	17.77	1,729	16.33	1,295	16.43	332	15.26	102	19.14	1,879	16.13
	Yorkshire & The Humber	0	0.00	26	5.08	277	2.62	225	2.85	39	1.79	13	2.44	303	2.60
	East Midlands	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	West Midlands	111	20.29	46	8.98	1,026	9.69	771	9.78	228	10.48	27	5.07	1,183	10.16
	East of England	3	0.55	8	1.56	795	7.51	579	7.35	201	9.24	15	2.81	806	6.92
	South West	81	14.81	72	14.06	1,305	12.32	953	12.09	314	14.44	38	7.13	1,458	12.52
	South Central	141	25.78	81	15.82	1,543	14.57	1,033	13.11	426	19.59	84	15.76	1,765	15.15
	London	6	1.10	29	5.66	1,640	15.49	1,211	15.36	328	15.08	101	18.95	1,675	14.38
	South East Coast	146	26.69	159	31.05	2,088	19.72	1,670	21.19	275	12.64	143	26.83	2,393	20.54
	England	547	100.00	512	100.00	10,590	100.00	7,882	100.00	2,175	100.00	533	100.00	11,649	100.00
	Northern Ireland														
	Scotland														
	Wales														

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] The Other LABD group includes Other LAMA, Other LABA, and Other LABA/LAMA

[3] Unless otherwise specified.

[4] Follow-up time from index date until censoring or study end (inclusive) .

[5] Where discontinuation is considered after a break of 91 days. Current exposure for patients censored between 31 and 90 days after their last prescription will end 30 days after the last prescription.

NB. Text in grey is optional and dependent on sufficient sample size.

Demographic characteristics at baseline, by index LABD group
CPRD-GOLD+THIN Cohort - With concomitant maintenance therapy at the index date

		Cohort of Patients (N=27,500)1							
		UMEC N = 2,648		UMEC/VI N = 485		Other LABD N = 27,313		All N = 30,446	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Age (in years) at index date	mean (SD)	68.68	10.78	68.64	11.02	66.27	14.13	66.51	13.85
	≥65 years	1,800	67.98	325	67.01	16,728	61.25	18,853	61.92
	<65 years	848	32.02	160	32.99	10,585	38.75	11,593	38.08
	<18 years	0	0.00	0	0.00	394	1.44	394	1.29
	18-34 years	12	0.45	1	0.21	380	1.39	393	1.29
	35-64 years	836	31.57	159	32.78	9,811	35.92	10,806	35.49
Gender	female	1,377	52.00	251	51.75	13,965	51.13	15,593	51.22
	male	1,271	48.00	234	48.25	13,348	48.87	14,853	48.78
Smoking status	current smoker	1,085	40.97	169	34.85	10,866	39.78	12,120	39.81
	ex-smoker	1,340	50.60	270	55.67	12,370	45.29	13,980	45.92
	no/never smoker	223	8.42	46	9.48	3,867	14.16	4,136	13.58
	missing[3]	0	0.00	0	0.00	210	0.77	210	0.69
Body Mass Index (kg/m^2)	mean (SD)	27.91	6.57	28.82	6.90	28.09	6.77	28.09	6.75
	underweight <18.5	136	5.14	16	3.30	1,152	4.22	1,304	4.28
	normal 18.5-24.9	790	29.83	134	27.63	8,034	29.41	8,958	29.42
	overweight 25.0-29.9	831	31.38	149	30.72	8,332	30.51	9,312	30.59
	obese ≥30	864	32.63	183	37.73	8,782	32.15	9,829	32.28
	missing[3]	27	1.02	3	0.62	1,013	3.71	1,043	3.43
Area based deprivation quintile[4]	Q1 (least deprived)								
	Q2								
	Q3								
	Q4								
	Q5 (most deprived)								
	missing[3]								

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

2 Unless otherwise specified

3 Percentages were calculated separately for those with missing and without missing data

4 Area based deprivation is measured using patient-level Townsend quintile

Demographic characteristics at baseline, by index LABD group
CPRD-GOLD+THIN Cohort - Without concomitant maintenance therapy at the index date

		Cohort of Patients (N=8,009)1							
		UMEC N = 1,227		UMEC/VI N = 1,739		Other LABD N = 5,496		All N = 8,462	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Age (in years) at index date	mean (SD)	68.92	10.86	69.12	10.62	62.81	18.17	64.99	16.23
	≥65 years	822	66.99	1,207	69.41	3,009	54.75	5,038	59.54
	<65 years	405	33.01	532	30.59	2,487	45.25	3,424	40.46
	<18 years	0	0.00	0	0.00	215	3.91	215	2.54
	18-34 years	4	0.33	5	0.29	220	4.00	229	2.71
	35-64 years	401	32.68	527	30.30	2,052	37.34	2,980	35.22
Gender	female	607	49.47	804	46.23	2,758	50.18	4,169	49.27
	male	620	50.53	935	53.77	2,738	49.82	4,293	50.73
Smoking status	current smoker	571	46.54	714	41.06	2,241	40.78	3,526	41.67
	ex-smoker	546	44.50	882	50.72	2,065	37.57	3,493	41.28
	no/never smoker	109	8.88	142	8.17	1,080	19.65	1,331	15.73
	missing[3]	1	0.08	1	0.06	110	2.00	112	1.32
Body Mass Index (kg/m^2)	mean (SD)	27.79	6.38	28.21	6.19	27.59	6.32	27.76	6.30
	underweight <18.5	53	4.32	66	3.80	215	3.91	334	3.95
	normal 18.5-24.9	372	30.32	481	27.66	1,646	29.95	2,499	29.53
	overweight 25.0-29.9	397	32.36	583	33.53	1,655	30.11	2,635	31.14
	obese ≥30	380	30.97	587	33.76	1,544	28.09	2,511	29.67
	missing[3]	25	2.04	22	1.27	436	7.93	483	5.71
Area based deprivation quintile[4]	Q1 (least deprived)								
	Q2								
	Q3								
	Q4								
	Q5 (most deprived)								
	missing[3]								

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

2 Unless otherwise specified

3 Percentages were calculated separately for those with missing and without missing data

4 Area based deprivation is measured using patient-level Townsend quintile

Demographic characteristics at baseline, by index LABD group
CPRD-GOLD+THIN Cohort

		Cohort of Patients (N=34,516)1							
		UMEC N = 3,875		UMEC/VI N = 2,224		Other LABD N = 32,809		All N = 38,908	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Age (in years) at index date	mean (SD)	68.75	10.80	69.02	10.71	65.69	14.94	66.18	14.41
	≥65 years	2,622	67.66	1,532	68.88	19,737	60.16	23,891	61.40
	<65 years	1,253	32.34	692	31.12	13,072	39.84	15,017	38.60
	<18 years	0	0.00	0	0.00	609	1.86	609	1.57
	18-34 years	16	0.41	6	0.27	600	1.83	622	1.60
	35-64 years	1,237	31.92	686	30.85	11,863	36.16	13,786	35.43
Gender	female	1,984	51.20	1,055	47.44	16,723	50.97	19,762	50.79
	male	1,891	48.80	1,169	52.56	16,086	49.03	19,146	49.21
Smoking status	current smoker	1,656	42.74	883	39.70	13,107	39.95	15,646	40.21
	ex-smoker	1,886	48.67	1,152	51.80	14,435	44.00	17,473	44.91
	no/never smoker	332	8.57	188	8.45	4,947	15.08	5,467	14.05
	missing[3]	1	0.03	1	0.04	320	0.98	322	0.83
Body Mass Index (kg/m^2)	mean (SD)	27.87	6.51	28.35	6.36	28.01	6.70	28.02	6.66
	underweight <18.5	189	4.88	82	3.69	1,367	4.17	1,638	4.21
	normal 18.5-24.9	1,162	29.99	615	27.65	9,680	29.50	11,457	29.45
	overweight 25.0-29.9	1,228	31.69	732	32.91	9,987	30.44	11,947	30.71
	obese ≥30	1,244	32.10	770	34.62	10,326	31.47	12,340	31.72
	missing[3]	52	1.34	25	1.12	1,449	4.42	1,526	3.92
Area based deprivation quintile[4]	Q1 (least deprived)								
	Q2								
	Q3								
	Q4								
	Q5 (most deprived)								
	missing[3]								

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] Unless otherwise specified

[3] Percentages were calculated separately for those with missing and without missing data

[4] Area based deprivation is measured using patient-level Townsend quintile

Demographic characteristics at baseline, by index LABD group
CPRD-GOLD Cohort

		Cohort of Patients (N=24,815)1							
		UMEC N = 2,486		UMEC/VI N = 1,645		Other LABD N = 23,825		All N = 27,956	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Age (in years) at index date	mean (SD)	69.16	10.99	69.31	10.77	65.77	15.03	66.28	14.54
	≥65 years	1,697	68.26	1,150	69.91	14,340	60.19	17,187	61.48
	<65 years	789	31.74	495	30.09	9,485	39.81	10,769	38.52
	<18 years	0	0.00	0	0.00	449	1.88	449	1.61
	18-34 years	12	0.48	4	0.24	431	1.81	447	1.60
	35-64 years	777	31.26	491	29.85	8,605	36.12	9,873	35.32
Gender	female	1,294	52.05	773	46.99	12,063	50.63	14,130	50.54
	male	1,192	47.95	872	53.01	11,762	49.37	13,826	49.46
Smoking status	current smoker	1,081	43.48	665	40.43	9,375	39.35	11,121	39.78
	ex-smoker	1,205	48.47	834	50.70	10,582	44.42	12,621	45.15
	no/never smoker	199	8.00	145	8.81	3,634	15.25	3,978	14.23
	missing[3]	1	0.04	1	0.06	234	0.98	236	0.84
Body Mass Index (kg/m^2)	mean (SD)	27.82	6.60	28.32	6.45	28.03	6.72	28.03	6.70
	underweight <18.5	131	5.27	65	3.95	997	4.18	1,193	4.27
	normal 18.5-24.9	747	30.05	458	27.84	7,020	29.46	8,225	29.42
	overweight 25.0-29.9	794	31.94	543	33.01	7,267	30.50	8,604	30.78
	obese ≥30	786	31.62	562	34.16	7,524	31.58	8,872	31.74
	missing[3]	28	1.13	17	1.03	1,017	4.27	1,062	3.80
Area based deprivation quintile[4]	Q1 (least deprived)	89	3.58	98	5.96	1,912	8.03	2,099	7.51
	Q2	101	4.06	111	6.75	1,972	8.28	2,184	7.81
	Q3	140	5.63	92	5.59	2,369	9.94	2,601	9.30
	Q4	126	5.07	124	7.54	2,547	10.69	2,797	10.01
	Q5 (most deprived)	90	3.62	87	5.29	1,786	7.50	1,963	7.02
	missing[3]	1,940	78.04	1,133	68.88	13,239	55.57	16,312	58.35

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

2 Unless otherwise specified

3 Percentages were calculated separately for those with missing and without missing data

4 Area based deprivation is measured using patient-level Townsend quintile

Demographic characteristics at baseline, by index LABD group
THIN Cohort

		Cohort of Patients (N=9,701)1							
		UMEC N = 1,389		UMEC/VI N = 579		Other LABD N = 8,984		All N = 10,952	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Age (in years) at index date	mean (SD)	68.04	10.43	68.18	10.50	65.47	14.71	65.94	14.07
	≥65 years	925	66.59	382	65.98	5,397	60.07	6,704	61.21
	<65 years	464	33.41	197	34.02	3,587	39.93	4,248	38.79
	<18 years	0	0.00	0	0.00	160	1.78	160	1.46
	18-34 years	4	0.29	2	0.35	169	1.88	175	1.60
	35-64 years	460	33.12	195	33.68	3,258	36.26	3,913	35.73
Gender	female	690	49.68	282	48.70	4,660	51.87	5,632	51.42
	male	699	50.32	297	51.30	4,324	48.13	5,320	48.58
Smoking status	current smoker	575	41.40	218	37.65	3,732	41.54	4,525	41.32
	ex-smoker	681	49.03	318	54.92	3,853	42.89	4,852	44.30
	no/never smoker	133	9.58	43	7.43	1,313	14.61	1,489	13.60
	missing[3]	0	0.00	0	0.00	86	0.96	86	0.79
Body Mass Index (kg/m^2)	mean (SD)	27.97	6.35	28.42	6.09	27.96	6.64	27.99	6.57
	underweight <18.5	58	4.18	17	2.94	370	4.12	445	4.06
	normal 18.5-24.9	415	29.88	157	27.12	2,660	29.61	3,232	29.51
	overweight 25.0-29.9	434	31.25	189	32.64	2,720	30.28	3,343	30.52
	obese ≥30	458	32.97	208	35.92	2,802	31.19	3,468	31.67
	missing[3]	24	1.73	8	1.38	432	4.81	464	4.24
Area based deprivation quintile[4]	Q1 (least deprived)								
	Q2								
	Q3								
	Q4								
	Q5 (most deprived)								
	missing[3]								

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

2 Unless otherwise specified

3 Percentages were calculated separately for those with missing and without missing data

4 Area based deprivation is measured using patient-level Townsend quintile

Demographic characteristics at baseline, by index LABD group
CPRD-GOLD+HES+ONS Cohort

		Cohort of Patients (N=10,646)1							
		UMEC N = 547		UMEC/VI N = 512		Other LABD N = 10,590		All N = 11,649	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Age (in years) at index date	mean (SD)	70.50	11.27	70.08	11.32	65.67	15.78	66.09	15.48
	≥65 years	404	73.86	376	73.44	6,436	60.77	7,216	61.95
	<65 years	143	26.14	136	26.56	4,154	39.23	4,433	38.05
	<18 years	0	0.00	0	0.00	242	2.29	242	2.08
	18-34 years	4	0.73	2	0.39	232	2.19	238	2.04
	35-64 years	139	25.41	134	26.17	3,680	34.75	3,953	33.93
Gender	female	245	44.79	233	45.51	5,277	49.83	5,755	49.40
	male	302	55.21	279	54.49	5,313	50.17	5,894	50.60
Smoking status	current smoker	208	38.03	190	37.11	3,807	35.95	4,205	36.10
	ex-smoker	282	51.55	273	53.32	4,799	45.32	5,354	45.96
	no/never smoker	57	10.42	48	9.38	1,854	17.51	1,959	16.82
	missing[3]	0	0.00	1	0.20	130	1.23	131	1.12
Body Mass Index (kg/m^2)	mean (SD)	27.56	6.44	28.01	6.39	28.02	6.66	28.00	6.64
	underweight <18.5	26	4.75	23	4.49	432	4.08	481	4.13
	normal 18.5-24.9	178	32.54	154	30.08	3,110	29.37	3,442	29.55
	overweight 25.0-29.9	185	33.82	165	32.23	3,261	30.79	3,611	31.00
	obese ≥30	151	27.61	162	31.64	3,308	31.24	3,621	31.08
	missing[3]	7	1.28	8	1.56	479	4.52	494	4.24
Area based deprivation quintile[4]	Q1 (least deprived)	89	16.27	98	19.14	1,911	18.05	2,098	18.01
	Q2	101	18.46	111	21.68	1,972	18.62	2,184	18.75
	Q3	140	25.59	92	17.97	2,369	22.37	2,601	22.33
	Q4	126	23.03	124	24.22	2,547	24.05	2,797	24.01
	Q5 (most deprived)	90	16.45	86	16.80	1,786	16.86	1,962	16.84
	missing[3]	1	0.18	1	0.20	5	0.05	7	0.06

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

2 Unless otherwise specified

3 Percentages were calculated separately for those with missing and without missing data

4 Area based deprivation is measured using patient-level Townsend quintile

Past history of comorbidities recorded in primary care, by index LABD group
CPRD-GOLD+THIN Cohort - With concomitant maintenance therapy at the index date

	Cohort of Patients (N=27,500)1							
	UMEC N = 2,648		UMEC/VI N = 485		Other LABD N = 27,313		All N = 30,446	
	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Cardio- and cerebrovascular disease (ever before)	1,719	64.92	307	63.30	16,759	61.36	18,785	61.70
Beta-blocker prescribing (in year prior to index date)	415	15.67	83	17.11	5,318	19.47	5,816	19.10
Pneumonia (ever before)	219	8.27	36	7.42	1,960	7.18	2,215	7.28
Gastroesophageal reflux disease (ever before)	621	23.45	114	23.51	6,261	22.92	6,996	22.98
Diabetes (ever before)	511	19.30	98	20.21	4,989	18.27	5,598	18.39
Acute and chronic renal disease (ever before)	570	21.53	88	18.14	4,919	18.01	5,577	18.32
Cancer (ever before)	394	14.88	57	11.75	3,531	12.93	3,982	13.08

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

2 Unless otherwise specified.

Past history of comorbidities recorded in primary care, by index LABD group
CPRD-GOLD+THIN Cohort - Without concomitant maintenance therapy at the index date

	Cohort of Patients (N=8,009)1							
	UMEC		UMEC/VI		Other LABD		All	
	N =	1,227	N =	1,739	N =	5,496	N =	8,462
	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Cardio- and cerebrovascular disease (ever before)	791	64.47	1,146	65.90	2,952	53.71	4,889	57.78
Beta-blocker prescribing (in year prior to index date)	292	23.80	402	23.12	1,073	19.52	1,767	20.88
Pneumonia (ever before)	65	5.30	124	7.13	352	6.40	541	6.39
Gastroesophageal reflux disease (ever before)	269	21.92	411	23.63	1,179	21.45	1,859	21.97
Diabetes (ever before)	242	19.72	312	17.94	874	15.90	1,428	16.88
Acute and chronic renal disease (ever before)	256	20.86	350	20.13	964	17.54	1,570	18.55
Cancer (ever before)	170	13.85	256	14.72	756	13.76	1,182	13.97

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

2 Unless otherwise specified.

Past history of comorbidities recorded in primary care, by index LABD group
CPRD+THIN Cohort

	Cohort of Patients (N=34,516)1							
	UMEC N = 3,875		UMEC/VI N = 2,224		Other LABD N = 32,809		All N = 38,908	
	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Cardio- and cerebrovascular disease (ever before)	2,510	64.77	1,453	65.33	19,711	60.08	23,674	60.85
Beta-blocker prescribing (in year prior to index date)	707	18.25	485	21.81	6,391	19.48	7,583	19.49
Pneumonia (ever before)	284	7.33	160	7.19	2,312	7.05	2,756	7.08
Gastroesophageal reflux disease (ever before)	890	22.97	525	23.61	7,440	22.68	8,855	22.76
Diabetes (ever before)	753	19.43	410	18.44	5,863	17.87	7,026	18.06
Acute and chronic renal disease (ever before)	826	21.32	438	19.69	5,883	17.93	7,147	18.37
Cancer (ever before)	564	14.55	313	14.07	4,287	13.07	5,164	13.27

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] Unless otherwise specified.

Respiratory medication use in year prior to index date, by index LABD group
CPRD+THIN Cohort

		Cohort of Patients (N=34,516)1											
		UMEC N = 3,875			UMEC/VI N = 2,224			Other LABD N = 32,809			All N = 38,908		
		Patients with prescription(s) N (%)		Total no. prescriptions	Patients with prescription(s) N (%)		Total no. prescriptions	Patients with prescription(s) N (%)		Total no. prescriptions	Patients with prescription(s) N (%)		Total no. prescriptions
SABD[2]	1+ prescription(s)[3]	3,357	86.63	24,700	1,789	80.44	11,186	26,120	79.61	158,232	31,266	80.36	194,118
	4+ prescriptions[3]	2,345	60.52	n/a	1,079	48.52	n/a	15,285	46.59	n/a	18,709	48.09	n/a
ICS	Any ICS	2,768	71.43	21,635	928	41.73	6,228	17,711	53.98	118,858	21,407	55.02	146,721
	ICS (in a single device)	274	7.07	1,150	196	8.81	847	5,829	17.77	23,084	6,299	16.19	25,081
	ICS/LABA (fixed combination)	2,588	66.79	20,485	774	34.80	5,381	13,245	40.37	95,774	16,607	42.68	121,640
	ICS/SABA (fixed combination)	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00	0
LABA	Any	2,713	70.01	21,529	1,056	47.48	7,269	14,773	45.03	106,404	18,542	47.66	135,202
	LABA (in a single device)	165	4.26	908	305	13.71	1,735	2,018	6.15	10,181	2,488	6.39	12,824
	ICS/LABA (fixed combination)	2,588	66.79	20,485	774	34.80	5,381	13,245	40.37	95,774	16,607	42.68	121,640
	LABA/LAMA (fixed combination)	43	1.11	136	59	2.65	153	173	0.53	449	275	0.71	738
LAMA	Any	2,289	59.07	17,236	1,129	50.76	7,505	7,489	22.83	48,755	10,907	28.03	73,496
	LAMA (in a single device)	2,279	58.81	17,100	1,108	49.82	7,352	7,417	22.61	48,306	10,804	27.77	72,758
	LABA/LAMA (fixed combination)	43	1.11	136	59	2.65	153	173	0.53	449	275	0.71	738
Theophylline (or derivatives)		211	5.45	1,909	54	2.43	605	837	2.55	7,170	1,102	2.83	9,684
Roflimulast		1	0.03	12	0	0.00	0	2	0.01	2	3	0.01	14
OCS	Chronic use[4]	295	7.61	n/a	115	5.17	n/a	1,705	5.20	n/a	2,115	5.44	n/a

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] Includes the following asthma "reliever" medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA.

[3] Categories are not mutually exclusive.

[4] Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days.

Notes This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

COPD disease burden at baseline and within year prior to index date, by index LABD group
CPRD-GOLD+THIN Cohort - With concomitant maintenance therapy at the index date

		Cohort of Patients (N=27,500)1							
		UMEC N = 2648		UMEC/VI N = 485		Other LABD N = 27313		All N = 30446	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Moderate COPD exacerbations (recorded in primary care only)	Rate per person year (95% CI)	1.34	(1.29, 1.38	1.25	(1.16, 1.36	0.88	(0.87, 0.89	0.93	(0.92, 0.94)
	0 events	1,040	39.27	210	43.30	14,157	51.83	15,407	50.60
	1 event	701	26.47	123	25.36	7,210	26.40	8,034	26.39
	2+ events	907	34.25	152	31.34	5,946	21.77	7,005	23.01
Moderate and Severe COPD exacerbations (recorded in primary and/or secondary care)	Rate per person year (95% CI) 0 events 1 event 2+ events	Only for CPRD-GOLD cohort of patients eligible for linkage with CPRD-HES and CPRD-ONS							
Dyspnoea (MRC Grade)	mean (SD)	2.95	0.94	2.89	0.93	2.66	0.96	2.70	0.96
	MRC Grade 1	89	4.18	17	4.40	1,350	8.76	1,456	8.12
	MRC Grade 2	638	30.00	126	32.64	6,040	39.19	6,804	37.96
	MRC Grade 3	778	36.58	138	35.75	4,921	31.93	5,837	32.56
	MRC Grade 4	534	25.11	93	24.09	2,631	17.07	3,258	18.17
	MRC Grade 5	88	4.14	12	3.11	471	3.06	571	3.19
	missing[3]	521	19.68	99	20.41	11,900	43.57	12,520	41.12
FEV_1 percent predicted	mean (SD)	55.42	19.29	55.90	20.01	59.04	19.25	58.65	19.30
	mild, Grade 1 (≥80%)	184	9.84	45	12.00	2,311	13.06	2,540	12.74
	moderate, Grade 2 (≥50% to <80%)	915	48.96	178	47.47	9,604	54.28	10,697	53.65
	severe, Grade 3 (≥30% to <50%)	622	33.28	114	30.40	4,723	26.69	5,459	27.38
	very severe, Grade 4 (<30%)	148	7.92	38	10.13	1,057	5.97	1,243	6.23
	missing[3]	779	29.42	110	22.68	9,618	35.21	10,507	34.51
FEV_1/FVC ratio	mean (SD)	57.55	16.39	58.49	16.33	61.64	15.86	61.22	15.96
	<70%	1,227	80.56	260	79.51	11,175	73.23	12,662	74.00
	≥70%	296	19.44	67	20.49	4,086	26.77	4,449	26.00
	missing[3]	1,125	42.48	158	32.58	12,052	44.13	13,335	43.80

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] Unless otherwise specified.

[3] Percentages were calculated separately for those with missing and without missing data

Notes MRC - Medical Research Council
FEV_1 - Forced Expired Volume in 1 second
FEV_1/FVC - Forced Expired Volume / Forced Vital Capacity

COPD disease burden at baseline and within year prior to index date, by index LABD group
CPRD-GOLD+THIN Cohort - Without concomitant maintenance therapy at the index date

		Cohort of Patients (N=8,009)1							
		UMEC N = 1227		UMEC/VI N = 1739		Other LABD N = 5496		All N = 8462	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Moderate COPD exacerbations (recorded in primary care only)	Rate per person year (95% CI)	0.56	(0.52, 0.60	0.63	(0.60, 0.67	0.57	(0.55, 0.59	0.58	(0.57, 0.60)
	0 events	786	64.06	1,047	60.21	3,472	63.17	5,305	62.69
	1 event	283	23.06	440	25.30	1,325	24.11	2,048	24.20
	2+ events	158	12.88	252	14.49	699	12.72	1,109	13.11
Moderate and Severe COPD exacerbations (recorded in primary and/or secondary care)	Rate per person year (95% CI) 0 events 1 event 2+ events	Only for CPRD-GOLD cohort of patients eligible for linkage with CPRD-HES and CPRD-ONS							
Dyspnoea (MRC Grade)	mean (SD)	2.42	0.90	2.63	0.88	2.50	0.97	2.52	0.93
	MRC Grade 1	107	12.01	83	6.40	293	12.27	483	10.56
	MRC Grade 2	432	48.48	554	42.71	1,051	44.03	2,037	44.52
	MRC Grade 3	240	26.94	447	34.46	665	27.86	1,352	29.55
	MRC Grade 4	95	10.66	185	14.26	304	12.74	584	12.77
	MRC Grade 5	17	1.91	28	2.16	74	3.10	119	2.60
	missing[3]	336	27.38	442	25.42	3,109	56.57	3,887	45.93
FEV_1 percent predicted	mean (SD)	64.37	17.55	61.24	18.47	64.62	19.45	63.73	18.96
	mild, Grade 1 (≥80%)	145	17.68	181	14.48	571	19.60	897	18.00
	moderate, Grade 2 (≥50% to <80%)	512	62.44	737	58.96	1,708	58.61	2,957	59.33
	severe, Grade 3 (≥30% to <50%)	146	17.80	287	22.96	543	18.63	976	19.58
	very severe, Grade 4 (<30%)	17	2.07	45	3.60	92	3.16	154	3.09
	missing[3]	407	33.17	489	28.12	2,582	46.98	3,478	41.10
FEV_1/FVC ratio	mean (SD)	61.78	14.22	60.94	13.41	65.04	13.73	63.48	13.85
	<70%	525	75.76	870	77.26	1,691	65.54	3,086	70.15
	≥70%	168	24.24	256	22.74	889	34.46	1,313	29.85
	missing[3]	534	43.52	613	35.25	2,916	53.06	4,063	48.01

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] Unless otherwise specified.

[3] Percentages were calculated separately for those with missing and without missing data

Notes MRC - Medical Research Council
FEV_1 - Forced Expired Volume in 1 second
FEV_1/FVC - Forced Expired Volume / Forced Vital Capacity

COPD disease burden at baseline and within year prior to index date, by index LABD group
CPRD-GOLD+THIN Cohort

		Cohort of Patients (N=34,516)1							
		UMEC N = 3,875		UMEC/VI N = 2,224		Other LABD N = 32,809		All N = 38,908	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Moderate COPD exacerbations (recorded in primary care only)	Rate per person year (95% CI)	1.09 (1.06, 1.12		0.77 (0.73, 0.81		0.83 (0.82, 0.84		0.85 (0.84, 0.86)	
	0 events	1,826	47.12	1,257	56.52	17,629	53.73	20,712	53.23
	1 event	984	25.39	563	25.31	8,535	26.01	10,082	25.91
	2+ events	1,065	27.48	404	18.17	6,645	20.25	8,114	20.85
Moderate and Severe COPD exacerbations (recorded in primary and/or secondary care)	Rate per person year (95% CI) 0 events 1 event 2+ events	Only for CPRD-GOLD cohort of patients eligible for linkage with CPRD-HES and CPRD-ONS							
Dyspnoea (MRC Grade)	mean (SD)	2.79	0.96	2.69	0.90	2.64	0.96	2.67	0.96
	MRC Grade 1	196	6.49	100	5.94	1,643	9.23	1,939	8.62
	MRC Grade 2	1,070	35.45	680	40.40	7,091	39.84	8,841	39.29
	MRC Grade 3	1,018	33.73	585	34.76	5,586	31.38	7,189	31.95
	MRC Grade 4	629	20.84	278	16.52	2,935	16.49	3,842	17.07
	MRC Grade 5	105	3.48	40	2.38	545	3.06	690	3.07
	missing[3]	857	22.12	541	24.33	15,009	45.75	16,407	42.17
FEV_1 percent predicted	mean (SD)	58.15	19.22	60.00	18.96	59.83	19.37	59.66	19.34
	mild, Grade 1 (≥80%)	329	12.24	226	13.91	2,882	13.98	3,437	13.79
	moderate, Grade 2 (≥50% to <80%)	1,427	53.07	915	56.31	11,312	54.89	13,654	54.78
	severe, Grade 3 (≥30% to <50%)	768	28.56	401	24.68	5,266	25.55	6,435	25.82
	very severe, Grade 4 (<30%)	165	6.14	83	5.11	1,149	5.58	1,397	5.61
	missing[3]	1,186	30.61	599	26.93	12,200	37.18	13,985	35.94
FEV_1/FVC ratio	mean (SD)	58.87	15.86	60.39	14.15	62.13	15.62	61.68	15.58
	<70%	1,752	79.06	1,130	77.77	12,866	72.11	15,748	73.21
	≥70%	464	20.94	323	22.23	4,975	27.89	5,762	26.79
	missing[3]	1,659	42.81	771	34.67	14,968	45.62	17,398	44.72

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] Unless otherwise specified.

[3] Percentages were calculated separately for those with missing and without missing data

Notes MRC - Medical Research Council

FEV_1 - Forced Expired Volume in 1 second

FEV_1/FVC - Forced Expired Volume / Forced Vital Capacity

COPD disease burden at baseline and within year prior to index date, by index LABD group
CPRD-GOLD+HES+ONS Cohort

		Cohort of Patients (N=10,646)1							
		UMEC N = 547		UMEC/VI N = 512		Other LABD N = 10590		All N = 11649	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Moderate COPD exacerbations (recorded in primary care only)	Rate per person year (95% CI)	1.28	(1.19, 1.38	0.93	(0.85, 1.02	0.87	(0.85, 0.89	0.89	(0.87, 0.91)
	0 events	221	40.40	266	51.95	5543	52.34	6030	51.76
	1 event	152	27.79	129	25.20	2762	26.08	3043	26.12
	2+ events	174	31.81	117	22.85	2285	21.58	2576	22.11
Moderate and Severe COPD exacerbations (recorded in primary and/or secondary care)	Rate per person year (95% CI)	1.47	(1.37, 1.58	1.11	(1.02, 1.21	1.03	(1.01, 1.05	1.05	(1.03, 1.07)
	0 events	188	40.40	*222*	51.95	*4873*	52.34	*6030*	51.76
	1 event	154	27.79	144	25.20	2937	26.08	3043	26.12
	2+ events	205	31.81	146	22.85	2780	21.58	2576	22.11
Dyspnoea (MRC Grade)	mean (SD)	2.76	1.05	2.70	0.94	2.62	0.96	2.64	0.96
	MRC Grade 1	43	9.89	33	8.38	548	9.75	624	9.68
	MRC Grade 2	149	34.25	141	35.79	2213	39.38	2503	38.81
	MRC Grade 3	138	31.72	145	36.80	1822	32.42	2105	32.64
	MRC Grade 4	79	18.16	63	15.99	874	15.55	1016	15.75
	MRC Grade 5	26	5.98	12	3.05	163	2.90	201	3.12
	missing[3]	112	20.48	118	23.05	4970	46.93	5200	44.64
FEV_1 percent predicted	mean (SD)	56.12	18.90	58.05	20.06	60.88	19.69	60.46	19.70
	mild, Grade 1 (≥80%)	47	10.68	43	10.62	1068	15.29	1158	14.79
	moderate, Grade 2 (≥50% to <80%)	222	50.45	223	55.06	3859	55.24	4304	54.96
	severe, Grade 3 (≥30% to <50%)	139	31.59	114	28.15	1703	24.38	1956	24.98
	very severe, Grade 4 (<30%)	32	7.27	25	6.17	356	5.10	413	5.27
	missing[3]	107	19.56	107	20.90	3604	34.03	3818	32.78
FEV_1/FVC ratio	mean (SD)	57.31	15.09	59.17	15.54	62.84	15.72	62.32	15.75
	<70%	330	84.83	309	80.89	4331	70.58	4970	71.96
	≥70%	59	15.17	73	19.11	1805	29.42	1937	28.04
	missing[3]	158	28.88	130	25.39	4454	42.06	4742	40.71

[1] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[2] Unless otherwise specified.

[3] Percentages were calculated separately for those with missing and without missing data

Notes MRC - Medical Research Council
FEV_1 - Forced Expired Volume in 1 second
FEV_1/FVC - Forced Expired Volume / Forced Vital Capacity

Figure 1: Time (in days) from index date to first myocardial infarction in UMEC and UMEC/VI initiators [Kaplan Meier plot]

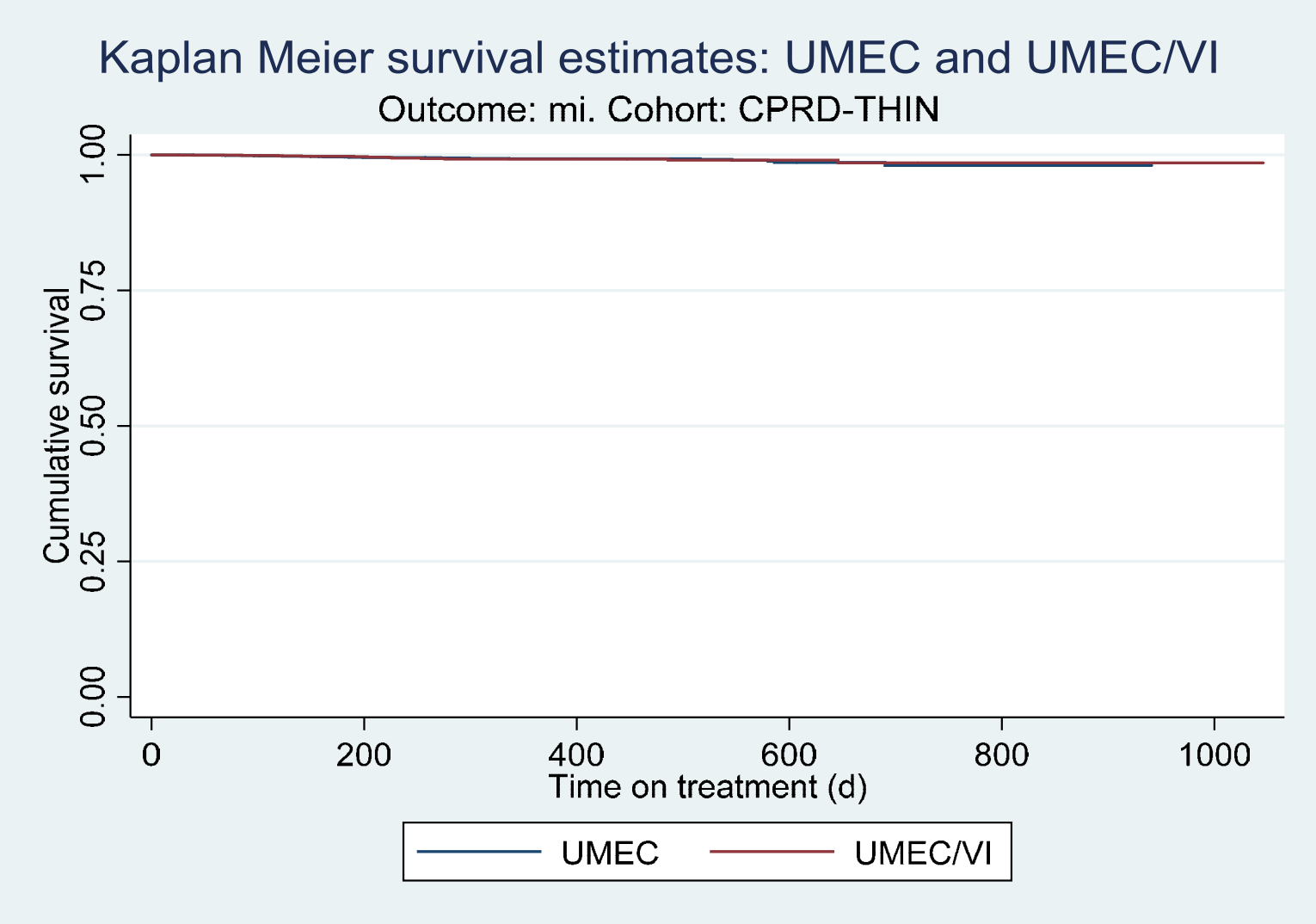


Figure 2: Time (in days) from index date to first stroke in UMEC and UMEC/VI initiators
[Kaplan Meier plot]

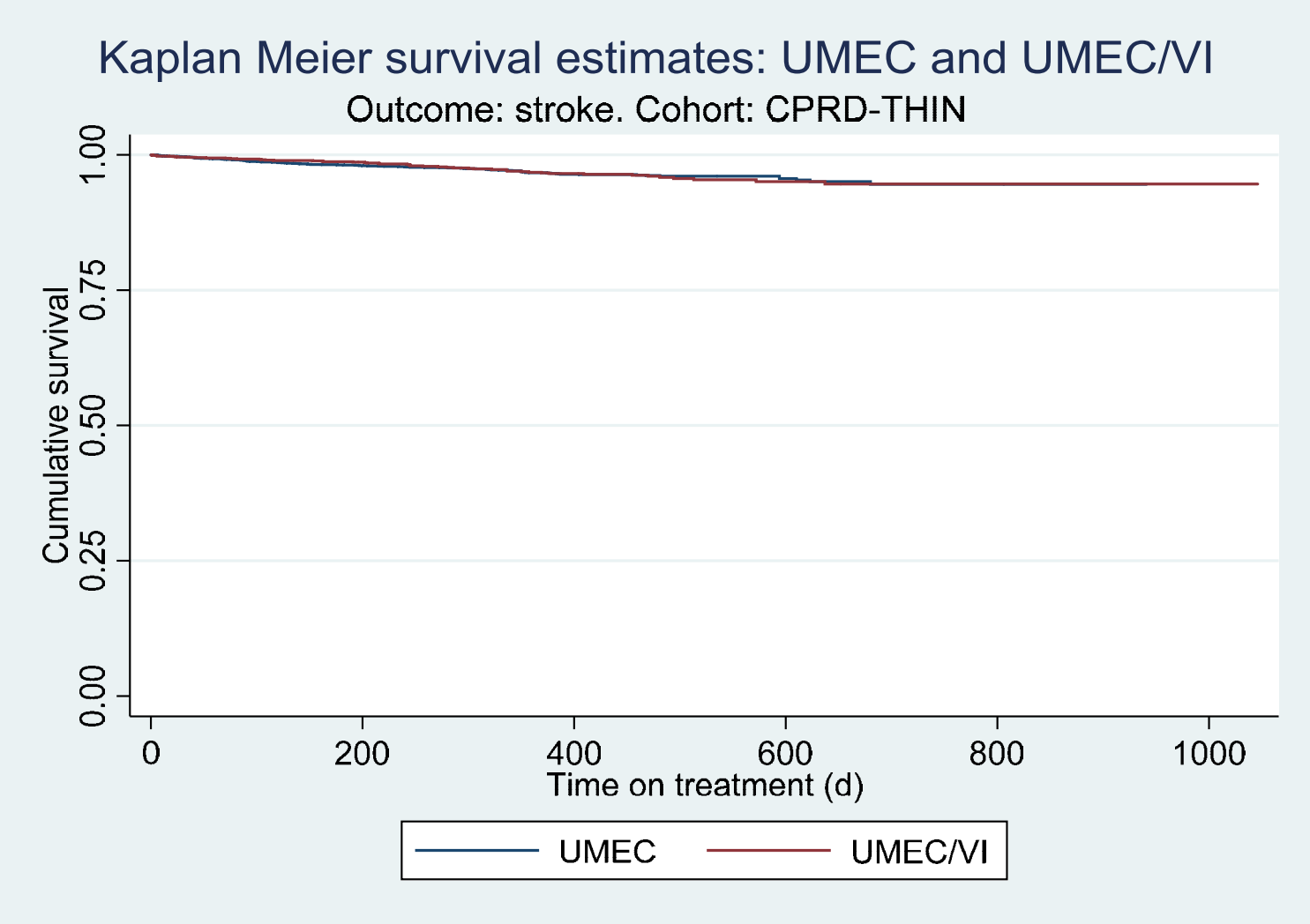


Figure 3: Time (in days) from index date to newly diagnosed congestive heart failure in UMEC and UMEC/VI initiators [Kaplan Meier plot]

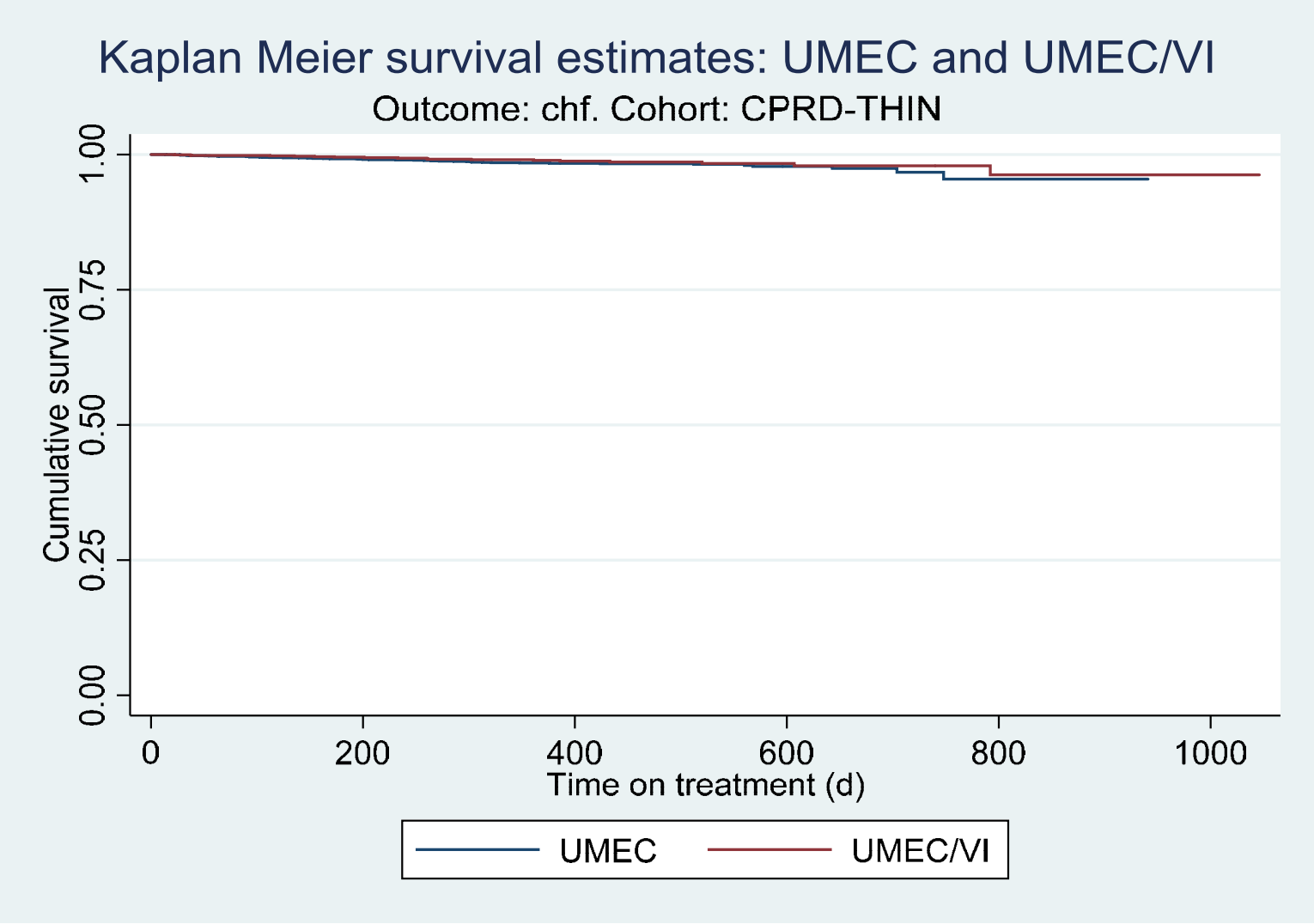


Figure 4: Time (in days) from index date to first pneumonia in UMEC and UMEC/VI initiators
[Kaplan Meier plot]

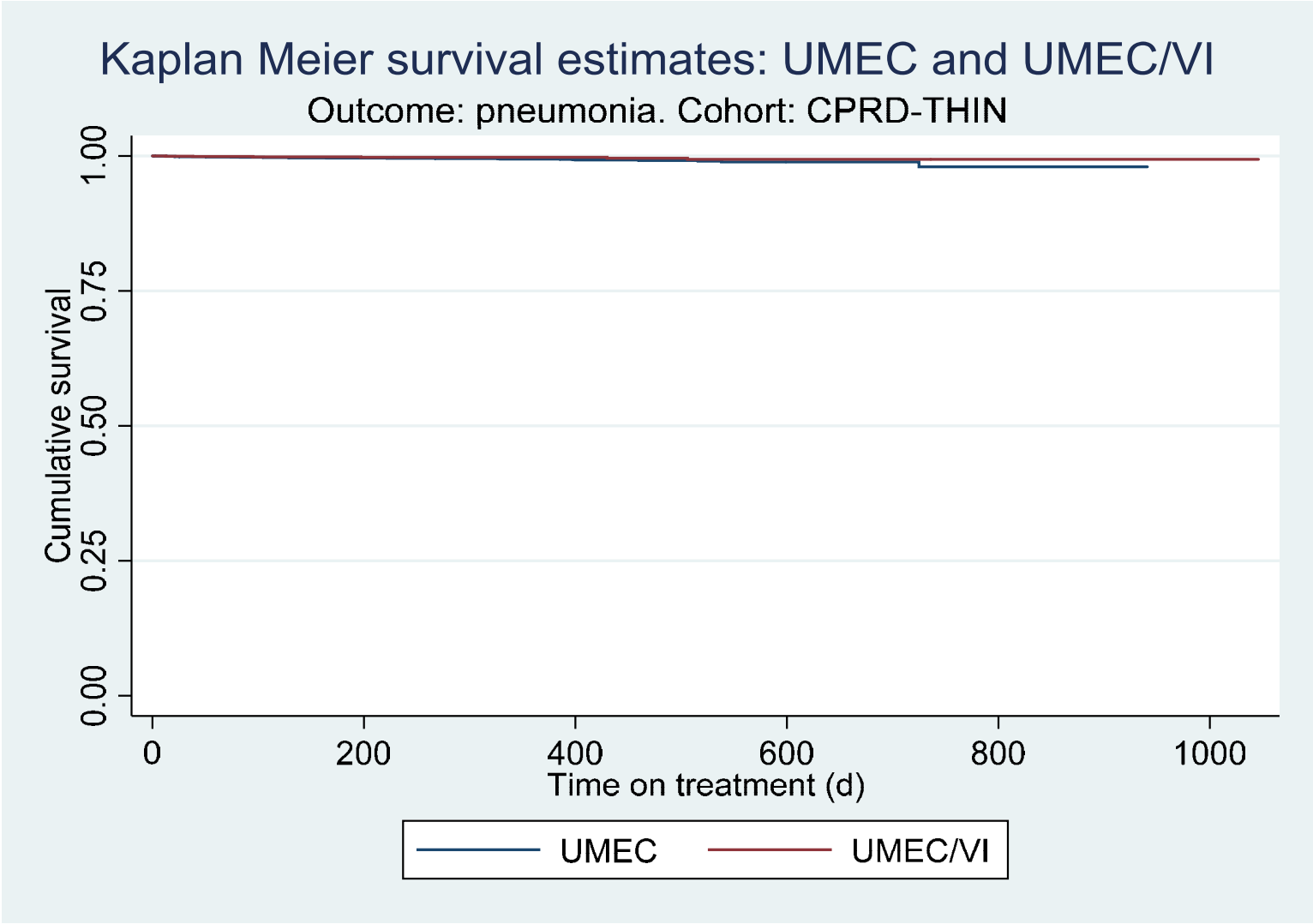


Figure 5: Time (in days) from index date to death of any cause in UMEC and UMEC/VI initiators
[Kaplan Meier plot]

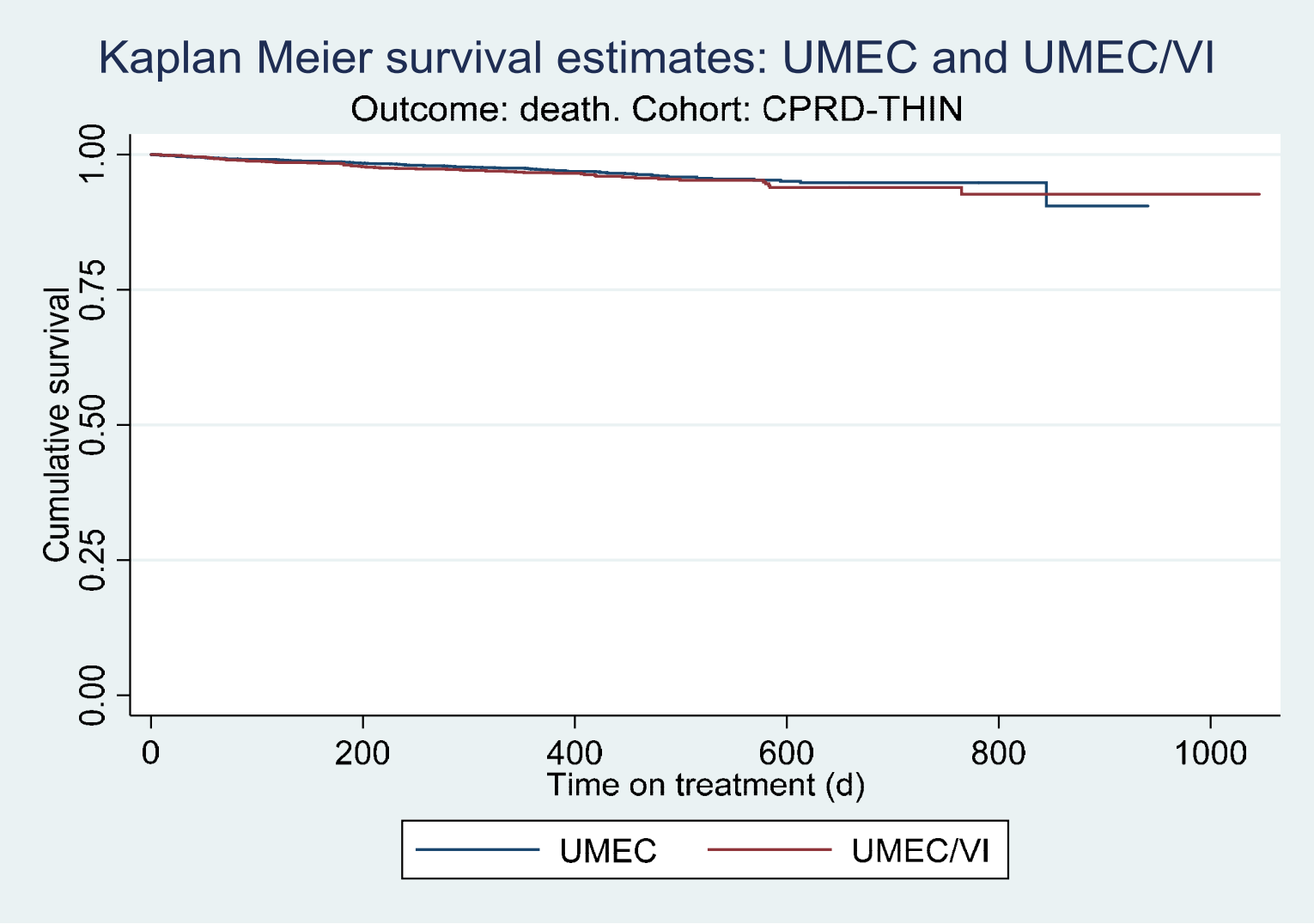


Figure 6: Time (in days) from index date to first myocardial infarction in UMEC and UMEC/VI initiators [Kaplan Meier plot]

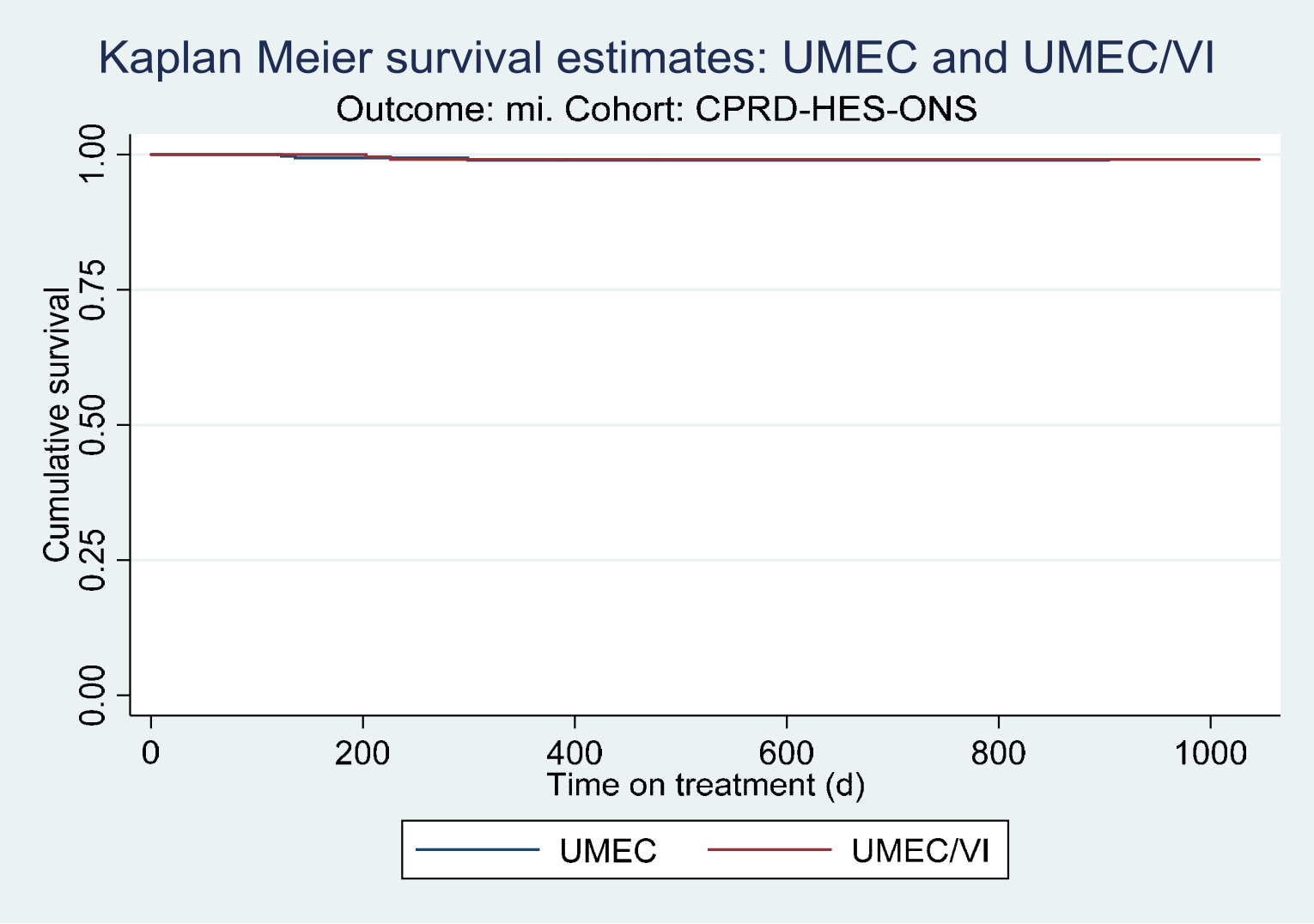


Figure 7: Time (in days) from index date to first stroke in UMEC and UMEC/VI initiators
[Kaplan Meier plot]

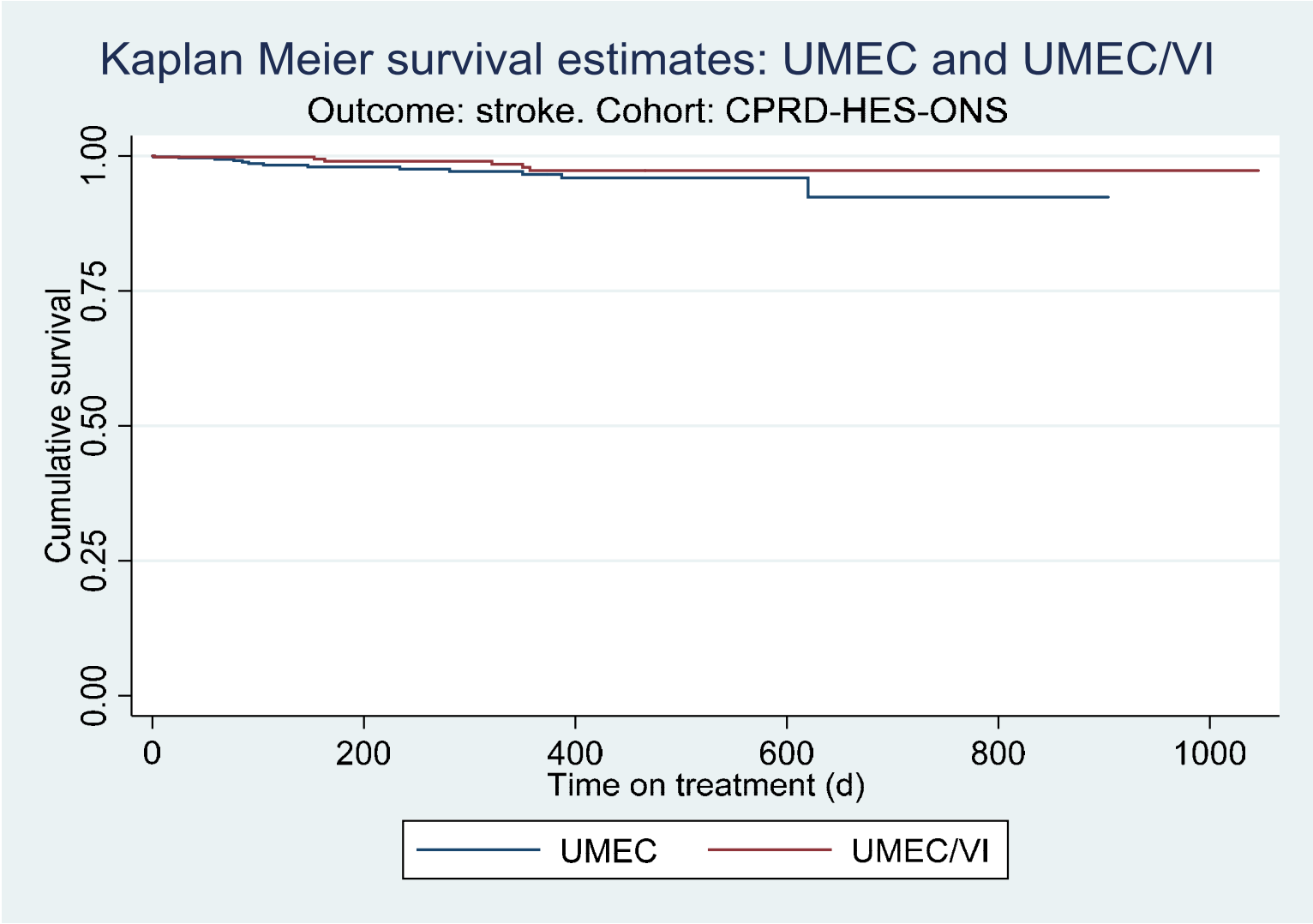


Figure 8: Time (in days) from index date to newly diagnosed congestive heart failure in UMEC and UMEC/VI initiators [Kaplan Meier plot]

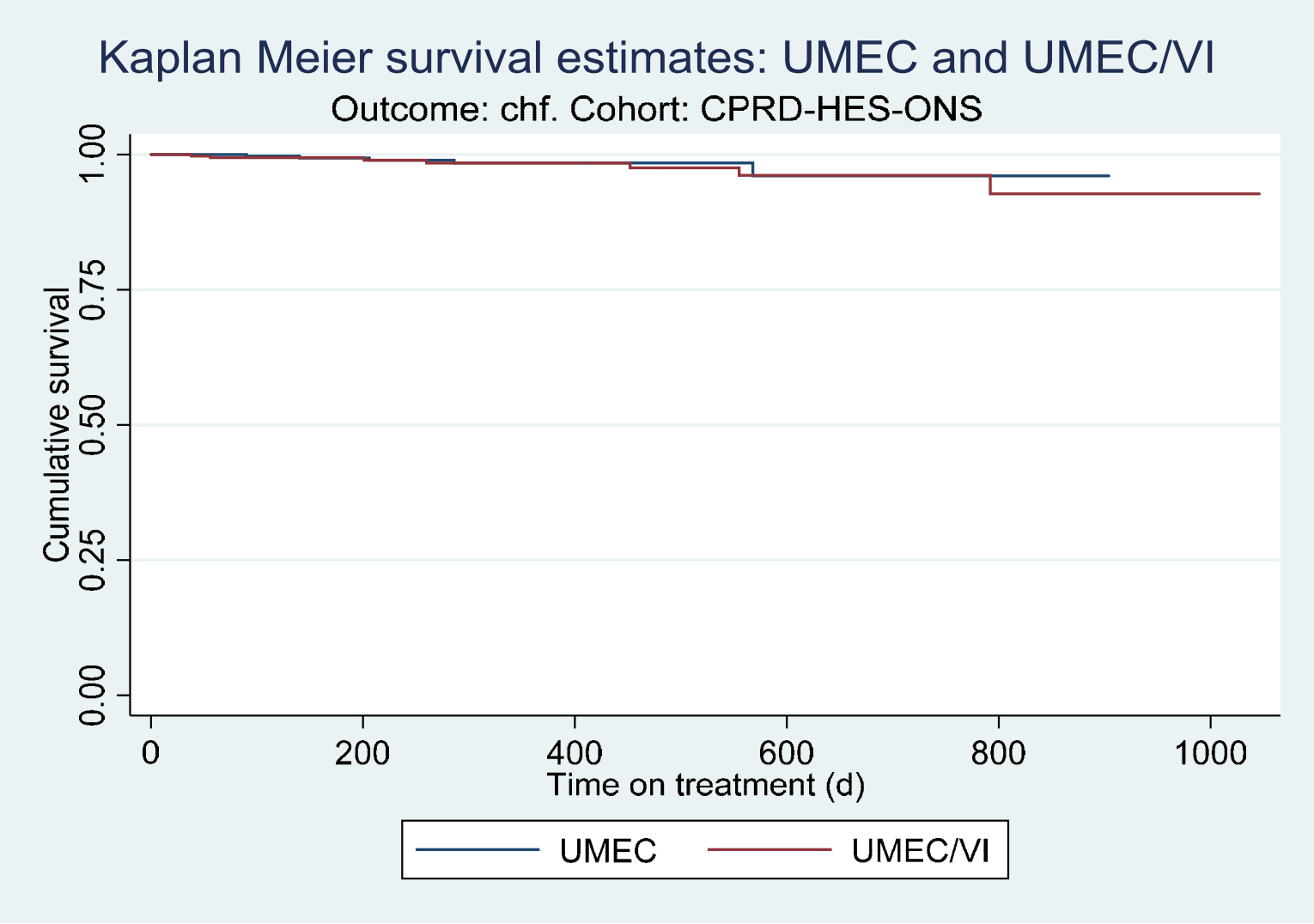


Figure 9: Time (in days) from index date to first pneumonia in UMEC and UMEC/VI initiators
[Kaplan Meier plot]

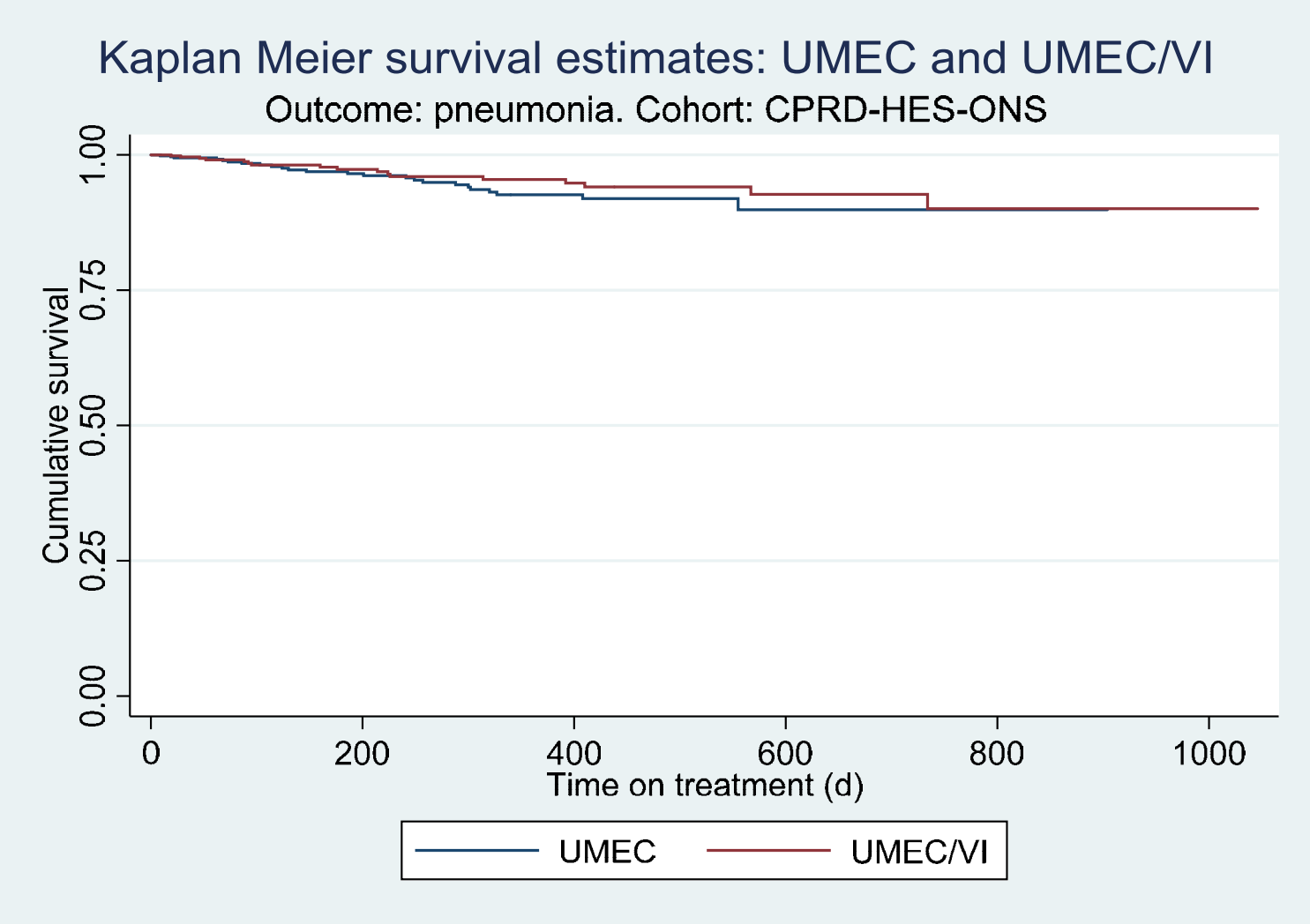


Figure 10a: Time (in days) from index date to death of any cause in UMEC and UMEC/VI initiators [Kaplan Meier plot]

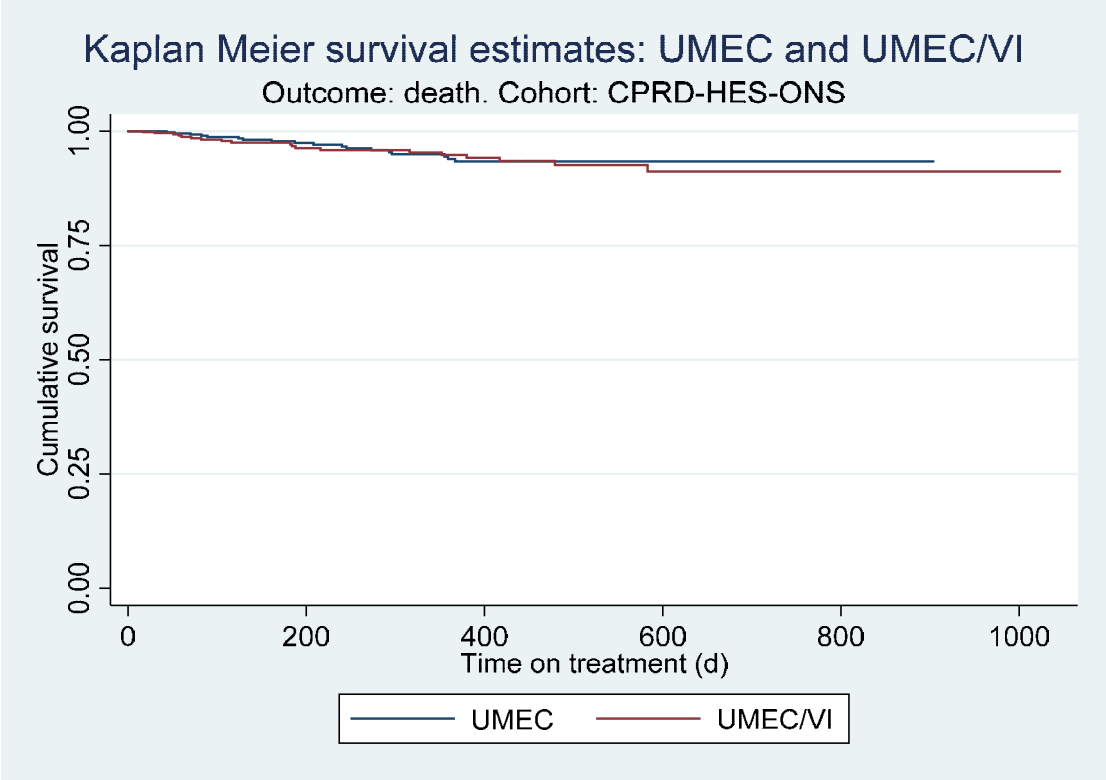


Figure 10b: Time (in days) from index date to death of cardiovascular death in UMEC and UMEC/VI initiators [Kaplan Meier plot]

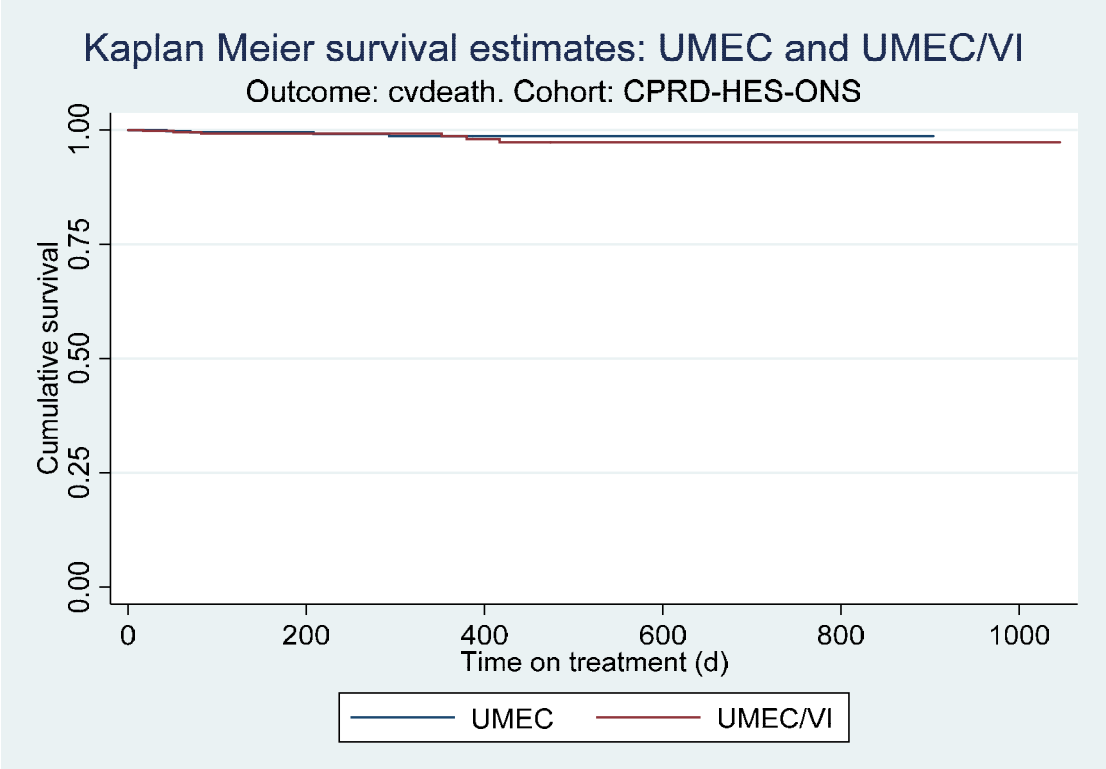


Figure 1: Time (in days) to first treatment change in UMEC initiators with no concomitant use of another maintenance therapy at initiation, by type of change
[Kaplan Meier plot]

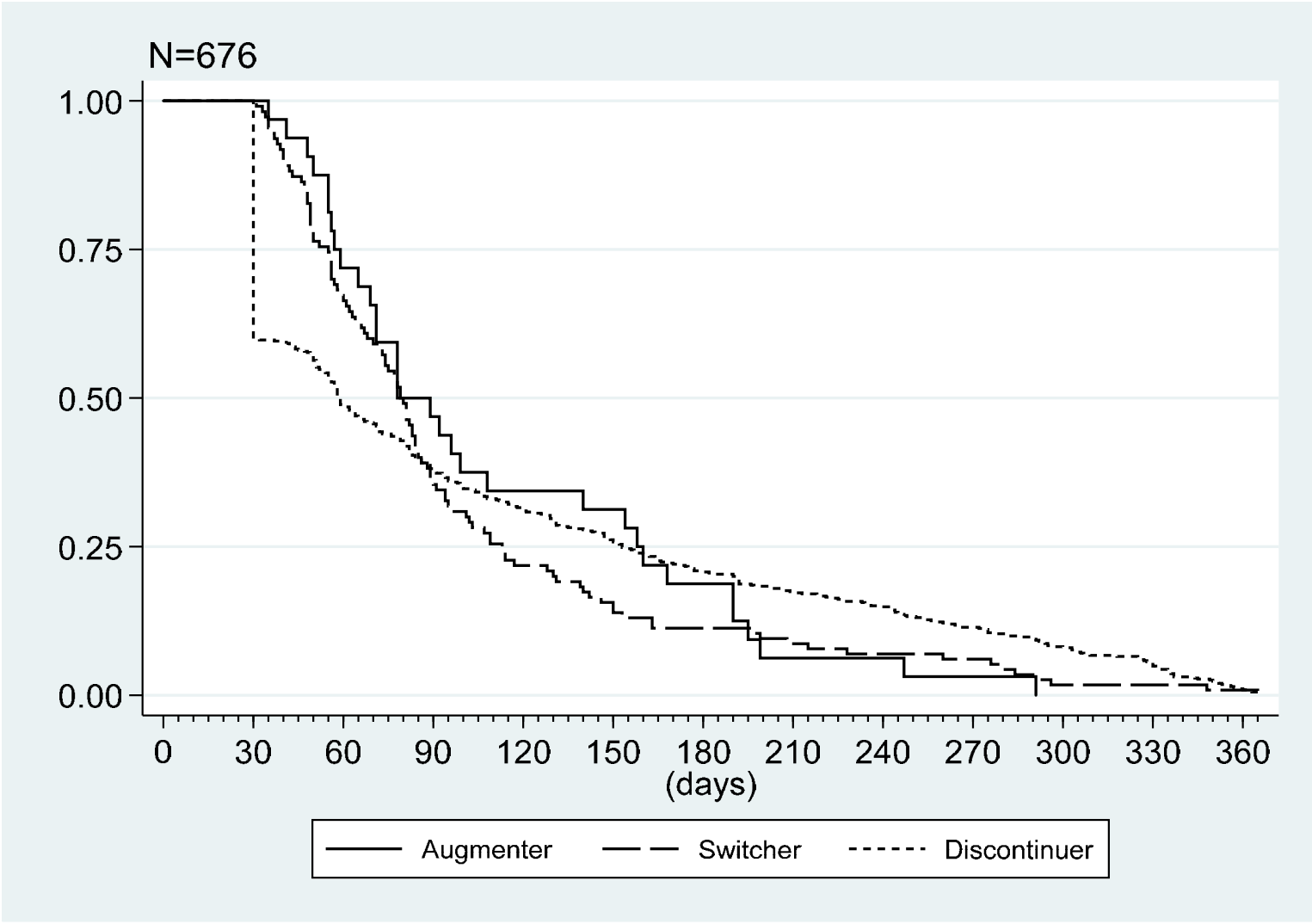


Figure 2: Time (in days) to first treatment change in UMEC initiators with concomitant use of another maintenance therapy at initiation, by type of change
[Kaplan Meier plot]

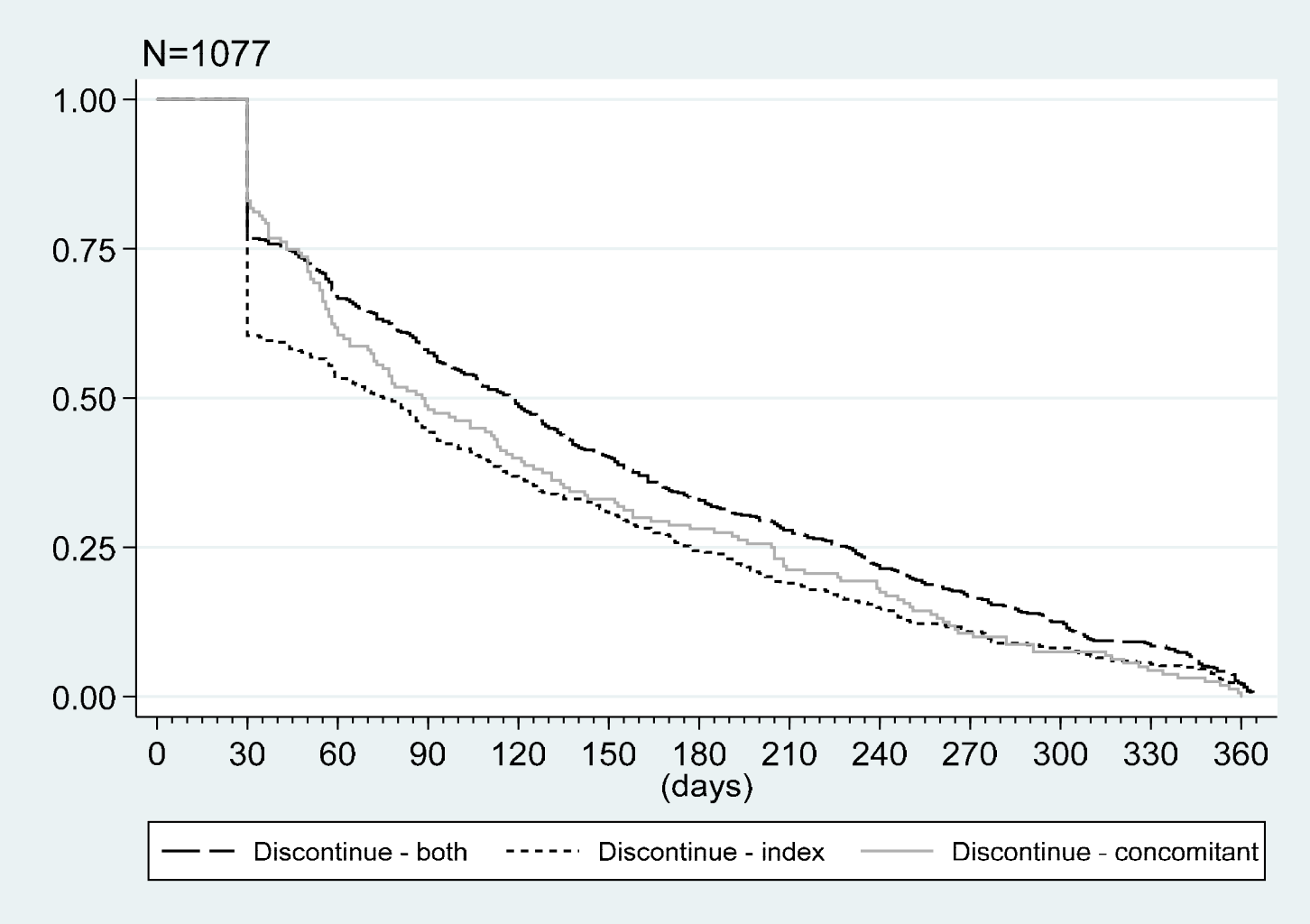


Figure 3: Time (in days) to first treatment change in UMEC/VI initiators with no concomitant use of another maintenance therapy at initiation, by type of change
[Kaplan Meier plot]

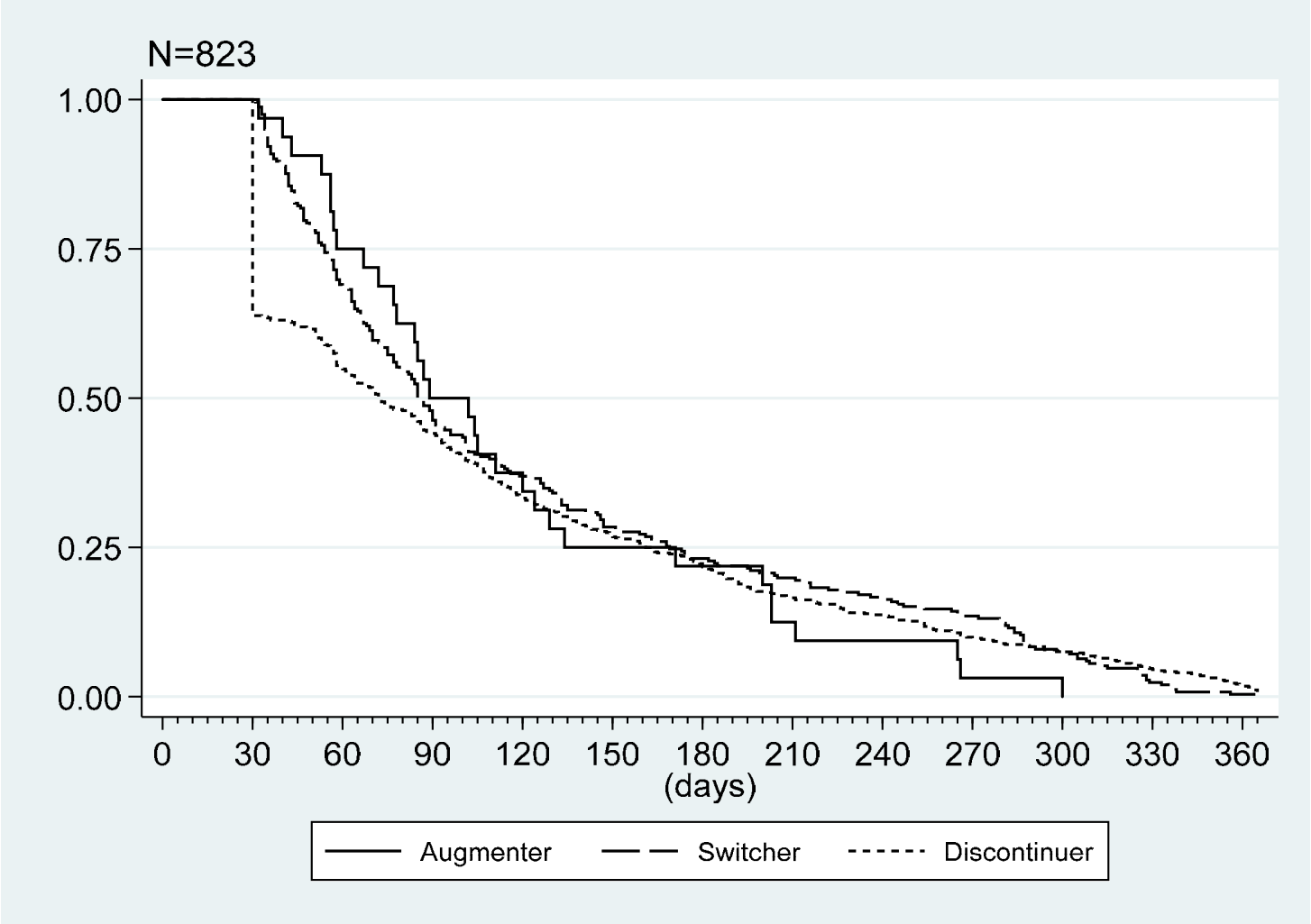
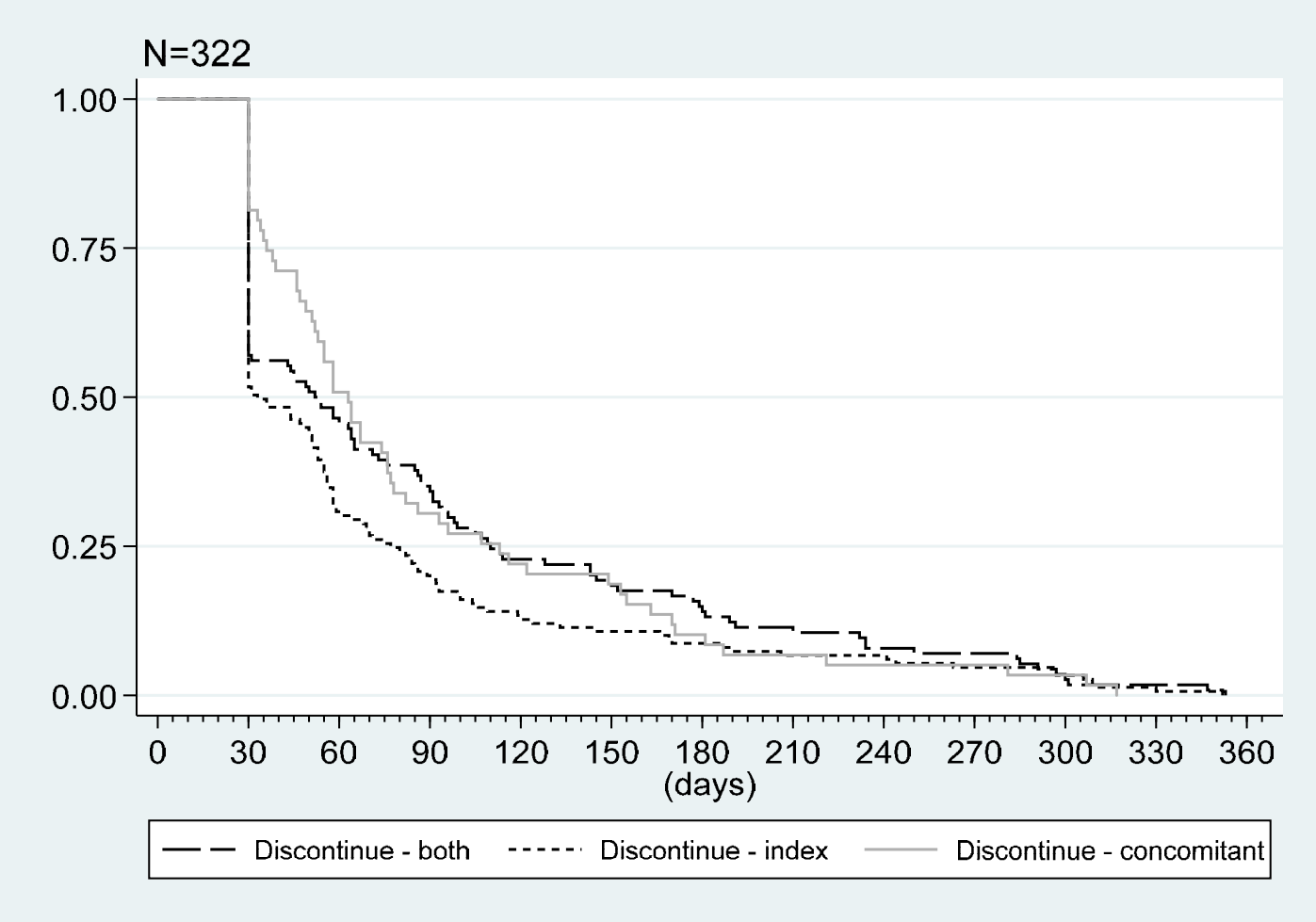


Figure 4: Time (in days) to first treatment change in UMEC/VI initiators with concomitant use of another maintenance therapy at initiation, by type of change
[Kaplan Meier plot]



1 Treatment patterns only considered in patients with at least 12 months follow-up after initiation.

Recorded "indication" for patients newly initiating UMEC, UMEC/VI or other LABD
CPRD GOLD+THIN Cohort

		Cohort of Patients (N=34,516)1					
		COPD N= 31000		Asthma (not COPD) N= 4876		Other (not COPD not asthma) N= 3032	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
UMEC	all	3,604		130		141	
	with concomitant ICS[3]	2,437	67.62	96	73.85	43	30.50
	without concomitant ICS[3]	1,167	32.38	34	26.15	98	69.50
	indication recorded anytime on or before index date	3,495	96.98	119	91.54		
	indication recorded >6 months before index date	2,955	81.99	104	80.00		
	indication recorded >3 to ≤6 months before index date	67	1.86	5	3.85		
	indication recorded ≤0 to ≤3 months before index date	473	13.12	10	7.69		
	indication recorded after index date	109	3.02	11	8.46		
	indication recorded >0 to ≤3 months after index date	63	1.75	4	3.08		
	indication recorded >3 to ≤6 months after index date	10	0.28	2	1.54		
	indication recorded >6 months after index date	36	1.00	5	3.85		
UMEC/VI	all	2,029		69		126	
	with concomitant ICS[3]	284	14.00	30	43.48	6	4.76
	without concomitant ICS[3]	1,745	86.00	39	56.52	120	95.24
	indication recorded anytime on or before index date	1,948	96.01	63	91.30		
	indication recorded >6 months before index date	1,508	74.32	55	79.71		
	indication recorded >3 to ≤6 months before index date	63	3.10	4	5.80		
	indication recorded ≤0 to ≤3 months before index date	377	18.58	4	5.80		
	indication recorded after index date	81	3.99	6	8.70		
	indication recorded >0 to ≤3 months after index date	45	2.22	2	2.90		
	indication recorded >3 to ≤6 months after index date	8	0.39	1	1.45		
	indication recorded >6 months after index date	28	1.38	3	4.35		
Other LABD[4]	all	25,367		4,677		2,765	
	with concomitant ICS[3]	9,509	37.49	2,848	60.89	482	17.43
	without concomitant ICS[3]	15,858	62.51	1,829	39.11	2,283	82.57
	indication recorded anytime on or before index date	22,961	90.52	4,294	91.81		
	indication recorded >6 months before index date	15,657	61.72	3,567	76.27		
	indication recorded >3 to ≤6 months before index date	958	3.78	199	4.25		
	indication recorded ≤0 to ≤3 months before index date	6,346	25.02	528	11.29		
	indication recorded after index date	2,406	9.48	383	8.19		
	indication recorded >0 to ≤3 months after index date	1,160	4.57	167	3.57		
	indication recorded >3 to ≤6 months after index date	346	1.36	65	1.39		
	indication recorded >6 months after index date	900	3.55	151	3.23		
Other LAMA	all	19,655		2,327		2,143	
	with concomitant ICS[3]	8,751	44.52	1,708	73.40	420	19.60
	without concomitant ICS[3]	10,904	55.48	619	26.60	1,723	80.40
	indication recorded anytime on or before index date	17,638	89.74	2,130	91.53		
	indication recorded >6 months before index date	11,562	58.82	1,903	81.78		
	indication recorded >3 to ≤6 months before index date	718	3.65	83	3.57		
	indication recorded ≤0 to ≤3 months before index date	5,358	27.26	144	6.19		
	indication recorded after index date	2,017	10.26	197	8.47		
	indication recorded >0 to ≤3 months after index date	992	5.05	71	3.05		
	indication recorded >3 to ≤6 months after index date	280	1.42	43	1.85		
	indication recorded >6 months after index date	745	3.79	83	3.57		
Other LABA	all	3,458		2,278		482	
	with concomitant ICS[3]	413	11.94	1,108	48.64	59	12.24
	without concomitant ICS[3]	3,045	88.06	1,170	51.36	423	87.76
	indication recorded anytime on or before index date	3,178	91.90	2,098	92.10		
	indication recorded >6 months before index date	2,308	66.74	1,604	70.41		
	indication recorded >3 to ≤6 months before index date	168	4.86	115	5.05		
	indication recorded ≤0 to ≤3 months before index date	702	20.30	379	16.64		
	indication recorded after index date	280	8.10	180	7.90		
	indication recorded >0 to ≤3 months after index date	118	3.41	95	4.17		
	indication recorded >3 to ≤6 months after index date	46	0.39	21	1.45		
	indication recorded >6 months after index date	116	3.35	64	2.81		
Other LAMA/LABA	all	2,254		72		140	
	with concomitant ICS[3]	345	15.31	32	44.44	3	2.14
	without concomitant ICS[3]	1,909	84.69	40	55.56	137	97.86
	indication recorded anytime on or before index date	2,145	95.16	66	91.67		
	indication recorded >6 months before index date	1,787	79.28	60	83.33		
	indication recorded >3 to ≤6 months before index date	72	3.19	1	1.39		
	indication recorded ≤0 to ≤3 months before index date	286	12.69	5	6.94		
	indication recorded after index date	109	4.84	6	8.33		
	indication recorded >0 to ≤3 months after index date	50	2.22	1	1.39		
	indication recorded >3 to ≤6 months after index date	20	0.89	1	1.39		
	indication recorded >6 months after index date	39	1.73	4	5.56		

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
2 Unless otherwise specified.
3 At index date
4 The Other LABD group includes Other LAMA, Other LABA, and Other LABA/LAMA

Recorded "indication" for patients newly initiating UMEC, UMEC/VI, other LAMA, other LABA and other LABA/LAMA

CPRD GOLD+THIN Cohort

		Cohort of Patients (N=34,516)1											
		COPD		Asthma (not COPD)		Other (not COPD not asthma)		Off-label (Definition 1)[2]		Off-label (Definition 2)[3]		Off-label (Definition 3)[4]	
		N=	31000	N=	4876	N=	3032	N=	7908	N=	24125	N=	6218
Index therapy	Total No.	No.[5]	(%)[5]	No.[5]	(%)[5]	No.[5]	(%)[5]	No.[5]	(%)[5]	No.[5]	(%)[5]	No.[5]	(%)[5]
UMEC	3,875	3,604	11.63	130	2.67	141	4.65	271	6.99				
UMEC/VI	2,224	2,029	6.55	69	1.42	126	4.16	195	8.77				
other LAMA	24,125	19,655	63.40	2,327	47.72	2,143	70.68	4,470	18.53	3,980	16.50		
other LABA	6,218	3,458	11.15	2,278	46.72	482	15.90	2,760	44.39			1,727	27.77
other LABA/LAMA	2,466	2,254	7.27	72	1.48	140	4.62	212	8.60				

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

2 Primary definition: Patients without evidence of COPD.

3 Other LAMA group only: Prescribing in patients without evidence of COPD unless they had 1) an index prescription for 2.5mg tiotropium on or after 13/09/2014 and 2) were in the asthma category, and 3) had concomitant ICS+LABA

4 Other LABA group only: Prescribing in patients without evidence of COPD unless they had 1) were in the asthma category, and 2) had concomitant ICS

5 Unless otherwise specified.

Characteristics of patients initiating LABD therapy, with breakdown by recorded "indication" - UMEC only
CPRD GOLD+THIN Cohort

		Cohort of Patients (N=3,875)1							
		COPD N= 3,604		Asthma (not COPD) N= 130		Other (not COPD not asthma N= 141		Off-label (Definition 1)[2] N= 271	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Demographics at baseline									
Age (in years) at index date	mean (SD)	69.02	10.31	60.18	15.86	69.84	13.79	65.2	15.56
	≥65 years	2,464	68.37	59	45.38	99	70.21	158	58.3
	<65 years	1,140	31.63	71	54.62	42	29.79	113	41.7
	<18 years	0	0	0	0	0	0	0	0
	18-64 years	1,140	31.63	71	54.62	42	29.79	113	41.7
Gender	female	1,829	50.75	75	57.69	80	56.74	155	57.2
	male	1,775	49.25	55	42.31	61	43.26	116	42.8
Smoking status	current smoker	1,555	43.15	42	32.31	59	42.14	101	37.41
	ex-smoker	1,788	49.61	44	33.85	54	38.57	98	36.3
	no/never smoker	261	7.24	44	33.85	27	19.29	71	26.3
	missing[4]	0	0	0	0	1	0.71	1	0.37
Body Mass Index (kg/m2)	mean (SD)	27.78	6.41	30.9	7.85	27.56	7.08	29.18	7.64
	underweight <18.5	180	5.06	1	0.78	8	5.93	9	3.42
	normal 18.5-24.9	1,087	30.53	28	21.88	47	34.81	75	28.52
	overweight 25.0-29.9	1,145	32.16	40	31.25	43	31.85	83	31.56
	obese ≥30	1,148	32.25	59	46.09	37	27.41	96	36.5
	missing[4]	44	1.22	2	1.54	6	4.26	8	2.95
Area based deprivation[5]	Q1 (least deprived)	80	16.19	5	21.74	4	13.79	9	17.31
	Q2	91	18.42	6	26.09	4	13.79	10	19.23
	Q3	130	26.32	3	13.04	7	24.14	10	19.23
	Q4	109	22.06	6	26.09	11	37.93	17	32.69
	Q5 (most deprived)	84	17	3	13.04	3	10.34	6	11.54
	missing[4]	3,110	86.29	107	82.31	112	79.43	219	80.81
COPD burden at baseline and within year prior to in									
Moderate COPD exacerbations (recorded in primary care	Rate per person year (95% CI)	1.12 (1.08, 1.15							
	0 events	1,687	46.81						
	1 event	904	25.08						
	2+ events	1,013	28.11						
Dyspnoea (MRC Grade)	mean (SD)	2.79	0.96	2.71	0.99	3.38	0.87	3.04	0.98
	MRC Grade 1	195	6.52	1	7.14	0	0	1	3.7
	MRC Grade 2	1,062	35.51	6	42.86	2	15.38	8	29.63
	MRC Grade 3	1,010	33.77	3	21.43	5	38.46	8	29.63
	MRC Grade 4	620	20.73	4	28.57	5	38.46	9	33.33
	MRC Grade 5	104	3.48	0	0	1	7.69	1	3.7
	missing[4]	613	17.01	116	89.23	128	90.78	244	90.04
FEV1 percent predicted	mean (SD)	57.93	19.16	67.88	18.76	64.05	21.16	65.99	19.93
	mild, Grade 1 (≥80%)	312	11.93	9	24.32	8	22.22	17	23.29
	moderate, Grade 2 (≥50% to <80%)	1,387	53.02	21	56.76	19	52.78	40	54.79
	severe, Grade 3 (≥30% to <50%)	755	28.86	6	16.22	7	19.44	13	17.81
	very severe, Grade 4 (<30%)	162	6.19	1	2.7	2	5.56	3	4.11
	missing[4]	988	27.41	93	71.54	105	74.47	198	73.06
FEV1/FVC ratio	mean (SD)	58.57	15.85	70.28	11.78	68.59	13.05	69.5	12.31
	<70%	1,722	79.91	16	48.48	14	50	30	49.18
	≥70%	433	20.09	17	51.52	14	50	31	50.82
	missing[4]	1,449	40.21	97	74.62	113	80.14	210	77.49
Past history of comorbidities									
Cardio- and cerebrovascular disease (ever before)		2,345	65.07	67	51.54	98	69.5	165	60.89
Beta-blocker prescribing (in year prior to index date)		651	18.06	18	13.85	38	26.95	56	20.66
Pneumonia (ever before)		262	7.27	10	7.69	12	8.51	22	8.12
Gastroesophageal reflux disease (ever before)		808	22.42	47	36.15	35	24.82	82	30.26
Diabetes (ever before)		696	19.31	28	21.54	29	20.57	57	21.03
Acute and chronic renal disease (ever before)		756	20.98	30	23.08	40	28.37	70	25.83
Cancer (ever before)		519	14.4	14	10.77	31	21.99	45	16.61
Respiratory medication use in year prior to index da									
SABD[6]	1+ prescription(s)	3,155	87.54	120	92.31	82	58.16	202	74.54
	4+ prescriptions	2,220	61.6	91	70	34	24.11	125	46.13
ICS	Any ICS	2,609	72.39	117	90	42	29.79	159	58.67
	ICS (in a single device)	250	6.94	16	12.31	8	5.67	24	8.86
	ICS/LABA (fixed combination)	2,443	67.79	111	85.38	34	24.11	145	53.51
LABA	Any	2,565	71.17	111	85.38	37	26.24	148	54.61
	LABA (in a single device)	157	4.36	5	3.85	3	2.13	8	2.95
	ICS/LABA (fixed combination)	2,443	67.79	111	85.38	34	24.11	145	53.51
	LABA/LAMA (fixed combination)	43	1.19	0	0	0	0	0	0
LAMA	Any	2,221	61.63	43	33.08	25	17.73	68	25.09
	LAMA (in a single device)	2,211	61.35	43	33.08	25	17.73	68	25.09
	LABA/LAMA (fixed combination)	43	1.19	0	0	0	0	0	0
Theophylline (or derivatives)		203	5.63	7	5.38	1	0.71	8	2.95
OCS	Chronic use[7]	279	7.74	8	6.15	8	5.67	16	5.9

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
2 Primary definition: Patients with (on-label) or without (off-label) evidence of COPD.
3 Unless otherwise specified.
4 Percentages were calculated separately for those with missing and without missing data
5 Area based deprivation is measured using patient-level Townsend quintile
6 Includes the following asthma "reliever" medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA.
7 Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days.
8 Roflumilast and ICS/SABA data were investigated but counts were very low (<5) so data are not presented
Note This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

Characteristics of patients initiating LABD therapy, with breakdown by recorded "indication" - UMEC/VI only
CPRD GOLD+THIN Cohort

		Cohort of Patients (N=2,224)1							
		COPD N= 2,029		Asthma (not COPD) N= 69		Other (not COPD not asthma N= 126		Off-label (Definition 1)[2] N= 195	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Demographics at baseline									
Age (in years) at index date	mean (SD)	69.29	10.19	62.25	15.02	68.36	14.33	66.19	14.83
	≥65 years	1,421	70.03	33	47.83	78	61.9	111	56.92
	<65 years	608	29.97	36	52.17	48	38.1	84	43.08
	<18 years	0	0	0	0	0	0	0	0
	18-64 years	608	29.97	36	52.17	48	38.1	84	43.08
Gender	female	947	46.67	47	68.12	61	48.41	108	55.38
	male	1,082	53.33	22	31.88	65	51.59	87	44.62
Smoking status	current smoker	819	40.38	16	23.19	48	38.1	64	32.82
	ex-smoker	1,080	53.25	26	37.68	46	36.51	72	36.92
	no/never smoker	129	6.36	27	39.13	32	25.4	59	30.26
	missing[4]	1	0.05	0	0	0	0	0	0
Body Mass Index (kg/m2)	mean (SD)	28.25	6.31	30.31	6.7	28.81	6.78	29.36	6.77
	underweight <18.5	80	3.98	0	0	2	1.67	2	1.06
	normal 18.5-24.9	564	28.06	14	20.29	37	30.83	51	26.98
	overweight 25.0-29.9	670	33.33	27	39.13	35	29.17	62	32.8
	obese ≥30	696	34.63	28	40.58	46	38.33	74	39.15
	missing[4]	19	0.94	0	0	6	4.76	6	3.08
Area based deprivation[5]	Q1 (least deprived)	93	20.09	2	14.29	3	8.57	5	10.2
	Q2	106	22.89	2	14.29	3	8.57	5	10.2
	Q3	79	17.06	4	28.57	9	25.71	13	26.53
	Q4	107	23.11	1	7.14	16	45.71	17	34.69
	Q5 (most deprived)	78	16.85	5	35.71	4	11.43	9	18.37
	missing[4]	1,566	77.18	55	79.71	91	72.22	146	74.87
COPD burden at baseline and within year prior to in									
Moderate COPD exacerbations (recorded in primary care	Rate per person year (95% CI)	0.79 (0.75, 0.83							
	0 events	1,136	55.99						
	1 event	513	25.28						
	2+ events	380	18.73						
Dyspnoea (MRC Grade)	mean (SD)	2.69	0.9	2.67	0.82	2.56	0.7	2.58	0.72
	MRC Grade 1	100	6.03	0	0	0	0	0	0
	MRC Grade 2	667	40.2	3	50	10	55.56	13	54.17
	MRC Grade 3	577	34.78	2	33.33	6	33.33	8	33.33
	MRC Grade 4	275	16.58	1	16.67	2	11.11	3	12.5
	MRC Grade 5	40	2.41	0	0	0	0	0	0
	missing[4]	370	18.24	63	91.3	108	85.71	171	87.69
FEV1 percent predicted	mean (SD)	59.61	18.73	76.55	21.71	70.05	22.22	72.05	22.06
	mild, Grade 1 (≥80%)	210	13.35	6	37.5	10	27.78	16	30.77
	moderate, Grade 2 (≥50% to <80%)	886	56.33	9	56.25	20	55.56	29	55.77
	severe, Grade 3 (≥30% to <50%)	395	25.11	1	6.25	5	13.89	6	11.54
	very severe, Grade 4 (<30%)	82	5.21	0	0	1	2.78	1	1.92
	missing[4]	456	22.47	53	76.81	90	71.43	143	73.33
FEV1/FVC ratio	mean (SD)	59.96	13.95	73.68	12.49	72.97	15.01	73.17	14.23
	<70%	1,112	79.09	4	30.77	14	41.18	18	38.3
	≥70%	294	20.91	9	69.23	20	58.82	29	61.7
	missing[4]	623	30.7	56	81.16	92	73.02	148	75.9
Past history of comorbidities									
Cardio- and cerebrovascular disease (ever before)		1,333	65.7	37	53.62	83	65.87	120	61.54
Beta-blocker prescribing (in year prior to index date)		434	21.39	7	10.14	44	34.92	51	26.15
Pneumonia (ever before)		145	7.15	4	5.8	11	8.73	15	7.69
Gastroesophageal reflux disease (ever before)		475	23.41	21	30.43	29	23.02	50	25.64
Diabetes (ever before)		372	18.33	14	20.29	24	19.05	38	19.49
Acute and chronic renal disease (ever before)		398	19.62	8	11.59	32	25.4	40	20.51
Cancer (ever before)		277	13.65	7	10.14	29	23.02	36	18.46
Respiratory medication use in year prior to index da									
SABD[6]	1+ prescription(s)	1,658	81.72	64	92.75	67	53.17	131	67.18
	4+ prescriptions	1,006	49.58	42	60.87	31	24.6	73	37.44
ICS	Any ICS	839	41.35	60	86.96	29	23.02	89	45.64
	ICS (in a single device)	166	8.18	23	33.33	7	5.56	30	15.38
	ICS/LABA (fixed combination)	706	34.8	46	66.67	22	17.46	68	34.87
LABA	Any	977	48.15	49	71.01	30	23.81	79	40.51
	LABA (in a single device)	292	14.39	6	8.7	7	5.56	13	6.67
	ICS/LABA (fixed combination)	706	34.8	46	66.67	22	17.46	68	34.87
	LABA/LAMA (fixed combination)	55	2.71	2	2.9	2	1.59	4	2.05
LAMA	Any	1,089	53.67	15	21.74	25	19.84	40	20.51
	LAMA (in a single device)	1,071	52.78	13	18.84	24	19.05	37	18.97
	LABA/LAMA (fixed combination)	55	2.71	2	2.9	2	1.59	4	2.05
Theophylline (or derivatives)		52	2.56	2	2.9	0	0	2	1.03
OCS	Chronic use[7]	97	4.78	7	10.14	11	8.73	18	9.23

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
2 Primary definition: Patients with (on-label) or without (off-label) evidence of COPD.
3 Unless otherwise specified.
4 Percentages were calculated separately for those with missing and without missing data
5 Area based deprivation is measured using patient-level Townsend quintile
6 Includes the following asthma "reliever" medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA.
7 Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days.
8 Roflumilast and ICS/SABA data were investigated but counts were very low (<5) so data are not presented
Note This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

Characteristics of patients initiating LABD therapy, with breakdown by recorded "indication" - all therapies

CPRD GOLD+THIN Cohort

		Cohort of Patients (N=34,516)1							
		COPD N= 31,000		Asthma (not COPD) N= 4,876		Other (not COPD not asthma N= 3,032		Off-label (Definition 1)[2] N= 7,908	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Demographics at baseline									
Age (in years) at index date	mean (SD)	68.5	10.79	50.74	21.94	67.31	16.16	57.09	21.49
	≥65 years	20,439	65.93	1,495	30.66	1,957	64.54	3,452	43.65
	<65 years	10,561	34.07	3,381	69.34	1,075	35.46	4,456	56.35
	<18 years	0	0	559	11.46	50	1.65	609	7.7
	18-64 years	10,561	34.07	2,822	57.88	1,025	33.81	3,847	48.65
Gender	female	15,274	49.27	3,097	63.52	1,391	45.88	4,488	56.75
	male	15,726	50.73	1,779	36.48	1,641	54.12	3,420	43.25
Smoking status	current smoker	13,579	43.82	975	21.15	1,092	36.57	2,067	27.21
	ex-smoker	14,943	48.22	1,293	28.05	1,237	41.43	2,530	33.31
	no/never smoker	2,468	7.96	2,342	50.8	657	22	2,999	39.48
	missing[4]	10	0.03	266	5.46	46	1.52	312	3.95
Body Mass Index (kg/m2)	mean (SD)	27.72	6.47	30.05	7.47	28.27	6.92	29.33	7.3
	underweight <18.5	1,475	4.84	51	1.25	112	4.01	163	2.37
	normal 18.5-24.9	9,615	31.53	1,006	24.58	836	29.9	1,842	26.74
	overweight 25.0-29.9	9,734	31.92	1,303	31.83	910	32.55	2,213	32.12
	obese ≥30	9,669	31.71	1,733	42.34	938	33.55	2,671	38.77
	missing[4]	507	1.64	783	16.06	236	7.78	1,019	12.89
Area based deprivation[5]	Q1 (least deprived)	1,513	17.39	374	20.38	212	19.1	586	19.9
	Q2	1,579	18.15	395	21.53	210	18.92	605	20.54
	Q3	1,945	22.36	408	22.23	248	22.34	656	22.28
	Q4	2,107	24.22	400	21.8	290	26.13	690	23.43
	Q5 (most deprived)	1,555	17.88	258	14.06	150	13.51	408	13.85
	missing[4]	22,301	71.94	3,041	62.37	1,922	63.39	4,963	62.76
COPD burden at baseline and within year prior to in									
Moderate COPD exacerbations (recorded in primary care	Rate per person year (95% CI)	0.9 (0.89, 0.92							
	0 events	15,991	51.58						
	1 event	8,092	26.1						
	2+ events	6,917	22.31						
Dyspnoea (MRC Grade)	mean (SD)	2.67	0.96	2.3	1.01	2.64	1	2.46	1.02
	MRC Grade 1	1,861	8.43	56	24.78	22	10.95	78	18.27
	MRC Grade 2	8,683	39.34	81	35.84	77	38.31	158	37
	MRC Grade 3	7,071	32.03	57	25.22	61	30.35	118	27.63
	MRC Grade 4	3,778	17.12	30	13.27	34	16.92	64	14.99
	MRC Grade 5	681	3.09	2	0.88	7	3.48	9	2.11
	missing[4]	8,926	28.79	4,650	95.37	2,831	93.37	7,481	94.6
FEV1 percent predicted	mean (SD)	58.61	18.88	74.69	19.88	69.63	20.15	72.69	20.14
	mild, Grade 1 (≥80%)	2,775	12.03	439	39.13	223	30.34	662	35.65
	moderate, Grade 2 (≥50% to <80%)	12,701	55.06	566	50.45	387	52.65	953	51.32
	severe, Grade 3 (≥30% to <50%)	6,219	26.96	104	9.27	112	15.24	216	11.63
	very severe, Grade 4 (<30%)	1,371	5.94	13	1.16	13	1.77	26	1.4
	missing[4]	7,934	25.59	3,754	76.99	2,297	75.76	6,051	76.52
FEV1/FVC ratio	mean (SD)	60.67	15.29	74.01	13.52	71.99	15.13	73.21	14.21
	<70%	15,109	76.39	352	33.65	287	41.9	639	36.92
	≥70%	4,670	23.61	694	66.35	398	58.1	1,092	63.08
	missing[4]	11,221	36.2	3,830	78.55	2,347	77.41	6,177	78.11
Past history of comorbidities									
Cardio- and cerebrovascular disease (ever before)		19,834	63.98	1,898	38.93	1,942	64.05	3,840	48.56
Beta-blocker prescribing (in year prior to index date)		6,274	20.24	391	8.02	918	30.28	1,309	16.55
Pneumonia (ever before)		2,271	7.33	267	5.48	218	7.19	485	6.13
Gastroesophageal reflux disease (ever before)		7,079	22.84	1,120	22.97	656	21.64	1,776	22.46
Diabetes (ever before)		5,688	18.35	661	13.56	677	22.33	1,338	16.92
Acute and chronic renal disease (ever before)		5,907	19.05	539	11.05	701	23.12	1,240	15.68
Cancer (ever before)		4,172	13.46	383	7.85	609	20.09	992	12.54
Respiratory medication use in year prior to index da									
SABD[6]	1+ prescription(s)	25,171	81.2	4,522	92.74	1,573	51.88	6,095	77.07
	4+ prescriptions	15,522	50.07	2,686	55.09	501	16.52	3,187	40.3
ICS	Any ICS	16,316	52.63	4,369	89.6	722	23.81	5,091	64.38
	ICS (in a single device)	3,463	11.17	2,468	50.62	368	12.14	2,836	35.86
	ICS/LABA (fixed combination)	13,806	44.54	2,389	49	412	13.59	2,801	35.42
LABA	Any	15,571	50.23	2,512	51.52	459	15.14	2,971	37.57
	LABA (in a single device)	2,223	7.17	208	4.27	57	1.88	265	3.35
	ICS/LABA (fixed combination)	13,806	44.54	2,389	49	412	13.59	2,801	35.42
	LABA/LAMA (fixed combination)	261	0.84	6	0.12	8	0.26	14	0.18
LAMA	Any	10,495	33.85	229	4.7	183	6.04	412	5.21
	LAMA (in a single device)	10,404	33.56	223	4.57	177	5.84	400	5.06
	LABA/LAMA (fixed combination)	261	0.84	6	0.12	8	0.26	14	0.18
Theophylline (or derivatives)		868	2.8	219	4.49	15	0.49	234	2.96
OCS	Chronic use[7]	1,701	5.49	290	5.95	124	4.09	414	5.24

1 Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
2 Primary definition: Patients with (on-label) or without (off-label) evidence of COPD.
3 Unless otherwise specified.
4 Percentages were calculated separately for those with missing and without missing data
5 Area based deprivation is measured using patient-level Townsend quintile
6 Includes the following asthma "reliever" medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA.
7 Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days.
8 Roflumilast and ICS/SABA data were investigated but counts were very low (<5) so data are not presented
Note This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

Incidence of outcomes of interest whilst currently exposed[1] to UMEC therapy
CPRD GOLD-THIN Cohort

Outcomes of interest recorded in primary care data		All UMEC				UMEC with concomitant ICS therapy at index date				UMEC without concomitant ICS therapy at index date			
		No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		3875				2576				1299			
Any Myocardial infarction (MI)[2]	Total	27	6.9 (4.4 to 10.2)	184		19	6.7 (3.9 to 10.7)	199		8	7.4 (3.0 to 15.3)	150	
	Any prior events	6	20.4 (7.5 to 44.3)	170		6	28.8 (10.6 to 62.6)	170		0	0.0 (0.0 to 42.9)	--	
	No prior events	21	5.6 (3.3 to 8.9)	264.5		13	4.7 (2.3 to 8.4)	298		8	8.2 (3.3 to 16.8)	150	
	1 prior event	6	28.9 (10.6 to 63.0)	170		6	41.4 (15.2 to 90.1)	170		0	0.0 (0.0 to 59.2)	--	
	2+ prior events	0	0.0 (0.0 to 42.2)	--		0	0.0 (0.0 to 57.9)	--		0	0.0 (0.0 to 155.8)	--	
MI without concomitant use of beta-blockers[2]	Total	16	4.8 (2.6 to 8.1)	298.5		12	4.6 (2.2 to 8.5)	407		4	5.4 (1.5 to 13.9)	230.5	
	Any prior events	1	7.8 (0.2 to 43.4)	186		1	10.0 (0.3 to 55.5)	186		0	0.0 (0.0 to 132.0)	--	
	No prior events	15	4.7 (2.5 to 8.0)	299		11	4.4 (2.0 to 8.3)	516		4	5.7 (1.5 to 14.5)	230.5	
	1 prior event	1	10.5 (0.3 to 58.6)	186		1	13.3 (0.3 to 74.3)	186		0	0.0 (0.0 to 183.6)	--	
	2+ prior events	0	0.0 (0.0 to 110.9)	--		0	0.0 (0.0 to 145.1)	--		0	0.0 (0.0 to 470.0)	--	
MI with concomitant use of beta-blockers[2]	Total	11	16.7 (8.0 to 30.7)	126		7	17.8 (7.2 to 36.7)	158		4	14.5 (3.0 to 42.3)	102	
	Any prior events	5	30.1 (9.8 to 70.2)	158		5	46.2 (15.0 to 107.8)	158		0	0.0 (0.0 to 63.5)	--	
	No prior events	6	11.5 (3.7 to 26.9)	102		2	7.0 (0.9 to 25.4)	148		4	20.1 (4.1 to 58.8)	102	
	1 prior event	5	44.6 (14.5 to 104.0)	158		5	71.5 (23.2 to 166.9)	158		0	0.0 (0.0 to 87.4)	--	
	2+ prior events	0	0.0 (0.0 to 68.1)	--		0	0.0 (0.0 to 96.3)	--		0	0.0 (0.0 to 233.0)	--	
Any stroke[2]	Total	171	30.9 (25.3 to 37.4)	140.5		113	26.7 (20.7 to 33.9)	136		58	42.3 (30.1 to 57.9)	148	
	Any prior events	140	278.4 (219.7 to 347.9)	141		92	220.6 (162.6 to 292.5)	138.5		48	491.7 (329.3 to 706.1)	148	
	No prior events	31	9.2 (6.2 to 13.2)	140		21	8.3 (5.0 to 12.9)	91		10	11.6 (5.6 to 21.3)	187	
	1 prior event	24	84.4 (38.6 to 160.2)	91		18	68.6 (25.2 to 149.4)	75		6	155.7 (32.1 to 455.0)	91	
	2+ prior events	116	400.2 (310.8 to 507.3)	149.5		74	322.6 (232.5 to 436.0)	146		42	654.7 (427.6 to 959.2)	172.5	
Stroke without concomitant use of beta-blockers[2]	Total	142	30.7 (24.6 to 37.8)	136		99	26.9 (20.4 to 34.8)	129		43	41.8 (28.2 to 59.7)	162	
	Any prior events	116	303.2 (232.4 to 388.6)	138.5		81	242.4 (173.2 to 330.1)	132.5		35	556.6 (348.8 to 842.7)	162	
	No prior events	26	9.5 (6.1 to 14.0)	134		18	8.7 (5.1 to 13.9)	91		8	11.8 (5.1 to 23.2)	184	
	1 prior event	23	97.4 (42.1 to 192.0)	88		17	73.4 (23.8 to 171.4)	59		6	214.1 (44.1 to 625.6)	91	
	2+ prior events	93	441.2 (331.4 to 575.6)	144.5		64	361.2 (251.6 to 502.4)	136		29	744.8 (448.4 to 1163.0)	197	
Stroke with concomitant use of beta-blockers[2]	Total	29	32.0 (19.3 to 50.0)	151		14	25.6 (12.3 to 47.2)	224.5		15	44.3 (20.2 to 84.0)	140	
	Any prior events	24	208.1 (116.5 to 343.2)	151		11	152.0 (65.6 to 299.5)	224.5		13	359.8 (144.6 to 741.2)	101	
	No prior events	5	7.7 (2.1 to 19.7)	367		3	5.9 (0.7 to 21.4)	318.5		2	10.9 (1.3 to 39.3)	375	
	1 prior event	1	40.7 (1.0 to 226.8)	91		1	51.8 (1.3 to 288.5)	91		0	0.0 (0.0 to 702.1)	--	
	2+ prior events	23	294.6 (161.1 to 494.4)	216		10	210.1 (84.5 to 433.0)	298		13	492.8 (198.1 to 1015.4)	101	
Any newly diagnosed congestive heart		48	14.8 (10.9 to 19.6)	195.5		35	14.9 (10.4 to 20.7)	196		13	14.5 (7.7 to 24.8)	163	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		28	10.2 (6.8 to 14.7)	195.5		21	10.3 (6.4 to 15.8)	196		7	9.8 (3.9 to 20.1)	163	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		20	40.8 (24.9 to 63.0)	184.5		14	44.9 (24.6 to 75.4)	184.5		6	33.6 (12.3 to 73.2)	208.5	
Pneumonia[2]	Total	25	6.9 (4.4 to 10.2)	147.5		21	7.8 (4.8 to 12.1)	245		4	4.2 (1.2 to 10.9)	63	
	Any prior events	5	16.0 (4.4 to 41.0)	189		4	14.7 (3.0 to 43.0)	327		1	21.8 (0.6 to 121.3)	51	
	No prior events	20	6.2 (3.8 to 9.5)	147.5		17	7.2 (4.2 to 11.6)	222		3	3.3 (0.7 to 9.8)	75	
	1 prior event	3	13.7 (2.8 to 40.0)	51		2	11.4 (1.4 to 41.3)	280		1	22.7 (0.6 to 126.6)	51	
	2+ prior events	2	32.4 (0.8 to 180.4)	327		2	34.5 (0.9 to 192.3)	327		0	0.0 (0.0 to 1933.1)	--	
Moderate COPD exacerbation[4]		3409	0.98 (0.93 to 1.03)	--		2919	1.16 (1.10 to 1.22)	--		490	0.53 (0.47 to 0.61)	--	
All cause mortality		105	29.9 (24.5 to 36.2)	--	2.71%	77	30.1 (23.7 to 37.6)	--	2.99%	28	29.6 (19.7 to 42.8)	--	2.16%

[1] Currently exposed defined as exposure time starting from the index date and continuing until the earliest of discontinuation, censoring or switching
[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.
[3] Counts and incidence include first ever events (only) following initiation.
[4] Counts and incidence include all events following initiation.

Incidence of outcomes of interest whilst currently exposed[1] to UMEC/VI therapy

CPRD GOLD-THIN Cohort

Outcomes of interest recorded in primary care data		All UMEC/VI				UMEC/VI with concomitant ICS therapy at index date				UMEC/VI without concomitant ICS therapy at index date			
		No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		2224				320				1904			
Any Myocardial infarction (MI)[2]	Total	13	6.8 (3.5 to 11.9)	213.5		0	0.0 (0.0 to 21.6)	--		13	7.5 (3.9 to 13.2)	213.5	
	Any prior events	1	7.3 (0.2 to 40.7)	224		0	0.0 (0.0 to 538.9)	--		1	7.7 (0.2 to 42.9)	224	
	No prior events	12	6.8 (3.4 to 12.1)	203		0	0.0 (0.0 to 22.5)	--		12	7.5 (3.8 to 13.5)	203	
	1 prior event	1	9.6 (0.2 to 53.2)	224		0	0.0 (0.0 to 580.8)	--		1	10.2 (0.3 to 56.7)	224	
	2+ prior events	0	0.0 (0.0 to 114.7)	--		0	0.0 (0.0 to 7485.4)	--		0	0.0 (0.0 to 116.5)	--	
MI without concomitant use of beta-blockers[2]	Total	10	6.5 (3.0 to 12.3)	226		0	0.0 (0.0 to 25.8)	--		10	7.2 (3.3 to 13.7)	226	
	Any prior events	0	0.0 (0.0 to 91.9)	--		0	0.0 (0.0 to 1438.0)	--		0	0.0 (0.0 to 98.2)	--	
	No prior events	10	6.7 (3.1 to 12.7)	226		0	0.0 (0.0 to 26.2)	--		10	7.4 (3.4 to 14.1)	226	
	1 prior event	0	0.0 (0.0 to 107.9)	--		0	0.0 (0.0 to 1485.5)	--		0	0.0 (0.0 to 116.4)	--	
	2+ prior events	0	0.0 (0.0 to 620.9)	--		0	0.0 (0.0 to 44912.1)	--		0	0.0 (0.0 to 629.6)	--	
MI with concomitant use of beta-blockers[2]	Total	3	8.1 (1.7 to 23.6)	203		0	0.0 (0.0 to 133.8)	--		3	8.7 (1.8 to 25.5)	203	
	Any prior events	1	10.3 (0.3 to 57.6)	224		0	0.0 (0.0 to 862.0)	--		1	10.8 (0.3 to 60.3)	224	
	No prior events	2	7.3 (0.9 to 26.3)	161		0	0.0 (0.0 to 158.4)	--		2	7.9 (1.0 to 28.7)	161	
	1 prior event	1	14.2 (0.4 to 79.1)	224		0	0.0 (0.0 to 953.5)	--		1	15.0 (0.4 to 83.7)	224	
	2+ prior events	0	0.0 (0.0 to 140.7)	--		0	0.0 (0.0 to 8982.4)	--		0	0.0 (0.0 to 142.9)	--	
Any stroke[2]	Total	84	30.5 (22.8 to 39.8)	216		7	23.7 (6.5 to 60.7)	113		77	31.2 (23.1 to 41.2)	242	
	Any prior events	57	250.0 (173.1 to 349.3)	197.5		6	311.4 (64.2 to 910.0)	35		51	245.3 (166.7 to 348.2)	216	
	No prior events	27	11.8 (7.1 to 18.5)	286		1	6.3 (0.2 to 35.0)	286		26	12.5 (7.4 to 19.7)	285.5	
	1 prior event	6	58.1 (12.0 to 169.9)	204		0	0.0 (0.0 to 693.4)	--		6	64.8 (13.4 to 189.4)	204	
	2+ prior events	51	367.3 (249.6 to 521.4)	191		6	695.3 (143.4 to 2031.9)	35		45	349.6 (232.3 to 505.3)	229	
Stroke without concomitant use of beta-blockers[2]	Total	63	27.0 (19.0 to 37.2)	215		7	28.3 (7.7 to 72.5)	113		56	26.8 (18.4 to 37.6)	242	
	Any prior events	43	246.1 (159.3 to 363.3)	191		6	363.9 (75.0 to 1063.5)	35		37	235.7 (147.7 to 356.9)	223	
	No prior events	20	9.4 (4.9 to 16.5)	278.5		1	7.5 (0.2 to 41.9)	286		19	9.7 (4.8 to 17.3)	271	
	1 prior event	3	51.1 (6.2 to 184.7)	290		0	0.0 (0.0 to 901.2)	--		3	57.1 (6.9 to 206.3)	290	
	2+ prior events	40	368.2 (233.4 to 552.5)	163		6	722.8 (149.1 to 2112.3)	35		34	343.0 (209.5 to 529.7)	202.5	
Stroke with concomitant use of beta-blockers[2]	Total	21	43.5 (24.9 to 70.7)	230.5		0	0.0 (0.0 to 133.8)	--		21	47.1 (26.9 to 76.4)	230.5	
	Any prior events	14	261.4 (119.5 to 496.2)	216		0	0.0 (0.0 to 2652.3)	--		14	272.4 (124.6 to 517.1)	216	
	No prior events	7	21.0 (8.4 to 43.3)	305		0	0.0 (0.0 to 140.9)	--		7	22.8 (9.2 to 47.0)	305	
	1 prior event	3	80.0 (2.0 to 445.8)	162		0	0.0 (0.0 to 3007.5)	--		3	88.7 (2.2 to 494.3)	162	
	2+ prior events	11	364.7 (157.5 to 718.7)	230.5		0	0.0 (0.0 to 22456.1)	--		11	367.5 (158.7 to 724.1)	230.5	
Any newly diagnosed congestive heart		18	11.0 (6.5 to 17.4)	246.5		0	0.0 (0.0 to 23.8)	--		18	12.2 (7.2 to 19.2)	246.5	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		10	7.4 (3.6 to 13.7)	310.5		0	0.0 (0.0 to 27.1)	--		10	8.3 (4.0 to 15.2)	310.5	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		8	27.8 (12.0 to 54.8)	187		0	0.0 (0.0 to 191.1)	--		8	29.8 (12.9 to 58.7)	187	
Pneumonia[2]	Total	6	3.4 (1.2 to 7.4)	146		2	11.7 (1.4 to 42.4)	53.5		4	2.5 (0.7 to 6.4)	313.5	
	Any prior events	1	7.6 (0.2 to 42.6)	95		1	62.0 (1.6 to 345.5)	95		0	0.0 (0.0 to 32.1)	--	
	No prior events	5	3.1 (1.0 to 7.1)	197		1	6.5 (0.2 to 36.1)	12		4	2.7 (0.7 to 6.9)	313.5	
	1 prior event	1	9.1 (0.2 to 50.6)	95		1	76.0 (1.9 to 423.7)	95		0	0.0 (0.0 to 38.1)	--	
	2+ prior events	0	0.0 (0.0 to 176.7)	--		0	0.0 (0.0 to 1239.5)	--		0	0.0 (0.0 to 206.0)	--	
Moderate COPD exacerbation[4]		1275	0.75 (0.69 to 0.81)	--		231	1.34 (1.10 to 1.63)	--		1044	0.67 (0.62 to 0.74)	--	
All cause mortality		62	35.1 (26.9 to 44.9)	--	2.79%	5	29.3 (9.5 to 68.3)	--	1.56%	57	35.7 (27.0 to 46.2)	--	2.99%

[1] Currently exposed defined as exposure time starting from the index date and continuing until the earliest of discontinuation, censoring or switching

[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.

[3] Counts and incidence include first ever events (only) following initiation.

[4] Counts and incidence include all events following initiation.

Incidence of outcomes of interest whilst currently exposed[1] to UMEC therapy

CPRD GOLD-HES-ONS Cohort

Outcomes of interest recorded in primary and/or secondary care data		All UMEC				UMEC with concomitant ICS therapy at index date				UMEC without concomitant ICS therapy at index date			
		No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		547				351				196			
Any Myocardial infarction (MI)[2]	Total	5	8.0 (1.7 to 23.4)	136		4	7.6 (0.9 to 27.5)	129.5		1	9.0 (0.2 to 49.9)	299	
	Any prior events	2	40.2 (1.0 to 224.1)	136		2	54.8 (1.4 to 305.1)	136		0	0.0 (0.0 to 558.4)	--	
	No prior events	3	5.7 (0.7 to 20.7)	211		2	4.1 (0.1 to 22.8)	123		1	9.5 (0.2 to 53.0)	299	
	1 prior event	0	0.0 (0.0 to 219.1)	--		0	0.0 (0.0 to 297.7)	--		0	0.0 (0.0 to 830.2)	--	
	2+ prior events	2	124.5 (3.2 to 693.8)	136		2	170.4 (4.3 to 949.6)	136		0	0.0 (0.0 to 1705.5)	--	
MI without concomitant use of beta-blockers[2]	Total	3	6.3 (0.8 to 22.7)	211		2	4.4 (0.1 to 24.7)	123		1	10.8 (0.3 to 60.4)	299	
	Any prior events	0	0.0 (0.0 to 459.5)	--		0	0.0 (0.0 to 599.4)	--		0	0.0 (0.0 to 1969.8)	--	
	No prior events	3	6.4 (0.8 to 23.3)	211		2	4.6 (0.1 to 25.4)	123		1	11.1 (0.3 to 61.6)	299	
	1 prior event	0	0.0 (0.0 to 493.2)	--		0	0.0 (0.0 to 657.9)	--		0	0.0 (0.0 to 1969.8)	--	
	2+ prior events	0	0.0 (0.0 to 6736.8)	--		0	0.0 (0.0 to 6736.8)	--		0	--	--	
MI with concomitant use of beta-blockers[2]	Total	2	17.9 (0.5 to 99.8)	136		2	27.5 (0.7 to 153.1)	136		0	0.0 (0.0 to 190.0)	--	
	Any prior events	2	59.4 (1.5 to 330.9)	136		2	82.6 (2.1 to 460.3)	136		0	0.0 (0.0 to 779.3)	--	
	No prior events	0	0.0 (0.0 to 94.7)	--		0	0.0 (0.0 to 151.9)	--		0	0.0 (0.0 to 251.2)	--	
	1 prior event	0	0.0 (0.0 to 394.3)	--		0	0.0 (0.0 to 543.7)	--		0	0.0 (0.0 to 1434.9)	--	
	2+ prior events	2	133.6 (3.4 to 744.6)	136		2	188.0 (4.8 to 1047.4)	136		0	0.0 (0.0 to 1705.5)	--	
Any stroke[2]	Total	19	35.4 (18.9 to 60.6)	105		14	31.1 (13.4 to 61.4)	98		5	45.5 (14.8 to 106.3)	234	
	Any prior events	15	345.3 (157.9 to 655.4)	91		12	314.2 (115.3 to 683.9)	84		3	430.4 (88.8 to 1257.8)	281	
	No prior events	4	11.7 (3.2 to 30.1)	190.5		2	8.4 (1.0 to 30.4)	383.5		2	19.4 (2.4 to 70.3)	129.5	
	1 prior event	3	190.0 (23.0 to 686.3)	72		2	121.6 (3.1 to 677.7)	59		1	433.8 (11.0 to 2416.9)	85	
	2+ prior events	12	450.4 (181.1 to 928.1)	105		10	459.8 (149.3 to 1073.0)	91		2	428.7 (51.9 to 1548.6)	334	
Stroke without concomitant use of beta-blockers[2]	Total	17	35.3 (17.6 to 63.2)	105		13	31.7 (12.8 to 65.4)	105		4	44.1 (12.0 to 112.8)	159.5	
	Any prior events	13	355.4 (142.9 to 732.2)	91		11	305.4 (99.2 to 712.8)	91		2	600.7 (72.8 to 2170.1)	236	
	No prior events	4	13.7 (3.7 to 35.1)	190.5		2	9.8 (1.2 to 35.4)	383.5		2	22.9 (2.8 to 82.6)	129.5	
	1 prior event	3	202.2 (24.5 to 730.6)	72		2	122.9 (3.1 to 684.5)	59		1	571.6 (14.5 to 3184.7)	85	
	2+ prior events	10	509.7 (165.5 to 1189.5)	105		9	486.0 (132.4 to 1244.4)	98		1	633.0 (16.0 to 3526.9)	387	
Stroke with concomitant use of beta-blockers[2]	Total	2	36.1 (4.4 to 130.4)	179		1	27.5 (0.7 to 153.3)	77		1	52.5 (1.3 to 292.7)	281	
	Any prior events	2	314.1 (38.0 to 1134.5)	179		1	366.7 (9.3 to 2043.2)	77		1	274.6 (7.0 to 1530.1)	281	
	No prior events	0	0.0 (0.0 to 75.3)	--		0	0.0 (0.0 to 109.7)	--		0	0.0 (0.0 to 239.6)	--	
	1 prior event	0	0.0 (0.0 to 5782.7)	--		0	0.0 (0.0 to 44912.1)	--		0	0.0 (0.0 to 6637.3)	--	
	2+ prior events	2	349.0 (42.3 to 1260.8)	179		1	378.1 (9.6 to 2106.7)	77		1	324.1 (8.2 to 1805.7)	281	
Any newly diagnosed congestive heart		5	14.6 (4.7 to 34.0)	206		5	21.0 (6.8 to 49.0)	206		0	0.0 (0.0 to 35.2)	--	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		5	16.6 (5.4 to 38.7)	206		5	23.8 (7.7 to 55.6)	206		0	0.0 (0.0 to 40.2)	--	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		0	0.0 (0.0 to 88.5)	--		0	0.0 (0.0 to 129.8)	--		0	0.0 (0.0 to 278.4)	--	
Pneumonia[2]	Total	25	66.0 (42.3 to 98.2)	166.5		21	78.6 (48.0 to 121.3)	193.5		4	36.7 (10.0 to 94.0)	100	
	Any prior events	9	203.1 (92.9 to 385.6)	147		9	276.8 (126.6 to 525.4)	147		0	0.0 (0.0 to 312.9)	--	
	No prior events	16	47.0 (26.3 to 77.5)	186		12	49.5 (24.7 to 88.6)	201		4	41.2 (11.2 to 105.4)	100	
	1 prior event	8	216.5 (93.5 to 426.6)	217.5		8	281.5 (121.5 to 554.7)	217.5		0	0.0 (0.0 to 432.3)	--	
	2+ prior events	1	136.0 (3.4 to 757.6)	62		1	244.0 (6.2 to 1359.4)	62		0	0.0 (0.0 to 1133.2)	--	
Moderate/Severe COPD exacerbation[4]		554	1.48 (1.33 to 1.66)	--		437	1.66 (1.47 to 1.87)	--		117	1.09 (0.83 to 1.43)	--	
Mortality	All cause	18	48.0 (28.5 to 75.9)	--	3.29%	12	45.6 (23.6 to 79.7)	--	3.42%	6	53.8 (19.7 to 117.0)	--	3.06%
	Cardiovascular	4	10.7 (2.9 to 27.3)	--	0.73%	2	7.6 (0.9 to 27.5)	--	0.57%	2	17.9 (2.2 to 64.7)	--	1.02%

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[4] Counts and incidence include all events following initiation.

Incidence of outcomes of interest whilst currently exposed[1] to UMEC/VI therapy

CPRD GOLD-HES-ONS Cohort

Outcomes of interest recorded in primary and/or secondary care data		All UMEC/VI				UMEC/VI with concomitant ICS therapy at index date				UMEC/VI without concomitant ICS therapy at index date			
		No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		512				95				417			
Any Myocardial infarction (MI)[2]	Total	2	5.5 (0.7 to 19.9)	214.5		0	0.0 (0.0 to 71.8)	--		2	6.4 (0.8 to 23.2)	214.5	
	Any prior events	0	0.0 (0.0 to 139.8)	--		0	0.0 (0.0 to 8749.1)	--		0	0.0 (0.0 to 142.1)	--	
	No prior events	2	5.9 (0.7 to 21.5)	214.5		0	0.0 (0.0 to 72.4)	--		2	7.0 (0.8 to 25.3)	214.5	
	1 prior event	0	0.0 (0.0 to 210.0)	--		0	0.0 (0.0 to 8749.1)	--		0	0.0 (0.0 to 215.1)	--	
	2+ prior events	0	0.0 (0.0 to 418.4)	--		0	--	--		0	0.0 (0.0 to 418.4)	--	
MI without concomitant use of beta-blockers[2]	Total	1	3.3 (0.1 to 18.6)	226		0	0.0 (0.0 to 82.0)	--		1	3.9 (0.1 to 21.9)	226	
	Any prior events	0	0.0 (0.0 to 392.9)	--		0	0.0 (0.0 to 8749.1)	--		0	0.0 (0.0 to 411.4)	--	
	No prior events	1	3.5 (0.1 to 19.2)	226		0	0.0 (0.0 to 82.8)	--		1	4.1 (0.1 to 22.7)	226	
	1 prior event	0	0.0 (0.0 to 407.2)	--		0	0.0 (0.0 to 8749.1)	--		0	0.0 (0.0 to 427.1)	--	
	2+ prior events	0	0.0 (0.0 to 11228.0)	--		0	--	--		0	0.0 (0.0 to 11228.0)	--	
MI with concomitant use of beta-blockers[2]	Total	1	15.6 (0.4 to 87.1)	203		0	0.0 (0.0 to 577.5)	--		1	17.4 (0.4 to 96.8)	203	
	Any prior events	0	0.0 (0.0 to 217.0)	--		0	--	--		0	0.0 (0.0 to 217.0)	--	
	No prior events	1	21.3 (0.5 to 118.7)	203		0	0.0 (0.0 to 577.5)	--		1	24.7 (0.6 to 137.4)	203	
	1 prior event	0	0.0 (0.0 to 433.5)	--		0	--	--		0	0.0 (0.0 to 433.5)	--	
	2+ prior events	0	0.0 (0.0 to 434.6)	--		0	--	--		0	0.0 (0.0 to 434.6)	--	
Any stroke[2]	Total	13	16.5 (6.1 to 36.0)	242		1	19.5 (0.5 to 108.8)	321		12	16.0 (5.2 to 37.4)	163	
	Any prior events	8	136.7 (28.2 to 399.5)	153		0	0.0 (0.0 to 847.9)	--		8	170.5 (35.2 to 498.3)	153	
	No prior events	5	8.8 (1.8 to 25.7)	350		1	21.3 (0.5 to 118.9)	321		4	6.8 (0.8 to 24.5)	353.5	
	1 prior event	0	0.0 (0.0 to 425.7)	--		0	0.0 (0.0 to 1296.8)	--		0	0.0 (0.0 to 633.8)	--	
	2+ prior events	8	225.9 (46.6 to 660.3)	153		0	0.0 (0.0 to 2449.8)	--		8	254.8 (52.6 to 744.7)	153	
Stroke without concomitant use of beta-blockers[2]	Total	9	10.0 (2.1 to 29.3)	321		1	22.3 (0.6 to 124.3)	321		8	7.9 (1.0 to 28.4)	256.5	
	Any prior events	5	55.8 (1.4 to 311.0)	163		0	0.0 (0.0 to 1150.6)	--		5	68.0 (1.7 to 378.8)	163	
	No prior events	4	7.1 (0.9 to 25.7)	335.5		1	24.0 (0.6 to 133.8)	321		3	4.2 (0.1 to 23.2)	350	
	1 prior event	0	0.0 (0.0 to 495.9)	--		0	0.0 (0.0 to 2169.7)	--		0	0.0 (0.0 to 642.8)	--	
	2+ prior events	5	95.4 (2.4 to 531.8)	163		0	0.0 (0.0 to 2449.8)	--		5	111.5 (2.8 to 621.0)	163	
Stroke with concomitant use of beta-blockers[2]	Total	4	47.0 (9.7 to 137.3)	153		0	0.0 (0.0 to 577.5)	--		4	52.2 (10.8 to 152.5)	153	
	Any prior events	3	496.6 (60.1 to 1793.9)	77.5		0	0.0 (0.0 to 3223.4)	--		3	693.7 (84.0 to 2506.0)	77.5	
	No prior events	1	16.7 (0.4 to 93.1)	357		0	0.0 (0.0 to 703.6)	--		1	18.3 (0.5 to 102.0)	357	
	1 prior event	0	0.0 (0.0 to 3007.5)	--		0	0.0 (0.0 to 3223.4)	--		0	0.0 (0.0 to 44912.1)	--	
	2+ prior events	3	714.1 (86.5 to 2579.5)	77.5		0	--	--		3	714.1 (86.5 to 2579.5)	77.5	
Any newly diagnosed congestive heart		7	20.5 (8.3 to 42.3)	260		1	20.2 (0.5 to 112.5)	56		6	20.6 (7.6 to 44.8)	356	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		3	10.3 (2.1 to 30.2)	260		1	23.0 (0.6 to 127.9)	56		2	8.1 (1.0 to 29.3)	407.5	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		4	79.2 (21.6 to 202.9)	326.5		0	0.0 (0.0 to 618.6)	--		4	89.8 (24.5 to 230.0)	326.5	
Pneumonia[2]	Total	18	47.3 (27.5 to 75.7)	176		1	19.5 (0.5 to 108.8)	95		17	51.9 (29.6 to 84.2)	195	
	Any prior events	10	161.0 (73.6 to 305.7)	214		1	167.2 (4.2 to 931.4)	95		9	160.3 (69.2 to 315.8)	219	
	No prior events	8	26.3 (11.4 to 51.9)	106		0	0.0 (0.0 to 81.6)	--		8	30.9 (13.4 to 60.9)	106	
	1 prior event	7	136.2 (50.0 to 296.4)	219		0	0.0 (0.0 to 699.9)	--		7	154.7 (56.8 to 336.7)	219	
	2+ prior events	3	253.5 (52.3 to 740.7)	95		1	1404.8 (35.6 to 7827.1)	95		2	179.8 (21.8 to 649.5)	157	
Moderate/Severe COPD exacerbation[4]		421	1.17 (1.01 to 1.35)	--		103	1.93 (1.43 to 2.62)	--		318	1.03 (0.88 to 1.20)	--	
Mortality	All cause	19	52.0 (31.3 to 81.2)	--	3.71%	3	58.4 (12.0 to 170.7)	--	3.16%	16	50.9 (29.1 to 82.7)	--	3.84%
	Cardiovascular	6	16.4 (6.0 to 35.7)	--	1.17%	0	0.0 (0.0 to 71.8)	--	<0.01%	6	19.1 (7.0 to 41.6)	--	1.44%

[1] Currently exposed defined as exposure time starting from the index date and continuing until the earliest of discontinuation, censoring or switching

[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.

[3] Counts and incidence include first ever events (only) following initiation.

[4] Counts and incidence include all events following initiation.

Incidence of outcomes of interest whilst currently AND previously exposed[1] to UMEC therapy

CPRD GOLD+THIN Cohort

Outcomes of interest recorded in primary care data		All UMEC				UMEC with concomitant ICS therapy at index date				UMEC without concomitant ICS therapy at index date			
		No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		3875				2576				1299			
Any Myocardial infarction (MI)[2]	Total	36	6.5 (4.4 to 9.1)	194.5		23	6.0 (3.7 to 9.3)	277.5		13	7.4 (3.8 to 12.9)	156	
	Any prior events	8	18.6 (8.0 to 36.7)	184		7	26.4 (10.6 to 54.3)	182		1	6.1 (0.2 to 34.0)	455	
	No prior events	28	5.3 (3.4 to 7.9)	277.5		16	4.3 (2.3 to 7.3)	365		12	7.5 (3.8 to 13.5)	150	
	1 prior event	7	22.3 (9.0 to 45.9)	186		6	31.4 (11.5 to 68.2)	184		1	8.2 (0.2 to 45.5)	455	
	2+ prior events	1	8.6 (0.2 to 48.2)	93		1	13.5 (0.3 to 75.0)	93		0	0.0 (0.0 to 89.1)	--	
MI without concomitant use of beta-blockers[2]	Total	23	4.9 (3.0 to 7.6)	321.5		16	4.6 (2.5 to 7.9)	365		7	5.6 (2.2 to 11.5)	190	
	Any prior events	2	10.9 (1.3 to 39.4)	139.5		2	15.4 (1.9 to 55.5)	139.5		0	0.0 (0.0 to 69.5)	--	
	No prior events	21	4.6 (2.7 to 7.3)	350.5		14	4.1 (2.0 to 7.3)	516		7	5.8 (2.3 to 12.0)	190	
	1 prior event	1	7.4 (0.2 to 41.2)	186		1	10.3 (0.3 to 57.3)	186		0	0.0 (0.0 to 97.0)	--	
	2+ prior events	1	20.9 (0.5 to 116.2)	93		1	30.4 (0.8 to 169.4)	93		0	0.0 (0.0 to 245.0)	--	
MI with concomitant use of beta-blockers[2]	Total	13	13.6 (7.1 to 23.8)	154		7	13.7 (5.5 to 28.3)	182		6	13.5 (4.4 to 31.5)	110	
	Any prior events	6	24.4 (8.9 to 53.0)	190.5		5	36.9 (12.0 to 86.2)	182		1	9.0 (0.2 to 50.3)	455	
	No prior events	7	9.5 (3.5 to 20.6)	106		2	5.3 (0.6 to 19.3)	148		5	15.4 (4.2 to 39.5)	106	
	1 prior event	6	33.6 (12.3 to 73.1)	190.5		5	53.1 (17.3 to 124.0)	182		1	11.8 (0.3 to 65.9)	455	
	2+ prior events	0	0.0 (0.0 to 54.5)	--		0	0.0 (0.0 to 89.2)	--		0	0.0 (0.0 to 140.1)	--	
Any stroke[2]	Total	245	32.0 (27.2 to 37.5)	193		144	27.0 (21.6 to 33.2)	186		101	42.4 (32.9 to 53.9)	200	
	Any prior events	190	269.2 (221.2 to 324.4)	192.5		111	210.2 (160.4 to 270.6)	190		79	405.7 (301.1 to 534.9)	195.5	
	No prior events	55	10.2 (7.4 to 13.6)	193		33	9.4 (6.3 to 13.6)	182.5		22	11.7 (6.8 to 18.7)	252	
	1 prior event	29	82.8 (44.1 to 141.6)	176		19	62.0 (24.9 to 127.8)	91		10	136.0 (49.9 to 296.0)	177	
	2+ prior events	161	385.4 (312.6 to 470.2)	197		92	307.2 (230.1 to 401.8)	191		69	556.1 (404.1 to 746.6)	198.5	
Stroke without concomitant use of beta-blockers[2]	Total	197	30.4 (25.2 to 36.3)	189		122	26.5 (20.7 to 33.3)	162		75	39.3 (29.0 to 52.2)	204.5	
	Any prior events	151	283.2 (225.6 to 351.1)	194		94	224.1 (165.2 to 297.1)	160.5		57	443.6 (309.0 to 616.9)	200	
	No prior events	46	10.3 (7.3 to 14.1)	182.5		28	9.8 (6.4 to 14.5)	182		18	11.4 (6.1 to 19.5)	234	
	1 prior event	28	104.0 (53.7 to 181.6)	177		18	70.1 (25.7 to 152.7)	149.5		10	200.8 (73.7 to 437.1)	177	
	2+ prior events	123	399.6 (312.1 to 504.1)	197		76	326.5 (235.3 to 441.3)	160.5		47	591.6 (396.2 to 849.6)	209	
Stroke with concomitant use of beta-blockers[2]	Total	48	39.5 (27.4 to 55.2)	236		22	29.9 (16.7 to 49.3)	298		26	53.0 (31.9 to 82.7)	172	
	Any prior events	39	233.6 (153.9 to 339.9)	191		17	168.4 (87.0 to 294.2)	302		22	338.3 (189.4 to 558.0)	139	
	No prior events	9	9.4 (3.8 to 19.4)	252		5	7.0 (1.4 to 20.4)	246		4	12.7 (3.5 to 32.6)	417.5	
	1 prior event	1	24.0 (0.6 to 134.0)	91		1	36.6 (0.9 to 203.7)	91		0	0.0 (0.0 to 259.1)	--	
	2+ prior events	38	351.4 (229.5 to 514.8)	210		16	250.6 (125.1 to 448.4)	306		22	498.4 (278.9 to 822.0)	139	
Any newly diagnosed congestive heart		60	13.1 (10.0 to 16.8)	254.5		41	13.4 (9.6 to 18.2)	231		19	12.4 (7.5 to 19.4)	336	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		38	9.8 (7.0 to 13.5)	255.5		26	9.8 (6.4 to 14.4)	249.5		12	9.9 (5.1 to 17.3)	330.5	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		22	30.5 (19.1 to 46.2)	244.5		15	37.1 (20.8 to 61.2)	200		7	22.1 (8.9 to 45.6)	336	
Pneumonia[2]	Total	46	8.9 (6.5 to 12.0)	262.5		34	9.7 (6.6 to 13.6)	310.5		12	7.4 (3.8 to 12.9)	133	
	Any prior events	10	26.3 (12.0 to 49.9)	181		8	26.1 (10.5 to 53.9)	294		2	26.9 (3.3 to 97.2)	79.5	
	No prior events	36	7.6 (5.3 to 10.6)	268		26	8.2 (5.3 to 12.1)	329		10	6.5 (3.1 to 11.9)	139	
	1 prior event	7	23.2 (9.3 to 47.7)	181		5	21.6 (7.0 to 50.4)	294		2	28.4 (3.4 to 102.5)	79.5	
	2+ prior events	3	49.9 (6.0 to 180.3)	254		3	55.2 (6.7 to 199.5)	254		0	0.0 (0.0 to 960.3)	--	
Moderate COPD exacerbation[4]		4663	0.94 (0.90 to 0.98)	--		3848	1.16 (1.10 to 1.21)	--		815	0.50 (0.45 to 0.56)	--	
All cause mortality		271	54.6 (48.3 to 61.5)	--	7.00%	181	54.3 (46.7 to 62.9)	--	7.03%	90	55.2 (44.4 to 67.8)	--	6.93%

[1] Currently exposed defined as exposure time starting from the index date and continuing until the earliest of discontinuation, censoring or switching. Previous exposure defined as exposure time starting from the discontinuation or switch date and continuing until either the censoring date or the date the patient resumes taking the same index medication.

[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.

[3] Counts and incidence include first ever events (only) following initiation.

[4] Counts and incidence include all events following initiation.

Incidence of outcomes of interest whilst currently AND previously exposed[1] to UMEC/VI therapy

CPRD GOLD+THIN Cohort

Outcomes of interest recorded in primary care data		All UMEC/VI				UMEC/VI with concomitant ICS therapy at index date				UMEC/VI without concomitant ICS therapy at index date			
		No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		2224				320				1904			
Any Myocardial infarction (MI)[2]	Total	23	7.3 (4.6 to 11.1)	247		1	2.1 (0.1 to 11.7)	602		22	8.3 (5.1 to 12.7)	240	
	Any prior events	5	20.5 (6.6 to 47.7)	277		0	0.0 (0.0 to 130.0)	--		5	23.1 (7.5 to 54.0)	277	
	No prior events	18	6.2 (3.6 to 9.9)	226		1	2.2 (0.1 to 12.4)	602		17	6.9 (4.0 to 11.2)	214.5	
	1 prior event	3	15.6 (3.2 to 45.6)	240		0	0.0 (0.0 to 155.3)	--		3	17.8 (3.7 to 52.1)	240	
	2+ prior events	2	38.2 (4.6 to 137.9)	311.5		0	0.0 (0.0 to 799.6)	--		2	41.9 (5.1 to 151.2)	311.5	
MI without concomitant use of beta-blockers[2]	Total	17	6.7 (3.9 to 10.9)	265		1	2.5 (0.1 to 14.0)	602		16	7.6 (4.2 to 12.5)	254	
	Any prior events	1	12.7 (0.3 to 70.6)	277		0	0.0 (0.0 to 327.9)	--		1	14.8 (0.4 to 82.3)	277	
	No prior events	16	6.5 (3.7 to 10.8)	254		1	2.6 (0.1 to 14.4)	602		15	7.3 (4.0 to 12.3)	240	
	1 prior event	0	0.0 (0.0 to 55.6)	--		0	0.0 (0.0 to 359.9)	--		0	0.0 (0.0 to 65.8)	--	
	2+ prior events	1	79.0 (2.0 to 440.3)	277		0	0.0 (0.0 to 3691.4)	--		1	85.8 (2.2 to 478.0)	277	
MI with concomitant use of beta-blockers[2]	Total	6	9.5 (3.5 to 20.7)	232		0	0.0 (0.0 to 45.9)	--		6	10.9 (4.0 to 23.7)	232	
	Any prior events	4	24.2 (6.6 to 61.9)	258.5		0	0.0 (0.0 to 215.5)	--		4	27.0 (7.3 to 69.0)	258.5	
	No prior events	2	4.3 (0.5 to 15.5)	161		0	0.0 (0.0 to 58.4)	--		2	5.0 (0.6 to 17.9)	161	
	1 prior event	3	23.9 (4.9 to 69.7)	240		0	0.0 (0.0 to 273.1)	--		3	26.7 (5.5 to 78.1)	240	
	2+ prior events	1	25.2 (0.6 to 140.2)	346		0	0.0 (0.0 to 1020.7)	--		1	27.7 (0.7 to 154.2)	346	
Any stroke[2]	Total	142	30.4 (24.5 to 37.4)	277.5		13	17.0 (7.3 to 33.4)	238.5		129	33.0 (26.2 to 40.9)	277.5	
	Any prior events	102	263.3 (200.5 to 339.7)	245		11	191.0 (70.1 to 415.7)	143		91	275.1 (206.1 to 359.9)	257	
	No prior events	40	11.3 (7.7 to 16.1)	357		2	4.5 (0.6 to 16.4)	460		38	12.6 (8.5 to 18.2)	357	
	1 prior event	20	127.9 (66.1 to 223.5)	361		1	66.9 (1.7 to 372.7)	371		19	139.5 (69.6 to 249.6)	351	
	2+ prior events	82	360.8 (265.1 to 479.8)	244		10	303.7 (98.6 to 708.8)	95		72	369.1 (266.0 to 498.9)	251	
Stroke without concomitant use of beta-blockers[2]	Total	106	27.4 (21.1 to 34.9)	275		12	17.8 (7.2 to 36.7)	286		94	29.3 (22.2 to 38.0)	271	
	Any prior events	77	266.8 (193.9 to 358.2)	251		10	189.9 (61.7 to 443.2)	191		67	281.4 (200.1 to 384.7)	257	
	No prior events	29	9.2 (5.6 to 14.2)	375		2	5.4 (0.7 to 19.7)	460		27	10.0 (5.9 to 15.7)	375	
	1 prior event	16	147.9 (70.9 to 271.9)	373.5		1	84.2 (2.1 to 469.0)	371		15	161.4 (73.8 to 306.5)	376	
	2+ prior events	61	349.5 (242.0 to 488.4)	244.5		9	276.9 (75.4 to 708.9)	113		52	362.2 (244.4 to 517.0)	251	
Stroke with concomitant use of beta-blockers[2]	Total	36	42.1 (27.5 to 61.6)	290.5		1	12.8 (0.3 to 71.3)	95		35	46.3 (30.0 to 68.3)	305	
	Any prior events	25	253.6 (141.9 to 418.3)	216		1	196.6 (5.0 to 1095.3)	95		24	259.0 (141.6 to 434.5)	246	
	No prior events	11	19.7 (9.8 to 35.2)	357		0	0.0 (0.0 to 50.5)	--		11	22.6 (11.3 to 40.5)	357	
	1 prior event	4	76.4 (9.3 to 276.1)	256.5		0	0.0 (0.0 to 1200.9)	--		4	86.6 (10.5 to 312.8)	256.5	
	2+ prior events	21	394.1 (209.8 to 673.9)	216		1	496.3 (12.6 to 2765.0)	95		20	387.5 (200.2 to 676.8)	246	
Any newly diagnosed congestive heart		36	13.0 (9.1 to 17.9)	263.5		3	6.8 (1.4 to 20.0)	148		33	14.1 (9.7 to 19.8)	266	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		22	9.6 (6.0 to 14.6)	278		3	7.9 (1.6 to 23.0)	148		19	10.0 (6.0 to 15.6)	290	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		14	28.3 (15.5 to 47.5)	251.5		0	0.0 (0.0 to 63.1)	--		14	32.1 (17.6 to 53.9)	251.5	
Pneumonia[2]	Total	18	5.3 (3.0 to 8.6)	251		5	8.4 (2.3 to 21.5)	182		13	4.7 (2.4 to 8.3)	258	
	Any prior events	4	18.9 (5.2 to 48.5)	251		3	89.1 (18.4 to 260.4)	269		1	5.6 (0.1 to 31.4)	233	
	No prior events	14	4.3 (2.2 to 7.5)	241.5		2	2.3 (0.1 to 12.6)	12		12	4.7 (2.3 to 8.4)	283	
	1 prior event	3	16.9 (3.5 to 49.5)	233		2	67.2 (8.1 to 242.9)	182		1	6.8 (0.2 to 37.8)	233	
	2+ prior events	1	29.5 (0.7 to 164.4)	366		1	254.9 (6.5 to 1420.1)	366		0	0.0 (0.0 to 123.1)	--	
Moderate COPD exacerbation[4]		2241	0.74 (0.69 to 0.79)	--		567	1.21 (1.06 to 1.38)	--		1674	0.65 (0.61 to 0.71)	--	
All cause mortality		176	58.3 (50.0 to 67.6)	--	7.91%	24	50.2 (32.2 to 74.7)	--	7.50%	152	59.8 (50.7 to 70.1)	--	7.98%

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[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.

[3] Counts and incidence include first ever events (only) following initiation.

[4] Counts and incidence include all events following initiation.

Incidence of outcomes of interest whilst currently AND previously exposed[1] to UMEC therapy

CPRD GOLD-HES-ONS Cohort

Outcomes of interest recorded in primary and/or secondary care data		All UMEC				UMEC with concomitant ICS therapy at index date				UMEC without concomitant ICS therapy at index date			
		No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		547				351				196			
Any Myocardial infarction (MI)[2]	Total	8	11.0 (4.0 to 24.0)	129.5		6	11.3 (3.1 to 29.0)	129.5		2	10.5 (1.3 to 37.8)	310	
	Any prior events	3	57.8 (7.0 to 208.8)	111.5		3	92.4 (11.2 to 333.9)	111.5		0	0.0 (0.0 to 284.6)	--	
	No prior events	5	7.8 (2.1 to 20.1)	212		3	6.0 (0.7 to 21.8)	212		2	11.2 (1.4 to 40.5)	310	
	1 prior event	0	0.0 (0.0 to 156.1)	--		0	0.0 (0.0 to 236.6)	--		0	0.0 (0.0 to 459.1)	--	
	2+ prior events	3	182.2 (22.1 to 658.2)	111.5		3	330.7 (40.0 to 1194.6)	111.5		0	0.0 (0.0 to 748.5)	--	
MI without concomitant use of beta-blockers[2]	Total	6	11.0 (3.6 to 25.7)	123		4	9.8 (2.0 to 28.6)	123		2	13.4 (1.6 to 48.6)	310	
	Any prior events	1	111.8 (2.8 to 623.1)	87		1	145.2 (3.7 to 809.2)	87		0	0.0 (0.0 to 1794.1)	--	
	No prior events	5	9.0 (2.4 to 23.0)	212		3	6.7 (0.8 to 24.2)	212		2	13.6 (1.7 to 49.3)	310	
	1 prior event	0	0.0 (0.0 to 441.2)	--		0	0.0 (0.0 to 585.0)	--		0	0.0 (0.0 to 1794.1)	--	
	2+ prior events	1	1722.9 (43.6 to 9599.3)	87		1	1722.9 (43.6 to 9599.3)	87		0	--	--	
MI with concomitant use of beta-blockers[2]	Total	2	11.1 (0.3 to 61.8)	136		2	21.0 (0.5 to 116.9)	136		0	0.0 (0.0 to 86.8)	--	
	Any prior events	2	39.0 (1.0 to 217.1)	136		2	67.8 (1.7 to 377.7)	136		0	0.0 (0.0 to 338.2)	--	
	No prior events	0	0.0 (0.0 to 57.2)	--		0	0.0 (0.0 to 112.1)	--		0	0.0 (0.0 to 116.9)	--	
	1 prior event	0	0.0 (0.0 to 241.7)	--		0	0.0 (0.0 to 397.3)	--		0	0.0 (0.0 to 616.9)	--	
	2+ prior events	2	96.2 (2.4 to 536.0)	136		2	182.9 (4.6 to 1019.0)	136		0	0.0 (0.0 to 748.5)	--	
Any stroke[2]	Total	25	35.3 (21.2 to 55.1)	162		18	34.3 (17.7 to 60.0)	154.5		7	37.0 (14.9 to 76.2)	234	
	Any prior events	19	252.4 (134.4 to 431.6)	118		15	258.1 (118.0 to 489.9)	118		4	240.4 (65.5 to 615.6)	196.5	
	No prior events	6	12.3 (4.5 to 26.8)	198		3	9.5 (2.0 to 27.9)	162		3	17.4 (3.6 to 50.8)	234	
	1 prior event	3	106.8 (12.9 to 385.8)	72		2	93.8 (2.4 to 522.3)	59		1	124.1 (3.1 to 691.5)	85	
	2+ prior events	16	335.5 (167.5 to 600.3)	191		13	330.5 (142.7 to 651.2)	154.5		3	349.6 (72.1 to 1021.8)	281	
Stroke without concomitant use of beta-blockers[2]	Total	21	33.4 (18.7 to 55.1)	147		16	33.1 (15.9 to 61.0)	132.5		5	33.9 (11.0 to 79.2)	234	
	Any prior events	15	273.4 (125.0 to 519.0)	105		13	262.5 (105.5 to 540.9)	105		2	319.8 (38.7 to 1155.3)	236	
	No prior events	6	14.4 (5.3 to 31.4)	198		3	10.9 (2.2 to 31.9)	162		3	21.3 (4.4 to 62.1)	234	
	1 prior event	3	155.6 (18.8 to 561.9)	72		2	108.2 (2.7 to 602.6)	59		1	276.9 (7.0 to 1542.9)	85	
	2+ prior events	12	348.9 (140.3 to 719.0)	118		11	344.5 (126.4 to 749.8)	111.5		1	378.5 (9.6 to 2108.9)	387	
Stroke with concomitant use of beta-blockers[2]	Total	4	44.7 (12.2 to 114.4)	236		2	41.9 (5.1 to 151.4)	248.5		2	47.8 (5.8 to 172.8)	196.5	
	Any prior events	4	215.1 (58.6 to 550.8)	236		2	243.7 (29.5 to 880.2)	248.5		2	192.6 (23.3 to 695.7)	196.5	
	No prior events	0	0.0 (0.0 to 52.0)	--		0	0.0 (0.0 to 93.3)	--		0	0.0 (0.0 to 117.4)	--	
	1 prior event	0	0.0 (0.0 to 628.7)	--		0	0.0 (0.0 to 2596.1)	--		0	0.0 (0.0 to 829.7)	--	
	2+ prior events	4	314.3 (85.6 to 804.8)	236		2	294.7 (35.7 to 1064.5)	248.5		2	336.8 (40.8 to 1216.6)	196.5	
Any newly diagnosed congestive heart		9	18.1 (8.3 to 34.3)	231		8	24.7 (10.7 to 48.7)	258.5		1	5.7 (0.1 to 31.9)	225	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		8	18.5 (8.0 to 36.5)	255.5		7	24.5 (9.8 to 50.4)	286		1	6.8 (0.2 to 38.1)	225	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		1	15.2 (0.4 to 84.7)	231		1	26.7 (0.7 to 148.7)	231		0	0.0 (0.0 to 130.4)	--	
Pneumonia[2]	Total	38	65.7 (45.8 to 91.4)	183		31	81.3 (54.0 to 117.5)	190.5		7	37.2 (15.0 to 76.7)	156	
	Any prior events	17	230.0 (128.7 to 379.3)	156		15	269.4 (143.4 to 460.6)	179		2	117.9 (14.3 to 425.8)	137.5	
	No prior events	21	42.8 (26.2 to 66.1)	225		16	50.6 (28.3 to 83.5)	257		5	29.2 (9.5 to 68.2)	183	
	1 prior event	14	236.3 (125.8 to 404.0)	156		12	254.3 (126.9 to 455.0)	179		2	169.9 (20.6 to 613.8)	137.5	
	2+ prior events	3	196.0 (23.7 to 708.0)	121.5		3	399.4 (48.4 to 1442.8)	121.5		0	0.0 (0.0 to 709.9)	--	
Moderate/Severe COPD exacerbation[4]		778	1.45 (1.30 to 1.60)	--		597	1.69 (1.51 to 1.89)	--		181	0.98 (0.78 to 1.23)	--	
Mortality	All cause	37	67.5 (47.5 to 93.0)	--	6.76%	24	67.3 (43.1 to 100.2)	--	6.84%	13	67.8 (36.1 to 115.9)	--	6.63%
	Cardiovascular	8	14.6 (6.3 to 28.7)	--	1.46%	3	8.4 (1.7 to 24.6)	--	0.85%	5	26.1 (8.5 to 60.8)	--	2.55%

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[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.

[3] Counts and incidence include first ever events (only) following initiation.

[4] Counts and incidence include all events following initiation.

Incidence of outcomes of interest whilst currently AND previously exposed[1] to UMEC/VI therapy

CPRD GOLD-HES-ONS Cohort

Outcomes of interest recorded in primary and/or secondary care data		All UMEC/VI				UMEC/VI with concomitant ICS therapy at index date				UMEC/VI without concomitant ICS therapy at index date			
		No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		512				95				417			
Any Myocardial infarction (MI)[2]	Total	7	7.7 (2.5 to 18.1)	203		0	0.0 (0.0 to 28.3)	--		7	9.7 (3.2 to 22.6)	203	
	Any prior events	0	0.0 (0.0 to 85.2)	--		0	0.0 (0.0 to 8749.1)	--		0	0.0 (0.0 to 86.0)	--	
	No prior events	7	8.3 (2.7 to 19.4)	203		0	0.0 (0.0 to 28.3)	--		7	10.6 (3.4 to 24.7)	203	
	1 prior event	0	0.0 (0.0 to 128.9)	--		0	0.0 (0.0 to 8749.1)	--		0	0.0 (0.0 to 130.8)	--	
	2+ prior events	0	0.0 (0.0 to 251.1)	--		0	--	--		0	0.0 (0.0 to 251.1)	--	
MI without concomitant use of beta-blockers[2]	Total	6	7.4 (2.0 to 19.1)	184		0	0.0 (0.0 to 31.3)	--		6	9.5 (2.6 to 24.4)	184	
	Any prior events	0	0.0 (0.0 to 240.0)	--		0	0.0 (0.0 to 8749.1)	--		0	0.0 (0.0 to 246.8)	--	
	No prior events	6	7.7 (2.1 to 19.6)	184		0	0.0 (0.0 to 31.4)	--		6	9.9 (2.7 to 25.3)	184	
	1 prior event	0	0.0 (0.0 to 282.8)	--		0	0.0 (0.0 to 8749.1)	--		0	0.0 (0.0 to 292.3)	--	
	2+ prior events	0	0.0 (0.0 to 1587.0)	--		0	--	--		0	0.0 (0.0 to 1587.0)	--	
MI with concomitant use of beta-blockers[2]	Total	1	9.2 (0.2 to 51.3)	203		0	0.0 (0.0 to 288.1)	--		1	10.4 (0.3 to 58.2)	203	
	Any prior events	0	0.0 (0.0 to 132.0)	--		0	--	--		0	0.0 (0.0 to 132.0)	--	
	No prior events	1	12.4 (0.3 to 69.1)	203		0	0.0 (0.0 to 288.1)	--		1	14.7 (0.4 to 82.1)	203	
	1 prior event	0	0.0 (0.0 to 236.8)	--		0	--	--		0	0.0 (0.0 to 236.8)	--	
	2+ prior events	0	0.0 (0.0 to 298.3)	--		0	--	--		0	0.0 (0.0 to 298.3)	--	
Any stroke[2]	Total	20	17.2 (8.6 to 30.7)	163		2	15.5 (1.9 to 56.1)	224		18	17.6 (8.0 to 33.4)	163	
	Any prior events	11	103.9 (28.3 to 266.1)	158		0	0.0 (0.0 to 337.9)	--		11	145.1 (39.5 to 371.4)	158	
	No prior events	9	11.6 (4.7 to 23.9)	321		2	17.0 (2.1 to 61.3)	224		7	10.3 (3.3 to 24.1)	350	
	1 prior event	0	0.0 (0.0 to 250.1)	--		0	0.0 (0.0 to 557.2)	--		0	0.0 (0.0 to 453.8)	--	
	2+ prior events	11	168.5 (45.9 to 431.4)	158		0	0.0 (0.0 to 858.2)	--		11	205.7 (56.1 to 526.7)	158	
Stroke without concomitant use of beta-blockers[2]	Total	12	11.2 (4.1 to 24.4)	242		2	17.2 (2.1 to 62.3)	224		10	9.5 (2.6 to 24.4)	256.5	
	Any prior events	6	65.6 (7.9 to 236.9)	270.5		0	0.0 (0.0 to 388.1)	--		6	95.3 (11.5 to 344.2)	270.5	
	No prior events	6	7.9 (2.2 to 20.3)	224		2	18.8 (2.3 to 67.9)	224		4	5.0 (0.6 to 18.1)	237.5	
	1 prior event	0	0.0 (0.0 to 299.5)	--		0	0.0 (0.0 to 708.4)	--		0	0.0 (0.0 to 518.8)	--	
	2+ prior events	6	110.0 (13.3 to 397.4)	270.5		0	0.0 (0.0 to 858.2)	--		6	144.1 (17.4 to 520.5)	270.5	
Stroke with concomitant use of beta-blockers[2]	Total	8	47.3 (15.4 to 110.4)	153		0	0.0 (0.0 to 288.1)	--		8	53.8 (17.5 to 125.6)	153	
	Any prior events	5	250.2 (30.3 to 903.7)	77.5		0	0.0 (0.0 to 2611.2)	--		5	303.9 (36.8 to 1097.7)	77.5	
	No prior events	3	30.7 (6.3 to 89.7)	357		0	0.0 (0.0 to 323.8)	--		3	34.7 (7.2 to 101.6)	357	
	1 prior event	0	0.0 (0.0 to 1517.3)	--		0	0.0 (0.0 to 2611.2)	--		0	0.0 (0.0 to 3621.9)	--	
	2+ prior events	5	359.5 (43.5 to 1298.6)	77.5		0	--	--		5	359.5 (43.5 to 1298.6)	77.5	
Any newly diagnosed congestive heart		14	23.3 (12.7 to 39.1)	235		1	8.0 (0.2 to 44.6)	56		13	27.3 (14.5 to 46.7)	260	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		7	13.6 (5.5 to 28.0)	260		1	8.7 (0.2 to 48.2)	56		6	15.0 (5.5 to 32.6)	263	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		7	82.2 (33.0 to 169.3)	210		0	0.0 (0.0 to 399.1)	--		7	92.2 (37.1 to 190.0)	210	
Pneumonia[2]	Total	34	48.8 (33.1 to 69.2)	199		6	46.4 (17.0 to 101.0)	282.5		28	49.4 (31.9 to 72.9)	176	
	Any prior events	15	149.6 (79.7 to 255.8)	224		3	175.2 (36.1 to 511.9)	150		12	143.3 (68.7 to 263.6)	225	
	No prior events	19	32.8 (19.4 to 51.8)	179.5		3	26.8 (5.5 to 78.2)	390		16	34.3 (19.2 to 56.6)	152	
	1 prior event	10	111.7 (48.2 to 220.1)	228.5		0	0.0 (0.0 to 238.7)	--		10	142.4 (61.5 to 280.6)	228.5	
	2+ prior events	5	327.7 (106.4 to 764.7)	150		3	1793.4 (369.8 to 5241.0)	150		2	147.2 (17.8 to 531.8)	157	
Moderate/Severe COPD exacerbation[4]		778	1.21 (1.09 to 1.35)	--		234	1.87 (1.52 to 2.31)	--		544	1.05 (0.93 to 1.19)	--	
Mortality	All cause	46	70.8 (51.8 to 94.4)	--	8.98%	8	61.3 (26.5 to 120.7)	--	8.42%	38	73.2 (51.8 to 100.5)	--	9.11%
	Cardiovascular	9	13.8 (6.3 to 26.3)	--	1.76%	0	0.0 (0.0 to 28.3)	--	<0.01%	9	17.3 (7.9 to 32.9)	--	2.16%

[1] Currently exposed defined as exposure time starting from the index date and continuing until the earliest of discontinuation, censoring or switching. Previous exposure defined as exposure time starting from the discontinuation or switch date and continuing until either the censoring date or the date the patient resumes taking the same index medication.

[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.

[3] Counts and incidence include first ever events (only) following initiation.

[4] Counts and incidence include all events following initiation.

Incidence of outcomes of interest whilst currently exposed[1] to UMEC therapy
CPRD GOLD+THIN Cohort

Outcomes of interest recorded in primary care data		All UMEC				Follow up while currently exposed to UMEC AND OTHER COPD MAINTENANCE THERAPY[6] (i.e. concurrent treatment)				Follow up while currently exposed to UMEC ONLY (i.e. no concurrent treatment with other COPD maintenance therapy[6])			
		No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		3875				3151				1337			
Any Myocardial infarction (MI)[2]	Total	27	6.9 (4.4 to 10.2)	184		19	6.4 (3.7 to 10.2)	199		8	8.4 (3.4 to 17.4)	150	
	Any prior events	6	20.4 (7.5 to 44.3)	170		6	27.4 (10.0 to 59.6)	170		0	0.0 (0.0 to 48.9)	--	
	No prior events	21	5.6 (3.3 to 8.9)	264.5		13	4.5 (2.2 to 8.0)	298		8	9.3 (3.7 to 19.1)	150	
	1 prior event	6	28.9 (10.6 to 63.0)	170		6	39.3 (14.4 to 85.5)	170		0	0.0 (0.0 to 67.8)	--	
	2+ prior events	0	0.0 (0.0 to 42.2)	--		0	0.0 (0.0 to 55.6)	--		0	0.0 (0.0 to 175.6)	--	
MI without concomitant use of beta-blockers[2]	Total	16	4.8 (2.6 to 8.1)	298.5		12	4.4 (2.1 to 8.2)	407		4	6.2 (1.7 to 15.9)	230.5	
	Any prior events	1	7.8 (0.2 to 43.4)	186		1	9.7 (0.2 to 54.0)	186		0	0.0 (0.0 to 146.5)	--	
	No prior events	15	4.7 (2.5 to 8.0)	299		11	4.2 (1.9 to 7.9)	516		4	6.5 (1.8 to 16.6)	230.5	
	1 prior event	1	10.5 (0.3 to 58.6)	186		1	12.9 (0.3 to 71.8)	186		0	0.0 (0.0 to 210.4)	--	
	2+ prior events	0	0.0 (0.0 to 110.9)	--		0	0.0 (0.0 to 144.0)	--		0	0.0 (0.0 to 482.6)	--	
MI with concomitant use of beta-blockers[2]	Total	11	16.7 (8.0 to 30.7)	126		7	16.9 (6.8 to 34.9)	158		4	16.1 (3.3 to 47.0)	91	
	Any prior events	5	30.1 (9.8 to 70.2)	158		5	43.1 (14.0 to 100.6)	158		0	0.0 (0.0 to 73.4)	--	
	No prior events	6	11.5 (3.7 to 26.9)	102		2	6.7 (0.8 to 24.3)	148		4	22.0 (4.5 to 64.3)	91	
	1 prior event	5	44.6 (14.5 to 104.0)	158		5	66.4 (21.6 to 155.1)	158		0	0.0 (0.0 to 99.9)	--	
	2+ prior events	0	0.0 (0.0 to 68.1)	--		0	0.0 (0.0 to 90.5)	--		0	0.0 (0.0 to 276.0)	--	
Any stroke[2]	Total	171	30.9 (25.3 to 37.4)	140.5		124	28.6 (22.5 to 35.9)	136		47	38.2 (25.9 to 54.2)	148	
	Any prior events	140	278.4 (219.7 to 347.9)	141		103	248.9 (188.0 to 323.3)	138.5		37	406.7 (251.7 to 621.6)	148	
	No prior events	31	9.2 (6.2 to 13.2)	140		21	7.9 (4.8 to 12.4)	91		10	13.1 (6.3 to 24.2)	169	
	1 prior event	24	84.4 (38.6 to 160.2)	91		18	79.8 (32.1 to 164.5)	91		6	105.4 (12.8 to 380.8)	130.5	
	2+ prior events	116	400.2 (310.8 to 507.3)	149.5		85	357.0 (264.1 to 472.0)	151		31	581.6 (350.2 to 908.3)	148	
Stroke without concomitant use of beta-blockers[2]	Total	142	30.7 (24.6 to 37.8)	136		106	28.1 (21.5 to 36.0)	128		36	39.7 (25.7 to 58.6)	176	
	Any prior events	116	303.2 (232.4 to 388.6)	138.5		89	269.5 (197.3 to 359.4)	132.5		27	473.3 (270.5 to 768.6)	162	
	No prior events	26	9.5 (6.1 to 14.0)	134		17	7.9 (4.5 to 12.8)	89.5		9	15.1 (6.9 to 28.7)	198	
	1 prior event	23	97.4 (42.1 to 192.0)	88		17	88.5 (32.5 to 192.6)	75		6	139.8 (16.9 to 504.8)	130.5	
	2+ prior events	93	441.2 (331.4 to 575.6)	144.5		72	388.7 (277.7 to 529.3)	138.5		21	718.2 (392.6 to 1205.0)	185	
Stroke with concomitant use of beta-blockers[2]	Total	29	32.0 (19.3 to 50.0)	151		18	31.6 (16.8 to 54.1)	298		11	32.9 (12.1 to 71.6)	120.5	
	Any prior events	24	208.1 (116.5 to 343.2)	151		14	184.3 (88.4 to 339.0)	224.5		10	280.4 (91.0 to 654.3)	101	
	No prior events	5	7.7 (2.1 to 19.7)	367		4	8.4 (1.7 to 24.6)	413		1	6.1 (0.2 to 33.9)	140	
	1 prior event	1	40.7 (1.0 to 226.8)	91		1	50.2 (1.3 to 279.9)	91		0	0.0 (0.0 to 791.6)	--	
	2+ prior events	23	294.6 (161.1 to 494.4)	216		13	262.1 (119.8 to 497.5)	298		10	379.5 (123.2 to 885.7)	101	
Any newly diagnosed congestive heart		48	14.8 (10.9 to 19.6)	195.5		36	14.6 (10.3 to 20.3)	182.5		12	15.3 (7.9 to 26.7)	213.5	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		28	10.2 (6.8 to 14.7)	195.5		21	9.9 (6.1 to 15.1)	196		7	11.2 (4.5 to 23.1)	163	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		20	40.8 (24.9 to 63.0)	184.5		15	45.6 (25.5 to 75.2)	169		5	31.0 (10.1 to 72.4)	264	
Pneumonia[2]	Total	25	6.9 (4.4 to 10.2)	147.5		22	7.9 (4.9 to 12.0)	222		3	3.6 (0.7 to 10.5)	75	
	Any prior events	5	16.0 (4.4 to 41.0)	189		5	18.9 (5.1 to 48.3)	179.5		0	0.0 (0.0 to 97.3)	--	
	No prior events	20	6.2 (3.8 to 9.5)	147.5		17	6.9 (4.0 to 11.1)	222		3	3.8 (0.8 to 11.0)	75	
	1 prior event	3	13.7 (2.8 to 40.0)	51		3	16.2 (3.3 to 47.4)	32		0	0.0 (0.0 to 107.9)	--	
	2+ prior events	2	32.4 (0.8 to 180.4)	327		2	36.8 (0.9 to 205.2)	327		0	0.0 (0.0 to 988.5)	--	
Moderate/Severe COPD exacerbation[4]		3409	0.98 (0.93 to 1.03)	--		3025	1.14 (1.09 to 1.20)	--		384	0.51 (0.44 to 0.58)	--	
Mortality	All cause	105	29.9 (24.5 to 36.2)	--	2.71%	77	28.8 (22.7 to 36.0)	--	2.44%	28	33.6 (22.3 to 48.5)	--	2.09%

[1] Currently exposed defined as exposure time starting from the index date and continuing until the earliest of discontinuation, censoring or switching.
[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.
[3] Counts and incidence include first ever events (only) following initiation.
[4] Counts and incidence include all events following initiation.
[5] Patients may contribute person time both with and without concurrent maintenance therapy therefore counts may exceed total number of patients
[6] Other COPD maintenance therapy defined as one or more of the following drug classes: ICS, ICS+SABA, theophylline, LABA, ICS+LABA, Other LAMA, Other LABA/LAMA,

Incidence of outcomes of interest whilst currently exposed[1] to UMEC/VI therapy
CPRD GOLD+THIN Cohort

Outcomes of interest recorded in primary care data		All UMEC/VI				Follow up while currently exposed to UMEC/VI AND OTHER COPD MAINTENANCE THERAPY[6] (i.e. concurrent treatment)				Follow up while currently exposed to UMEC/VI ONLY (i.e. no concurrent treatment with other COPD maintenance therapy[5])			
		No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		2224				1252				1807			
Any Myocardial infarction (MI)[2]	Total	13	6.8 (3.5 to 11.9)	213.5		3	11.7 (2.4 to 34.1)	141		10	6.0 (2.7 to 11.4)	216	
	Any prior events	1	7.3 (0.2 to 40.7)	224		0	0.0 (0.0 to 277.9)	--		1	8.1 (0.2 to 45.1)	216	
	No prior events	12	6.8 (3.4 to 12.1)	203		3	12.3 (2.5 to 36.0)	141		9	5.8 (2.5 to 11.4)	220	
	1 prior event	1	9.6 (0.2 to 53.2)	224		0	0.0 (0.0 to 364.8)	--		1	10.6 (0.3 to 58.9)	216	
	2+ prior events	0	0.0 (0.0 to 114.7)	--		0	0.0 (0.0 to 1166.5)	--		0	0.0 (0.0 to 127.2)	--	
MI without concomitant use of beta-blockers[2]	Total	10	6.5 (3.0 to 12.3)	226		3	14.3 (2.9 to 41.6)	141		7	5.1 (1.9 to 11.1)	253	
	Any prior events	0	0.0 (0.0 to 91.9)	--		0	0.0 (0.0 to 858.2)	--		0	0.0 (0.0 to 103.0)	--	
	No prior events	10	6.7 (3.1 to 12.7)	226		3	14.5 (3.0 to 42.5)	141		7	5.3 (1.9 to 11.4)	253	
	1 prior event	0	0.0 (0.0 to 107.9)	--		0	0.0 (0.0 to 1086.6)	--		0	0.0 (0.0 to 119.8)	--	
	2+ prior events	0	0.0 (0.0 to 620.9)	--		0	0.0 (0.0 to 4082.9)	--		0	0.0 (0.0 to 732.3)	--	
MI with concomitant use of beta-blockers[2]	Total	3	8.1 (1.7 to 23.6)	203		0	0.0 (0.0 to 79.3)	--		3	9.2 (1.9 to 26.9)	143	
	Any prior events	1	10.3 (0.3 to 57.6)	224		0	0.0 (0.0 to 411.0)	--		1	11.4 (0.3 to 63.5)	216	
	No prior events	2	7.3 (0.9 to 26.3)	161		0	0.0 (0.0 to 98.3)	--		2	8.4 (1.0 to 30.4)	131	
	1 prior event	1	14.2 (0.4 to 79.1)	224		0	0.0 (0.0 to 549.3)	--		1	15.7 (0.4 to 87.4)	216	
	2+ prior events	0	0.0 (0.0 to 140.7)	--		0	0.0 (0.0 to 1633.2)	--		0	0.0 (0.0 to 153.9)	--	
Any stroke[2]	Total	84	30.5 (22.8 to 39.8)	216		10	27.2 (11.0 to 56.1)	37		74	31.0 (22.7 to 41.4)	214	
	Any prior events	57	250.0 (173.1 to 349.3)	197.5		10	339.1 (136.3 to 698.7)	37		47	234.0 (154.2 to 340.5)	182	
	No prior events	27	11.8 (7.1 to 18.5)	286		0	0.0 (0.0 to 15.6)	--		27	13.9 (8.4 to 21.7)	241	
	1 prior event	6	58.1 (12.0 to 169.9)	204		0	0.0 (0.0 to 411.4)	--		6	70.4 (14.5 to 205.6)	182	
	2+ prior events	51	367.3 (249.6 to 521.4)	191		10	599.5 (241.0 to 1235.1)	37		41	330.0 (211.5 to 491.1)	184	
Stroke without concomitant use of beta-blockers[2]	Total	63	27.0 (19.0 to 37.2)	215		8	23.7 (7.7 to 55.4)	167		55	27.5 (18.8 to 38.9)	208.5	
	Any prior events	43	246.1 (159.3 to 363.3)	191		8	301.7 (97.9 to 704.0)	167		35	235.3 (143.7 to 363.4)	168.5	
	No prior events	20	9.4 (4.9 to 16.5)	278.5		0	0.0 (0.0 to 19.0)	--		20	11.1 (5.8 to 19.5)	243	
	1 prior event	3	51.1 (6.2 to 184.7)	290		0	0.0 (0.0 to 531.5)	--		3	62.2 (7.5 to 224.6)	279	
	2+ prior events	40	368.2 (233.4 to 552.5)	163		8	519.0 (168.5 to 1211.1)	167		32	340.7 (201.9 to 538.5)	135.5	
Stroke with concomitant use of beta-blockers[2]	Total	21	43.5 (24.9 to 70.7)	230.5		2	43.1 (5.2 to 155.8)	21		19	43.6 (23.8 to 73.1)	227	
	Any prior events	14	261.4 (119.5 to 496.2)	216		2	491.6 (59.5 to 1775.8)	21		12	230.5 (92.7 to 475.0)	213	
	No prior events	7	21.0 (8.4 to 43.3)	305		0	0.0 (0.0 to 87.2)	--		7	24.1 (9.7 to 49.6)	241	
	1 prior event	3	80.0 (2.0 to 445.8)	162		0	0.0 (0.0 to 1820.8)	--		3	95.5 (2.4 to 532.0)	162	
	2+ prior events	11	364.7 (157.5 to 718.7)	230.5		2	979.2 (118.6 to 3537.3)	21		9	301.7 (110.7 to 656.6)	229	
Any newly diagnosed congestive heart		18	11.0 (6.5 to 17.4)	246.5		1	4.2 (0.1 to 23.5)	155		17	12.2 (7.1 to 19.5)	233	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		10	7.4 (3.6 to 13.7)	310.5		1	4.9 (0.1 to 27.4)	155		9	7.9 (3.6 to 15.0)	335	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		8	27.8 (12.0 to 54.8)	187		0	0.0 (0.0 to 109.3)	--		8	31.5 (13.6 to 62.1)	187	
Pneumonia[2]	Total	6	3.4 (1.2 to 7.4)	146		2	7.7 (0.9 to 27.9)	53.5		4	2.7 (0.7 to 6.8)	305.5	
	Any prior events	1	7.6 (0.2 to 42.6)	95		1	48.3 (1.2 to 269.2)	95		0	0.0 (0.0 to 33.5)	--	
	No prior events	5	3.1 (1.0 to 7.1)	197		1	4.2 (0.1 to 23.4)	12		4	2.9 (0.8 to 7.3)	305.5	
	1 prior event	1	9.1 (0.2 to 50.6)	95		1	58.9 (1.5 to 328.3)	95		0	0.0 (0.0 to 39.6)	--	
	2+ prior events	0	0.0 (0.0 to 176.7)	--		0	0.0 (0.0 to 989.3)	--		0	0.0 (0.0 to 215.1)	--	
Moderate/Severe COPD exacerbation[4]		1275	0.75 (0.69 to 0.81)	--		302	1.11 (0.96 to 1.29)	--		973	0.66 (0.60 to 0.73)	--	
Mortality	All cause	62	35.1 (26.9 to 44.9)	--	2.79%	9	34.8 (15.9 to 66.0)	--	0.72%	53	35.1 (26.3 to 45.9)	--	2.93%

[1] Currently exposed defined as exposure time starting from the index date and continuing until the earliest of discontinuation, censoring or switching.
[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.
[3] Counts and incidence include first ever events (only) following initiation.
[4] Counts and incidence include all events following initiation.
[5] Patients may contribute person time both with and without concurrent maintenance therapy therefore counts may exceed total number of patients
[6] Other COPD maintenance therapy defined as one or more of the following drug classes: ICS, ICS+SABA, theophylline, LABA, ICS+LABA, Other LAMA, Other LABA/LAMA,

Incidence of outcomes of interest whilst currently exposed[1] to UMEC therapy
CPRD GOLD-HES-ONS Cohort

Outcomes of interest recorded in primary and/or secondary care data		All UMEC				Follow up while currently exposed to UMEC/VI AND OTHER COPD MAINTENANCE THERAPY[6] (i.e. concurrent treatment)				Follow up while currently exposed to UMEC/VI ONLY (i.e. no concurrent treatment with other COPD maintenance therapy[5])			
		No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		547				439				194			
Any Myocardial infarction (MI)[2]	Total	5	8.0 (1.7 to 23.4)	136		4	7.3 (0.9 to 26.3)	129.5		1	10.0 (0.3 to 55.9)	299	
	Any prior events	2	40.2 (1.0 to 224.1)	136		2	57.5 (1.5 to 320.4)	136		0	0.0 (0.0 to 493.4)	--	
	No prior events	3	5.7 (0.7 to 20.7)	211		2	3.9 (0.1 to 21.7)	123		1	10.8 (0.3 to 60.4)	299	
	1 prior event	0	0.0 (0.0 to 219.1)	--		0	0.0 (0.0 to 320.2)	--		0	0.0 (0.0 to 694.2)	--	
	2+ prior events	2	124.5 (3.2 to 693.8)	136		2	170.4 (4.3 to 949.6)	136		0	0.0 (0.0 to 1705.5)	--	
MI without concomitant use of beta-blockers[2]	Total	3	6.3 (0.8 to 22.7)	211		2	4.2 (0.1 to 23.4)	123		1	12.5 (0.3 to 69.5)	299	
	Any prior events	0	0.0 (0.0 to 459.5)	--		0	0.0 (0.0 to 570.7)	--		0	0.0 (0.0 to 2359.7)	--	
	No prior events	3	6.4 (0.8 to 23.3)	211		2	4.3 (0.1 to 24.1)	123		1	12.7 (0.3 to 70.8)	299	
	1 prior event	0	0.0 (0.0 to 493.2)	--		0	0.0 (0.0 to 623.5)	--		0	0.0 (0.0 to 2359.7)	--	
	2+ prior events	0	0.0 (0.0 to 6736.8)	--		0	0.0 (0.0 to 6736.8)	--		0	--	--	
MI with concomitant use of beta-blockers[2]	Total	2	17.9 (0.5 to 99.8)	136		2	27.5 (0.7 to 153.3)	136		0	0.0 (0.0 to 189.4)	--	
	Any prior events	2	59.4 (1.5 to 330.9)	136		2	91.5 (2.3 to 510.0)	136		0	0.0 (0.0 to 623.8)	--	
	No prior events	0	0.0 (0.0 to 94.7)	--		0	0.0 (0.0 to 145.2)	--		0	0.0 (0.0 to 272.1)	--	
	1 prior event	0	0.0 (0.0 to 394.3)	--		0	0.0 (0.0 to 658.2)	--		0	0.0 (0.0 to 983.5)	--	
	2+ prior events	2	133.6 (3.4 to 744.6)	136		2	188.0 (4.8 to 1047.4)	136		0	0.0 (0.0 to 1705.5)	--	
Any stroke[2]	Total	19	35.4 (18.9 to 60.6)	105		14	29.8 (12.8 to 58.6)	98		5	51.1 (16.6 to 119.2)	198	
	Any prior events	15	345.3 (157.9 to 655.4)	91		12	307.1 (112.7 to 668.5)	84		3	459.2 (94.7 to 1342.1)	281	
	No prior events	4	11.7 (3.2 to 30.1)	190.5		2	8.0 (1.0 to 29.0)	383.5		2	21.9 (2.7 to 79.1)	106.5	
	1 prior event	3	190.0 (23.0 to 686.3)	72		2	117.1 (3.0 to 652.5)	59		1	503.1 (12.7 to 2803.1)	85	
	2+ prior events	12	450.4 (181.1 to 928.1)	105		10	454.7 (147.7 to 1061.2)	91		2	440.1 (53.3 to 1589.6)	326	
Stroke without concomitant use of beta-blockers[2]	Total	17	35.3 (17.6 to 63.2)	105		13	30.1 (12.1 to 62.0)	105		4	50.8 (13.8 to 130.0)	141.5	
	Any prior events	13	355.4 (142.9 to 732.2)	91		11	298.5 (96.9 to 696.5)	91		2	678.9 (82.2 to 2452.4)	228	
	No prior events	4	13.7 (3.7 to 35.1)	190.5		2	9.3 (1.1 to 33.5)	383.5		2	26.4 (3.2 to 95.2)	106.5	
	1 prior event	3	202.2 (24.5 to 730.6)	72		2	118.3 (3.0 to 659.2)	59		1	695.7 (17.6 to 3876.3)	85	
	2+ prior events	10	509.7 (165.5 to 1189.5)	105		9	481.9 (131.3 to 1233.8)	98		1	662.9 (16.8 to 3693.4)	371	
Stroke with concomitant use of beta-blockers[2]	Total	2	36.1 (4.4 to 130.4)	179		1	27.5 (0.7 to 153.5)	77		1	52.4 (1.3 to 291.9)	281	
	Any prior events	2	314.1 (38.0 to 1134.5)	179		1	359.5 (9.1 to 2003.0)	77		1	278.8 (7.1 to 1553.5)	281	
	No prior events	0	0.0 (0.0 to 75.3)	--		0	0.0 (0.0 to 110.1)	--		0	0.0 (0.0 to 238.0)	--	
	1 prior event	0	0.0 (0.0 to 5782.7)	--		0	0.0 (0.0 to 42105.1)	--		0	0.0 (0.0 to 6703.3)	--	
	2+ prior events	2	349.0 (42.3 to 1260.8)	179		1	371.2 (9.4 to 2068.1)	77		1	329.4 (8.3 to 1835.0)	281	
Any newly diagnosed congestive heart		5	14.6 (4.7 to 34.0)	206		5	20.1 (6.5 to 46.8)	206		0	0.0 (0.0 to 39.2)	--	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		5	16.6 (5.4 to 38.7)	206		5	22.6 (7.3 to 52.7)	206		0	0.0 (0.0 to 46.1)	--	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		0	0.0 (0.0 to 88.5)	--		0	0.0 (0.0 to 133.6)	--		0	0.0 (0.0 to 262.4)	--	
Pneumonia[2]	Total	25	66.0 (42.3 to 98.2)	166.5		21	75.0 (45.8 to 115.9)	193.5		4	41.3 (11.2 to 105.6)	100	
	Any prior events	9	203.1 (92.9 to 385.6)	147		9	256.8 (117.4 to 487.6)	147		0	0.0 (0.0 to 398.3)	--	
	No prior events	16	47.0 (26.3 to 77.5)	186		12	47.5 (23.7 to 85.0)	201		4	45.6 (12.4 to 116.8)	100	
	1 prior event	8	216.5 (93.5 to 426.6)	217.5		8	276.4 (119.3 to 544.7)	217.5		0	0.0 (0.0 to 460.6)	--	
	2+ prior events	1	136.0 (3.4 to 757.6)	62		1	163.9 (4.2 to 913.4)	62		0	0.0 (0.0 to 2941.8)	--	
Moderate/Severe COPD exacerbation[4]		554	1.48 (1.33 to 1.66)	--		455	1.65 (1.46 to 1.86)	--		99	1.03 (0.78 to 1.35)	--	
Mortality	All cause	18	48.0 (28.5 to 75.9)	--	3.29%	13	47.3 (25.2 to 80.8)	--	2.96%	5	50.2 (16.3 to 117.1)	--	2.58%
	Cardiovascular	4	10.7 (2.9 to 27.3)	--	0.73%	2	7.3 (0.9 to 26.3)	--	0.46%	2	20.1 (2.4 to 72.5)	--	1.03%

[1] Currently exposed defined as exposure time starting from the index date and continuing until the earliest of discontinuation, censoring or switching.
[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.
[3] Counts and incidence include first ever events (only) following initiation.
[5] Patients may contribute person time both with and without concurrent maintenance therapy therefore counts may exceed total number of patients
[6] Other COPD maintenance therapy defined as one or more of the following drug classes: ICS, ICS+SABA, theophylline, LABA, ICS+LABA, Other LAMA, Other LABA/LAMA,

Incidence of outcomes of interest whilst currently exposed[1] to UMEC/VI therapy
CPRD GOLD-HES-ONS Cohort

Outcomes of interest recorded in primary and/or secondary care data		All UMEC/VI				Follow up while currently exposed to UMEC AND OTHER COPD MAINTENANCE THERAPY[6] (i.e. concurrent treatment)				Follow up while currently exposed to UMEC ONLY (i.e. no concurrent treatment with other COPD maintenance therapy[6])			
		No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients[5]	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		512				299				402			
Any Myocardial infarction (MI)[2]	Total	2	5.5 (0.7 to 19.9)	214.5		1	14.2 (0.4 to 78.9)	226		1	3.4 (0.1 to 19.0)	143	
	Any prior events	0	0.0 (0.0 to 139.8)	--		0	0.0 (0.0 to 1469.3)	--		0	0.0 (0.0 to 154.5)	--	
	No prior events	2	5.9 (0.7 to 21.5)	214.5		1	14.7 (0.4 to 81.8)	226		1	3.7 (0.1 to 20.7)	143	
	1 prior event	0	0.0 (0.0 to 210.0)	--		0	0.0 (0.0 to 1665.5)	--		0	0.0 (0.0 to 240.3)	--	
	2+ prior events	0	0.0 (0.0 to 418.4)	--		0	0.0 (0.0 to 12475.6)	--		0	0.0 (0.0 to 433.0)	--	
MI without concomitant use of beta-blockers[2]	Total	1	3.3 (0.1 to 18.6)	226		1	16.4 (0.4 to 91.5)	226		0	0.0 (0.0 to 15.5)	--	
	Any prior events	0	0.0 (0.0 to 392.9)	--		0	0.0 (0.0 to 2397.4)	--		0	0.0 (0.0 to 470.0)	--	
	No prior events	1	3.5 (0.1 to 19.2)	226		1	16.8 (0.4 to 93.8)	226		0	0.0 (0.0 to 16.0)	--	
	1 prior event	0	0.0 (0.0 to 407.2)	--		0	0.0 (0.0 to 2397.4)	--		0	0.0 (0.0 to 490.5)	--	
	2+ prior events	0	0.0 (0.0 to 11228.0)	--		0	--	--		0	0.0 (0.0 to 11228.0)	--	
MI with concomitant use of beta-blockers[2]	Total	1	15.6 (0.4 to 87.1)	203		0	0.0 (0.0 to 381.3)	--		1	18.4 (0.5 to 102.7)	143	
	Any prior events	0	0.0 (0.0 to 217.0)	--		0	0.0 (0.0 to 3795.4)	--		0	0.0 (0.0 to 230.2)	--	
	No prior events	1	21.3 (0.5 to 118.7)	203		0	0.0 (0.0 to 423.8)	--		1	26.1 (0.7 to 145.7)	143	
	1 prior event	0	0.0 (0.0 to 433.5)	--		0	0.0 (0.0 to 5454.9)	--		0	0.0 (0.0 to 470.9)	--	
	2+ prior events	0	0.0 (0.0 to 434.6)	--		0	0.0 (0.0 to 12475.6)	--		0	0.0 (0.0 to 450.3)	--	
Any stroke[2]	Total	13	16.5 (6.1 to 36.0)	242		1	13.9 (0.4 to 77.5)	321		12	17.2 (5.6 to 40.1)	155	
	Any prior events	8	136.7 (28.2 to 399.5)	153		0	0.0 (0.0 to 630.5)	--		8	186.4 (38.4 to 544.8)	131	
	No prior events	5	8.8 (1.8 to 25.7)	350		1	15.1 (0.4 to 84.4)	321		4	7.3 (0.9 to 26.3)	353.5	
	1 prior event	0	0.0 (0.0 to 425.7)	--		0	0.0 (0.0 to 921.6)	--		0	0.0 (0.0 to 791.2)	--	
	2+ prior events	8	225.9 (46.6 to 660.3)	153		0	0.0 (0.0 to 1996.1)	--		8	262.5 (54.1 to 767.0)	131	
Stroke without concomitant use of beta-blockers[2]	Total	9	10.0 (2.1 to 29.3)	321		1	16.1 (0.4 to 89.6)	321		8	8.4 (1.0 to 30.5)	252.5	
	Any prior events	5	55.8 (1.4 to 311.0)	163		0	0.0 (0.0 to 803.4)	--		5	75.0 (1.9 to 418.1)	155	
	No prior events	4	7.1 (0.9 to 25.7)	335.5		1	17.4 (0.4 to 96.7)	321		3	4.5 (0.1 to 24.9)	350	
	1 prior event	0	0.0 (0.0 to 495.9)	--		0	0.0 (0.0 to 1278.3)	--		0	0.0 (0.0 to 810.2)	--	
	2+ prior events	5	95.4 (2.4 to 531.8)	163		0	0.0 (0.0 to 2162.7)	--		5	114.0 (2.9 to 635.2)	155	
Stroke with concomitant use of beta-blockers[2]	Total	4	47.0 (9.7 to 137.3)	153		0	0.0 (0.0 to 381.3)	--		4	55.4 (11.4 to 161.8)	131	
	Any prior events	3	496.6 (60.1 to 1793.9)	77.5		0	0.0 (0.0 to 2929.1)	--		3	722.6 (87.5 to 2610.1)	66.5	
	No prior events	1	16.7 (0.4 to 93.1)	357		0	0.0 (0.0 to 438.3)	--		1	19.4 (0.5 to 108.3)	357	
	1 prior event	0	0.0 (0.0 to 3007.5)	--		0	0.0 (0.0 to 3302.4)	--		0	0.0 (0.0 to 33684.1)	--	
	2+ prior events	3	714.1 (86.5 to 2579.5)	77.5		0	0.0 (0.0 to 25910.8)	--		3	752.3 (91.1 to 2717.6)	66.5	
Any newly diagnosed congestive heart		7	20.5 (8.3 to 42.3)	260		3	44.8 (9.2 to 131.0)	137		4	14.6 (4.0 to 37.4)	326.5	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		3	10.3 (2.1 to 30.2)	260		3	50.4 (10.4 to 147.2)	137		0	0.0 (0.0 to 16.0)	--	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		4	79.2 (21.6 to 202.9)	326.5		0	0.0 (0.0 to 499.6)	--		4	92.8 (25.3 to 237.6)	326.5	
Pneumonia[2]	Total	18	47.3 (27.5 to 75.7)	176		5	57.5 (15.7 to 147.1)	91.5		13	44.8 (23.9 to 76.6)	203	
	Any prior events	10	161.0 (73.6 to 305.7)	214		4	280.5 (57.9 to 819.8)	95		6	132.7 (48.7 to 288.9)	208.5	
	No prior events	8	26.3 (11.4 to 51.9)	106		1	17.0 (0.4 to 94.6)	52		7	28.6 (11.5 to 58.9)	133	
	1 prior event	7	136.2 (50.0 to 296.4)	219		1	0.0 (0.0 to 414.4)	--		6	170.7 (62.6 to 371.4)	208.5	
	2+ prior events	3	253.5 (52.3 to 740.7)	95		3	1672.9 (345.0 to 4888.9)	95		0	0.0 (0.0 to 367.3)	--	
Moderate/Severe COPD exacerbation[4]		421	1.17 (1.01 to 1.35)	--		118	1.60 (1.28 to 2.00)	--		303	1.05 (0.89 to 1.23)	--	
Mortality	All cause	19	52.0 (31.3 to 81.2)	--	3.71%	3	41.6 (8.6 to 121.7)	--	1.00%	16	54.5 (31.2 to 88.5)	--	3.98%
	Cardiovascular	6	16.4 (6.0 to 35.7)	--	1.17%	0	0.0 (0.0 to 51.2)	--	0.00%	6	20.4 (7.5 to 44.5)	--	1.49%

[1] Currently exposed defined as exposure time starting from the index date and continuing until the earliest of discontinuation, censoring or switching.
[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.
[3] Counts and incidence include first ever events (only) following initiation.
[5] Patients may contribute person time both with and without concurrent maintenance therapy therefore counts may exceed total number of patients
[6] Other COPD maintenance therapy defined as one or more of the following drug classes: ICS, ICS+SABA, theophylline, LABA, ICS+LABA, Other LAMA, Other LABA/LAMA,

Incidence of outcomes of interest whilst currently exposed [1] to UMEC or UMEC/VI therapy
CPRD GOLD-THIN Cohort

Outcomes of interest recorded in primary care data		UMEC with possible "on-label" prescribing				UMEC with possible "off-label" prescribing				UMEC/VI with possible "on-label" prescribing				UMEC/VI with possible "off-label" prescribing			
		No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		3604				271				2029				195			
Any Myocardial infarction (MI)[2]	Total	25	7.0 (4.4 to 10.4)	182		2	5.3 (0.1 to 29.3)	586		13	7.3 (3.7 to 12.7)	213.5		0	0.0 (0.0 to 34.9)	--	
	Any prior events	6	21.4 (7.8 to 46.5)	170		0	0.0 (0.0 to 266.8)	--		1	7.9 (0.2 to 43.8)	224		0	0.0 (0.0 to 384.5)	--	
	No prior events	19	5.6 (3.3 to 9.0)	257		2	5.7 (0.1 to 31.6)	586		12	7.2 (3.6 to 12.9)	203		0	0.0 (0.0 to 38.3)	--	
	1 prior event	6	30.6 (11.2 to 66.5)	170		0	0.0 (0.0 to 335.8)	--		1	10.1 (0.3 to 56.2)	224		0	0.0 (0.0 to 675.0)	--	
	2+ prior events	0	0.0 (0.0 to 43.6)	--		0	0.0 (0.0 to 1298.0)	--		0	0.0 (0.0 to 131.6)	--		0	0.0 (0.0 to 893.5)	--	
MI without concomitant use of beta-blockers[2]	Total	14	4.7 (2.5 to 8.1)	298		2	6.6 (0.2 to 36.9)	586		10	6.9 (3.1 to 13.0)	226		0	0.0 (0.0 to 48.5)	--	
	Any prior events	1	8.1 (0.2 to 44.9)	186		0	0.0 (0.0 to 876.0)	--		0	0.0 (0.0 to 95.7)	--		0	0.0 (0.0 to 2359.7)	--	
	No prior events	13	4.6 (2.4 to 8.0)	298.5		2	6.8 (0.2 to 37.9)	586		10	7.1 (3.2 to 13.4)	226		0	0.0 (0.0 to 49.6)	--	
	1 prior event	1	10.9 (0.3 to 60.9)	186		0	0.0 (0.0 to 1017.6)	--		0	0.0 (0.0 to 112.1)	--		0	0.0 (0.0 to 2879.0)	--	
	2+ prior events	0	0.0 (0.0 to 112.9)	--		0	0.0 (0.0 to 6296.1)	--		0	0.0 (0.0 to 651.8)	--		0	0.0 (0.0 to 13081.2)	--	
MI with concomitant use of beta-blockers[2]	Total	11	17.8 (8.5 to 32.8)	126		0	0.0 (0.0 to 95.2)	--		3	8.8 (1.8 to 25.6)	203		0	0.0 (0.0 to 123.7)	--	
	Any prior events	5	31.9 (10.4 to 74.5)	158		0	0.0 (0.0 to 383.6)	--		1	11.3 (0.3 to 62.8)	224		0	0.0 (0.0 to 459.4)	--	
	No prior events	6	12.4 (4.0 to 28.9)	102		0	0.0 (0.0 to 126.5)	--		2	7.9 (1.0 to 28.5)	161		0	0.0 (0.0 to 169.3)	--	
	1 prior event	5	47.7 (15.5 to 111.3)	158		0	0.0 (0.0 to 501.3)	--		1	15.1 (0.4 to 84.1)	224		0	0.0 (0.0 to 881.8)	--	
	2+ prior events	0	0.0 (0.0 to 71.1)	--		0	0.0 (0.0 to 1635.1)	--		0	0.0 (0.0 to 164.9)	--		0	0.0 (0.0 to 959.0)	--	
Any stroke[2]	Total	166	31.1 (25.4 to 37.8)	148		5	26.5 (8.6 to 61.9)	91		80	30.0 (22.2 to 39.6)	216		4	38.0 (10.4 to 97.4)	219	
	Any prior events	137	286.4 (224.9 to 359.6)	144.5		3	164.5 (33.9 to 480.6)	56		54	246.0 (167.2 to 349.2)	204		3	299.6 (61.8 to 875.6)	116	
	No prior events	29	9.0 (6.0 to 13.2)	148		2	11.7 (1.4 to 42.4)	112.5		26	11.9 (7.1 to 18.8)	278.5		1	10.5 (0.3 to 58.6)	357	
	1 prior event	24	92.0 (42.1 to 174.7)	91		0	0.0 (0.0 to 415.7)	--		6	61.4 (12.7 to 179.3)	204		0	0.0 (0.0 to 1355.5)	--	
	2+ prior events	113	404.9 (312.5 to 516.0)	151		3	320.2 (66.0 to 935.8)	56		48	363.1 (241.3 to 524.8)	203.5		3	411.5 (84.9 to 1202.5)	116	
Stroke without concomitant use of beta-blockers[2]	Total	138	30.9 (24.6 to 38.3)	141		4	26.7 (7.3 to 68.4)	112.5		61	27.0 (18.8 to 37.5)	215		2	26.4 (3.2 to 95.4)	219	
	Any prior events	114	311.4 (237.7 to 400.9)	138.5		2	168.7 (20.4 to 609.3)	198		41	243.9 (154.6 to 365.9)	191		2	275.2 (33.3 to 994.3)	219	
	No prior events	24	9.2 (5.8 to 13.8)	148		2	14.5 (1.8 to 52.4)	112.5		20	10.0 (5.2 to 17.4)	278.5		0	0.0 (0.0 to 53.9)	--	
	1 prior event	23	104.0 (44.9 to 204.8)	88		0	0.0 (0.0 to 716.3)	--		3	53.0 (6.4 to 191.5)	290		0	0.0 (0.0 to 2657.5)	--	
	2+ prior events	91	449.4 (335.7 to 589.4)	144.5		2	298.2 (36.1 to 1077.1)	198		38	371.1 (229.7 to 567.3)	163		2	340.2 (41.2 to 1229.1)	219	
Stroke with concomitant use of beta-blockers[2]	Total	28	32.5 (19.2 to 51.3)	216		1	25.8 (0.7 to 143.7)	56		19	41.4 (22.6 to 69.4)	230.5		2	68.1 (8.2 to 245.9)	179.5	
	Any prior events	23	213.1 (116.5 to 357.5)	216		1	156.6 (4.0 to 872.7)	56		13	252.5 (109.0 to 497.5)	230.5		1	364.2 (9.2 to 2029.0)	2	
	No prior events	5	8.2 (2.2 to 21.0)	367		0	0.0 (0.0 to 113.9)	--		6	19.6 (7.2 to 42.6)	204.5		1	37.5 (1.0 to 209.2)	357	
	1 prior event	1	48.0 (1.2 to 267.3)	91		0	0.0 (0.0 to 990.7)	--		3	89.6 (2.3 to 499.0)	162		0	0.0 (0.0 to 2766.7)	--	
	2+ prior events	22	289.8 (154.3 to 495.6)	281		1	375.8 (9.5 to 2093.7)	56		10	341.1 (137.2 to 702.9)	245		1	707.8 (17.9 to 3943.9)	2	
Any newly diagnosed congestive heart failure (CHF)**		47	15.3 (11.2 to 20.3)	196		1	5.9 (0.1 to 32.7)	63		16	10.4 (6.0 to 16.9)	260.5		2	20.8 (2.5 to 75.0)	67	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		28	10.7 (7.1 to 15.5)	195.5		0	0.0 (0.0 to 26.2)	--		9	7.1 (3.2 to 13.4)	361		1	13.5 (0.3 to 75.3)	22	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		19	41.3 (24.9 to 64.5)	200		1	33.6 (0.8 to 187.0)	63		7	26.4 (10.6 to 54.3)	201		1	44.8 (1.1 to 249.4)	112	
Pneumonia[2]	Total	22	6.4 (3.9 to 9.7)	222		3	15.8 (3.3 to 46.2)	75		6	3.6 (1.3 to 7.9)	146		0	0.0 (0.0 to 34.9)	--	
	Any prior events	5	16.9 (4.6 to 43.4)	189		0	0.0 (0.0 to 267.3)	--		1	8.3 (0.2 to 46.2)	95		0	0.0 (0.0 to 359.3)	--	
	No prior events	17	5.5 (3.2 to 8.9)	222		3	17.1 (3.5 to 49.9)	75		5	3.2 (1.1 to 7.6)	197		0	0.0 (0.0 to 38.6)	--	
	1 prior event	3	14.6 (3.0 to 42.7)	51		0	0.0 (0.0 to 267.3)	--		1	9.9 (0.2 to 54.9)	95		0	0.0 (0.0 to 432.7)	--	
	2+ prior events	2	32.4 (0.8 to 180.4)	327		0	--	--		0	0.0 (0.0 to 192.7)	--		0	0.0 (0.0 to 2118.5)	--	
Moderate/Severe COPD exacerbation[4]		3297	1.00 (0.95 to 1.05)	--		112	0.60 (0.46 to 0.79)	--		1229	0.77 (0.71 to 0.84)	--		46	0.41 (0.29 to 0.58)	--	
Mortality	All cause	96	28.9 (23.4 to 35.3)	--	2.66%	9	47.4 (21.7 to 89.9)	--	3.32%	49	29.5 (21.8 to 39.0)	--	2.41%	13	122.9 (65.4 to 210.1)	--	6.67%

[1] Currently exposed defined as exposure time starting from the index date and continuing until the earliest of discontinuation, censoring or switching.
[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.
[3] Counts and incidence include first ever events (only) following initiation.
[4] Counts and incidence include all events following initiation.

Incidence of outcomes of interest whilst currently exposed [1] to UMEC or UMEC/VI therapy
CPRD GOLD-HES-ONS Cohort

Outcomes of interest recorded in primary and/or secondary care data		UMEC with possible "on-label" prescribing				UMEC with possible "off-label" prescribing				UMEC/VI with possible "on-label" prescribing				UMEC/VI with possible "off-label" prescribing			
		No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.	No. patients	Incidence rate (95% CI)	Time to first event (in days)	Prop.
All patients		494				53				462				50			
Any Myocardial infarction (MI)[2]	Total	5	8.6 (1.8 to 25.3)	136		0	0.0 (0.0 to 136.6)	--		2	6.0 (0.7 to 21.5)	214.5		0	0.0 (0.0 to 134.7)	--	
	Any prior events	2	43.0 (1.1 to 239.5)	136		0	0.0 (0.0 to 2307.1)	--		0	0.0 (0.0 to 182.8)	--		0	0.0 (0.0 to 594.6)	--	
	No prior events	3	6.2 (0.7 to 22.3)	211		0	0.0 (0.0 to 145.2)	--		2	6.3 (0.8 to 22.9)	214.5		0	0.0 (0.0 to 174.2)	--	
	1 prior event	0	0.0 (0.0 to 242.1)	--		0	0.0 (0.0 to 2307.1)	--		0	0.0 (0.0 to 221.9)	--		0	0.0 (0.0 to 3905.4)	--	
	2+ prior events	2	124.5 (3.2 to 693.8)	136		0	--	--		0	0.0 (0.0 to 1037.2)	--		0	0.0 (0.0 to 701.4)	--	
MI without concomitant use of beta-blockers[2]	Total	3	6.8 (0.8 to 24.6)	211		0	0.0 (0.0 to 149.3)	--		1	3.6 (0.1 to 19.9)	226		0	0.0 (0.0 to 191.2)	--	
	Any prior events	0	0.0 (0.0 to 459.5)	--		0	--	--		0	0.0 (0.0 to 417.1)	--		0	0.0 (0.0 to 6770.7)	--	
	No prior events	3	7.0 (0.8 to 25.3)	211		0	0.0 (0.0 to 149.3)	--		1	3.7 (0.1 to 20.6)	226		0	0.0 (0.0 to 196.7)	--	
	1 prior event	0	0.0 (0.0 to 493.2)	--		0	--	--		0	0.0 (0.0 to 429.1)	--		0	0.0 (0.0 to 7972.6)	--	
	2+ prior events	0	0.0 (0.0 to 6736.8)	--		0	--	--		0	0.0 (0.0 to 14970.7)	--		0	0.0 (0.0 to 44912.1)	--	
MI with concomitant use of beta-blockers[2]	Total	2	18.7 (0.5 to 104.1)	136		0	0.0 (0.0 to 1605.9)	--		1	17.9 (0.5 to 99.7)	203		0	0.0 (0.0 to 456.3)	--	
	Any prior events	2	65.6 (1.7 to 365.6)	136		0	0.0 (0.0 to 2307.1)	--		0	0.0 (0.0 to 325.4)	--		0	0.0 (0.0 to 651.8)	--	
	No prior events	0	0.0 (0.0 to 96.4)	--		0	0.0 (0.0 to 5283.8)	--		1	22.5 (0.6 to 125.1)	203		0	0.0 (0.0 to 1520.7)	--	
	1 prior event	0	0.0 (0.0 to 475.6)	--		0	0.0 (0.0 to 2307.1)	--		0	0.0 (0.0 to 459.5)	--		0	0.0 (0.0 to 7655.5)	--	
	2+ prior events	2	133.6 (3.4 to 744.6)	136		0	--	--		0	0.0 (0.0 to 1114.4)	--		0	0.0 (0.0 to 712.5)	--	
Any stroke[2]	Total	19	38.3 (20.4 to 65.4)	105		0	0.0 (0.0 to 136.6)	--		11	11.9 (3.2 to 30.5)	242		2	74.2 (9.0 to 268.1)	179.5	
	Any prior events	15	377.5 (172.6 to 716.6)	91		0	0.0 (0.0 to 1657.3)	--		7	104.8 (12.7 to 378.6)	158		1	349.5 (8.8 to 1947.4)	2	
	No prior events	4	12.7 (3.5 to 32.4)	190.5		0	0.0 (0.0 to 148.8)	--		4	6.3 (0.8 to 22.8)	335.5		1	41.5 (1.1 to 231.3)	357	
	1 prior event	3	206.1 (25.0 to 744.4)	72		0	0.0 (0.0 to 4491.2)	--		0	0.0 (0.0 to 429.8)	--		0	0.0 (0.0 to 44912.1)	--	
	2+ prior events	12	495.2 (199.1 to 1020.3)	105		0	0.0 (0.0 to 2626.4)	--		7	190.5 (23.1 to 688.1)	158		1	359.9 (9.1 to 2005.0)	2	
Stroke without concomitant use of beta-blockers[2]	Total	17	38.4 (19.2 to 68.7)	105		0	0.0 (0.0 to 149.3)	--		9	10.7 (2.2 to 31.3)	321		0	0.0 (0.0 to 191.2)	--	
	Any prior events	13	391.1 (157.3 to 805.9)	91		0	0.0 (0.0 to 2047.7)	--		5	60.7 (1.5 to 338.3)	163		0	0.0 (0.0 to 2547.0)	--	
	No prior events	4	14.9 (4.1 to 38.1)	190.5		0	0.0 (0.0 to 161.0)	--		4	7.6 (0.9 to 27.4)	335.5		0	0.0 (0.0 to 206.7)	--	
	1 prior event	3	218.6 (26.5 to 789.6)	72		0	0.0 (0.0 to 4990.2)	--		0	0.0 (0.0 to 501.4)	--		0	0.0 (0.0 to 44912.1)	--	
	2+ prior events	10	571.6 (185.6 to 1333.9)	105		0	0.0 (0.0 to 3472.6)	--		5	109.8 (2.8 to 611.5)	163		0	0.0 (0.0 to 2700.1)	--	
Stroke with concomitant use of beta-blockers[2]	Total	2	37.7 (4.6 to 136.1)	179		0	0.0 (0.0 to 1605.9)	--		2	17.8 (0.5 to 99.1)	153		2	261.3 (31.6 to 943.8)	179.5	
	Any prior events	2	336.5 (40.7 to 1215.5)	179		0	0.0 (0.0 to 8692.7)	--		2	382.5 (9.7 to 2130.9)	153		1	707.8 (17.9 to 3943.9)	2	
	No prior events	0	0.0 (0.0 to 78.2)	--		0	0.0 (0.0 to 1969.8)	--		0	0.0 (0.0 to 68.8)	--		1	160.2 (4.1 to 892.6)	357	
	1 prior event	0	0.0 (0.0 to 6637.3)	--		0	0.0 (0.0 to 44912.1)	--		0	0.0 (0.0 to 3007.5)	--		0	--	--	
	2+ prior events	2	371.2 (45.0 to 1340.9)	179		0	0.0 (0.0 to 10778.9)	--		2	720.4 (18.2 to 4013.9)	153		1	707.8 (17.9 to 3943.9)	2	
Any newly diagnosed congestive heart failure (CHF)**		5	15.7 (5.1 to 36.6)	206		0	0.0 (0.0 to 152.2)	--		5	15.9 (5.2 to 37.0)	260		2	77.5 (9.4 to 280.1)	254	
Newly diagnosed CHF without concomitant use of beta-blockers[3]		5	17.9 (5.8 to 41.8)	206		0	0.0 (0.0 to 164.4)	--		2	7.4 (0.9 to 26.6)	407.5		1	51.8 (1.3 to 288.8)	56	
Newly diagnosed CHF with concomitant use of beta-blockers[3]		0	0.0 (0.0 to 92.5)	--		0	0.0 (0.0 to 2047.7)	--		3	68.2 (14.1 to 199.3)	201		1	153.8 (3.9 to 856.9)	452	
Pneumonia[2]	Total	20	59.2 (36.2 to 91.4)	193.5		5	155.9 (42.5 to 399.1)	93.5		15	42.1 (23.0 to 70.6)	168		3	111.0 (22.9 to 324.3)	314	
	Any prior events	8	204.8 (88.4 to 403.5)	135.5		1	190.8 (4.8 to 1063.2)	288		9	177.5 (76.6 to 349.7)	195		1	92.5 (2.3 to 515.2)	314	
	No prior events	12	40.2 (20.8 to 70.1)	221		4	146.9 (30.3 to 429.4)	73		6	20.9 (7.7 to 45.4)	106		2	123.3 (14.9 to 445.5)	219	
	1 prior event	7	219.9 (88.4 to 453.1)	147		1	195.3 (4.9 to 1088.3)	288		6	131.5 (42.7 to 306.8)	214		1	165.8 (4.2 to 923.8)	314	
	2+ prior events	1	138.2 (3.5 to 770.3)	62		0	0.0 (0.0 to 30621.9)	--		3	425.4 (87.7 to 1243.1)	95		0	0.0 (0.0 to 771.2)	--	
Moderate/Severe COPD exacerbation[4]		527	1.53 (1.36 to 1.72)	--		27	0.96 (0.61 to 1.51)	--		414	1.25 (1.08 to 1.44)	--		7	0.26 (0.12 to 0.54)	--	
Mortality	All cause	13	37.4 (19.9 to 63.9)	--	2.63%	5	185.3 (60.2 to 432.4)	--	9.43%	16	47.3 (27.0 to 76.8)	--	3.46%	3	109.6 (22.6 to 320.2)	--	6.00%
	Cardiovascular	3	8.6 (1.8 to 25.2)	--	0.61%	1	37.0 (0.9 to 206.3)	--	1.89%	5	14.8 (4.8 to 34.5)	--	1.08%	1	36.5 (0.9 to 203.5)	--	2.00%

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[2] Counts include first and subsequent events, whilst incidence rate considers only the first occurrence following initiation.
[3] Counts and incidence include first ever events (only) following initiation.
[4] Counts and incidence include all events following initiation.

Treatment patterns of inhaled COPD maintenance therapies in the first 12 months[1] following initiation of UMEC and UMEC/VI

CPRD-GOLD+THIN cohort

		UMEC (n=3240)			UMEC/VI (n=1822)		
		No.	(%)	Mean (SD) time in days to first change	No.	(%)	Mean (SD) time in days to first change
No concomitant use of another maintenance therapy at initiation	All[1]	1,047	[redacted]		1,478	[redacted]	
	Continuous user	371	35.43		655	44.32	
	Augmenter	32	3.06	110.69 (65.64)	32	2.17	118.19 (72.01)
	Immediate switcher	114	10.89	96.17 (66.68)	249	16.85	120.67 (88.81)
	Discontinuer	530	50.62	106.52 (98.52)	542	36.67	111.34 (95.92)
	True discontinuer	216	40.75	96.15 (98.22)	177	32.66	84.42 (89.74)
	Discontinuer with drug hiatus	279	52.64	121.26 (100.72)	359	66.24	125.54 (96.54)
	Discontinuer with latent switch	35	6.60	53.11 (40.95)	6	1.11	55.83 (31.49)
Concomitant use of another maintenance therapy at initiation	All[1]	2,193	[redacted]		344	[redacted]	
	Continuous use of both drugs	1,116	50.89		22	6.40	
	Discontinuation of index drug only	553	25.22	143.24 (105.92)	115	33.43	87.25 (81.83)
	Discontinuation of concomitant drug only	364	16.60	114.74 (99.37)	148	43.02	68.39 (70.39)
	Discontinuation of both drugs	160	7.30	125.36 (97.76)	59	17.15	87.27 (69.57)

1 Treatment patterns only considered in patients with at least 12 months follow-up after initiation

Adherence to UMEC and UMEC/VI therapy in the first 12 months[1] following initiation of UMEC and UMEC/VI

CPRD-GOLD+THIN cohort

		UMEC		UMEC/VI	
		No.[2]	Proportion[2]	No.[2]	Proportion[2]
Medication Possession Ratio (MPR)	Total patients[1]	2,716		1,432	
	mean (SD)	0.92	0.75	0.99	1.43
	≥80%	1,734	63.84	921	64.32
	<80%	982	36.16	511	35.68
Proportion Days Covered (PDC)	Total patients[1]	3,240		1,822	
	mean (SD)	0.63	0.33	0.55	0.34
	≥80%	1,332	41.11	599	32.88
	<80%	1,908	58.89	1,223	67.12

1 Adherence only measured in patients with at least 12 months follow-up after initiation.

2 Unless otherwise specified.

Characteristics of patients adherent and non-adherent to UMEC and UMEC/VI therapy in the first 12 months[1] following initiation, where adherence is defined using Medication Possession Ratio and Proportion of Days Covered
CPRD-GOLD+THIN cohort

		UMEC								UMEC/VI							
		adherent (MPR≥80%)		non-adherent (MPR<80%)		adherent (PDC≥80%)		non-adherent (PDC<80%)		adherent (MPR≥80%)		non-adherent (MPR<80%)		adherent (PDC≥80%)		non-adherent (PDC<80%)	
		No.[2]	Proportion[2]	No.[2]	Proportion[2]	No.[2]	Proportion[2]	No.[2]	Proportion[2]	No.[2]	Proportion[2]	No.[2]	Proportion[2]	No.[2]	Proportion[2]	No.[2]	Proportion[2]
Total[1]		1,734		982		1,332		1,908		921		511		599		1,223	
Demographics at baseline																	
Age (in years) at index date	mean (SD)	68.74	10.46	67.01	10.92	68.42	10.26	68.05	10.97	69.29	10.22	67.47	10.23	69.57	10.40	67.81	10.49
	≥65 years	1,174	67.70	606	61.71	889	66.74	1,247	65.36	647	70.25	322	63.01	422	70.45	799	65.33
	<65 years	560	32.30	376	38.29	443	33.26	661	34.64	274	29.75	189	36.99	177	29.55	424	34.67
	<18 years																
	18-64 years	560	32.30	376	38.29	443	33.26	661	34.64	274	29.75	189	36.99	177	29.55	424	34.67
Gender	male	848	48.90	483	49.19	670	50.30	900	47.17	502	54.51	271	53.03	321	53.59	624	51.02
	female	886	51.10	499	50.81	662	49.70	1,008	52.83	419	45.49	240	46.97	278	46.41	599	48.98
Smoking status	current smoker	752	43.37	440	44.81	565	42.42	837	43.87	373	40.50	207	40.51	255	42.57	479	39.17
	ex-smoker	834	48.10	467	47.56	661	49.62	904	47.38	484	52.55	269	52.64	302	50.42	637	52.09
	no/never smoker	148	8.54	75	7.64	106	7.96	167	8.75	64	6.95	35	6.85	42	7.01	107	8.75
	missing[3]																
Body Mass Index (kg/m^2)	mean (SD)	28.08	6.45	27.82	6.48	28.03	6.63	27.94	6.30	28.50	6.42	29.03	6.39	28.19	6.45	28.77	6.29
	underweight <18.5	75	4.38	49	5.04	65	4.94	73	3.87	38	4.16	38	1.39	28	4.74	166	2.56
	normal 18.5-24.9	505	29.48	291	29.94	387	29.38	567	30.08	239	26.18	129	25.60	166	28.09	318	26.22
	overweight 25.0-29.9	559	32.63	310	31.89	427	32.42	629	33.37	300	32.86	186	36.90	196	33.16	411	33.88
	obese ≥30	574	33.51	322	33.13	438	33.26	616	32.68	336	36.80	182	36.11	201	34.01	453	37.35
	missing[3]	21	1.21	10	1.02	15	1.13	23	1.21	8	0.87	7	1.37	8	1.34	10	0.82
Area based deprivation[4]	Q1 (least deprived)	33	16.42	12	22.64	18	11.54	37	24.03	35	19.77	11	17.19	19	15.57	46	21.20
	Q2	39	19.40	7	13.21	31	19.87	27	17.53	36	20.34	11	17.19	24	19.67	43	19.82
	Q3	51	25.37	14	26.42	43	27.56	36	23.38	30	16.95	16	25.00	26	21.31	35	16.13
	Q4	43	21.39	12	22.64	34	21.79	30	19.48	42	23.73	17	26.56	33	27.05	46	21.20
	Q5 (most deprived)	35	17.41	8	15.09	30	19.23	24	15.58	34	19.21	9	14.06	20	16.39	47	21.66
	missing[3]	1,533	88.41	929	94.60	1,176	88.29	1,754	91.93	744	80.78	447	87.48	477	79.63	1,006	82.26
COPD burden at baseline and within year prior to index date																	
COPD exacerbations (recorded in primary care only)	Rate per xxxx person years (95% CI)	1.11 (1.06, 1.16)		1.09 (1.02, 1.15)		1.10 (1.05, 1.16)		1.05 (1.00, 1.10)		0.81 (0.75, 0.87)		0.67 (0.61, 0.75)		0.76 (0.69, 0.83)		0.77 (0.72, 0.82)	
	0 events	793	45.73	489	49.80	623	46.77	930	48.74	519	56.35	291	56.95	348	58.10	678	55.44
	1 event	446	25.72	223	22.71	323	24.25	486	25.47	230	24.97	141	27.59	150	25.04	314	25.67
	2+ events	495	28.55	270	27.49	386	28.98	492	25.79	172	18.68	79	15.46	101	16.86	231	18.89
Dyspnoea (MRC Grade)	mean (SD)	3	0.92	3	0.98	3	2.75	1	0.97	3	0.90	3	0.85	3	0.87	3	0.89
	MRC Grade 1	70	5.14	60	7.65	56	5.24	107	7.20	39	5.56	25	6.31	22	4.84	63	6.70
	MRC Grade 2	493	36.20	277	35.33	369	34.55	560	37.69	281	40.03	164	41.41	190	41.76	377	40.06
	MRC Grade 3	484	35.54	243	30.99	389	36.42	468	31.49	244	34.76	141	35.61	163	35.82	328	34.86
	MRC Grade 4	272	19.97	182	23.21	225	21.07	302	20.32	120	17.09	64	16.16	69	15.16	157	16.68
	MRC Grade 5	43	3.16	22	2.81	29	2.72	49	3.30	18	2.56	2	0.51	11	2.42	16	1.70
	missing[3]	372	21.45	198	20.16	264	19.82	422	22.12	219	23.78	115	22.50	144	24.04	282	23.06
FEV_1 percent predicted	mean (SD)	57.57	19.36	59.21	18.75	56.93	19.31	60.11	18.99	58.76	19.88	61.29	17.49	58.93	20.23	60.89	18.51
	mild, Grade 1 (≥80%)	146	11.90	81	12.05	103	10.97	181	13.80	94	14.01	50	13.02	58	13.58	134	14.68
	moderate, Grade 2 (≥50% to <80%)	627	51.10	389	57.89	485	51.65	733	55.87	352	52.46	238	61.98	230	53.86	527	57.72
	severe, Grade 3 (≥30% to <50%)	381	31.05	161	23.96	291	30.99	334	25.46	182	27.12	83	21.61	112	26.23	213	23.33
	very severe, Grade 4 (<30%)	73	5.95	41	6.10	60	6.39	64	4.88	43	6.41	13	3.39	27	6.32	39	4.27
	missing[3]	507	29.24	310	31.57	393	29.50	596	31.24	250	27.14	127	24.85	172	28.71	310	25.35
FEV_1/FVC ratio	mean (SD)	58.61	16.02	58.92	16.36	58.12	16.65	59.59	15.04	59.97	15.40	60.95	12.32	59.79	15.59	61.04	13.64
	<70%	810	80.52	439	79.39	626	82.26	839	77.40	474	77.70	257	78.12	307	79.53	613	75.87
	≥70%	196	19.48	114	20.61	135	17.74	245	22.60	136	22.30	72	21.88	79	20.47	195	24.13
	missing[3]	728	41.98	429	43.69	571	42.87	824	43.19	311	33.77	182	35.62	213	35.56	415	33.93
Past history of comorbidities																	
Cardio- and cerebrovascular disease (ever before)		1,126	64.94	602	61.30	863	64.79	1,207	63.26	610	66.23	334	65.36	402	67.11	775	63.37
Beta-blocker prescribing (in year prior to index date)		298	17.19	184	18.74	207	15.54	366	19.18	187	20.30	119	23.29	115	19.20	273	22.32
Pneumonia (ever before)		122	7.04	72	7.33	97	7.28	136	7.13	72	7.82	39	7.63	47	7.85	81	6.62
Gastroesophageal reflux disease (ever before)		379	21.86	249	25.36	282	21.17	462	24.21	201	21.82	123	24.07	122	20.37	303	24.78
Diabetes (ever before)		339	19.55	187	19.04	253	18.99	357	18.71	185	20.09	103	20.16	112	18.70	229	18.72
Acute and chronic renal disease (ever before)		352	20.30	190	19.35	259	19.44	377	19.76	170	18.46	80	15.66	107	17.86	212	17.33
Cancer (ever before)		239	13.78	121	12.32	173	12.99	271	14.20	113	12.27	75	14.68	80	13.36	157	12.84
Respiratory medication use in year prior to index date																	
SABD[5]	1+ prescription(s)[6]	1,534	88.47	845	86.05	1,182	88.74	1,636	85.74	752	81.65	417	81.60	492	82.14	986	80.62
	4+ prescriptions[6]	1,149	66.26	557	56.72	929	69.74	1,044	54.72	495	53.75	217	42.47	330	55.09	561	45.87
ICS	Any ICS	1,293	74.57	693	70.57	1,041	78.15	1,285	67.35	426	46.25	184	36.01	251	41.90	538	43.99
	ICS (in a single device)	130	7.50	60	6.11	99	7.43	130	6.81	88	9.55	38	7.44	61	10.18	112	9.16
	ICS/LABA (fixed combination)	1,213	69.95	653	66.50	980	73.57	1,198	62.79	358	38.87	155	30.33	204	34.06	451	36.88
	ICS/SABA (fixed combination)																
LABA	Any	1,271	73.30	678	69.04	1,020	76.58	1,263	66.19	464	50.38	228	44.62	282	47.08	599	48.98
	LABA (in a single device)	76	4.38	30	3.05	51	3.83	89	4.66	123	13.36	77	15.07	89	14.86	161	13.16
	ICS/LABA (fixed combination)	1,213	69.95	653	66.50	980	73.57	1,198	62.79	358	38.87	155	30.33	204	34.06	451	36.88
	LABA/LAMA (fixed combination)	18	1.04	16	1.63	12	0.90	25	1.31	18	1.95	17	3.33	11	1.84	36	2.94
LAMA	Any	1,113	64.19	609	62.02	908	68.17	1,058	55.45	498	54.07	251	49.12	333	55.59	591	48.32
	LAMA (in a single device)	1,110	64.01	604	61.51	906	68.02	1,051	55.08	492	53.42	245	47.95	330	55.09	579	47.34
	LABA/LAMA (fixed combination)	18	1.04	16	1.63	12	0.90	25	1.31	18	1.95	17	3.33	11	1.84	36	2.94
Theophylline (or derivatives)		108	6.23	53	5.40	82	6.16	98	5.14	26	2.82	7	1.37	12	2.00	31	2.53
Roflumilast		0	0.00	0	0.00	0	0.00	0	0.00								
OCS	Chronic use[7]	140	8.07	71	7.23	103	7.73	129	6.76	52	5.65	22	4.31	27	4.51	61	4.99

1 Adherence only measured in patients with at least 12 months follow-up after initiation.
2 Unless otherwise specified.
3 Percentages were calculated separately for those with missing and without missing data
4 Area based deprivation is measured using patient-level Townsend quintile
5 Includes the following asthma "reliever" medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA.
6 Categories are not mutually exclusive.
7 Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days.

NB. This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

Treatment patterns of inhaled COPD maintenance therapies in the first 12 months[1] following initiation of UMEC and UMEC/VI in patients with and without a recorded COPD diagnosis

CPRD-GOLD+THIN cohort

		Patients with a recorded COPD diagnosis "possible on label"						Patients without a recorded COPD diagnosis "possible off label"					
		UMEC			UMEC/VI			UMEC			UMEC/VI		
		No.	(%)	Mean (SD) time in days to first change	No.	(%)	Mean (SD) time in days to first change	No.	(%)	Mean (SD) time in days to first change	No.	(%)	Mean (SD) time in days to first change
No concomitant use of another maintenance therapy at initiation	All[1]	954	[redacted]		1,365	[redacted]		93			113		
	Continuous user	342	35.85		623	45.64		29	31.18		32	28.32	
	Augmenter	29	3.04	106.86 (66.78)	28	2.05	128.54 (71.06)	3	3.23	147.67 (45.83)	4	3.54	45.75 (11.90)
	Immediate switcher	104	10.90	97.87 (68.93)	227	16.63	121.96 (89.64)	10	10.75	78.50 (32.84)	22	19.47	107.45 (80.36)
	Discontinuer	479	50.21	108.20 (100.39)	487	35.68	115.59 (97.31)	51	54.84	90.75 (77.98)	55	48.67	73.73 (73.12)
	True discontinuer	185	38.62	98.90 (101.21)	142	29.16	89.42 (93.93)	31	60.78	79.74 (77.34)	35	63.64	64.14 (67.62)
	Discontinuer with drug hiatus	263	54.91	121.64 (101.91)	339	69.61	127.61 (97.09)	16	31.37	114.94 (81.00)	20	36.36	90.50 (80.91)
	Discontinuer with latent switch	31	6.47	49.74 (37.16)	6	1.23	55.83 (31.49)	4	7.84	79.25 (64.59)	0	0.00	
Concomitant use of another maintenance therapy at initiation	All[1]	2,093	[redacted]		319	[redacted]		100			25		
	Continuous use of both drugs	1,075	51.36		21	6.58		41	41.00		1	4.00	
	Discontinuation of index drug only	523	24.99	142.16 (105.16)	101	31.66	88.84 (81.74)	30	30.00	162.03 (118.79)	14	56.00	75.79 (84.67)
	Discontinuation of concomitant drug only	341	16.29	114.28 (99.17)	141	44.20	69.73 (71.69)	23	23.00	121.48 (104.33)	7	28.00	41.43 (23.61)
	Discontinuation of both drugs	154	7.36	122.34 (97.30)	56	17.55	88.46 (71.22)	6	6.00	203.00 (81.55)	3	12.00	65.00 (8.19)

1 Treatment patterns only considered in patients with at least 12 months follow-up after initiation.

Adherence to UMEC and UMEC/VI therapy in the first 12 months[1] following initiation in patients with and without a recorded COPD diagnosis

CPRD-GOLD+THIN cohort

		Patients with a recorded COPD diagnosis "possible on label"				Patients without a recorded COPD diagnosis "possible off label"			
		UMEC		UMEC/VI		UMEC		UMEC/VI	
		No.[2]	Proportion[2]	No.[2]	Proportion[2]	No.[2]	Proportion[2]	No.[2]	Proportion[2]
Medication Possession Ratio (MPR)	Total patients[1]	2,563		1,349		153		83	
	mean (SD)	0.92	0.76	1.00	1.47	0.97	0.52	0.90	0.32
	≥80%	1,635	63.79	866	64.20	99	64.71	55	66.27
	<80%	928	36.21	483	35.80	54	35.29	28	33.73
Proportion Days Covered (PDC)	Total patients[1]	3,047		1,684		193		138	
	mean (SD)	0.63	0.33	0.56	0.34	0.57	0.34	0.41	0.34
	≥80%	1,267	41.58	568	33.73	65	33.68	31	22.46
	<80%	1,780	58.42	1,116	66.27	128	66.32	107	77.54

1 Adherence only measured in patients with at least 12 months follow-up after initiation.

2 Unless otherwise specified.

ANNEX 2: Study Protocol and Statistical Analysis Plan

Document ID	
1	Study Protocol: Epi-Protect_WWE117397
2	Statistical Analysis Plan (SAP)

TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	WWE117397: Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting- Amendment 2

Compound Number:	GSK573719, GW642444
Development Phase	IV
Effective Date:	09-DEC-2019
Subject:	Drug Utilization Study, Post-Authorization Safety Study, Chronic Obstructive Pulmonary Disease, Electronic Medical Records, Long-Acting Muscarinic Antagonists, Long-Acting Beta-2-Agonists
Author(s):	PPD

PASS information

Title	Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting
Protocol version identifier	1.2
Date of last version of protocol	24 June 2016
EU PAS register number	ENCEPP/SDPP/7761
Active substance	Umeclidinium bromide/Vilanterol trifenatate (UMEC/VI) ATC R03AL03: Adrenergics in combination with anticholinergics Umeclidinium bromide (UMEC) ATC R03BB07: Anticholinergics
Medicinal product	UMEC (Incruse Ellipta™Rolufta Ellipta™), UMEC/VI (Anoro Ellipta™ /Laventair Ellipta™) OTHER long-acting bronchodilators will be included in the study analysis, provided they will be available to prescribers, inclusive but not limited to medications containing: Tiotropium Glycopyrronium Glycopyrronium/Indacaterol Aclidinium Indacaterol Formoterol Salmeterol

Product reference	The EU Marketing Authorisation numbers are: Anoro Ellipta EU/1/14/898/001 EU/1/14/898/002 EU/1/14/898/003 Laventair Ellipta: EU/1/14/899/001 EU/1/14/899/002 EU/1/14/899/003 Incruse Ellipta: EU/1/14/922/001 EU/1/14/922/002 EU/1/14/922/003 Rolufta Ellipta: EU/1/17/1174/001 EU/1/17/1174/002 EU/1/17/1174/003
Procedure number	Incruse Ellipta: EMEA/H/C/002809/0000 Rolufta Ellipta: EMEA/H/C/004654/0000 Anoro Ellipta: EMEA/H/C/002751/0000/ Laventair Ellipta: EMEA/H/C/003754
Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford Middlesex, TW8 9GS UK
Joint PASS	No

Research question and objectives	In the initial period of up to 24-months from the start of UMEC/VI and UMEC availability in the UK, we will identify patients newly prescribed long-acting bronchodilators (LABD) from a set of the UK primary care Electronic Medical Records (EMR) databases and conduct drug utilization review focusing on the following aims: Objective 1: In new users of UMEC/VI, UMEC, or other LABD report the proportion of patients with possible off-label prescribing and characterize them, using information available prior to and at the time of index prescription initiation, in respect to patient demographics, disease burden, co-morbidity, and COPD or asthma medication use. Objective 2: In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality, pneumonia, and rate of exacerbations of COPD during follow-up. Objective 3: In new users of UMEC/VI or UMEC describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up.
Country(-ies) of study	United Kingdom
Author	PPD Director, Worldwide Epidemiology R&D Projects, Clinical Platforms & Sciences GlaxoSmithKline Building 9, Iron Bridge Road, Stockley Park West, Uxbridge, Middlesex, UB11 1BT Tel. PPD PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS UK
MAH contact person	PPD Manager, Respiratory Therapeutic Group Global Regulatory Affairs GlaxoSmithKline Research & Development Ltd

TABLE OF CONTENTS

PAGE

1. LIST OF ABBREVIATIONS

AE	Adverse Event
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
CAG	Confidentiality Advisory Group
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CPRD-GOLD	CPRD database derived from Vision GP software
CV	Cardiovascular
CVD	Cardiovascular Disease
EMR	Electronic Medical Records
EHR	Electronic Healthcare Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU-RMP	European Union – Risk Management Plan
FEV1	Forced Expiratory Volume (in one second)
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GSK	GlaxoSmithKline
HES	Hospital Episodes Statistics
HRA	Health Research Authority
ICS	Inhaled Corticosteroids
ISAC	Independent Scientific Advisory Committee
LABA	Long-Acting Beta2-Agonists
LABD	Long-Acting Bronchodilator
LAMA	Long-Acting Muscarinics Antagonist
LRTI	Lower Respiratory Tract Infections
LTRA	Leukotriene Receptor Antagonists
MAH	Marketing Authorization Holder
MINAP	Myocardial Ischaemia National Audit Project
MPR	Medication Possession Ratio
MRC	Medical Research Council
OCS	Oral Corticosteroids
ONS	Office for National Statistics
PASS	Post Authorisation Safety Study
PDC	Proportion of Days Covered
SABA	Short-Acting Beta2-Agonists
SABD	Short-Acting Bronchodilators
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonists
SD	Standard Deviation
THIN	The Health Information Network

UK	United Kingdom
UMEC	Umeclidinium bromide
VI	Vilanterol trifenatate

Trademark Information

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2. RESPONSIBLE PARTIES

Sponsor

The Marketing Authorization Holder (MAH) will serve as the sponsor of this study. It is the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

Role/Title: Manager, Respiratory Therapeutic Group, Global Regulatory Affairs

Name: PPD

Address: GlaxoSmithKline Research & Development Ltd.

Study Coordination

The MAH has contracted with Clinical Practice Research Datalink (CPRD), a research organisation specialising in observational studies and a managing body of the CPRD database, as a partner to provide scientific leadership and to conduct the study. The CPRD will conduct the study with review and input from the MAH. A Scientific Committee (SC) will provide expert medical and epidemiological input and advice, review the interim and final reports and monitor the overall study progress through regular teleconferences and meetings. The responsibilities of the SC are further described below.

CPRD:
5th Floor,
151 Buckingham Palace Road,
London,
SW1W 9SZ

Study Scientific Committee

The SC consists of epidemiologists and clinicians with expertise in designing observational studies in EMR databases. It consists of three external members with relevant clinical and epidemiologic experience, as well as three GSK employees, and two representatives from the CPRD. This group is assisting with protocol development, and will develop and review the statistical analysis plan, provide technical input during study development, and assist with interpretation and dissemination of study results. Further clinical and methodological advice can be sought with other members of academia on an ad-hoc basis.

The SC will convene on a regular basis in association with important study milestones: protocol development, statistical plan approval, annual interim analysis and final study report.

External Members

PPD (Professor, Head of the Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine).

PPD (Professor, Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, The Netherlands)

Dr PPD (Consultant in Chest Medicine and Clinical Senior Lecturer in Respiratory Epidemiology, Imperial College)

CPRD Members

PPD (Senior Researcher, CPRD)

PPD (Senior Researcher, CPRD)

GSK Members

PPD (Manager, Real World Evidence & Epidemiology)

PPD (Director, Real World Evidence & Epidemiology)

SPONSOR SIGNATORY:

PPD

Robert Reynolds
VP, Epidemiology R&D Value Evidence & Outcomes.

9/20/19
Date

PPD

SPONSOR INFORMATION PAGE

WWEpi Project Identifier:

WWE117397 (GSK Epidemiology: WEUSKOP6679)

GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor Contact Information: Not Applicable

Sponsor Serious Adverse Events (SAE) Contact Information:

Case Management Group,
GCSP –Stockley Park, UK
Email: PPD
Fax: PPD

Regulatory Agency Identifying Number(s): n/a

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Daniel Dedman

Investigator Signature	Date

3. ABSTRACT

Title

Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting

Short title: Retrospective EMR distributed network LABD drug utilization study

Rationale and background

This study primarily aims to collect data reflecting the 'real-world' experience with umeclidinium/vilanterol (UMEC/VI) and umeclidinium (UMEC) in the post-approval setting. UMEC/VI and UMEC as well as other medications containing only long-acting bronchodilators (LABD) are indicated for the treatment of Chronic Obstructive Pulmonary Disease (COPD). They are not indicated for the treatment of asthma without a concomitant treatment with inhaled steroids (ICS); such use is considered off-label. In addition, both LABD classes of drugs, the long-acting beta2-agonists (LABA) and long-acting antimuscarinics (LAMA) have been associated with some increased risk of cardiovascular events that warrants further investigation. This study will describe the patient population newly prescribed with 1) UMEC/VI, 2) UMEC and 3) other LABD and determine the frequency of possible off label prescribing as well as evaluate feasibility of undertaking potential future risk-benefit studies.

This study fulfils a voluntary commitment made in the European Union – Risk Management Plans (EU-RMP) for UMEC/VI and UMEC to examine the utilisation (including possible off-label prescribing) of these medications in a real-world, post-approval setting.

Research question and objectives

In the initial post-approval period of up to 24 months from the start of UMEC/VI and UMEC availability in the UK, we will identify patients newly prescribed long-acting bronchodilators (LABD) from a set of the UK primary care Electronic Medical Records (EMR) databases and conduct drug utilization review focusing on the following aims:

Objective 1: In new users of UMEC/VI, UMEC, or other LABD report the proportion of patients with possible off-label prescribing and characterize them, using information available prior to and at the time of index prescription initiation, in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Objective 2: In new users of UMEC/VI or UMEC quantify incidence of major cardiovascular and cerebrovascular events, mortality, pneumonia, and rate of exacerbations of COPD during follow-up.

Objective 3: In new users of UMEC/VI or UMEC with 12 or more months of follow-up following initiation, describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up.

Study design

Retrospective longitudinal non-interventional observational study of new users of UMEC/VI, UMEC, or other LABD and followed-up from their index prescription date until censoring at death, leaving GP practice, the practice's last collection date or end of follow-up on June 30, 2017.

Population

To address Objective 1, new users of UMEC/VI, UMEC or other LABD will be included, while Objectives 2 and 3 will be limited to new users of UMEC/VI or UMEC only.

Variables

Exposures

We will identify all new users of UMEC/VI, UMEC or other LABD during the identification period of July 1, 2014 to June 30, 2016, corresponding with a period up to 24 months of UMEC/VI or UMEC availability to prescribers in the UK (See Section 8.3.1 for exposure definition). New use is defined as never having had a prescription for the same medication (UMEC/VI, UMEC or specific active substance of other LABD) ever recorded in the past. The first day of the first qualifying new use prescriptions will be the index date. Prior or concomitant use of respiratory medications containing a *different active substance to the one being initiated* will be allowed. A single patient is able to contribute more than one qualifying new use medication (UMEC/VI, UMEC or other LABD) during the exposure identification period of July 1, 2014 to June 30, 2016 if they meet the definition of new use for multiple medications.

The other LABD group will be analysed as a single combined group, and where appropriate and sample size allows, stratified as LAMA, LABA, and LAMA/LABA. No other LABD drugs will be analysed individually.

Outcomes

To address Objective 1, we will flag possible cases of off-label prescribing by reporting a proportion of new UMEC/VI, UMEC, or other LABD users who were diagnosed with (a) COPD (b) asthma or (c) neither COPD nor asthma. For Objective 2 we will quantify incident events of myocardial infarction, heart failure, or stroke in patients at risk during the follow-up period based on their available history. Further, events of death, pneumonia, and exacerbations of COPD will be counted. For Objective 3 we will describe treatment patterns and adherence to inhalation therapy.

Data sources

Data will be derived from the Clinical Practice Research Datalink (CPRD)-GOLD database and the Health Information Network (THIN) database.

Study size

This is a descriptive study. A sample size of 1,000 new users in each group produces a 95% confidence interval equal to the sample proportion plus or minus 1.3% when the estimated proportion of possible off-label prescribing is 5%. As this study is non-interventional, we cannot influence how many patients will initiate UMEC/VI, UMEC, or other LABD.

Data Analysis

Objective 1: Patients in the new user UMEC/VI, UMEC, or other LABD cohorts will be split according to presence or absence of a respiratory diagnosis record for (a) COPD (b) asthma or (c) neither COPD nor asthma, and described by their demographics, co-morbidity, disease burden, and other COPD or asthma medication use in the period prior to (and including) the initiation of their treatment with UMEC/VI, UMEC, or other LABD.

Objective 2: In new users of UMEC/VI or UMEC, we will enumerate count and incidence (new events/person-time) of myocardial infarction, heart failure, or stroke as well as events of death, pneumonia, and rate of exacerbations of COPD during follow-up. All analyses will be descriptive.

Objective 3: Among new users of UMEC/VI or UMEC with 12 or more months of follow-up following initiation, we will describe treatment patterns and adherence to treatment using medication possession ratio during total follow-up and proportion of days covered during the 0-12 months of follow-up.

Milestones

Start of periodic data evaluation: March 2015

Statistical and Operational analysis plan finalised: July 2016

Interim report: February 2018 (Drug utilization, possible off-label prescribing (up to relevant time period achieved)

Final report completed: By Q4 2019 (All objectives)

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	05 August 2016	3; 7; 8.1; 8.2.1.2; 8.3.2.2; 8.3.2.3; 8.7.1.3; 8.7.1.4	Objectives 2 and 3 to be conducted in all new users (not specifically in those with COPD).	There may be differences in the patient characteristics and safety endpoints between patients who are potentially prescribed ANORO off-label and on label users and thus it is valuable to include both populations and stratify results by off label/on label use.
2	05 August 2016	3; 7; 8.1; 8.2.1.2; 8.3.2.2; 8.7.1.3	Objective 2 to be conducted in only UMEC/VI and UMEC cohorts; removing other LABD cohort from this objective.	Objective 2 is a secondary aim of this study, intended to evaluate feasibility of undertaking potential future risk-benefit studies of events that have been associated with the LABA and LAMA class of drugs, such as cardio- and cerebrovascular events and pneumonia. In order to accomplish this, it is planned to descriptively quantify the frequency of these events in our sample of 1,000 UMEC and UMEC/VI users, thus generating inputs for power/sample size calculations for future comparative study protocols, if required. It is not the intention of Objective 2 to serve as a comparative analysis of the risk of these events against users of "other LABD", as this study is neither powered for such comparison nor designed to ensure patient or disease characteristics, which may

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
				influence the risk of these outcomes, is balanced between the "other LABD" group and the UMEC and UMEC/VI groups, respectively. As such, the SSC felt that it was out of scope and scientifically inappropriate for the WWE117397 study to report outputs associated with Objective 2 in the "other LABD" group. GSK is conducting a second post-approval safety study (Study #201038), which is a longitudinal prospective observational non-interventional study specifically designed to address the comparative risk of cardiovascular events of interest versus Tiotropium. This study is prospective in nature and employs appropriate propensity score balanced analysis and adequate study size to detect differences in the study primary endpoints.
3	05 August 2016	3; 8.3.2.1; 8.7.1.2; 8.7.2	Definitions of COPD and asthma edited to reflect diagnosis of these conditions in an EMR database scenario, so as to identify more precisely the primary endpoint	Due to potential delays in the recording of COPD in an EMR database, the definition of COPD was edited to allow capture of cases diagnosed before and after the index medication. Further, the definition of asthma was simplified to better reflect how asthma

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			(possible off-label prescribing).	is captured in an EMR database. Lastly, the group of patients that meet neither the COPD nor asthma definitions will be characterised in an "other category" but will not be further defined as specific respiratory diseases as we expect small patient numbers for specific other respiratory diseases.
4	05 August 2016	3; 8.1; 8.3.1.1	Definition of new user refined to allow patients to qualify for more than one active treatment.	The original protocol allowed patients to enter into the study for only the first qualifying drug (UMEC/VI, UMEC or other LABD). This requirement had the potential to create an immortal time bias within the study population and thus was edited to allow for patients to contribute data for all medications which meet the "new use" definition during the identification period.
5	05 August 2016	3; 8.1; 8.3.1.3; 8.3.2.3; 8.7.1.3; 8.7.1.4 8.7.2	Patient follow-up period and drug exposed period during follow-up redefined; discontinuation incorporated into this definition and removed as part of treatment patterns objective.	The definitions of the total follow-up period until censoring and the drug exposed periods during follow-up have been further refined. This includes simplification of the potential reasons for censoring a patient during follow-up and provides greater detail around exposed person-time for the purposes of calculation of (incidence) rates of study endpoints.
6	05 August	3; 7;	Removed descriptive	There are limitations to using the number of GP

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
	2016	8.3.2.2; 8.3.3; 8.7.1.2; 8.7.1.3; 8.7.1.4;	endpoint "health care resources utilization".	visits as a proxy for health status as each time a record is opened to add information about that visit (i.e. to add lab values, etc), it appears as a consultation and thus there is a potential for misclassification of the true number of GP visits. Further, capturing hospitalizations for causes other than COPD will add limited value since most hospitalization in this population will be for COPD and will therefore be adequately captured in the severe COPD exacerbation endpoint.
7	05 August 2016	3; 6.2; 7; 8.3.2.2; 8.3.3; 8.7.1.3; 8.9	Removed descriptive endpoint lower respiratory tract infections (LRTI) from pneumonia/LRTI category, so that this category represents pneumonia only.	Clinically and technically, using LRTI medical diagnosis codes in the CPRD primary care, electronic health record (EHR) database (used in this study) is likely to a result in a classification of acute exacerbations of COPD (AECOPD) events as LRTI. 1) Clinically, it is estimated that 50-70% of AECOPD are due to LRTI [Millet 2013; Sapey 2006]. Hence, AECOPD represent a substantial proportion of LRTI events among COPD patients and a combined endpoint of LRTI/pneumonia would in fact mostly represent AECOPD/pneumonia events. This was not seen

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
				as desirable, because AECOPD are reported as a separate outcome associated with Objective 2. Moreover, the exposure with respiratory medications may lead to a reduction of AECOPD, whereas incidence of pneumonia is not impacted or increased, depending on the respiratory medications class. Therefore, a composite endpoint of LRTI/pneumonia does not allow for reporting of a specific estimate of physician-recorded pneumonia, which is most of interest as a safety concern. 2) Technically, GPs are recording AECOPD as LRTI without further specification in EHRs. A recently completed validation study conducted in the CPRD compared recorded codes with the original GP records and detected that about 75% of LRTI recordings in COPD patients are actually confirmed as AECOPD (PPV~75%) [Rothnie, 2016]. Thus, in EHR type studies, LRTI is part of the definition used to identify AECOPD and therefore it is not appropriate to have these as separate endpoints.
8	05	8.3.2.2;	Remove acute	There is a high potential to

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
	August 2016	8.7.1.3	worsening of heart failure descriptive endpoint.	misclassify acute worsening of heart failure with an acute exacerbation of COPD in an EMR database. [Valk, 2015] As such, only newly diagnosed heart failure will be described in this study.
9	05 August 2016	8.2; 8.3.2.2; 8.4	Potential linkage to MINAP registry for CVD outcomes removed.	Linkage to the MINAP registry is not necessary in order to adequately capture the CVD events of interest in this study [Herrett, 2013] and requiring this linkage will decrease the number of datasets to potentially include in the distributed network design as not all databases link to MINAP.
10	05 August 2016	8.2; 8.3.2.2; 8.4	Linkage to ONS death registry will be used in Objective 2 in an analysis of cardiovascular death among patients eligible for linkage.	Cardiovascular death is an informative endpoint. However, cardiovascular death cannot be explored in the full study population as not all patients are eligible for linked data. Analysis of this endpoint will therefore be confined to those patients for are eligible for linkage.
11	05 August 2016	8.3.3	Charlson score comorbidity variable removed. Instead, the following comorbidities will be examined at baseline: peripheral vascular disease, gastroesophageal reflux disease, renal disease (acute and chronic),	Charlson score is redundant as it does not provide additional information above the key specific COPD-related morbidities that will individually studied.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			pneumonia, and cancer.	
12	05 August 2016	8.3.3 (Table 4)	Oxygen use removed as a covariate to describe prior COPD medication use at baseline.	Oxygen is poorly recorded in UK EMR and any estimate of oxygen use is likely to be underestimated when using EMR alone.
	05 August 2016	8.3.3 (Table 4)	Leukotriene receptor antagonists (LTRA) and anti-IgE medications removed from medication list in Table 4 (medication use at baseline).	These drugs were removed as they are typically used to treat asthma and the revised definition of asthma does not require medication use.
13	05 August 2016	8.3.3; 8.7.1.3	Including past history of beta-blocker prescribing as a covariate. Stratification of analyses for cardiovascular endpoints in objective 2 by concomitant beta-blocker prescribing.	Patients prescribed beta-blockers are likely to have fewer adverse cardiovascular events. It is therefore important to understand the effects of cardiovascular endpoints conditional on beta-blocker prescribing for patients in the UMEC and UMEC/VI groups for objective 2.
14	05 August 2016	8.3.2; 8.3.2.3; 8.7.1.4	In objective 3, treatment patterns will be explored for inhalation therapies only and only among patients who are not censored 31 to 90 days after their last prescription within the initial 12 months follow-up.	It is not possible to determine whether a patient discontinues if they are censored 31-90 days after their last prescription (see section 8.3.1.3). Inhalation therapies are of greatest interest.
15	05 August	8.3.2; 8.3.2.3;	Treatment patterns for objective 3	Treatment patterns needed to be mutually exclusive

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
	2016	8.7.1.4	have been refined (see Figures 3 and 4 in section 8.3.2.3) and will be examined in first 12 months following index date among patients with a full 12 months of follow-up. Adherence for objective 3 also examined in first 12 months following index date among patients with a full 12 months of follow-up.	and cover all potential treatment changes. Time limit means patients who initiate early in the study period, and are therefore followed up for longer, did not have spuriously high rates of switching, augmentation and discontinuation relative to patients who initiate late and are followed up for less time. Adherence patterns have been changed so that all analyses for objective 3 conducted amongst same group of eligible patients.
16	05 August 2016	8.3.3;	COPD exacerbations at baseline will be identified in two ways (a) using primary-care data for all patients and (b) using primary- and secondary-care data for patients eligible for linkage.	During the recent development of an updated algorithm for identification of COPD exacerbations [Rothnie, 2016], it was established that the CPRD (and thus other primary-care databases) is an insufficient source to identify all instances of hospitalized exacerbations of COPD. Therefore, the most reliable way of capturing COPD exacerbation events is to supplement primary care data with information from secondary care (HES).
17	05 August 2016	8.3.2.2; 8.7.1.3	For objective 2, the primary analysis will identify events using information recorded in primary care, secondary care (HES) and	The most reliable way of capturing cardiovascular, pneumonia, death and COPD exacerbation events is to supplement primary care data with information from secondary care

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			mortality data (ONS). This analysis will be conducted using the subset of patients who are eligible for linkage with HES and ONS data. A secondary analysis will be conducted among all (eligible) patients using information from primary care only.	(HES) and mortality data (ONS). The secondary analysis conducted among all patients will provide information on the extent of under-recording of these events in primary care data. Additionally, as death events are well recorded in primary care data, the secondary analysis of death (where all patients are included) will provide greater confidence in estimates of survival rate.
18	05 August 2016	8.3.3	Removed region covariate used to describe new users of UMEC, UMEC/VI and other LABD.	Region variable not available in all partner databases.
19	05 August 2016	8.3.3	Removed derived variable for COPD severity which classifies patients into GOLD groups A, B, C and D.	Previous studies of COPD using CPRD data suggest a very high proportion of patients will have missing information for this variable.
20	05 August 2016	10	Explanation added in line with SOP 52214 as to why adverse events cannot be reported from this study.	Because this study uses anonymised electronic medical records, the minimum criteria for reporting adverse events is not met. A statement to this effect was added.
21	14 Sept 2018	n/a	'off-label use' has been changed throughout the document to 'possible off-label prescribing'	As we only have information about prescriptions it is more appropriate employ 'possible prescribing' than 'use'.
22	14 Sept 2018	PASS information	The new trade names have been added:	The EMA approve the new tradenames in EU on 10th August 2018.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			Anoro Ellipta Incruse Ellipta Laventair Ellipta Rolufta Ellipta EU authorisation numbers and procedure number have been added for Rolufta Ellipta	Update information for Rolufta Ellipta
23	14 Sept 2018	5	Milestones- Interim report date modified	Interim report was submitted to the EMA as part of the PBRER (Periodic Benefit Risk Evaluation Report of Anoro/Laventair, number 2017N342954) on 23rd February 2018, so the date has been changed accordingly.
24	14 Sept 2018	6.1	We have added: "Only one LAMA, tiotropium, is currently approved as an add on-treatment for asthma for patients who are currently treated with the maintenance combination of ICS/LABA and who experienced one or more severe exacerbations in the previous year."	To reflect the authorisation of tiotropium in September 2014 to be used as an add on therapy to ICS/LABA for the treatment of asthma in patients with asthma exacerbations
25	14 Sept 2018	6.1	E.g. GOLD 2014, has been changed to GOLD 2018	References have been updated to more recent ones
26	14 Sept 2018	6.2	We have added: "This study fulfils a voluntary commitment made in the European Union – Risk	To clarify the intention of a voluntary commitment made in the European Union – Risk Management Plans (EU-RMP)

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			Management Plans (EU-RMP) for UMEC/VI and UMEC to examine the utilisation (including possible off-label prescribing) of these medications in a real-world, post-approval setting."	
27	14 Sept 2018	7	Change from "*a set*" of UK databases to just "*two"* UK databases	Initially a set of EMR databases was proposed however adequate sample size was reached with just two databases (CPRD and THIN)
28	14 Sept 2018	8.1	Figure 1 -we have added: 'only for new users of UMEC or UMEC/VI'	To clarify in the Figure 1 that the follow-up period to examine medication patterns and counts of events (objective 2 and 3), will be only done in new users of UMEC or UMEC/VI
29	14 Sept 2018	8.2	Information about potential data sources has been deleted and just left the two databases employed in the study	Initially a set of EMR databases was proposed however adequate sample size was reached with just two databases and therefore details of only those two databases have been included (CPRD and THIN)
30	14 Sept 2018	8.3.1.1	We have added: "For the LAMA/LABA sub group of other LABD, fixed dose combinations will be included as well	Clarification about considering the inclusion of fixed and open combinations.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			as open combinations of a LABA and a LAMA in two devices only if they are prescribed on the same exact date."	
31	14 Sept 2018	8.3.1.1	"A single patient is able to contribute more than one qualifying index medication during the ~~study~~ identification period"	Clarification about the contribution of a patient to more than one qualifying index medication, if they meet the definition of new use, will be only during the identification period, not during the whole study period.
32	14 Sept 2018	8.3.1.2	We have added: "Only single device or fixed dose combination maintenance therapies will be considered when defining concomitant maintenance medications."	Clarification about definition of concomitant maintenance medications
33	14 Sept 2018	8.3.1.3	Paragraphs explaining the exposure categories for the person-time exposed to UMEC or UMEC/VI during follow-up have been changed	Additional detail provided to ensure correct classification of UMEC or UMEC/VI patients into current and previous exposure time, taking into account all follow up time until censoring.
34	14 Sept 2018	8.3.2.1	"Patients will be considered to have asthma if their most recent asthma medical code is a maximum of two years prior to their	Clarification of Asthma definition

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			index date".	
35	14 Sept 2018	8.3.2.1	New paragraphs have been added to clarify this	Clarification of 'possible off-label prescribing' for the 3 exposure groups
36	14 Sept 2018	8.3.2.2	We have added: "in those currently or previously exposed to…"	To specify that the objective 2 will be performed in those currently or previously exposed to UMEC or UMEC/VI
37	14 Sept 2018	8.3.2.2	We have added: "HES/ONS"	Data linked with ONS data will be used as well as linked with HES
38	14 Sept 2018	8.3.2.3	We have added: "in new users of UMEC/VI or UMEC defined during the identification period"	Clarification that only new users of UMEC/VI or UMEC defined during the identification period will be considered.
39	14 Sept 2018	8.3.2.3; 8.7.1.4	We have changed the paragraph to one similar to the objective 2: "It will not be possible to determine whether a patient discontinues UMEC or UMEC/VI if they are censored between 31 and 90 days after their last prescription. These patients will be flagged, and the primary analysis will take a conservative approach for these patients and assume they were only exposed for	Objective 3, will follow the same approach that objective 2.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			the 30 days period following their last prescription."	
40	14 Sept 2018	8.3.2.3	Table with possible treatment switches or augmentations has been modified removing ICS/LAMA	Among the possible treatments ICS/LAMA have been removed as it is not a common treatment option
41	14 Sept 2018	8.3.2.3	Paragraph has changed to this: "treatment patterns that will be considered include continuous use of both drugs, discontinuation of the index medication (continue to use the concomitant medication), discontinuation of the concomitant medication (continue to use the index medication), discontinuation of both medications at the same time.	Options for switches or augmentations to calculate treatment patterns have been clarified
42	14 Sept 2018	8.3.2.3	More detailed explanation and formulae of the calculation for MPR and PRC have been added.	To ensure transparency in the calculation and which populations are included in each measure of adherence
43	14 Sept 2018	8.3.3.3	As part of the demographics baseline variables, we have added "Respiratory conditions"	For those with an indication of neither asthma nor COPD we want to explore which respiratory conditions they have
44	14 Sept 2018	8.3.3.3	COPD severity will be characterised by	COPD severity will be explored in the 24 months

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			lung function test and FEV_1/FVC ratio in the 24 months prior to index date	prior to index date, instead of in the 12 months prior, using much information available to better characterise patient's severity.
45	14 Sept 2018	8.3.3.3	COPD or asthma medication have been changed for 'Respiratory' medication	Respiratory medication is more adequate as general term
46	14 Sept 2018	8.3.3.3	Table 4 has been changed accordingly	For the purposes of this analysis, only fixed dose combinations will be considered.
47	14 Sept 2018	8.4	Some updated references and figures about CPRD have been added. As well a new paragraph about THIN database.	Information about CPRD has been updated. And, information about THIN database has been added
48	14 Sept 2018	8.7.1.2	We will select the first ever diagnosis code in their medical history	In case a patient has more than one diagnoses codes, clarify which code will be selected to calculate the proportion of patients with a diagnosis before or after their index medication
49	14 Sept 2018	8.7.1.2	We have added: "Further, the descriptive statistics will be repeated in the groups of patients who are identified as on label and potentially prescribed off label UMEC or UMEC/VI."	To add the possibility to repeat some tables by exposure groups.
50	14 Sept	8.7.1.3	Objective 2- We	To make this more

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
	2018		have changed the paragraph to: "First, using the full cohort of patients with identification of events in primary care data only (both CPRD and THIN data sources). And secondly, using information from primary care, secondary care (HES) and mortality data (ONS) in patients eligible for linkage with both HES and ONS data. Two secondary analyses will be carried out in both primary care data only and in those with linked to HES and ONS."	complete and straightforward, we edited this paragraph to essentially do these 3 analyses in both datasets.
51	14 Sept 2018	8.9	We have added: "By this design, new users of Other LABD who may have switched to either UMEC or UMEC/VI after the identification period during the *one-year follow-up window* will not have that UMEC or UMEC/VI exposure time counted in this	To acknowledge the limitation that the design of the study only assigns current and previously exposed follow-up time to users identified within the period of July 1, 2014 to June 30, 2016. Patients initially taken 'other LABD' will not be taken into account for the analyses if they switch to UMEC or UMEC/VI after the identification period.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			study’	
52	14 Sept 2018	8.9	The paragraph about the expected complexity of data analysis has been changed to “The final sets of databases, CPRD GOLD and THIN, are both based on the same GP software (Vision) and have comparable data structures and coding schemes. This reduces complexity in the analyses”	Initially a distributed network design was proposed, but finally only two final sets of databases have been used, therefore the complexity in the analyses have been reduced.

5. MILESTONES

Milestone	Planned date
Start of data collection	March 2015
End of data collection	June 30, 2017
Registration in the EU PAS register	October 2014
Interim report 1 (Drug Utilization, possible off-label prescribing) (up to relevant time period achieved)	February 23rd, 2018
Final report of study results (All objectives)	By Q4 2019

Interim and final analysis timings: due to dependence on the natural uptake of a medication by medical doctors, the actual interim and final analysis timings may differ. The study progress reports will provide regular information about physician prescribing and numbers of new users on a 6-monthly basis.

6. RATIONAL AND BACKGROUND

6.1. Background

Umeclidinium bromide/vilanterol trifenatate (UMEC/VI) fixed dose-combination LAMA/LABA and umeclidinium bromide (UMEC) LAMA monotherapy were recently approved by the European Commission for the treatment of COPD on May 2014 and April 2014, respectively. LAMA/LABA fixed-dose combinations are identified in the treatment guidance document for COPD, when severity warrants the use of both medications [GOLD, 2018]. Currently, other fixed-dose LAMA/LABA combination medication (glycopyrronium/indacaterol) was approved for COPD by the European Commission (approved prior to UMEC/VI). Additionally, several medications containing LAMA only and LABA only are available for treatment of COPD patients experiencing breathlessness, including medications containing salmeterol, formoterol, indacaterol, glycopyrronium, tiotropium, and aclidinium.

The safety and efficacy of mono component LABA and LAMA containing medication in COPD have been studied extensively. LAMA containing medications are considered a gold standard of bronchodilation in COPD patients demonstrating benefits of improved lung function and reduced dyspnoea [GOLD, 2018]. As there are fewer approved fixed dose LAMA/LABAs less is known about their risk/benefit profile.

There is a potential for off-label prescribing of UMEC/VI as a controller medication in asthma. However, the use of UMEC/VI for asthma would not be consistent with established guidance by the Global Initiative for Asthma [GINA, 2018]. Long-acting beta2-agonists are not recommended as monotherapy in asthma, as they do not influence airway inflammation and are potentially associated with a risk of asthma-related deaths [Bateman, 2008; Nelson, 2006; Sears, 2009; Morales, 2013]. LABAs are most effective when combined with glucocorticosteroids, and this combination is the preferred treatment

when glucocorticosteroid monotherapy fails to control asthma. Additionally, the benefits of LAMAs in asthma management have not yet been established. Only one LAMA, tiotropium, is currently approved as an add on-treatment for asthma for patients who are currently treated with the maintenance combination of ICS/LABA and who experienced one or more severe exacerbations in the previous year. There is a wide range of licensed and established controller treatment options available to physicians for the management of asthma including glucocorticosteroids, leukotriene modifiers, LABAs in combination with glucocorticosteroids, sustained-release theophylline, cromones and anti-IgE therapy [GINA, 2018].

We conducted a systematic review of observational studies describing the incidence or relative risk of major cardio- and cerebrovascular events in users of LAMA in COPD. Two out of the identified studies, using a single database source, reported incidence rates of events specified in Table 1 below in users of Tiotropium and LABA [Jara, 2012; Jara, 2007].

Table 1 Incidence rates (per 1,000 person-years) of Cardiovascular events among users of Tiotropium or LABA in the THIN database [Jara, 2012; Jara; 2007]

Outcome	Tiotropium (rate per 1,000 person-years)	LABA (rate per 1,000 person-years)
Atrial fibrillation & flutter	17.0 to 31.9	24.1 to 33.4
Heart failure	34.0 to 42.6	46.4 to 59.0
Myocardial Infarction	12.7 to 14.9	10.0 to 12.1
Tachycardia	5.40 to 19.1	4.80 to 24.1
Ventricular tachycardia	0.70	0.40

One study reported no difference in relative risk of cardiovascular events in users of tiotropium administered via Handihaler device vs. users of other respiratory medications [de Luise, 2007]. Three studies evaluated a relative risk of cardio- and cerebrovascular events in tiotropium (Handihaler) users vs. LABA users [Jara, 2012; Jara, 2007; Gershon, 2013], specified in Table 2. Only the risk of stroke was significantly increased in only one study among tiotropium users [Gershon, 2013].

Table 2 Risk of Cardio- and Cerebrovascular events among Tiotropium vs. LABA users [Jara, 2012; Jara, 2007; Gershon, 2013]

Outcome	Jara, 2012 HR (95% CI)	Jara, 2007 HR (95% CI)	Gershon, 2013 OR (95% CI)
Heart failure	0.85 (0.63 - 1.14)	0.65 (0.37 - 1.12)	1.08 (0.79 - 1.47)
Myocardial Infarction	1.26 (0.72 - 2.21)	1.29 (0.45 - 3.66)	1.10 (0.78 - 1.56)
Atrial fibrillation & flutter	0.99 (0.71 - 1.38)	0.60 (0.25 - 1.42)	
Stroke	1.49 (0.91 - 2.45)		1.73† (1.06 - 2.83)

†Statistically significant (p value of 0.03); All other estimates were Not statistically significant

Specific concerns were identified for users of tiotropium administrated via Respimat device. Tiotropium Respimat administration was repeatedly associated with an increased risk of cardiovascular events as compared to tiotropium administered via Handihaler in clinical and observational studies [Jenkins, 2013; Verhamme, 2013]. A large randomised clinical trial, TIOSPIR, designed to answer a question of the cardio- and cerebrovascular risks associated with tiotropium Respimat vs. Handihaler, reported noninferiority for the primary outcome of all-cause mortality; however, an imbalance of counts of some cardiovascular events was observed with Respimat administration [Wise, 2013].

Any risk of medication treatment related cardio- and cerebrovascular events in COPD needs to be interpreted taking into account an increased background prevalence of such events in COPD patients and their risk factors when compared with patients without COPD [Mullerova, 2012].

Respiratory infections, including pneumonia and lower respiratory tract infections (LRTI) [Mannino, 2009] often occur in patients with COPD. The incidence and prevalence of pneumonia in COPD patients can be difficult to estimate because of the application of different definitions of pneumonia (e.g. radiographic confirmation of pneumonia). In a COPD cohort of 40,414 patients in the UK, the incidence of pneumonia was 22.4 per 1,000 person-years and increased with disease severity [Mullerova, 2012]. Incidence rates of pneumonia were 18.2, 19.2, and 35.9 per 10,000 person-years for mild, moderate, and severe COPD patients respectively, where severity was estimated based on respiratory medication use [Mullerova, 2012].

Data from two large United States cardiovascular health studies observed that the rates of pneumonia requiring hospitalisation among patients with COPD ranged from 0.9 per 1000 person years for ages 45-49 and increased markedly with age (2.5, 5.4, 6.7, 12.2, and 19.5 per 1000 person years for patients 60-64, 65-71, 72-75, 76-79, ≥80) and GOLD stage (GOLD II: 6.9 per 1000 person years, GOLD III/IV: 22.7 per 1000 person years, normal lung function: 1.5 per 1000 person years) [Mannino, 2009].

6.2. Rationale

In the early post-approval period for UMEC/VI and UMEC, this study aims to collect data reflecting the 'real-world' experience of new users of LABD. We will focus on cohorts of new users of UMEC/VI and UMEC aiming to place the analysis output into context of experience of new users of other LABD. There is no a priori hypothesis to be tested. This study fulfils a voluntary commitment made in the European Union – Risk Management Plans (EU-RMP) for UMEC/VI and UMEC to examine the utilisation (including possible off-label prescribing) of these medications in a real-world, post-approval setting.

We will focus our investigation on characteristics (clinical, demographic) of new users of UMEC/VI, UMEC, or other LABD including whether pre-existing conditions like cardio- and cerebrovascular disease or pneumonia are impacting on physician's choice of maintenance therapy for COPD patients by informally comparing the distribution of comorbidities in the three cohorts at the time of index prescription.

Another specific focus is on quantifying and characterizing possible off-label prescribing in patients diagnosed with asthma alone (without COPD diagnosis) as LABD alone, including UMEC/VI and UMEC, without concomitant ICS use, are not indicated for the treatment of asthma.

In addition, as both the LABA and LAMA class of drugs have been associated with some increased risk of cardio- and cerebrovascular events, it is of interest to pursue evaluation of cardio- and cerebrovascular safety of UMEC/VI and UMEC during the post-approval stage. To enable rapid development of any possible future risk-benefit studies, as a feasibility evaluation, we will descriptively quantify incidence during follow-up of cardio- and cerebrovascular events of interest in patients using UMEC/VI and UMEC as well as report on the incidence of events of pneumonia.

We will also describe treatment patterns and adherence to medication among new users UMEC/VI and UMEC.

7. RESEARCH QUESTION AND OBJECTIVE(S)

In the initial post-approval period of up to 24 months from the start of UMEC/VI and UMEC availability in the UK, we will identify patients newly prescribed long-acting bronchodilators (LABD) from two UK primary care Electronic Medical Records (EMR) databases and conduct drug utilization review focusing on the following aims:

Objective 1: In new users of UMEC/VI, UMEC, or other LABD report the proportion of patients with a possible off-label prescribing and characterize them, using information available prior to and at the time of index prescription initiation, in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Objective 2: In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality and pneumonia, and rates of exacerbations of COPD during follow-up.

Objective 3: In new users of UMEC/VI or UMEC with 12 or more months of follow-up following initiation, describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up.

8. RESEARCH METHODS

8.1. Study Design

This study will take a naturalistic approach, capturing routine medical care using a retrospective longitudinal non-interventional observational design. The study will identify patients based on a new prescription (index prescription date) for UMEC/VI, UMEC, or other LABD who will be followed-up from their index prescription date until their censoring date which is the earliest of the following events:

1. Death
2. Leaving GP practice
3. the practice's last collection date or
4. End of follow-up on June 30, 2017.

We will identify all new users of UMEC/VI, UMEC or other LABD during the exposure identification period of July 1, 2014 to June 30, 2016, corresponding with a period up to 24 months of UMEC/VI or UMEC availability to prescribers in the UK (See Section 8.3.1, Figure 1, Figure 2).

A minimum period of at least 12 months prior to index prescription date, defined as being registered with the practice for at least one year, is required for all new users to allow for a standardised period of history to describe selected patient demographics, disease burden, and previous respiratory medication use (Figure 1, Figure 2).

To evaluate Objective 1, all patients newly prescribed UMEC/VI, UMEC, or other LABD will be included; Objectives 2 and 3 will be limited to new users of UMEC/VI or UMEC only.

Figure 1 Study Schematic: Individual patient history assessment

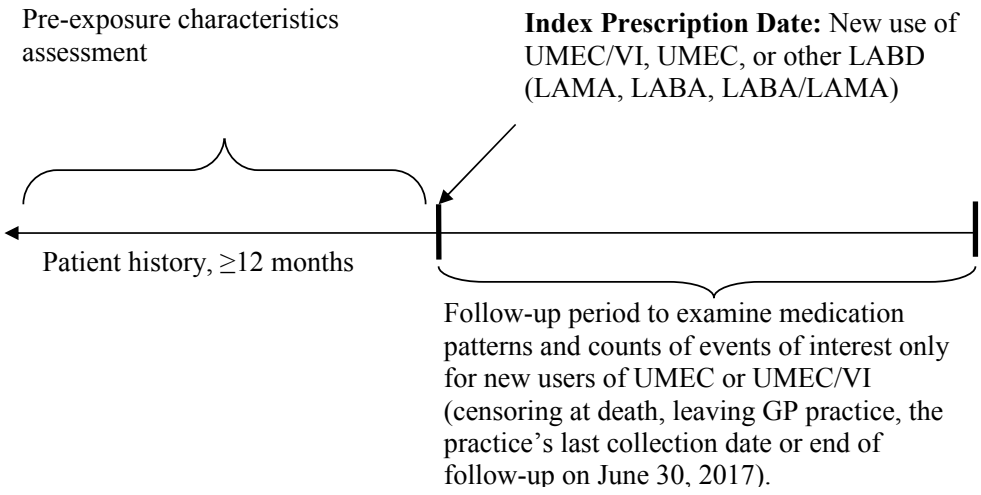
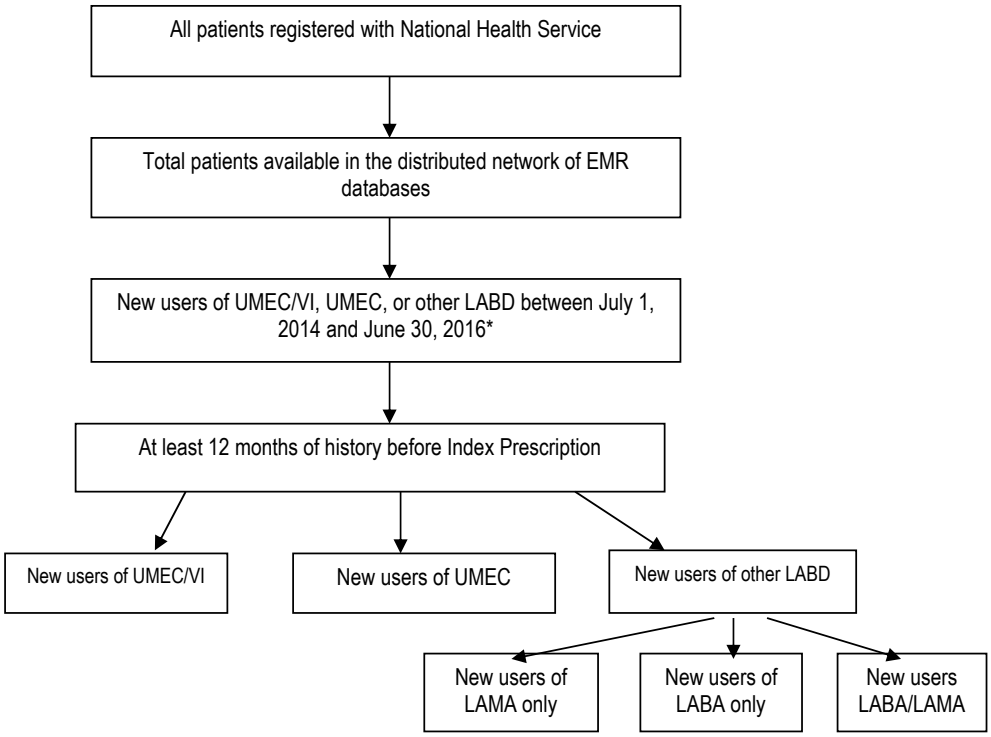


Figure 2 Consort Diagram Schematic: Cohort Selection



* A patient may qualify for more than one exposure category if they meet the "new user" definition for more than one drug during the exposure identification period.

8.2. Setting

The study population will be identified from two UK data sources, the Clinical Practice Research Datalink GOLD database (referred to hereafter as CPRD-GOLD) and The Health Improvement Network (referred to hereafter as THIN). The required sample size will be achieved using these two data sources. Each database currently comprises EMR data from a single vendor system, and the ones we will consider for inclusion were those databases which contain data from one of the three main systems which currently cover over 85% of UK general practices: Vision from In Practice Systems (InPS)As the co-coordinating centre for the study, CPRD will obtain and evaluate data from the THIN database, using criteria agreed in advance with GSK.

Patients in each database are unique at two levels. First, at the patient level we consider only so-called permanently registered patients; such patients can register with one GP practice at a time only. The movement across practices is considered to be low. Secondly, at the database level, we will use practice identifiers to ascertain if any practice is contributing to more than one system in the distributed network.

Primary care records of eligible patients only from the CPRD-GOLD will be linked where possible, to additional datasets such as the Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) mortality statistics database to potentially improve capture of study outcome events and obtain richer information about study outcome events.

These linked datasets, covering population of England only, will be used primarily for outcome ascertainment and validation. Further details on datasets are provided in Table 3 and Section 8.4.

Table 3 Summary of the characteristics for the EMR databases to be included in the study

	CPRD-GOLD	**THIN**
EMR System	**Vision (InPS)**	**Vision (InPS)**
Database size: **a) total patients** **b) current (or active) patients** **c) total practices** **d) current (or active) practices**	a) 14.2M b) 3.5M d) 406	a) 11.1M b) 3.7M c) 578 d) n/k
Patient geographical coverage	UK	UK
Linked data available	For a subset of English practices: HES, ONS, NICOR (MINAP)	A small subset of practices has been linked to HES
Regularity of data uploads	Monthly	Monthly
Allows obtaining further evidence from GP practice medical records	Yes (subset of practices)	Yes
Further specifications		~50% of flagged practices overlap with the CPRD.

8.2.1. Study Populations

The study population will consist of new users of UMEC/VI, UMEC or other LABD treatment (See Section 8.3.1 for exposure definition).

8.2.1.1. Inclusion Criteria

Patients are required to:

1. Have a record for a new prescription of UMEC/VI, UMEC, or other LABD between July 1, 2014 and June 30, 2016 (inclusive).
2. Have at least 12 months of recorded data prior to index prescription date to allow characterization of patient's status, demographics and clinical characteristics.

8.2.1.2. Exclusion Criteria

Having a prescription for the same exact substance (or combination) of LABD ever recorded in the past.

To evaluate Objective 1, all patients newly prescribed UMEC/VI, UMEC, or other LABD will be included; Objectives 2 and 3 will be limited to new users of UMEC/VI or UMEC only.

8.3. Variables

8.3.1. Exposure definition

8.3.1.1. New users (UMEC/VI, UMEC or other LABD)

We will identify all new users of UMEC/VI, UMEC or other LABD during the exposure identification period of July 1, 2014 to June 30, 2016, corresponding with a period up to 24 months of UMEC/VI or UMEC availability to prescribers in the UK. New use is defined as never having had a prescription for the same medication (UMEC/VI, UMEC or specific active substance (or combination) of other LABD) ever recorded in the past. The first day of the first qualifying new use prescriptions will be in the index date. Prior or concomitant use of respiratory medications containing a different specific active substance (or combination) then the new substance (or combination) being initiated will be allowed.

Other LABD includes but is not limited to medications containing: tiotropium, glycopyrronium, glycopyrronium/indacaterol, aclidinium, indacaterol, salmeterol, olodaterol, and formoterol, according to the availability. This list may need to be further modified depending on newly authorised medications in the class. For the LAMA/LABA sub group of other LABD, fixed dose combinations will be included as well as open combinations of a LABA and a LAMA in two devices only if they are prescribed on the same exact date. The other LABD group will be analysed as a single combined group, and where appropriate and sample size allows, stratified as LAMA, LABA, and LAMA/LABA. No other LABD drugs will be analysed individually. The new use of ICS/LABA combinations in a single device is not considered as new other LABD unless it is accompanied with a new prescription for LAMA.

All individual prescriptions will be given a *default length of 30 days per container prescribed* irrespective of whether they have a recorded value for script length (less than 1% had a value recorded).

A single patient is able to contribute more than one qualifying index medication during the identification period if they meet the definition of new use for multiple medications. A patient may qualify for new uses of both UMEC and UMEC/VI if that patient switches between the two during the identification period. A patient may also qualify for more than one ‘other LABD’ containing the same active substance (e.g. glycopyrronium and glycopyrronium/indacaterol) or an ‘other LABD’ (such as tiotropium) and UMEC or UMEC/VI.

Note: prescriptions are used as proxy for pharmacy dispensing, as it is known that a percentage of patients never take a prescription to the pharmacy or fail to collect a filled prescription.

8.3.1.2. Concomitant use of other medications at index date (UMEC/VI, UMEC)

Given the naturalistic nature of the study design, it is possible that some patients will initiate UMEC or UMEC/VI while on other maintenance medications. In some instances, these patients will be transitioning from the old medication to the new one and there is a

small overlap. In other cases, they may continue to take both medications for a period of time. Of particular interest is concomitant use of an ICS-containing medication along with the index medication, as this will be used as a stratification variable for several of the study objectives.

We will search the patient record and flag instances when patients are receiving concomitant COPD maintenance therapy at the time of the index prescription. Concomitant therapy will be defined as at least two continuous prescriptions for the other COPD maintenance therapy which start either before, or up to 30 days after the index date, and overlap for at least 30 days with the index treatment. Only single device or fixed dose combination maintenance therapies will be considered when defining concomitant maintenance medications.

8.3.1.3. Follow up period and person time (UMEC/VI, UMEC)

For Objective 2, new users of UMEC/VI and UMEC, defined in the identification period, will be followed from their index date until their censoring date (death, leaving the GP practice, the practice's last collection date or 30th June 2017) for disease outcomes. Person-time exposed to UMEC or UMEC/VI during follow-up will be classified in several exposure categories:

Currently exposed to UMEC/VI or UMEC: current exposure is person-time starting from the index date and continuing until the earliest of:

1. The censoring date (ie. patient continuously used the index medication during the whole study period)

   OR

2. Discontinuation of prescribing the index medication (UMEC or UMEC/VI) considered to have occurred if there is either:

   - A break of at least 91 days between prescriptions for the index medication. The discontinuation date is set at 30 days after the prescription prior to the break. (Note: After this break, the patient may resume the same index medication (drug hiatus) or switch to a different inhaled COPD medication (See Section 8.3.2.3).

     or

   - Complete discontinuation in prescribing of the index medication and no further inhaled COPD medication of any kind until the censoring date (See Section 8.3.2.3). The discontinuation date is set at 30 days after the final prescription.

   It will not be possible to determine whether a patient discontinues UMEC or UMEC/VI if they are censored between 31 and 90 days after their last prescription. These patients will be flagged, and the primary analysis will

take a conservative approach for these patients and assume they were only exposed for the 30 days period following their last prescription.

If a patient discontinues the index medication but resumes taking that index medication at a later date, the second exposure period will also be considered as part of "currently exposed" time.

OR

3. An immediate switch to another inhaled COPD medication (See Section 8.3.2.3)
    - Patient starts taking another inhaled COPD medication during an interval that is between ≤30 days before the discontinuation date for the index treatment and ≤60 days after the discontinuation date for the index treatment. The immediate switching date will be defined as the date of first prescription for the new therapy.

Previously exposed to UMEC/VI or UMEC: for patients with a defined discontinuation date or a switch date (see above), previous exposure to an index medication is all person-time starting from the discontinuation or switch date and continuing until either the censoring date (in instances of complete discontinuation or latent switch), or, the date the patient resumes taking the same index medication (in instances of a drug hiatus).

Note: Patients who continuously use their index medication through to censoring will have no "previously exposed time" defined.

Concurrent exposure to other COPD maintenance therapies: As it is possible that some patients will be taking another COPD maintenance therapy concomitantly at index date or will start up another COPD maintenance therapy at some time during follow up while still taking their index medication, we will also flag patients who have had periods of time where they are exposed to more than just the index medication. Concurrent exposure is person-time starting from the date of the first prescription for another COPD maintenance therapy (or the index date in the case of therapies started concomitant with the index medication), and continuing until the earliest of the censoring date, the discontinuation date for the other COPD maintenance therapy (if observed, i.e. complete cessation or a break of at least 91 days between prescriptions) or the discontinuation date for the index medication (if observed). After treatment patterns have been assessed, the most common concurrent medications observed will be considered for this analysis.

8.3.2. Outcome definitions

All codes and detailed algorithms will be reviewed by a clinician, agreed with the study Scientific Committee and summarised in the detailed statistical analysis plan.

8.3.2.1. Objective 1

For *Objective 1* to estimate possible off-label prescribing, new users of UMEC/VI, UMEC, or other LABD will be further split by a diagnosis of: (a) COPD, (b) asthma, or (c) neither COPD nor asthma, as described below. These definitions will be applied in a stepwise manner, whereby the definition of COPD will be applied first. For those who do not meet the COPD definition, we will then look to see if they fulfil the case definition of asthma. Lastly, patients who meet neither the COPD nor asthma definition will be captured in the third category.

1. **COPD:** Patients will be considered to have COPD if they have a COPD diagnosis recorded any time in their CPRD history up to and including the index UMEC/VI, UMEC, or other LABD prescription date through their censoring date and were age 35 years or older at the time of their first ever COPD medical code.
2. **Asthma:** Patients who did not fulfil the case definition of COPD as described above will be considered to have asthma if their most recent asthma medical code is a maximum of two years prior to their index date (up to and including the index UMEC/VI, UMEC, or other LABD prescription date through to their censoring date). The asthma code list is derived from a recently published asthma diagnosis validation study in CPRD [Nissen, 2017]).
3. **Neither COPD nor asthma:** Patients will be classified into this category if they did not meet either the definition of COPD or asthma above.

Different time periods for identification of the COPD or asthma diagnosis will be explored (See Section 8.7.2 for sensitivity analysis description).

For the purposes of this study, possible off-label prescribing is defined as use in a patient not classified as having COPD.

Possible off label prescribing of UMEC:

- **Proportion of all UMEC users in the asthma group or the neither asthma nor COPD group**

  $$\frac{\text{\# patients in “Asthma group” or “Neither asthma nor COPD group” with an index prescription for UMEC}}{\text{\# patients with an index prescription for UMEC}}$$

Possible off label prescribing of UMEC/VI:

- **Proportion of all UMEC/VI users in the asthma or the neither asthma nor COPD group**

  $$\frac{\text{\# patients in “Asthma group” or “Neither asthma nor COPD group” with an index prescription for UMEC/VI}}{\text{\# patients with an index prescription for UMEC/VI}}$$

Possible off label prescribing for the other LABD group will be calculated as described above separately for other LAMA, other LABA and other LAMA/LABA. Denominators in both cases will be all patients with an index prescription in that particular LABD group.

For the other LAMA subgroup only, a secondary definition will also be used to account for the September, 2014 authorisation of tiotropium to be used as an add on therapy to ICS/LABA for the treatment of asthma in patients with asthma exacerbations. Other LAMA sub-group off-label prescribing definition 2 will therefore be defined as prescribing of other LAMA in patients in the asthma or other diagnosis group *unless they had an asthma diagnosis and a prescription for 2.5mcg tiotropium along with a concomitant prescription of an ICS/LABA* on or after 13/09/2014.

For the other LABA subgroup only, a secondary definition will also be used to account for the fact that LABA plus an ICS in two devices might be an option utilized to treat asthma. Other LABA sub-group off-label prescribing definition 3 will therefore be defined as prescribing of an 'Other LABA' in the asthma or other diagnosis group *unless they had an asthma diagnosis and a concomitant ICS at index date along with their index Other LABA*.

8.3.2.2. Objective 2

For *Objective 2*, in those currently or previously exposed to UMEC/VI or UMEC we will enumerate all events that occur from index prescription date until censoring of the following incident events:

1. Myocardial infarction, Heart failure, Stroke

We will derive diagnoses for these events using Read Code or ICD-9 or ICD-10 code lists. Validated code lists have been published from multiple UK EMR databases, including CPRD, for myocardial infarction event [Hammad, 2008; Coloma, 2013; Herrett, 2013] and ischaemic stroke [Ruigomez, 2010]. In the primary analysis these outcomes will be defined using information recorded in primary care (i.e. the GP record) and supplemented with information from secondary care (HES/ONS). For heart failure, we will focus on recorded instances of newly diagnosed heart failure, i.e. first ever congestive heart failure diagnosis in the available history after the index date.

2. Pneumonia

We will derive diagnoses for these events using Read Code or ICD-9 or ICD-10 code lists based on a code list from a recently published study on pneumonia in COPD patients using the CPRD GOLD data [DiSantostefano, 2014].

In the primary analysis, pneumonia will be defined based on a recorded diagnosis in the GP record, and further supplemented with the HES record. A secondary analysis will consider pneumonia recorded only in the GP record.

3. Death

The event of death will be primarily derived from EMR databases using Read Code lists or specifics flags, depending on the database. The primary analysis will also consider cardiovascular death using data from ONS mortality statistics, where available.

4. Episodes of COPD exacerbations

The count and exacerbation rate per person year will be calculated. COPD exacerbations will be identified using a validated algorithm based on medical and treatment codes that have been shown to result in PPV of 86% and sensitivity of 63%: (1) a medical diagnosis of LRTI or acute exacerbations of COPD, or (2) a prescription of COPD-specific antibiotic combined with OCS for 5-14 days, or (3) a record of two or more respiratory symptoms of acute exacerbations of COPD along with a prescription of COPD-specific antibiotics and/or OCS on the same day [Rothnie, 2016]. These combined strategies will be used only after removing any acute exacerbation of COPD events occurring on the same date as codes suggestive of a visit for annual COPD review or provision of rescue packs for COPD-specific antibiotics or OCS.

In the primary analysis, exacerbations will be defined in the GP record and further supplemented with HES data. A secondary analysis will define exacerbations using only information in the GP record.

8.3.2.3. Objective 3

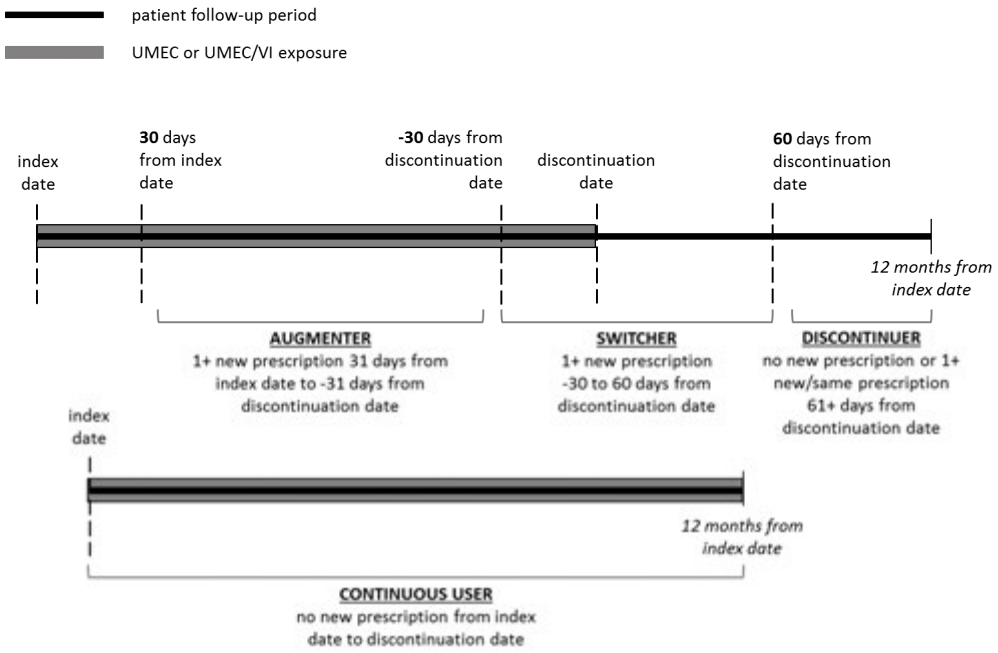
For *Objective 3*, in new users of UMEC/VI or UMEC defined during the identification period, with at least 12 months of recorded data following initiation, we will separately describe treatment patterns and adherence of inhalation therapies.

Treatment patterns

Treatment patterns will be considered only in patients with at least 12 months of follow-up after their index treatment. It will not be possible to determine whether a patient discontinues UMEC or UMEC/VI if they are censored between 31 and 90 days after their last prescription. These patients will be flagged, and the primary analysis will take a conservative approach for these patients and assume they were only exposed for the 30 days period following their last prescription.

For patients who are not taking a concomitant COPD (inhalation) maintenance therapy at the time of the index prescription, a number of mutually exclusive treatment patterns will be defined (as shown in Figure 3). We will describe the first change within the 12 months period following initiation.

Figure 3 Treatment patterns for patients who are not taking a concomitant COPD maintenance therapy



a. *Continuous Use:* Patient DOES NOT start taking another inhaled COPD maintenance therapy, and continues to use index treatment through the 12 months after the index date.

b. *Augmentation:* Patient starts taking another inhaled COPD maintenance therapy (1 or more prescriptions) and the new treatment starts ≥31 days after the index date and ≥31 days before the discontinuation date for the index treatment or the end of 12 months following the index date. The augmentation date will be defined as the date of first prescription for the new COPD maintenance therapy. Note: for patients who qualify for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication will be considered a switch and not an augmentation. This is in line with the decision to allow patients to enter the study separately for UMEC and UMEC/VI (i.e. they are considered as separate products).

c. *Immediate Switching:* Patient starts taking another inhaled COPD maintenance therapy (1 or more prescriptions) within 12 months of the index date, and the new treatment starts during an interval that is between ≤30 days before the discontinuation date for the index treatment and ≤60 days after the discontinuation date for the index treatment. The switching date will be defined as the date of first prescription for the new COPD maintenance therapy. Note: for patients who qualify for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication will always be considered a switch as described.

d. *Discontinuation:* Patient meets the definition of discontinuation as defined in 8.3.1.3 within 12 months of the index date.

Discontinuers will be followed until 12 months after the index date and classified according to whether they:

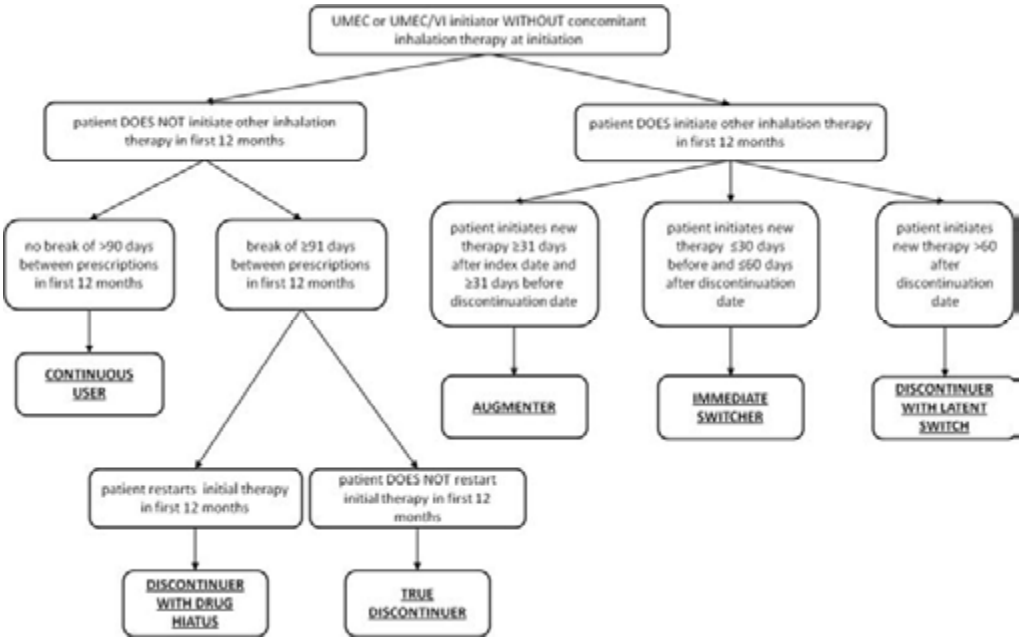
a) do not restart the index medication and do not start a new inhaled COPD maintenance treatment (i.e. true discontinuers)

b) restart the index medication (i.e. patients taking a drug hiatus)

c) start a new inhaled COPD maintenance treatment >60 days after discontinuation (i.e. latent switchers). Note: for patients who qualify for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication will be considered a latent switch based on the rationale described earlier.

The six mutually exclusive treatment groups will be identified using the algorithm shown in Figure 4.

Figure 4 Algorithm for identifying mutually exclusive groups of treatment patterns for patients who are not taking a concomitant COPD maintenance therapy at index date



The following treatment switches or augmentations may possibly occur:

Initial treatment	Treatment switch	Treatment augmentation
UMEC	LAMA[1]	LABA
	LABA	ICS/LABA[2]
UMEC/VI	ICS/LABA[3]	
	LABA	ICS/LABA[2]
	LAMA	
	LAMA/LABA[1]	
	ICS/LABA[2]	

1. LAMA and LAMA/LABA different to the index medication
2. Fixed Combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist

For patients who are taking a concomitant COPD (inhalation) maintenance therapy at the time of the index prescription, treatment patterns that will be considered include continuous use of both drugs, discontinuation of the index medication (continue to use the concomitant medication), discontinuation of the concomitant medication (continue to use the index medication), discontinuation of both medications at the same time.

We will only describe the first change within the 12 months period following initiation and may consider only those mostly commonly occurring concomitant medications at index date.

Treatment adherence

Treatment adherence will be assessed from the index UMEC/VI or UMEC prescription until the end of the 12 months after the index date. Treatment adherence will be measured in the first 12 months of follow-up, for patients with at least 12 months of follow-up after initiation of the index drug.

Medication possession ratio (MPR) will be calculated only in those with 12 complete months of follow-up from the index date and at least one additional UMEC or UMEC/VI prescription after the index prescription.

Calculated as follows:

$$\frac{\text{Number of days in possession of UMEC (or UMEC/VI) between last prescription date and index date}}{\text{Total number of days between index date and last prescription date}}$$

Where number of days in possession is calculated by multiplying the number of prescriptions in the period (minus the last prescription) by the assumed duration of 30 days and where last prescription date is the last prescription date recorded before the end of the follow-up period or discontinuation date, whichever occurs first. (Note: each patient will have a unique denominator). Additions to the index medication are allowed as long as the patient is still exposed to the index medication.

The MPR will be expressed as a percentage, with nonadherence defined as MPR <80% and adherence defined as MPR ≥80%.

Proportion of days covered (PDC) will be calculated in patients with 12 complete months of follow-up from the index date.

Calculated as follows:

$$\frac{\text{Number of days in possession of UMEC (or UMEC/VI) over 12 months follow-up period}}{\text{365 days}}$$

where number of days in possession is calculated by multiplying the number of prescriptions (at any dose) in the period (minus the last prescription) by the assumed duration of 30 days and where last prescription date is the last prescription date recorded before the end of the follow-up period or discontinuation date, whichever occurs first.

All eligible patients are included in the PDC calculation as only a single prescription of the index mediation is required.

The PDC will be expressed as a percentage. For the 0-12 months period, PDC values will range from a minimum of 8% (only had one index prescription over 365 days) to a maximum of 100% (had medication available every day for the 365 days study period). The PDC will also be dichotomised, with nonadherence defined as PDC <80% and adherence defined as PDC ≥80%.

8.3.3. Confounders and effect modifiers

The following variables will be used in Objective 1 to describe new users of UMEC/VI, UMEC, or other LABD in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Demographics at baseline

- **Age at index prescription date**: Mean (SD) and categories of: younger than 65, 65 years or older. For objective 1, we will also create two additional categories: younger than 18 years, 18 to 64 years.

- **Gender**: (female or male)

- **Smoking status**: categories of: current smoker, ex-smoker, no/never smoker, and missing. Smoking will be ascertained using records searched through all available history up to three months after the index date. Nearest record to index date will be used.

- **BMI:** Mean (SD) and categories of: Underweight <18.5, Normal 18.5 - 24.9, Overweight 25.0 - 29.9, and Obese ≥30.0. BMI is either taken as recorded in the database or calculated as weight in kilograms divided by height in meters squared. This value can occur any time before to three months after the index date; value taken nearest prior to index date will be used.

- **Area based deprivation measures:** the most recently available version of each national index of multiple deprivation (IMD) or Townsend deprivation data will be used to classify small areas according to quintiles or deciles of relative

deprivation. Patients will then be classified according to the deprivation level of their own area of residence.

- Region of practice at index date: The Strategic Health Authority for practice postcode within England, and the country i.e. Wales, Scotland, or Northern Ireland for the rest.

- Respiratory conditions: For the Neither Asthma nor COPD diagnosis group only, common Respiratory READ codes (Chapter H: Respiratory System Codes) occurring in the 12 months prior to index date will be analysed to describe other respiratory conditions.

Disease burden at baseline

- **COPD exacerbations** will be flagged in the 12 months prior to index date and the rate (per person-year) and 95% confidence interval will be calculated. Further, the total number of exacerbations will be described and also presented as 0, 1 and 2+ events This will be done in two groups, first using primary care data only for the full group of patients and second using both primary care and secondary care (HES) data for the subset of patients eligible for linkage. In this second group, we will further differentiate between those with moderate exacerbations (i.e. recorded only in primary care) and those with moderate and severe exacerbations (i.e. recorded in primary and/or secondary care). (See Section 8.3.2.2 for definition)
- **Dyspnoea** will be identified as having a code for Medical Research Council (MRC) dyspnoea in the 12 months prior to index date and will be characterised into MRC Grades 1-5 or MRC missing. The count and percent of patients in each group and the mean (SD) MRC will be reported. Value taken nearest prior to index date will be used.

- **COPD severity** will be characterised by airflow limitation as measured by lung function test (spirometry) in the 24 months prior to index date. Lung function parameter of forced expiratory volume in one second, FEV_1, percent predicted will be used and expressed as Mean (SD) and split in categories modified from the GOLD, 2006 classification of airflow limitation [GOLD, 2009], using cut points of FEV_1 ≥80% predicted for mild Grade 1, ≥50% to <80% FEV_1 predicted for moderate Grade 2, ≥30% to <50% FEV_1 predicted for severe Grade 3, and <30% FEV1 predicted for very severe Grade 4. Patients with missing values will be categorised as 'missing'. The count and percent of patients in each group will be reported. Value taken nearest prior to index date will be used.

  Further, the value for FEV_1/FVC ratio in the 24 months prior to index date will flagged and expressed as Mean (SD) and categorised as less than 70%, equal or more than 70%, and missing. Value taken nearest prior to index date will be used.

Comorbidity

- **Past history of cardio-and cerebrovascular diseases** will be flagged (Yes/No) in all available history prior to index date (See Section 8.3.2.2 for definition)

- **History of beta-blocker prescribing** will be identified in the one year period prior to index date (See Section 8.3.2.2 for definition). The proportion of patients with one or more prescriptions for a beta-blocker will be reported.

- **Past history of pneumonia, gastroesophageal reflux disease, diabetes, renal disease (acute and chronic) and cancer** (recorded only in primary care) will be flagged (Yes/No) in all available history prior to index date (See Section 8.3.2.2 for definition).

Prior use of respiratory medication at baseline

Utilization of other respiratory therapies in the 12 months prior to index date will be flagged and the count and percentage of patients with at least one prescription for that type of medication will be calculated. Further, the total number of prescriptions of each type of drug will be described. The types of COPD therapies to be ascertained are outlined in Table 4 below. For the purposes of this analysis, only fixed dose combinations will be considered.

Table 4 Categories of respiratory medications

Category	Description
SABD§	Short-Acting Beta2-Agonist (SABA), Short-Acting Anticholinergic (SAMA), Fixed Combinations of SABA/ Cromoglycate Fixed Combinations of SABA/SAMA
ICS and SABA/ICS*	Inhaled Corticosteroids OR Fixed Combination of Short-Acting Beta2-Agonist and Inhaled Corticosteroid
LABA	Long-Acting Beta2-Agonists
ICS/LABA*	Fixed Combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist
LAMA*	Long-Acting Anticholinergics
LAMA/LABA	Fixed Combination of Long-Acting Beta2-Agonist along with a Long-Acting Anticholinergic
Theophylline*	Theophylline and its derivates
Roflumilast	Roflumilast (Oral PDE4 inhibitor)
Oral corticosteroids*	

§ Asthma medications categorised as "reliever"
*Asthma medications categorised as "maintenance"

For SABD, we will also describe the count and percent of patients with more than four prescriptions.

For Oral Corticosteroids (OCS), we will describe only "chronic use" which is defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days.

8.4. Data sources

Primary care data

The study population will be identified in a distributed network of the UK Primary Care EMR databases, see Section 8.2 and Table 3.

CPRD-GOLD will serve as the main primary care database for development and benchmarking of analyses. It contains data extracted from Vision Primary Care EMR systems, and is described in more detail below. Other databases comprising data from the other main primary care EMR systems will vary to some extent. Nevertheless, a number of common factors constrain all systems such that there is a large degree of similarity in terms of both the information captured, and the data models:

- All systems capture information from the same underlying health system.
- All systems must comply with national NHS information standards and procedures. This includes implementing standard clinical and therapeutic terminologies, and communications with pathology laboratory systems.
- All systems are required to generate and report comparable information for national initiatives such as the Quality and Outcomes Framework, and National Diabetes Audits
- All systems are required to support some level of interoperability, exemplified by the GP2GP standard for electronic transfer of individual EMRs when a patient moves to a different practice.

CPRD-GOLD contains the anonymised, longitudinal medical records of patients registered with contributing primary care practices across the UK. The GOLD database covers approximately 3.6% of the current UK population, including practices in England, Northern Ireland, Scotland and Wales. As of July 2018 there were 738 GP practices and 15.5M acceptable (research quality) patients in GOLD, of which 2.3M are active (still alive and registered with the GP practice). Data has been collected from GP practices since 1987.The CPRD-GOLD database has been used previously for descriptive drug utilization studies for prescription medications in respiratory diseases [Ashworth, 2004; van Staa, 2003; DiSantostefano, 2014]. Descriptive and pharmacoepidemiological studies of patients with COPD have been conducted in CPRD, including validation of physician-recorded COPD diagnosis [Quint, 2014] and evaluation of COPD co-morbidities [Soriano, 2005].

The Health Improvement Network (THIN) was established in 2002 and facilitates the collection of non-identified patient data from UK General Practice (GP) clinical systems. IQVIA has a License Agreement to use the data collected by THIN for medical research and treatment analysis. As of January 2018, the THIN data available for research includes the Electronic Medical Records (EMRs) from over 17 million patients in the UK, 3.1 million of which are registered with an actively contributing THIN GP practice. All data are fully anonymised, processed and validated by CSD Medical Research UK [THIN 2017].

CPRD-GOLD and THIN contain patient registration information and all care events that general practice staff record in order to support the ongoing clinical care and management of their patients. This includes demographic information (age, sex, weight etc.), records of clinical events (medical diagnoses), referrals to specialists and secondary care settings, prescriptions issued in primary care, records of immunisations/vaccinations, diagnostic testing, lifestyle information (e.g. smoking and alcohol status), and all other types of care administered as part of routine GP practice. Furthermore, free text notes which are routinely entered in the comment field of the electronic patient record can also be accessed, once they have been anonymised. The NHS dictionary of medicines and devices (dm+d) is used as a dictionary containing unique identifiers (codes) and associated textual descriptions for representing medicines and medical devices in information systems and electronic communications (http://www.dmd.nhs.uk/). CPRD-GOLD and THIN contain data from the Vision EMR system which uses Read codes - specifically the Unified 5-byte Version 2 Read code set - as the basic means to record patient findings and procedures, and other relevant information.

Linked data

Linkage of CPRD-GOLD data to other patient level datasets including but not limited to HES, is possible for a subset of around 2 million patients. Patients in CPRD-GOLD are considered eligible for linkage if they are currently registered with the 224 consented English practices that continue to participate in the linkage scheme. Additionally, patients must have the necessary identifiers (e.g. NHS number) to enable linkage of the primary care data (CPRD-GOLD) with other patient level datasets.

- Hospital Episodes Statistics (HES): HES is a data warehouse containing details of all inpatient episodes of care (including day cases), outpatient appointments and A&E attendances at NHS hospitals in England. This data is collected during a patient's time primarily for administrative reasons, but is designed to enable secondary use. As well as patient demographic information and admission and discharge information, the inpatient data includes coded information about diagnoses (ICD-10) and procedures (OPCS 4 codes). Outpatient data contains information about appointment dates and times, and specialties, but much less coded clinical information. Further information is available at: http://www.hscic.gov.uk/hes.

- Office for National Statistics (ONS) Mortality statistics: Mortality data for England and Wales are based on the details collected when deaths are certified and registered. Details available in the linked data include underlying and contributory causes of death (ICD-10).

Monitoring uptake of study drugs

Regular data uploads will be used to evaluate LABD uptake by identifying patients taking UMEC/VI, UMEC or other LABD during the exposure identification period from July 1, 2014 until June 30, 2016. We will pilot various time intervals of data uploads depending on the upload frequency in each database participating in the distributed network. These data will also be useful in determining when the necessary sample size is expected to be reached.

Description of validated diagnoses

All code lists will be agreed with data partners across the distributed network of EMR databases and include review with at least one physician currently practicing in the UK. Where possible code lists already validated and published will be utilised. Further, a recently completed validation study in the CPRD will provide validated definitions of COPD diagnosis and COPD exacerbations for this study [Rothnie, 2016] and of asthma diagnosis [Nissen, 2018]. Availability of some validated code lists is indicated in the Section 8.3.2 Study Outcomes.

8.5. Study size

The three objectives of this study are descriptive in nature. Hence, we do not propose a formal hypothesis-driven specification of sample size.

If we assume 5% of patients will use UMEC/VI off-label, then a sample size of 1,000 new users in each group produces a 95% confidence interval equal to the sample proportion plus or minus 1.3% (NCSS PASS: Confidence interval of a proportion)

A recently conducted study (GSK protocol: WEUSKOP6976) identified nearly 40,000 (N=39,639) new users of COPD maintenance therapy with a long acting bronchodilator in a prevalent COPD cohort over a 4-year period (2009-2012) extracted from the CPRD GOLD. Fifty-four percent (N=21,366) of these new users were newly prescribed with LAMA containing treatment regimen. Therefore, we can expect at least 10,000 new LABD users in the CPRD GOLD alone over the up to 24 month of the patients' identification period.

We will conduct regular checks of the UMEC/VI and UMEC uptake, on a 6-monthly basis.

8.6. Data management

Data will be collected retrospectively from the selected databases. All programming will be performed using Stata (StataCorp. College Station, TX) or SAS (Cary, NC). A trained epidemiologist and database analyst will perform all programming and analysis work.

Selection of the data integration model will be dependent on the final choice of partner databases. We will evaluate all options including:

- A minimally integrated model where all data extraction, processing and analysis is conducted entirely separately for each database, with a pooled analysis of aggregate data undertaken by the co-ordinating centre.

- A maximally integrated model where data from each database is combined at the earliest opportunity using a common data model. Whether the integrated dataset exists

physically (in a single database), or virtually (with data stored in a number of structurally identical but physically separated databases), all subsequent processing analysis is carried out using a single suite of programs.

- In practice the level of data integration may fall between these two extremes, and may vary for different database partners.

For all data management and analysis tasks undertaken by database partners, we will encourage standardisation as far as possible through provision of detailed specifications including dataset specifications and variable naming conventions, algorithms and pseudo-code for derived variables, and sharing of Stata programs for complex analytical tasks.

8.6.1. Data handling conventions

Definitions and data handling conventions are described in other sections.

8.6.2. Resourcing needs

GSK will outsource this study to the CPRD. GSK will closely collaborate and monitor the deliverables including finalization of the study protocol, acquisition of data from data partners, development of the common data model, and development of programs and conducting the analysis, and finalizing the study report. Further, the Scientific Committee will provide an oversight of the study conduct including deliverables from the CPRD.

8.6.3. Timings of Assessment during follow-up

The proposed analysis design is descriptive using retrospective EMR cohort of patients newly prescribed with UMEC/VI, UMEC or other LABD. As this study is purely observational without any intervention, there are no specific assessments.

8.7. Data analysis

A detailed statistical analysis plan will be prepared and managed by the CPRD and agreed with GSK and Scientific Committee.

8.7.1. Essential analysis

8.7.1.1. Describing the exposure cohorts

Descriptive statistics (mean (SD); median (range)) on the duration of time until censoring and the reasons for censoring for the full cohort as well as by index medication group (UMEC, UMEC/VI or other LABD) will be described. Descriptive statistics will also be provided for all cohorts (CPRD+THIN, CPRD-GOLD only, THIN and CPRD-GOLD patients eligible for linkage with both HES and ONS data).

For the UMEC and UMEC/VI cohort, descriptive statistics (mean (SD); median (range)) on the duration of time *currently exposed* will be also described.

The proportion of patients contributing more than one index drug will also be described. For these patients the mean (SD) time in days between the discontinuation date of the first index medication and the index date of the subsequent medication (in cases where the two index medications do not overlap) or the mean (SD) time during which the two index medications overlap (in cases where the medication do overlap) will also be calculated.

Further, the proportion of UMEC and UMEC/VI users that were flagged as taking concomitant maintenance therapy at the index date (See Section 8.3.1.2 for definition) will be calculated and the type of concomitant drug described. Lastly, descriptive analysis using traits specified in Section 8.3.3 for each of the three drug groups (UMEC, UMEC/VI and other LABD) will be performed with count and percentage for categorical variables and mean (SD) for continuous variables. The total count of exacerbations will be categorised as described in Section 8.3.3. As well, the exacerbation rate (expressed per person-year) and 95% confidence interval will be calculated. For the rate calculations, the numerator will be the total number of exacerbations and the denominator will be all person time from 12 months prior to the prescription initiation date up to and including the prescription initiation date.

8.7.1.2. Objective 1

In new users of UMEC/VI, UMEC, or other LABD, report the proportion of patients with possible off-label prescribing and characterize them, using information available prior to and at the time of index prescription initiation, in respect to patient demographics, disease burden, co-morbidity, and COPD or asthma medication use.

This objective will be explored among all new users combined and for each cohort, UMEC/VI, UMEC, or other LABD separately. If sample size allows, patients in the other LABD cohort will be further stratified by type of index LABD (LAMA, LABA, LAMA/LABA).

Patients in each defined exposure category (UMEC/VI, UMEC, or other LABD) will be split into the three pre-defined disease categories of 1) COPD, 2) asthma, and 3) neither COPD nor asthma (see Section 8.3.2.1 for definitions) and frequencies tabulated. The proportion of patients with potential off-label prescribing will also be calculated as defined in Section 8.3.2.1.

As well, for the COPD and asthma groups, we will describe what proportion had the diagnosis before and after their medication index date (as a binary variable (before/after) and by distinct time periods before and after such as 0-3 months, 3-6 months, etc).

Descriptive analysis using traits specified in Section 8.3.3 will be reported for each of the three main disease categories of COPD, asthma, and neither COPD nor asthma with count and percentage for categorical variables and mean (SD) for continuous variables. Further, the descriptive statistics will be repeated in the groups of patients who are identified as on label and potentially prescribed off label UMEC or UMEC/VI.

The total count of exacerbations will be categorised (for patients with COPD) as described in Section 8.3.3 and a summary per category tabulated. As well, the exacerbation rate (expressed per person-year) and 95% confidence interval will be calculated. For the rate calculations, the numerator will be the total number of exacerbations and the denominator will be all person time from 12 months prior to the prescription initiation date up to and including the prescription initiation date.

8.7.1.3. Objective 2

In new users of UMEC/VI and UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality, pneumonia, and rate of exacerbations of COPD during follow-up.

We will enumerate counts and rates (new events/person-time) of pre-defined events (See Section 8.3.2.2 for definitions) within each of the new user cohorts of UMEC/VI and UMEC during follow-up. All analyses will be descriptive. Further, all analyses will be split by concomitant ICS-containing medication use at index date.

For the primary analysis, we will enumerate counts and rates for outcome events occurring during follow-up time classified as *currently exposed to UMEC or UMEC/VI* (see Section 8.3.1 for exposure definitions). First, using the full cohort of patients with identification of events in primary care data only (both CPRD and THIN data sources). And secondly, using information from primary care, secondary care (HES) and mortality data (ONS) in patients eligible for linkage with both HES and ONS data.

Two secondary analyses will be carried out in both primary care data only and in those with linked to HES and ONS:

1. enumerate counts and rates for outcome events occurring during follow-up classified as *currently AND previously exposed to UMEC or UMEC/VI*.

2. enumerate counts and rates for outcome events occurring during follow-up classified as *currently exposed* to UMEC or UMEC/VI in patients who have had a concurrent treatment with other maintenance therapy at any time (see Section 8.3.1.3 for definition of concurrent treatment), and separately, enumerate counts and incidence (or rate for COPD exacerbations) for outcome events occurring during *currently exposed* follow-up to UMEC or UMEC/VI in patients who have NOT had a concurrent treatment at any time.

For counts of myocardial infarction, first *and* subsequent events occurring during the relevant follow up will be included. For calculation of incidence rates with 95% confidence intervals, we will consider only the first occurrence of myocardial infarction for each patient, and censor the person time for any patient at the time of occurrence of the first outcome event. The incidence rate will be stratified by presence of past events of myocardial infarction as collected from available patients' history and stratified as none, one, and two or more prior events. Further, we will take the first event of myocardial

infarction and ascertain time from index date to the first event. The time to first event will be visualised using Kaplan-Meier plot.

Identical analysis will be conducted for the events of stroke and pneumonia.

For newly diagnosed congestive heart failure, only patients with new diagnosis of congestive heart failure will be placed in numerator. The denominator will only consist of patients at risk of incident congestive heart failure, i.e., excluding patients with ongoing management of heart failure at index date from the analysis.

Counts and incidence for cardiovascular outcomes will be stratified by concomitant beta-blocker prescribing at index date. Concomitant use will be defined as in Section 8.3.1.2 - at least two continuous prescriptions for a beta-blocker which start either before, or up to 30 days after the index date, and overlap for at least 30 days with the index treatment.

Death will be flagged and summarised as a proportion of patients who died. Further, we will calculate survival rate by dividing the total number of deaths by person-time from index date until date of death or other censoring. Survival time will be visualised using Kaplan-Meier plot. The primary analysis will additionally enumerate counts and incidence of cardiovascular death.

For exacerbations of COPD (as defined in Section 8.3.3) all events occurring during the relevant follow up will be included. For calculation of rates with 95% confidence intervals, the rate will be calculated as total count of exacerbation events divided by the relevant person-time and standardised per person year. To account for additional variability in exacerbation rates between individuals, negative binomial regression will be also considered to produce the rates as well as 95% confidence intervals [Glynn, 1996].

8.7.1.4. Objective 3

In new users of UMEC/VI or UMEC with at least 12 months of follow-up, describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered within the first 12 months of follow-up.

The following analyses will be undertaken separately for new users of UMEC and UMEC/VI. Only prescriptions for inhaler therapies will be considered.

1. Treatment patterns

Among patients that have at least 12 months of follow-up and that do not have concomitant use of another maintenance therapy at index date, describe the count and percentage of patients falling into the four main mutually exclusive categories defined in Section 8.3.2.3 (continuous users, augmenters, switchers and discontinuers). The count and percentage of discontinuers that (a) truly discontinue, (b) restart the index therapy after a break, and (c) start a new maintenance therapy after a break, will also be described. As well, the mean (SD) time (in days) from the index to the first change (among those with a change) will be reported and a Kaplan-Meier plot created.

For patients with at least 12 months of follow-up who are taking a concomitant COPD maintenance therapy at index date, the count and percentage of patients falling into the mutually exclusive categories defined in Section 8.3.2.3 will be described. Treatment patterns may be limited to only the commonly prescribed concomitant therapy groups may be described to ensure adequate sample size. As well, the mean (SD) time (in days) from the index date to the first change (among those with a change) will be calculated and a Kaplan-Meier plot will be created.

Note: As it is not possible to determine whether a patient discontinues UMEC or UMEC/VI if they are censored between 31 and 90 days after their last prescription, these patients will be flagged, and the primary analysis will take a conservative approach for these patients and assume they were only exposed for the 30 days period following their last prescription.

2. Treatment adherence

Calculate the count and percentage of patients who are adherent to the initially prescribed therapy during follow-up using the MPR and PDC as described in Section 8.3.2.3. As well as cut offs of >=80% for the MPR and PDC, the mean (SD) of these measures as continuous variables during follow-up will also be calculated.

The calculation of MPR requires that patients received at least two prescriptions during the required 12 months period of follow-up; the PDC can be calculated with only one prescription and also requires a fixed follow-up period of 12 months. Therefore, the denominator and the numbers of patients eligible for these two measures will differ.

Patients will first be stratified as adherent or non-adherent to initial therapy with UMEC or UMEC/VI based on (a) MPR >=80% and MPR <80% during follow-up, and (b) PDC >=80% and PDC <80% during the first 12 months of follow-up. Patient demographics, co-morbidity, disease burden, and other COPD and asthma medications (as defined in Section 8.3.3) will be described for adherent and non-adherent patient groups for each of MRC and PDC definitions with count and percentage for categorical variables and mean (SD) for continuous variables. Additional analyses and adjustments to the planned analysis may be performed as the data warrant.

8.7.2. Exploratory analysis

The following exploratory sensitivity analyses are planned:

1. For the definition of possible off-label prescribing in Objective 1, in addition to the definitions described in Section 8.3.2, an alternative time period to identify COPD or asthma diagnoses that spans the whole patient history until the prescription index date only, will be used.
2. For Objective 2, just the primary analysis will be further stratified by on-label and possible off-label prescribing.

3. For Objective 3 analyses will be further stratified by on-label and possible off-label prescribing.

8.7.3. General considerations for data analyses

Not Applicable

8.8. Quality control

CPRD-GOLD has been used previously for descriptive drug utilization studies for prescription medications in respiratory diseases [DiSantostefano, 2014; Ashworth, 2004; van Staa, 2003]. Validated code lists have been published from multiple databases including CPRD for myocardial infarction event [Hammad, 2008; Coloma, 2013; Herrett, 2013] and ischaemic stroke [Ruigomez, 2010].

The standard operating procedures of CPRD and of each research partner in the distributed network will guide the conduct of the study, and will include internal quality audits; following rules for secure storage and backup of confidential data and study documentation; quality control procedures for programming, and requirements for senior scientific review. All patients will be required to have data of acceptable research quality according to each database standards.

The QC of analysis will be performed in accordance with GSK Standard Operating Procedures (SOPs) and Guidance Documents, specifically the SOP_52213 (4.0) : Conducting Quality Control Review of Worldwide Epidemiology Study Results . The common data model will allow the use of one set of programming following creation of a standardised structure. Wherever feasible, all statistical programming will be independently reviewed by a second analyst, with oversight by a senior statistician. Key study documents, such as the ISAC Protocol, statistical analysis plan, and study reports will undergo quality-control checks and review by the Scientific Steering Committee. Archiving of the project materials will be performed in accordance with GSK SOPs for documentation and archiving of observational studies.

8.9. Limitations of the research methods

Sample size within a given timeframe is difficult to predict since it depends upon the rate of prescribing by primary care physicians and, hence, the study size and timelines are cautiously estimated.

Generalizability of the UK data to the other EU countries can represent a study limitation. GSK proposed this study in the UK environment, because of the presence of robust data and possibility to use a distributed design within one health-care system ensuring fast delivery. GSK will compare patient population characteristics (inclusive of gender, age,

COPD severity and prior treatment) in patients identified in this retrospective study with patients prospectively enrolled in the multi-country European study. If a different patient profile or pattern of use for UMEC/VI or UMEC among patients with COPD is observed, GSK will initiate additional drug utilization study representing other countries within the EU with high quality medical records data available.

Data on new exposure to UMEC/VI, UMEC, or other LABD are based on records of prescribed medications, rather than dispensed data. Currently, information on prescriptions initiated in hospitals or secondary care are not accessible for analysis. As such, the adherence measures proposed to be calculated in this study are not a "direct" measure of medication taking but rather reflect repeat prescribing.

We also assume that each prescribed medication will provide treatment for 30 days, which may introduce a bias, albeit one of a systematic nature, impacting on all medications.

As this study is primarily aimed to understand the rate of key patient outcomes specifically in new users of UMEC and UMEC/VI, the design of the study only assigns current and previously exposed follow-up time to only those users initiating one (or both) of these drugs in the identification period of July 1, 2014 to June 30, 2016. By this design, new users of Other LABD who may have switched to either UMEC or UMEC/VI after the identification period during the *one-year follow-up window* will not have that UMEC or UMEC/VI exposure time counted in this study. Despite this, we feel we still will have captured a broad cross section of new users of UMEC and UMEC/VI in the immediate post approval period for these mediations.

The final sets of databases, CPRD GOLD and THIN, are both based on the same GP software (Vision) and have comparable data structures and coding schemes. This reduces complexity in the analyses with CPRD performing the bulk of the post-extraction data processing and analysis tasks. This provides the greatest control over standardisation and quality assurance of the analyses.

There are no routine databases available to researchers capturing for secondary and tertiary care prescribing in the UK. Hence, we will not be able to ascertain exposure start accurately in the cases where the UMEC/VI, UMEC, or other LABD was initially prescribed by a chest specialist or at discharge from the hospital. There is only one pilot project managed by the IMS Company providing data on prescribing in secondary/tertiary care, but the link to primary care data is available only for a small subset of CPRD GOLD practices only resulting in a total of only few hundreds of COPD patients.

The ascertainment of the pneumonia events from GP records may lead into issues with misclassification of the event. We will not be able to access chest x-ray results or analysis of sputum samples to confirm the diagnosis and, therefore, the resulting event rates will need to interpret with caution. Similarly, heart failure may be misclassified as undiagnosed COPD [Valk, 2015].

Using information recorded in secondary care (HES) and at the time of death (ONS mortality data) will enable better capture of pneumonia, heart failure and other outcomes,

including acute exacerbations of COPD which may be under-recorded in GP records. However, better classification of these outcomes comes at a cost of reduced sample size as not all patients in the study will be eligible for linkage to HES and ONS.

8.9.1. Study closure/uninterpretability of results

If uptake of the UMEC/VI or UMEC is lower than expected and fewer than 500 patients per group is ascertained the descriptive information about off-label medication use and medication usage patterns may not be as robust. If identification of UMEC/VI patients results in fewer patients than anticipated, GSK will consider either extending the patient identification period beyond two years and/or add additional databases to the study.

8.10. Other aspects

Not Applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

CPRD and other similar EMR systems are databases of pseudonymised EMRs. Our approach to the study is naturalistic; we will not be conducting further diagnostic tests, alter disease management strategies, or collect data in addition to or above routine medical care. Where further information is likely to be helpful, for example for ascertaining cardiovascular endpoints, this will be sought from the patients' registered GP, usually via a structured questionnaire, and/or anonymised chart review (for example copies of hospital discharge letters). This is a well-established process co-ordinated and managed by a separate group within CPRD to ensure that researchers and analysts with access to the EMR database cannot identify individual general practices or patients.

Linkage of the primary care databases to other datasets such as HES is undertaken by a trusted third party (the Health and Social Care Information Centre). The identifiers (date of birth, gender, NHS number, postcode of residence) required for linkage are sent directly from the originating general practice to the trusted third party. CPRD holds only a local patient identifier which is meaningful only at the patients' registered general practice. This identifier is pseudonymised a second time before being made available to researchers and analysts with access to the database.

CPRD's processes have been reviewed by the Confidentiality Advisory Group (CAG) and approved by the Health Research Authority (HRA) and Secretary of State to process patient identifiable information without consent under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002. This effectively removes the obligation to obtain patient consent for the use of confidential patient information for

conducting purely observational research using CPRD databases, and associated linked datasets. This approval is conditional on approval of a study protocol by the CPRD Independent Scientific Advisory Committee (ISAC).

9.2. Subject confidentiality

CPRD and other EMR databases in the distributed network contain only fully de-identified patient data. No patient identifiable information will be available to the study team, or to GSK. All data held and processed by CPRD and any other partners in the distributed network will be done so in compliance with the relevant legal obligations including the Data Protection Act 1998.

All data will be held on a secure computer network, with access restricted to authorised users.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on the study objectives, it is unlikely that adverse events will be identified during this descriptive drug utilization study. Further, as the research utilises existing data sources of anonymised patient data, the minimum criteria needed to report serious and non-serious adverse events, pregnancy exposures, and other incidents related to a GSK product are not present in the data and thus there is no potential for reporting of adverse events, pregnancy exposures and other incidents in this study. The following minimum criteria for reporting are missing from the data sources: an identifiable patient.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The final report of this Post-Authorization Safety Study will be provided to the European Medicines Agency and reported in appropriate regulatory documents in accordance with regulations. This study will also be submitted for consideration in the published literature.

11.2. Study reporting and publications

External communications

Interim and Final study reports will lead into development of peer-reviewed publications in collaboration with Scientific Committee.

Internal communications

Interim and Final reports will be circulated and archived according to GSK SOPs.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Tables

Complete list of Tables will be determined in a separate document of the Statistical analysis plan.

Figures

Complete list of Figures will be determined in a separate document of the Statistical analysis plan.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:
WWE117397: Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting

Study reference number:
EUPAS7761

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Study progress report(s)	☒	☐	☐	5
1.1.4 Interim progress report(s)	☒	☐	☐	5
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6; 7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2.1

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	8.7.1.3
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	8.1
4.2.2 Age and sex?	☒	☐	☐	8.3.3
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	8.3.2.1
4.2.5 Duration of follow-up?	☒	☐	☐	8.3.1.3

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	8.3.1; 8.9
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	8.3.1.3
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	8.3.2; 8.9
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☒	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☐	☒	☐	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.3.2
9.1.3 Covariates?	☒	☐	☐	8.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3.2
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.3.2
9.3.3 Covariates?	☒	☐	☐	8.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	8.7.1
10.2 Are descriptive analyses included?	☒	☐	☐	8.7.1
10.3 Are stratified analyses included?	☒	☐	☐	8.7.1
10.4 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	8.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	11.1

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.2

Comments:

Ethical clearance is subject to approval of protocol by independent scientific advisory committee.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11.2

Comments:

Name of main author of study protocol: PPD

Date: / /

Signature: _____

Medicines & Healthcare products Regulatory Agency

CPRD More Dimensions to Data

Statistical Analysis Plan

WWE117397: Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting

Investigators: PPD PPD [GSK], PPD [GSK], PPD [GSK], PPD [GSK]

Authors: PPD [CPRD]; PPD [CPRD]

Reviewers: PPD [CPRD]

Date: 14th September 2018

Version: 1.3

ISAC Number: 17_023

Document control sheet

Version	Summary and rationale of change(s)	Prepared by	Date	Reviewed by	Date
0.1	First draft	PPD	04/12/2015		
0.2	Second draft, (now complete and with updated table shells)		07/01/2016	PPD PPD and PPD PPD PPD	
0.3	Third draft (with updated table shells)		22/01/2016	Discussed at Scientific Study Committee (SSC) meeting	
0.4	Incorporating changes following SSC meeting, including updated table shells		05/02/2016	PP and PPD	29/03/2016 and 20/04/2016
0.5	Incorporated changes following detailed client review		04/07/2016	PP	28/11/2016
0.6	Incorporated changes following second client review		06/12/2016	PP	07/12/2016
1.0	Cleaned, changes accepted.		15/12/2016		
1.1	Updated after April 2017 SSC meeting		24/05/2017		
1.2	Updated after Interim report completed		08/01/2018		
1.3	Updated after protocol update from GSK		14/09/2018	PP and PPD PPD PPD	

Table of contents

Scope

This statistical analysis plan (SAP) provides a detailed description of the statistical analyses planned for the delivery of the client's (GSK's) project which includes both interim and final reports. Section 1 lists the objectives of the project, section 2 outlines the data sources that will be used for the interim and final analyses, and sections 3 to 5 provide details of the study period, population and variable definitions. Section 6 gives details of the proposed statistical analysis for both the interim and final analysis. Finally, examples of tables for reporting the results of this study are provided in Annex 5.

1. Study details

Aims and rationale

This study primarily aims to collect data reflecting the 'real-world' experience with umeclidinium/vilanterol (UMEC/VI) and umeclidinium (UMEC) in the post-approval setting. UMEC/VI and UMEC as well as other medications containing only long-acting bronchodilators (LABD) are indicated for the treatment of Chronic Obstructive Pulmonary Disease (COPD). They are not indicated for the treatment of asthma without a concomitant treatment with inhaled steroids (ICS); such use is considered off-label. In addition, both LABD classes of drugs, the long-acting beta2-agonists (LABA) and long-acting antimuscarinics (LAMA) have been associated with an increased risk of cardiovascular events that warrants further investigation. This study will describe the patient population newly prescribed with UMEC/VI, UMEC and other LABD, determine the frequency of off-label use, and evaluate the feasibility of undertaking potential future risk-benefit studies.

Objectives

In the initial post-approval period of up to a maximum 24 months from the start of UMEC/VI and UMEC availability in the UK, we will identify patients newly prescribed long-acting bronchodilators (LABD) from a set of the UK primary care Electronic Medical Records (EMR) databases and conduct drug utilization review focusing on the following aims:

Objective 1: In new users of UMEC/VI, UMEC, or other LABD, report the proportion of patients with a possible off-label prescribing and characterise them, using information available prior to and at the time of index prescription initiation, in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Objective 2: In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality, pneumonia, and exacerbations of COPD occurring during follow-up.

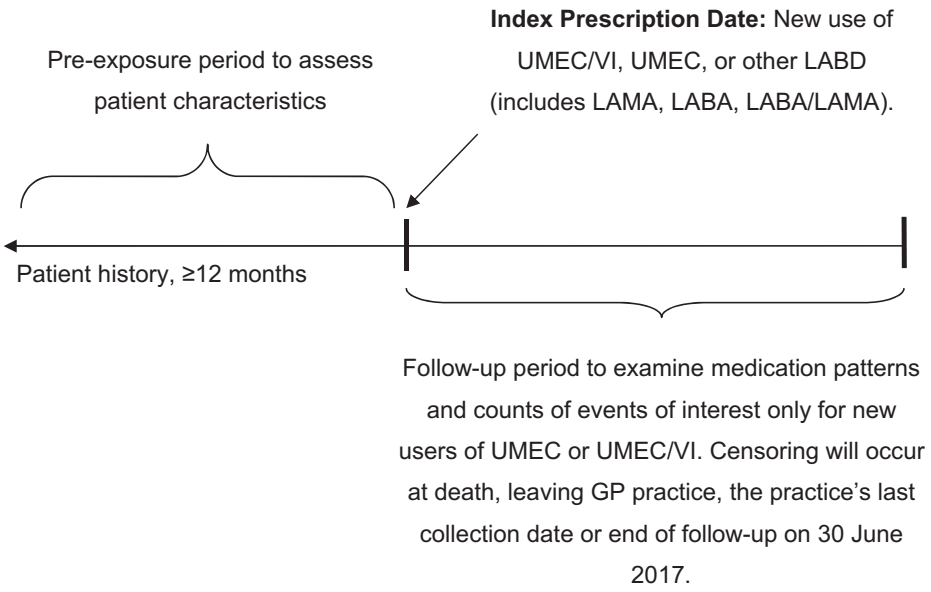
Objective 3: In new users of UMEC/VI or UMEC with 12 or more months of follow-up following initiation, describe treatment patterns and adherence including Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) during follow-up.

Study design

Retrospective longitudinal non-interventional observational study of new users of UMEC/VI, UMEC, or other LABD, identified based on a new prescription (index prescription date) and followed-up from their index prescription date until censoring at death, leaving their GP practice, the practice's last collection date or the end of follow-up on 30 June 2017.

The study schematic is provided in Figure 1.

Figure 1 - Study schematic



2. Data sources

The study will primarily use data from the Clinical Practice Research Datalink and The Health Improvement Network primary care databases (referred to hereafter as CPRD-GOLD and THIN).

Both CPRD-GOLD and THIN comprise the computerised medical records of general practitioners (GPs) who record information using Vision GP software. General practitioners play a key role in the UK health care system, as they are responsible for primary health care and specialist referrals. Individuals are semi-permanently affiliated to a practice, which centralises the medical information from the GPs, specialist referrals and hospitalisations. The data recorded include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. The CPRD-GOLD database currently includes 14.8 million individuals (with acceptable quality medical records) from 1987 onwards, of which data are currently being collected on 3.1 million. The THIN database includes over 12 million individuals of whom roughly 3.6 million are considered as actively contributing. Both CPRD-GOLD and THIN are dynamic databases where patients can join and leave at any time. Data dictionaries for CPRD-GOLD and THIN are available in Annex 1.

Additional analyses will use CPRD linked data sources including:

- Hospital Episodes Statistics (HES): HES is a data warehouse containing details of all inpatient episodes of care (including day cases), outpatient appointments and A&E attendances at NHS hospitals in England. These data are collected during a patient's time primarily for administrative reasons, but the data collection is designed to enable secondary use. As well as patient demographic information and admission and discharge information, the inpatient data includes coded information about diagnoses (ICD-10) and procedures (OPCS 4 codes). Outpatient data contains information about appointment dates and times, and specialties, but much less coded clinical information. This study will use inpatient admissions data only from the CPRD's basic version of HES, referred to hereafter as CPRD-HES. Additional information on CPRD-HES is available in Annex 1.

- Office for National Statistics (ONS) mortality statistics: Mortality data for England and Wales are based on the details collected when deaths are certified and registered. Details available in the linked data include underlying and contributory causes of death and are coded using ICD-9 prior to 2001 and ICD-10 from 2001 onwards. This study will use linked mortality data for England only, referred to hereafter as CPRD-ONS. Additional information on CPRD-ONS is available in Annex 1.

The data sources used for the primary and other analyses are shown in the table below.

Objective	Data source(s) for primary analysis	Data source(s) for other analyses
1: Off-label prescribing	CPRD-GOLD + THIN	CPRD-GOLD + THIN
2: Incidence of adverse events	CPRD-GOLD + THIN and CPRD-HES-ONS	CPRD-GOLD + THIN and CPRD-HES-ONS
3: Treatment patterns and adherence	CPRD-GOLD + THIN	CPRD-GOLD + THIN

Linkage of CPRD-GOLD data to HES and ONS is only possible for a subset of patients registered at English practices which participate in the linkage scheme. Matching of CPRD-GOLD data with the HES and ONS datasets is conducted by a trusted third party (NHS Digital formerly known as the Health and Social Care Information Centre, HSCIC) on an approximately quarterly basis. However, it is difficult to predict the exact coverage period available for the linked datasets prior to the end of the exposure identification period. Matching of CPRD-GOLD with HES and ONS data is based on a stepwise algorithm of 8 matching-steps using a combination of NHS number, date of birth, gender and postcode. Only records matched based on a combination of NHS number and at least one other variable will be considered as valid and successful linkages in this study (corresponding with matching-steps 1 to 5).

The following versions of primary care and linked data will be used:

Data source	Version	Coverage period
CPRD-GOLD	earliest version to include data through the end of the June 2017 (July 2018 build)	01/01/1987 – 30/06/2018
THIN	earliest version to include data through the end of June 2017 (May 2018 database)	01/01/1987 – 15/05/2018
CPRD-HES	earliest version to include data through end of June 2017 (Set 16)	01/04/1997 – 31/12/2017
CPRD-ONS	earliest version to include data through end of June 2017 (Set 16)	01/01/1998 – February/2018

An interim analysis will be conducted at the end of the exposure identification period. This analysis will use data from the earliest available versions of CPRD-GOLD and THIN which include follow-up through the end of June 2017.

All CPRD data, including CPRD-GOLD, CPRD-HES and CPRD-ONS, will be extracted by members of the CPRD Research Team according to the specification outlined in this SAP.

THIN data are to be supplied by the THIN data provider (IQVIA). However, CPRD will work with the THIN data provider to ensure that THIN data are extracted to the exact specification outlined in this SAP.

To address Objective 1, new users of UMEC/VI, UMEC or other LABD will be included, while Objectives 2 and 3 will be limited to new users of UMEC/VI or UMEC only.

3. Source populations

CPRD-GOLD source population

For the primary analysis, the source population will include all research-quality, acceptable[1] [accept=1], male [gender=1] and female [gender=2] patients in the version of CPRD-GOLD specified in section 2. Registration start and end will be defined for all patients in the source population as follows:

- Registration start [regstart] will be equal to the patient's current registration date [crd].
- Registration end [regend] will be equal to the earliest of a patient's transfer out date [todate], the patient's CPRD-GOLD derived date of death[2] [deathdate] and the practice's last collection date [lcd].

For analyses requiring CPRD linked data sets, the source population will be further restricted to patients who are eligible for linkage to HES and ONS data. Patients are considered eligible for linkage (irrespective of whether linkage is actually successful) to HES and ONS mortality data if they:

- are registered in practices contributing to the linkage scheme;
- had a valid NHS number when their identifiers were sent to CPRD's trusted third party (NHS Digital) for linkage; and,
- have not dissented from data transfer to the NHS Digital.

Patients eligible for linkage will be identified using the HES and ONS eligibility flags (hes_e and ons_e) in the linkage_eligibility.txt file. Additional registration start [regstart_link] and registration end [regend_link] variables will be created for patients eligible for linkage. These new variables may or may not be the same as the [regstart] and [regend] variables defined earlier. This is because registration time for patients in this restricted source population will additionally incorporate (and censor on) the start and end dates for the CPRD-HES and CPRD-ONS coverage periods, and registration time will not incorporate the CPRD-GOLD derived date of death [deathdate]. A minority of patients may have a recorded date of death in CPRD-GOLD but not in CPRD-ONS – in analyses

[1] Definition provided in Annex 2.

[2] Definition provided in Annex 2.

using CPRD-ONS and CPRD-HES these patients will be considered not to have died. Registration start and end will be defined as follows.

- Registration Start [regstart_link] will be equal to the latest of a patient's current registration date [crd], the start of CPRD-HES coverage, and the start of CPRD-ONS coverage.

- Registration End [regend_link] will be equal to the earliest of a patient's transfer out date [todate], the end of CPRD-HES coverage, the end of CPRD-ONS coverage, the patient's date of death in CPRD-ONS [dod] and the practice last collection date [lcd]. Occasionally, duplicate death dates can exist in CPRD-ONS when CPRD-GOLD patients are matched to more than patient in CPRD-ONS. In these instances, the nearest [dod] record to the CPRD-GOLD derived death date [deathdate] will be considered valid.

THIN source population

The THIN source population is tailored to replicate as closely as possible the CPRD source population. Patients will be included if they are permanently registered [regstat=02], male [sex=1] or female [sex=2] and have acceptable quality records[3] [patflag=A or patflag=C]. Patients registered with practices which contributed data to both CPRD and THIN during any part of the study period will be excluded from the THIN data.

Registration start and end variables for all patients in the source population will be created as follows:

- Registration start [regstart] will be equal to the latest of a patient's registration date [regdate].

- Registration end [regend] will be equal to the earliest of a patient's transfer out date [xferdate], the patient's date of death[4] as derived by IQVIA [deathdate], and the practice's last collection date [collectdate].

[3] Definition provided in Annex 2.

[4] Definition provided in Annex 2.

4. Study populations

Four main study populations will be identified:

1. CPRD-GOLD cohort
2. THIN cohort
3. Combined CPRD-GOLD and THIN cohort
4. CPRD-GOLD cohort of patients eligible for linkage to both CPRD-HES and CPRD-ONS.

These cohorts will include all patients in the CPRD-GOLD and/or THIN source populations that meet the inclusion and exclusion criteria below.

Inclusion criteria

Patients are required to:

1. Have a record for a prescription of UMEC/VI, UMEC, or other LABD in the 24 months' exposure identification period beginning on 1 July 2014 and ending on 30 June 2016 (inclusive).
2. CPRD-GOLD only - Have at least 12 months of up-to-standard (UTS) [utsdate][5] recorded data prior to first (index) prescription in the exposure identification period to allow characterisation of patient's status, demographics and clinical characteristics (i.e. between [regstart] and [indexdate]).
3. THIN only – Have at least 12 months of recorded data, prior to first (index) prescription and post the Acceptable Mortality Recording (AMR)[6] [amr] date, the date upon which the practice first began using computers to record clinical information [compdate], and the date when the practice first began using Vision GP software [visiondate].

[5] Definition provided in Annex 2.

[6] Definition provided in Annex 2.

Exclusion criteria

Patients will be excluded if they:

1. Have a prescription for the same exact substance (or combination) of LABD ever recorded in the past prior to index date [indexdate].
2. To evaluate Objective 1, all patients newly prescribed UMEC/VI, UMEC, or other LABD will be included; Objectives 2 and 3 will be limited to new users of UMEC/VI or UMEC only.
3. Patients in the 'Other LABD – LABA/LAMA' will be included based on:
   - a new prescription for a LABA/LAMA in one inhaler device, or
   - a new prescription for both LABA and LAMA (in separate devices) issued on the same day
   - The other LABD group will be analysed as a single combined group, and where appropriate and sample size allows, stratified as LAMA, LABA, and LAMA/LABA.
   - No other LABD drugs will be analysed individually.
   - The new use of ICS/LABA combinations in a single device is not considered as new other LABD unless it is accompanied with a new prescription for LAMA.

For LABA/LAMA products, the index date will be the date of prescription for the combination or separate devices. All prescriptions for LABD will be considered to last 30 days from the date of prescription. Specific rules to account for situations where multiple index prescriptions occur on the same day are listed below:

Qualifying index medication group	Category	Generic names	Brand names	Single** or combination ** substance LABD	Additional rules
The following LABD will be considered as index medications.					
UMEC/VI	LABA / LAMA	umeclidinium + vilanterol	anoro	combination	
UMEC	LAMA	umeclidinium	incruse, laventair	single	
UMEC & UMEC/VI*					New users in both UMEC and UMEC/VI
UMEC/VI & LABA/LAMA *					New user of UMEC/VI with Concomitant Other LABA/LAMA
UMEC/VI & LABA*					New user of UMEC/VI with Concomitant Other LABA

Qualifying index medication group	Category	Generic names	Brand names	Single** or combination ** substance LABD	Additional rules
The following LABD will be considered as index medications.					
UMEC/VI & LAMA*					New user of UMEC/VI with Concomitant Other LAMA
UMEC & LABA*					New user of UMEC with Concomitant Other LABA
Other LABD *[Other LABA]*	LABA	salmeterol	serevent, vertine, neovent	single	
	LABA	formoterol	oxis, foradil, atimos modulite, eformoterol	single	
	LABA	indacaterol	onbrez	single	
	LABA	olodaterol	striverdi	single	
Other LABD *[Other LAMA]*	LAMA	tiotropium	spiriva	single	
	LAMA	glycopyrroniu m	seebri	single	
	LAMA	aclidinium	eklira	single	
Other LABD *[Other LABA / LAMA]*	LABA / LAMA	glycopyrroniu m + indacaterol	ultibro, [seebri + onbrez]	combination	
	LABA / LAMA	formoterol + aclidinium	duaklir, [(oxis, foradil, atimos modulite, eformoterol , symbicort, duoresp spiromax, fostair, flutiform) + eklira]	combination	
	LABA / LAMA	tiotropium + olodaterol	spiolto, stiolto, [spiriva + stiverdi]	combination	
LABA/LAMA &					Other LABA/LAMA as index

Qualifying index medication group	Category	Generic names	Brand names	Single** or combination ** substance LABD	Additional rules
The following LABD will be considered as index medications.					
LABA/LAMA *					medication, counted only once
LABA/LAMA & LAMA					LABA/LAMA as index medication, counted only once
LABA/LAMA & LABA*					LABA/LAMA as index medication, counted only once
LAMA & LAMA*					Other LAMA as index medication, counted only once
LABA & LABA*					Other LABA as index medication, counted only once

** prescriptions on same day*

*** The term single here applies to a single LABD, irrespective of whether the product is in the same device as an inhaled corticosteroid (ICS). Similarly, the term combination here is used to refer to multiple LABDs, irrespective of whether the products are in the same device.*

Study follow-up

For Objectives 2 new users of UMEC/VI and UMEC, defined in the identification period in the CPRD-GOLD and THIN study populations will be followed from their index prescription date until their censoring date [censordate] which is the earliest of the patients' registration end [regend] (which incorporates death date and transfer out date), the practice's last collection date and the end of follow-up on 30 June 2017.

For patients in the CPRD-GOLD cohort of patients eligible for linkage to both CPRD-HES and CPRD-ONS, follow-up will continue until the earliest of [regend_link] and 30 June 2017.

Data extraction processes

CPRD data will be extracted as tab delimited text files using the version specified in section 2 of this SAP. Full data will be extracted for all patients meeting the inclusion criteria. These full data will then be used to identify and exclude patients with prior prescriptions for the same exact LABD or combination of LABD.

IQVIA will supply THIN data for patients meeting the inclusion criteria for the study. CPRD will filter these data to identify and exclude patients with prior prescriptions for the same exact LABD or combination of LABD.

Raw data will be manipulated separately in the CPRD-GOLD and THIN cohorts. THIN variables will be renamed using CPRD naming convention where possible to facilitate combining data at earliest point possible. Because patid is only unique by practice in THIN, a combined patid+prac variable will be used instead of patid for THIN data.

Data integration model for combined CPRD-GOLD and THIN cohort

A maximally integrated model will be developed where data from each database is combined at the earliest opportunity using variables and definitions described in section 5. At this point a variable will be created to indicate the source database for each patient ([source] = 1 for CPRD or [source] = 2 for THIN). All subsequent processing analysis will be carried out using a single suite of programs.

5. Variables and definitions

Exposure

Timings will be based on the prescription event date variables in CPRD [eventdate] and THIN [prscdate]. All prescriptions for LABD will be given a default length of 30 days per container prescribed, irrespective of whether the prescription has a recorded value for script length.

A single patient will be able to contribute more than one qualifying index medication during the identification period if they meet the definition of new use for multiple medications. A patient may qualify for new uses of both UMEC and UMEC/VI if that patient switches between the two during the identification period. A patient may also qualify for more than one 'Other LABD' containing the same active substance (e.g. glycopyrronium and glycopyrronium/indacaterol) or an 'Other LABD' (such as tiotropium) and UMEC or UMEC/VI.

Patients who contribute for a second or third qualifying index medication will be given a new identifier [patid] with a suffix of _2 or _3 to differentiate between their first, second and third qualifying index medications. Patients with multiple qualifying index medications will be considered as separate individuals in the analyses. Variables for these patients may or may not change depending on the two or more index dates of the patients.

Concomitant use of other medications at index date (UMEC/VI, UMEC)

Given the naturalistic nature of the study design, it is possible that some patients will initiate UMEC or UMEC/VI while on other maintenance medications. In some instances, these patients will be transitioning from the old medication to the new one and there is a small overlap. In other cases, they may continue to take both medications for a period of time. Of particular interest is concomitant use of an ICS-containing medication along with the index medication, as this will be used as a stratification variable for several of the study objectives.

We will search the patient record and flag instances when patients are receiving concomitant COPD maintenance therapy at the time of the index prescription. Concomitant therapy will be defined as at least two continuous prescriptions for the other COPD maintenance therapy which start either before, or up to 30 days after the index date, and overlap for at least 30 days with the index treatment. Only single device or fixed dose combination maintenance therapies will be considered when defining concomitant maintenance medications.

Concomitant medication at index date will be considered in new users of UMEC and UMEC/VI only.

Exposure period:

For Objective 2, exposure time will be categorised for UMEC/VI and UMEC users (only). Exposure time to UMEC or UMEC/VI during follow-up will be classified in several categories:

Currently exposed to UMEC/VI or UMEC*:* current exposure is exposure time starting from the index date and continuing until the earliest of:

1. The censoring date (i.e. patient continuously used the index medication during the whole study period)
   OR
2. Discontinuation of prescribing the index medication (UMEC or UMEC/VI) considered to have occurred if there is either:
   - A break of at least 91 days between prescriptions for the index medication. The discontinuation date is set at 30 days after the prescription prior to the break. (*Note: After this break, the patient may resume the same index medication (drug hiatus*) or switch to a different inhaled COPD medication.
     or
   - Complete discontinuation in prescribing of the index medication and no further inhaled COPD medication of any kind until the censoring date. The discontinuation date is set at 30 days after the final prescription.

   It will not be possible to determine whether a patient discontinues UMEC or UMEC/VI if they are censored between 31 and 90 days after their last prescription. These patients will be flagged, and the primary analysis will take a conservative approach for these patients and assume they were only exposed for the 30 day period following their last prescription.

   If a patient discontinues the index medication but resumes taking that index medication at a later date, the second exposure period will also be considered as part of “currently exposed” time.

OR

3. An immediate switch to another inhaled COPD medication
   - Patient starts taking another inhaled COPD medication during an interval that is between ≤30 days before the discontinuation date for the index treatment and ≤60 days after the discontinuation date for the index treatment. The immediate switching date will be defined as the date of first prescription for the new therapy.

***Previously exposed to UMEC/VI or UMEC**:* for patients with a defined discontinuation date or a switch date (see above), previous exposure to an index medication is all person-time starting from the discontinuation or switch date and continuing until either the censoring date (in instances of complete discontinuation), or, the date the patient resumes taking the same index medication (in instances of a drug hiatus).

Note: Patients who continuously use their index medication through to censoring will have no "previously exposed time" defined.

Concurrent exposure to other COPD maintenance therapies:

As it is possible that some patients will be taking another COPD maintenance therapy concomitantly at index date or will start up another COPD maintenance therapy at some time during follow up while still taking their index medication, we will also flag patients who have had periods of time where they are exposed to more than just the index medication. This flag will be used as a stratification variable in a secondary analysis for objective 2.

Concurrent exposure is any person-time starting from the date of the first prescription for another COPD maintenance therapy (or the index date in the case of therapies started concomitant with the index medication), and continuing until the earliest of the censoring date, the discontinuation date for the other COPD maintenance therapy (if observed, i.e. complete cessation or a break of at least 91 days between prescriptions) or the discontinuation date for the index medication (if observed).

The terms 'baseline' and 'at cohort entry' are used interchangeably in this SAP, and unless specified otherwise, refer to a patient's medical history up to (and sometimes including) the index date.

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
Index medication group	index_cat1	categorical *(never missing)*	1 = UMEC; 2 = UMEC/VI; 3 = other LABD	Category of qualifying index medication.	[prodcode] from ***all_labd*** group of code lists in therapy file	[drugcode] from ***all_labd*** group of code lists in therapy file
	index_cat2	categorical *(never missing)*	1 = UMEC; 2 = UMEC/VI; 3 = other LABD-LAMA; 4 = other LABD-LABA; 5 = other LABD-LAMA/LABA	Category of qualifying index medication.	[prodcode] from ***all_labd*** group of code lists in therapy file	[drugcode] from ***all_labd*** group of code lists in therapy file
	index_tio2_5	binary (never missing)	0 = no; 1 = yes;	Qualifying index medication is 2.5mcg tiotropium product.	[prodcode] from **tiotropium_25_June2018** code list in therapy file	[drugcode] form **tiotropium_25_THIN1801** code list in therapy file
Index date	indexdate	date *(never missing)*	date	First prescription for the qualifying index medication within 1 July 2014 and 30 June 2016. For patients who qualify with an open LABA/LAMA combination, the index date will be the date of first overlap between LABA and LAMA.	[prodcode] from ***all_labd*** group of code lists in therapy file	[drugcode] from ***all_labd*** group of code lists in therapy file
Censoring date	censordate	date *(never missing)*	date	Earliest of a patient's transfer out date, the patient's date of death as recorded in primary care, the practice's last collection date and 30 June 2017.	[todate] and [deathdate] in patient file; [lcd] in practice file	[xferdate] and [deathdate] in patient file; [collectdate] in practice file
	censordate_link	date *(never missing)*	date	Earliest of a patient's transfer out date, the end of CPRD-HES coverage, the end of CPRD-ONS coverage, the patient's date of death in CPRD-ONS, the practice last collection date and 30 June 2017.	[todate] in patient file; [lcd] in practice file; [dod] in CPRD-ONS	n/a
Reason for censoring	censor_cat	categorical *(never missing)*	1 = death (from primary care record); 2 = left (transferred out of) GP practice;	Type of record associated with reason for censoring. If multiple records on one day, priority is given as follows: death, leaving practice, last collection date, end of follow-up	[todate] and [deathdate] in patient file; [lcd] in practice file	[xferdate] and [deathdate] in patient file; [collectdate] in practice file

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
			3 = practice last collection date 4 = end of follow-up on 30 June 2017			
	censor_cat_link	categorical *(never missing)*	1 = death (from death certificate, CPRD-ONS); 2 = left (transferred out of) GP practice; 3 = practice last collection date 4 = end of follow-up on 30 June 2017	Type of record associated with reason for censoring. If multiple records on one day, priority is given as follows: death (from CPRD-ONS), leaving practice, last collection date, end of follow-up.	[todate] in patient file; [lcd] in practice file; [dod] in CPRD-ONS	n/a
Censored 31 to 90 days after last prescription of UMEC/VI or UMEC	censor_flag	binary *(never missing in patients in UMEC/VI or UMEC groups)*	0 = no; 1 = yes; . = missing	Indicates that last prescription (in patients not meeting definition of discontinuation) was issued between 31-90 days before censoring.	derived from [censordate] variable and date associated with [prodcode] from ***UMEC & UMEC/VI*** code lists in therapy file	derived [censordate] variable and date associated with [drugcode] from ***UMEC & UMEC/VI*** code lists in therapy file
	censor_flag_link	binary *(never missing in patients in UMEC/VI or UMEC groups)*	0 = no; 1 = yes; . = missing	Last prescription (in patients not meeting definition of discontinuation) is between 31-90 days before censoring.	derived from [censordate_link] variable and date associated with [prodcode] from ***UMEC & UMEC/VI*** code lists in therapy file	n/a
Date of discontinuation of the index medication (UMEC/VI or UMEC only)	disdate_N	date	date; . = missing	30 days after date of last prescription before a break of ≥91 days. Only for patients prescribed UMEC/VI or UMEC.	date associated with [prodcode] from ***UMEC & UMEC/VI*** code lists in therapy file	date associated with [drugcode] from ***UMEC & UMEC/VI*** code lists in therapy file

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
End of exposure period	CEEdate_N	date *(never missing in patients in UMEC/VI or UMEC groups)*	date; . = missing	Earliest of censor date (for patients with no discontinuation) or date of last prescription + 30 days.	derived from [censordate], [censor_flag] and [disdate_N] variables	derived [censordate], [censor_flag] and [disdate_N] variables
	CEEdate_N_link	date	date; . = missing	Earliest of censor date (for patients with no discontinuation) or date of last prescription + 30 days.	derived from [censordate_link] and [disdate_N] variables	n/a
Time period when index medication was initiated	timeperiod	categorical *(never missing)*	1 = 01/07/2014 – 30/09/2014; 2 = 01/10/2014 – 31/12/2014; 3 = 01/01/2015 – 31/03/2015; 4 = 01/04/2015 – 30/06/2015; 5 = 01/07/2015 – 30/09/2015 6 = 01/10/2015 – 31/12/2015 7 = 01/01/2016 – 31/03/2016 8 = 01/04/2016 – 30/06/2016	Time period when index medication was initiated.	derived from [indexdate] variable	derived [indexdate] variable
Concomitant prescribing of beta-blockers	beta_blocker_con	binary *(never missing in patients in UMEC/VI or UMEC groups)*	0 = no; 1 = yes	Two or more prescriptions which start either <[indexdate] or ≤[indexdate]+30 and overlap for ≥30 days with the index treatment.	[prodcode] from ***beta_blocker_June2018*** code list in therapy file	[drugcode] from ***beta_blocker_THIN1801*** code list in therapy file
Concomitant prescribing of other maintenance therapy at index date (UMEC & UMEC/VI only)	ics_con	binary *(never missing)*	0 = no; 1 = yes	Two or more prescriptions which start either <[indexdate] or ≤[indexdate]+30 and overlap for ≥30 days with the index treatment.	[prodcode] from ***ics_June2018*** code list in therapy file	[drugcode] from ***ics_THIN1801*** code list in therapy file
	icssaba_con	binary *(never missing)*	0 = no; 1 = yes	Two or more prescriptions which start either <[indexdate] or ≤[indexdate]+30 and overlap for ≥30 days with the index treatment.	[prodcode] from ***saba+ics_June2018*** code list in therapy file	[drugcode] from ***saba+ics_THIN1801*** code list in therapy file
	laba_con	binary	0 = no; 1 = yes;	Two or more prescriptions which start either <[indexdate] or ≤[indexdate]+30	[prodcode] from ***laba_June2018***	[drugcode] from ***laba_THIN1801***

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
			. = missing (if index medication is a LABA)	and overlap for ≥30 days with the index treatment.	code list in therapy file	code list in therapy file
	icslaba_con	binary	0 = no; 1 = yes; . = missing (if index medication is a LABA)	Two or more prescriptions which start either <[indexdate] or ≤[indexdate]+30 and overlap for ≥30 days with the index treatment.	[prodcode] from ***ics+laba_June2018*** o code lists in therapy file	[drugcode] from ***ics+laba_THIN1801*** code list in therapy file
	lama_con	binary	0 = no; 1 = yes; . = missing (if index medication is a LAMA)	Two or more prescriptions which start either <[indexdate] or ≤[indexdate]+30 and overlap for ≥30 days with the index treatment.	[prodcode] from ***lama_June2018*** code list in therapy file	[drugcode] from ***lama_THIN1801*** code list in therapy file
	labalama_con	binary	0 = no; 1 = yes; . = missing (if index medication is a LABA/LAMA)	Two or more prescriptions which start either <[indexdate] or ≤[indexdate]+30 and overlap for ≥30 days with the index treatment.	[prodcode] from ***laba+lama_June2018*** code list in therapy file	[drugcode] from ***laba+lama_THIN1801*** code list in therapy file
	theoph_con	binary *(never missing)*	0 = no; 1 = yes	Two or more prescriptions which start either <[indexdate] or ≤[indexdate]+30 and overlap for ≥30 days with the index treatment.	[prodcode] from ***theophylline_June2018*** code list in therapy file	[drugcode] from ***theophylline_THIN1801*** code list in therapy file
	any_con	binary *(never missing)*	0 = no; 1 = yes	Two or more prescriptions for any concomitant COPD maintenance therapy which start either <[indexdate] or ≤[indexdate]+30 and overlap for ≥30 days with the index treatment.	derived [ics_con], [icssaba_con], and [icslaba_con], [laba_con], [lama_con], [labalama_con], [theoph_con] variables	derived [ics_con], [icssaba_con], and [icslaba_con], [laba_con], [lama_con], [labalama_con], [theoph_con] variables
	anyics_con	binary *(never missing)*	0 = no; 1 = yes	Two or more prescriptions for any ICS therapy which start either <[indexdate] or ≤[indexdate]+30 and overlap for ≥30 days with the index treatment.	derived [ics_con], and [icslaba_con] variables	derived [ics_con], and [icslaba_con] variables

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
Gap (in days) between index medications	index_gap	count	≥0; . = missing	Number days between index date of new qualifying medication and discontinuation date for old qualifying medication, in patients who qualify for more than one medication and where last prescription date is before new index date.	derived [indexdate], [index_mult], [disdate_N] and [patid] variables	derived [indexdate], [index_mult], [disdate_N] and [patid] variables
Overlap (in days) between index medications	index_over	count	≥0; . = missing	Number days between discontinuation date for old qualifying medication and index date for new qualifying medication, in patients who qualify for more than one medication and where the discontinuation date is on or after the new index date.	derived [indexdate], [index_mult], [disdate_N] and [patid] variables	derived [indexdate], [index_mult], [disdate_N] and [patid] variables
Concurrent COPD maintenance therapy	any_concurrent	binary	0 = no; 1 = yes	Two or more maintenance therapy prescriptions which start during a period of current exposure to UMEC or UMEC/VI and overlap for ≥30 days with the index treatment. Event date is equal to the first prescription for another COPD maintenance therapy (or the index date in the case of therapies started concomitantly with the index medication), and continuing until the earliest of the censoring date, the discontinuation date for the other COPD maintenance therapy.	derived: [indexdate], [index_mult], [censordate], [disdate_N] and [patid] variables	derived: [indexdate], [index_mult], [censordate], [disdate_N] and [patid] variables

Outcomes

Outcome variables are grouped according to the three main study objectives. Unless otherwise specified, timings will be based on the event date ([eventdate] in CPRD-GOLD and THIN) or prescription date ([eventdate] in CPRD-GOLD and [prscdate] in THIN) variables in CPRD-GOLD and THIN. Timings in CPRD-HES will be based on the [admidate] variable.

Objective 1: Off-label prescribing (All patients) – CPRD-GOLD+THIN

Possible off-label prescribing will be flagged by reporting a proportion of new UMEC/VI, UMEC, or other LABD users with a diagnosis of: (a) COPD, (b) asthma, or (c) neither COPD nor asthma.

These definitions will be applied in a stepwise manner, whereby the definition of COPD will be applied first. For those who do not meet the COPD definition, we will then look to see if they fulfil the case definition of asthma. Lastly, patients who meet neither the COPD nor asthma definition will be captured in the third category.

1. **COPD:** Patients will be considered to have COPD if they have a COPD diagnosis recorded any time in their CPRD history up to and including the index UMEC/VI, UMEC, or other LABD prescription date through their censoring date and were age 35 years or older at the time of their first ever COPD medical code.
2. **Asthma:** Patients who did not fulfil the case definition of COPD as described above will be considered to have asthma if their most recent asthma medical code is a maximum of two years prior to their index date (up to and including the index UMEC/VI, UMEC, or other LABD prescription date through to their censoring date).
3. **Neither COPD nor asthma:** Patients will be classified into this category if they did not meet either the definition of COPD or asthma above.

Possible off-label definitions:

Possible off label prescribing of UMEC (primary definition):

- **Proportion of all UMEC users in the asthma group or the neither asthma nor COPD group**

$$\frac{\text{\# patients in “Asthma group” or “Neither asthma nor COPD group” with an index prescription for UMEC}}{\text{\# patients with an index prescription for UMEC}}$$

Possible off label prescribing of UMEC/VI (primary definition):

- **Proportion of all UMEC/VI users in the asthma or the neither asthma nor COPD group**

$$\frac{\text{\# patients in “Asthma group” or “Neither asthma nor COPD group” with an index prescription for UMEC/VI}}{\text{\# patients with an index prescription for UMEC/VI}}$$

Possible off label prescribing for the other LABD group will be calculated as described above separately for other LAMA, other LABA and other LAMA/LABA. Denominators in both cases will be all patients with an index prescription in that particular LABD group.

For the other LAMA subgroup only, a secondary definition will also be used to account for the September, 2014 authorisation of tiotropium to be used as an add on therapy to ICS/LABA for the treatment of asthma in patients with asthma exacerbations. Other LAMA sub-group off-label prescribing definition 2 will therefore be defined as prescribing of other LAMA in patients in the asthma or other diagnosis group *unless they had an asthma diagnosis and an index prescription for 2.5mcg tiotropium on or after 13/09/2014 and a concomitant prescription of an ICS/LABA at index date*

For the other LABA subgroup only, a secondary definition will also be used to account for the fact that LABA plus an ICS in two devices might be an option utilized to treat asthma. Other LABA sub-group off-label prescribing definition 3 will therefore be defined as prescribing of an Other LABA in the asthma or other diagnosis group *unless they had an asthma diagnosis and a concomitant ICS at index date along with their index Other LABA.*

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
Date of first COPD record (at any age)	d_copd_any	date	date; . = missing	date of earliest record of COPD prior to and including censor date (≤[censordate])	[eventdate] associated with [medcode] from ***copd_June2018*** code list in clinical and referral files	[eventdate] associated with [medcode] from ***copd_THIN1801*** code list in medical file
	d_copd_any_sens	date	date; . = missing	date of earliest record of COPD prior to and including the index date (≤[indexdate])	[eventdate] associated with [medcode] from ***copd_June2018*** code list in clinical and referral files	[eventdate] associated with [medcode] from ***copd_THIN1801*** code list in medical file
COPD	copd	binary *(never missing)*	0 = no; 1 = yes	patient is age ≥35 at time of earliest record of COPD [d_copd_any] prior to and including censor date (≤[censordate])	derived [d_copd_any] variable and [yob] in patient file	derived [d_copd_any] variable and [yob] in patient file
	copd_sens	binary *(never missing)*	0 = no; 1 = yes	patient is age ≥35 at time of earliest record of COPD [d_copd_any_sens] prior to and including the index date (≤[indexdate])	derived [d_copd_any_sens] variable and [yob] in patient file	derived [d_copd_any_sens] variable and [yob] in patient file
Date of first COPD record (in patients meeting COPD definition)	d_copd	date	date; . = missing (only if [copd]=0)	date of earliest record of COPD prior to and including censor date (≤[censordate]) in patients with COPD ([copd]=1)	derived [d_copd_any] and [copd] variables	derived [d_copd_any] and [copd] variables
	d_copd _sens	date	date; . = missing (only if [copd_sens] =0)	date of earliest record of COPD prior to and including index date (≤[indexdate]) in patients with COPD according to the sensitivity definition ([copd_sens] =1)	derived [d_copd_any_sens] and [copd_sens] variables	derived [d_copd_any_sens] and [copd_sens] variables
Timing of first COPD record in relation to	t_copd_cat1	categorical	0 = on / before; 1 = after; . = missing (only if [copd]=0)	relative timing (on/before or after) between date of earliest COPD record and index date [indexdate] in patients with [copd]=1	derived [d_copd] date and [indexdate]	derived [d_copd] date and [indexdate]

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
the index date	t_copd_cat2	categorical	1 = >6 months before 2 = >3 and ≤6 months before 3 = ≥0 and ≤3 months before; 4 = >0 and ≤3 months after; 5 = >3 and ≤6 months after; 6 = >6 months after; . = missing (only if [copd]=0)	relative timing in months (of 30 days) between date of earliest COPD record and index date [indexdate] in patients with [copd]=1	derived [d_copd] date and [indexdate]	derived [d_copd] date and [indexdate]
	t_copd_sens_cat2	categorical	1 = >6 months before 2 = >3 and ≤6 months before; 3 = ≥0 and ≤3 months before; . = missing	relative timing in months (of 30 days) between date of earliest COPD record and index date [indexdate] in patients with [copd_sens] =1	derived [d_copd_sens] date and [indexdate]	derived [d_copd_sens] date and [indexdate]
Asthma (not COPD)	asthma	binary *(never missing)*	0 = no; 1 = yes	no record of COPD ([copd]=0) AND record of asthma up to 2 years prior to their index date [indexdate-720 days] and up to the censor date (≤[censordate])	[medcode] from **asthma** code list in clinical or referral file; derived [copd] variable;	[medcode] from ***asthma_THIN1609*** code list in medical file; derived [copd] variable;
	asthma_sens	binary *(never missing)*	0 = no; 1 = yes	no record of COPD according to the sensitivity definition ([copd_sens]=0) AND record of asthma up to 2 years prior to their index date [indexdate-720 days]	[medcode] from **asthma** code list in clinical or referral file; derived [copd_sens] variable	[medcode] from ***asthma_THIN1609*** code list in medical file; derived [copd_sens] variable
Date of indexed asthma record (in patients meeting asthma definition)	d_asthma	date	date; . = missing (only if [asthma]=0)	date of earliest record of asthma no more than 2 years prior to index date in patients with asthma ([asthma=1])	[eventdate] associated with derived [asthma] variable in clinical and referral files	[eventdate] associated with derived [asthma] variable in medical file
	d_asthma_sens	date	date; . = missing (only if [asthma_sens] =0)	date of earliest record of asthma no more than 2 years prior to index date in patients with asthma according to the sensitivity definition ([asthma_sens=1])	[eventdate] associated with derived [asthma_sens] variable in clinical and referral files	[eventdate] associated with derived [asthma_sens] variable in medical file
Timing of first indexed asthma record in	t_asthma_cat1	categorical	0 = on / before; 1 = after; . = missing (only if [asthma]=0)	relative timing (on/before or after) between date of earliest asthma record and	derived [d_asthma] date and [indexdate]	derived [d_asthma] date and [indexdate]

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
relation to index date				index date in patients with [asthma]=1		
	t_asthma_cat2	categorical	1 = >6 months before; 2 = >3 and ≤6 months before; 3 = ≥0 and ≤3 months before; 4 = >0 and ≤3 months after; 5 = >3 and ≤6 months after; 6 = >6 months after; . = missing (only if [asthma]=0)	relative timing (in months of 30 days) between date of earliest asthma record and index date in patients with [asthma]=1	derived [d_asthma] date and [indexdate]	derived [d_asthma] date and [indexdate]
	t_asthma_sens_cat2	categorical	1 = >6 months before; 2 = >3 and ≤6 months before; 3 = ≥0 and ≤3 months before; . = missing	relative timing (in months of 30 days) between date of earliest asthma record and index date in patients with [asthma_sens] =1	derived [d_asthma_sens] date and [indexdate]	derived [d_asthma_sens] date and [indexdate]
Other (not COPD, not asthma)	other	binary *(never missing)*	0 = no; 1 = yes	no record of COPD ([copd]=0) AND no record of asthma ([asthma]=0)	derived [copd] variable and derived [asthma] variable	derived [copd] variable and derived [asthma] variable
	other_sens	binary *(never missing)*	0 = no; 1 = yes	no record of COPD according to the sensitivity definition ([copd_sens] =0) AND no record of asthma according to the sensitivity definition ([asthma_sens] =0)	derived [copd_sens] variable and derived [asthma_sens] variable	derived [copd_sens] variable and derived [asthma_sens] variable
Off-label prescribing	offlabel1	binary *(never missing)*	0 = no; 1 = yes	New users of UMEC, UMEC/VI, other LAMA, other LABA or other LAMA/LABA with no evidence of COPD ([copd]=0	derived [copd] & [index_cat2] variable	derived [copd] & [index_cat2] variable
	offlabel2	binary *(never missing)*	0 = no; 1 = yes	New users of other LAMA only, with no evidence of COPD ([copd]=0) unless, and patient has evidence of asthma ([asthma]=1) **and** an index prescription for 2.5mcg tiotropium on or after 13/10/2014 **and** a concomitant prescription	derived [copd] & [index_cat2], [asthma], [index_tio2_5] variables	derived [copd] & [index_cat2], [asthma], [index_tio2_5] variables

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
				ICS+LABA at the index date ([icslaba_con]=1)		
	offlabel3	binary *(never missing)*	0 = no; 1 = yes	New users of other LABA only, with no evidence of COPD *([copd]=0 recorded at any time between registration start (≥[regstart]) and the censor date (≤[censordate])* unless, the patient has evidence of asthma ([asthma]=1) **and** the patient is concomitantly prescribed ICS at the index date ([ics_con]=1)	derived [copd], [index_cat2], [ics_con] and [asthma], and [indexdate] variables	derived [copd], [icslaba_con] and [asthma], and [indexdate] variables

Objective 2 – Incidence of adverse events (UMEC & UMEC/VI ONLY) – CPRD+THIN and CPRD-HES-ONS

In new users of UMEC/VI and UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality, pneumonia, and rate of exacerbations of COPD during follow-up.

Enumerate counts and rates (new events/person-time) of outcomes within each of the new user cohorts of UMEC/VI and UMEC during follow-up. Further, all analyses will be split by concomitant ICS-containing medication use at index date.

Primary analysis:

Counts and rates for outcome events occurring during follow-up time classified as *currently exposed to UMEC or UMEC/VI* in 1) primary care data only (CPRD+THIN) and 2) primary care, secondary care (HES) and mortality data (ONS) (CPRD-HES-ONS).

Secondary analyses:

Carried out in both 1) primary care data only (CPRD+THIN) and 2) primary care, secondary care (HES) and mortality data (ONS) (CPRD-HES-ONS).

1. Counts and rates for outcome events occurring during follow-up classified as *currently **AND** previously exposed to UMEC or UMEC/VI*.
2. Counts and rates for outcome events occurring during follow-up classified as *currently exposed* to UMEC or UMEC/VI in patients **AND** stratified by patients who had or did not have a concurrent treatment with other maintenance therapy while currently exposed to UMEC or UMEC/VI.

NB. In order to differentiate between the occurrence of multiple adverse events and multiple records (in primary care or in primary and secondary care) for a single adverse event, the following windows will be used to group records into a single event episode:

- Congestive heart failure (CHF): only newly diagnosed (i.e. incident after the index date) CHF is of interest, and therefore no gaps are required to differentiate between multiple events and multiple records in primary/secondary care for a single event. For analyses using linked CPRD data, the earliest record of CHF in CPRD-GOLD or CPRD-HES will be selected. Only patients with new diagnosis of CHF will be placed in the numerator. The denominator will only consist of patients at risk of incident congestive heart failure, i.e., excluding patients with ongoing management of heart failure at index date from the analysis.

- myocardial infarction (MI): any records ≤7 days apart will be considered as part of the same episode[7].
- stroke: any records ≤7 days apart will be considered as part of the same episode
    - Counts and incidence for cardiovascular outcomes (MI, CHF and stroke) will be stratified by concomitant beta-blocker prescribing at index date. Concomitant beta-blocker is defined as at least two continuous prescriptions for a beta-blocker which start either before, or up to 30 days after the index date, and overlap for at least 30 days with the index treatment.
- pneumonia: any records ≤28 days apart will be considered as part of the same episode[8]
    - For counts of MI, stroke and pneumonia, first *and* subsequent events occurring during the relevant follow up will be included. For calculation of incidence rates with 95% confidence intervals, we will consider only the first occurrence for each patient and censor the person time for any patient at the time of occurrence of the first outcome event. The incidence rate will be stratified by presence of past events as collected from available patients' history and stratified as none, one, and two or more prior events. Further, we will take the first event and ascertain time from index date to the first event. The time to first event will be visualised using Kaplan-Meier plot.
- Death: Event of death will be derived from CPRD GOLD and THIN using Read Code lists or specifics flags. Death will be flagged and summarised as a proportion of patients who died. Further, we will calculate survival rate by dividing the total number of deaths by person-time from index date until date of death or other censoring. The primary analysis will additionally enumerate counts and incidence of cardiovascular death.
    - Cardiovascular death will use data from ONS mortality statistics in the linked cohort.
- Acute exacerbation of COPD (aecopd): any records ≤14 days apart will be considered as part of the same episode[9]. The full definition of an aecopd is provided in annex 4. All events occurring during the relevant follow up will be included. For calculation of rates with 95%

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[7] Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van ST et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ. 2013; 346:f2350.

[8] Millett ER, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PLoS One. 2013 Sep 11;8(9):e75131.

[9] Rothnie KJ, Müllerova H, Hurst JR, Smeeth L, Davis K, Thomas SL, Quint JK. Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare recrods., PLoS One, 2016 DOI: 10.1371/journal.pone.015135.

confidence intervals, the rate will be calculated as total count of exacerbation events divided by the relevant person-time and standardised per person year. To account for additional variability in exacerbation rates between individuals, negative binomial regression will be also considered to produce the rates as well as 95% confidence.

Full definition for acute exacerbation of COPD (AECOPD)

AECOPD will be defined in CPRD-GOLD and THIN using an algorithm developed by Jennifer Quint's research group.[10], with further refinements implemented by GSK. Briefly:

Primary care derived AECOPD, i.e. GP recording of COPD exacerbation, is defined as the presence of one of the four following events:

1. Prescriptions for antibiotics (ATB) AND oral corticosteroids (OCS) for a length of 5 to 14 days each (both prescriptions must have the same start date but each can last for a different number of days);
2. Presence of respiratory symptoms (codes suggesting an increase in two or more of: breathlessness, cough, or sputum volume and/or purulence recorded on the same date) and a prescription for ATB or OCS (or both) on the same day;
3. Lower Respiratory Tract Infection (LRTI) medical code;
4. AECOPD specific medical code:

Events of AECOPD requiring hospital admission, also called severe exacerbations, are identified in the Hospital Episodes Statistics (HES), using ICD-10 codes, which must appear in a relevant diagnostic position (i.e. primary diagnosis or any diagnosis).

Full details of both algorithms are included in Annex 4. This includes all code lists. Read code lists have been developed using CPRD-GOLD and will be translated to equivalent THIN codelists.

[10] Rothnie KJ, Müllerova H, Hurst JR, Smeeth L, Davis K, Thomas SL, Quint JK. Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare recrods., PLoS One, 2016 DOI: 10.1371/journal.pone.015135.

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
Myocardial infarction (MI) after index date	mi_current	count *(never missing)*	≥0	Number of MI events (recorded in primary care) following initiation and during follow-up classified as *currently* exposed to UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate])	[medcode] in ***mi_Dec2015*** in clinical or referral files	[medcode] in ***mi_THIN1505*** in medical file
	mi_prev	count *(never missing)*	≥0	Number of MI events (recorded in primary care) following initiation and during follow-up classified as *currently and previously* exposed to UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate])	[medcode] in ***mi_Dec2015*** in clinical or referral files	[medcode] in ***mi_THIN1505*** in medical file
	mi_current_hes	count *(never missing in those eligible for analysis)*	≥0; . = missing	Number of MI events (inpatient admissions or records in primary care) following initiation and during follow-up classified as *currently* exposed to UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate_link])	[ICD_PRIMARY] in ***mi_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***mi_Dec2015*** in clinical or referral files	n/a
	mi_prev_hes	count *(never missing in those eligible for analysis)*	≥0; . = missing	Number of MI events (inpatient admissions or records in primary care) following initiation and during follow-up classified as *currently and previously* exposed to UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate_link])	[ICD_PRIMARY] in ***mi_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***mi_Dec2015*** in clinical or referral files	n/a
Date of first MI after index date	d_mi_current	date	date; . = missing	Date of first MI (recorded in primary care) following initiation and during follow-up classified as *currently* exposed to, UMEC or UMEC/VI (i.e. [mi_current]≥1;])	[eventdate] associated with [medcode] for ***mi_Dec2015*** in clinical or referral files	[eventdate] associated with [medcode] in ***mi_THIN1505*** in medical file
	d_mi_prev	date	date; . = missing	Date of first MI (recorded in primary care) following initiation and during follow-up classified as *currently* and previously exposed	eventdate] associated with [medcode] for ***mi_Dec2015*** in clinical or referral files	[eventdate] associated with [medcode] in ***mi_THIN1505*** in medical file

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
				to, UMEC or UMEC/VI (i.e. [mi_prev]≥1;])		
	d_mi_current_hes	date	date; . = missing	Date of first MI event (inpatient admission or record in primary care) following initiation of, *and while currently exposed to, UMEC or UMEC/VI* (i.e. [mi_current_hes]≥1)	[admidate] associated with [ICD_PRIMARY] for ***mi_icd*** in HES_primary_diag_hosp.txt and [eventdate] associated with [medcode] for ***mi_Dec2015*** in clinical or referral files	n/a
	d_mi_prev_hes	date	date; . = missing	Date of first MI event (inpatient admission or record in primary care) following initiation of, *and while currently and previously exposed to, UMEC or UMEC/VI* (i.e. [mi_prev_hes]≥1)	[admidate] associated with [ICD_PRIMARY] for ***mi_icd*** in HES_primary_diag_hosp.txt and [eventdate] associated with [medcode] for ***mi_Dec2015*** in clinical or referral files	n/a
MI on or prior to index date	mi_base_cat1	categorical *(never missing)*	0 = no prior events; 1 = any prior events	Any MI (recorded in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	[medcode] in ***mi_Dec2015*** in clinical or referral files	[medcode] in ***mi_THIN1505*** in medical file
	mi_base_cat2	categorical *(never missing)*	0 = no prior events; 1 = 1 prior event; 2 = 2+ prior events	Number of MIs (recorded in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	[medcode] in ***mi_Dec2015*** in clinical or referral files	[medcode] in ***mi_THIN1505*** in medical file
	mi_hes_base_cat1	categorical *(never missing in those eligible for analysis)*	0 = no prior events; 1 = any prior events	Any MI (inpatient admission or record in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	ICD_PRIMARY] in ***mi_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***mi_Dec2015*** in clinical or referral files	n/a
	mi_hes_base_cat2	categorical *(never missing in those*	0 = no prior events; 1 = 1 prior event;	Number of MIs (inpatient admission or record in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	[ICD_PRIMARY in ***mi_icd*** in HES_primary_diag_hosp.txt and [medcode]	n/a

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
		eligible for analysis)	2 = 2+ prior events		in ***mi_Dec2015*** in clinical or referral files	
Stroke after index date	stroke_current	count *(never missing)*	≥0	Number of strokes (recorded in primary care) following initiation and during follow-up classified as *currently* exposed to, UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate])	[medcode] in ***stroke_Dec2015*** in clinical or referral files	[medcode] in ***stroke_THIN1505*** in medical file
	stroke_prev	count *(never missing)*	≥0	Number of strokes (recorded in primary care) following initiation and during follow-up classified as *currently and previously* exposed to, UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate])	[medcode] in ***stroke_Dec2015*** in clinical or referral files	[medcode] in ***stroke_THIN1505*** in medical file
	stroke_current_hes	count *(never missing in those eligible for analysis)*	≥0; . = missing	Number of strokes (inpatient admissions or records in primary care) following initiation and during follow-up classified as *currently* exposed *to UMEC or UMEC/VI* (i.e. all periods of exposure >[indexdate] and ≤[censordate_link])	[ICD_PRIMARY] in ***stroke_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***stroke_Dec2015*** in clinical or referral files	n/a
	stroke_prev_hes	count *(never missing in those eligible for analysis)*	≥0; . = missing	Number of strokes (inpatient admissions or records in primary care) following initiation and during follow-up classified as *currently and previously* exposed to *UMEC or UMEC/VI* (i.e. all periods of exposure >[indexdate] and ≤[censordate_link])	[ICD_PRIMARY] in ***stroke_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***stroke_Dec2015*** in clinical or referral files	n/a
Date of first stroke after index date	d_stroke_current	date	date; . = missing	Date of first stroke (recorded in primary care) following initiation and during follow-up classified as *currently* exposed to UMEC or UMEC/VI (i.e. [stroke_current]≥1)	[eventdate] associated with [medcode] for ***stroke_Dec2015*** in clinical or referral files	[eventdate] associated with [medcode] in ***stroke_THIN1505*** in medical file
	d_stroke_prev	date	date; . = missing	Date of first stroke (recorded in primary care) following initiation and during follow-up classified as	[eventdate] associated with [medcode] for	[eventdate] associated with [medcode] in

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
				currently and previously exposed to UMEC or UMEC/VI (i.e. [stroke_prev]≥1)	***stroke_Dec2015*** in clinical or referral files	***stroke_THIN1505*** in medical file
	d_stroke_current_hes	date	date; . = missing	Date of first stroke (inpatient admission or primary care record) following initiation and during follow-up classified as *currently* exposed to *UMEC or UMEC/VI* (i.e. [stroke_current_hes]≥1;)	[admidate] associated with [ICD_PRIMARY] for ***stroke_icd*** in HES_primary_diag_hosp.txt and [eventdate] associated with [medcode] for ***stroke_Dec2015*** in clinical or referral files	n/a
	d_stroke_prev_hes	date	date; . = missing	Date of first stroke (inpatient admission or primary care record) following initiation and during follow-up classified as *currently and previously* exposed to *UMEC or UMEC/VI* (i.e. [stroke_prev_hes]≥1;)	[admidate] associated with [ICD_PRIMARY] for ***stroke_icd*** in HES_primary_diag_hosp.txt and [eventdate] associated with [medcode] for ***stroke_Dec2015*** in clinical or referral files	n/a
Stroke on or prior to index date	stroke_base_cat1	categorical *(never missing)*	0 = no prior events; 1 = any prior events	Any stroke (recorded in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	[medcode] in ***stroke_Dec2015*** in clinical or referral files	[medcode] in ***stroke_THIN1505*** in medical file
	stroke_base_cat2	categorical *(never missing)*	0 = no prior events; 1 = 1 prior event; 2 = 2+ prior events	Number of strokes (recorded in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	[medcode] in ***stroke_Dec2015*** in clinical or referral files	[medcode] in ***stroke_THIN1505*** in medical file
	stroke_hes_base_cat1	categorical *(never missing in those eligible for analysis)*	0 = no prior events; 1 = any prior events	Any stroke (inpatient admission or record in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	[ICD_PRIMARY] in ***stroke_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***stroke_Dec2015*** in clinical or referral files	n/a
	stroke_hes_base_cat2	categorical *(never missing in*	0 = no prior events;	Number of strokes (inpatient admission or record in primary	[ICD_PRIMARY] in ***stroke_icd*** in HES_primary_diag_ho	n/a

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
		those eligible for analysis)	1 = 1 prior event; 2 = 2+ prior events	care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	sp.txt and [medcode] in ***stroke_Dec2015*** in clinical or referral files	
Existing congestive heart failure (CHF) at baseline	chf_base	binary *(never missing)*	0 = no; 1 = yes;	Primary care record of CHF at any time prior to and including the index date (i.e. ≤[indexdate])	[medcode] in ***chf_Dec2015*** in clinical or referral files	[medcode] in ***chf_THIN1505*** in medical file
	chf_hes_base	binary *(never missing in those eligible for analysis)*	0 = no; 1 = yes; . = missing	Record of CHF (in primary or secondary care) at any time prior to and including the index date (i.e. ≤[indexdate])	[ICD_PRIMARY] in ***chf_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***chf_Dec2015*** in clinical or referral files	n/a
New CHF (diagnosed after index date)	chf_current	binary *(never missing in those eligible for analysis)*	0 = no; 1 = yes; . = missing	Occurrence of CHF (recorded in primary care) following initiation and during follow-up classified as *currently* exposed to UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate]) amongst patients with no previous CHF (i.e. [chf_base]=0)	[medcode] in ***chf_Dec2015*** in clinical or referral files	[medcode] in ***chf_THIN1505*** in medical file
	chf_prev	binary *(never missing in those eligible for analysis)*	0 = no; 1 = yes; . = missing	Occurrence of CHF (recorded in primary care) following initiation and during follow-up classified as *currently and previously* exposed to UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate]) amongst patients with no previous CHF (i.e. [chf_base]=0)	[medcode] in ***chf_Dec2015*** in clinical or referral files	[medcode] in ***chf_THIN1505*** in medical file
	chf_current_hes	binary *(never missing in those eligible for analysis)*	0 = no; 1 = yes; . = missing	Record of CHF (in primary or secondary care) following initiation and during follow-up classified as *currently* exposed to UMEC or UMEC/VI (i.e.all periods of exposure >[indexdate] and ≤[censordate_link]) amongst patients with no previous CHF (i.e. [chf_hesgold_base]=0)	[ICD_PRIMARY] in ***chf_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***chf_Dec2015*** in clinical or referral files	n/a

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
	chf_prev_hes	binary *(never missing in those eligible for analysis)*	0 = no; 1 = yes; . = missing	Record of CHF (in primary or secondary care) following initiation and during follow-up classified as *currently and previously* exposed to UMEC or UMEC/VI (i.e.all periods of exposure >[indexdate] and ≤[censordate_link]) amongst patients with no previous CHF (i.e. [chf_hesgold_base]=0)	[ICD_PRIMARY] in ***chf_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***chf_Dec2015*** in clinical or referral files	n/a
Date of first CHF, if after index date	d_chf_current	date	date; . = missing	Date of CHF (recorded in primary care) if first CHF occurred following initiation and during follow-up classified as *currently* exposed to UMEC or UMEC/VI (i.e. [chf_current]=1)	[eventdate] associated with [medcode] for ***chf_Dec2015*** in clinical or referral files	[eventdate] associated with [medcode] in ***chf_THIN1505*** in medical file
	d_chf_prev	date	date; . = missing	Date of CHF (recorded in primary care) if first CHF occurred following initiation and during follow-up classified as *currently and previously* exposed to UMEC or UMEC/VI (i.e. [chf_prev]=1)	[eventdate] associated with [medcode] for ***chf_Dec2015*** in clinical or referral files	[eventdate] associated with [medcode] in ***chf_THIN1505*** in medical file
	d_chf_current_hes	date	date; . = missing	Date of first CHF (recorded in primary or secondary care) if first CHF inpatient admission occurred following initiation and during follow-up classified as *currently* exposed to UMEC or UMEC/VI (i.e. [chf_current_hes]=1])	[admidate] associated with [ICD_PRIMARY] for ***chf_icd*** in HES_primary_diag_hosp.txt and [eventdate] associated with [medcode] for ***chf_Dec2015*** in clinical or referral files	n/a
	d_chf_prev_hes	date	date; . = missing	Date of first CHF (recorded in primary or secondary care) if first CHF inpatient admission occurred following initiation and during follow-up classified as *currently* and previously exposed to UMEC or UMEC/VI (i.e. [chf_prev_hes]=1])	[admidate] associated with [ICD_PRIMARY] for ***chf_icd*** in HES_primary_diag_hosp.txt and [eventdate] associated with [medcode] for ***chf_Dec2015*** in clinical or referral files	n/a

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
Pneumonia after index date	pneumonia_current	count *(never missing)*	≥0	Number of episodes of pneumonia (recorded in primary care) following initiation and during follow-up classified as *currently* exposed *to* UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate])	[medcode] in ***pneumonia_Dec2015*** in clinical or referral files	[medcode] in ***pneumonia_THIN1505*** in medical file
	pneumonia_prev	count *(never missing)*	≥0	Number of episodes of pneumonia (recorded in primary care) following initiation and during follow-up classified as *currently and previously* exposed to *UMEC or UMEC/VI* UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate])	[medcode] in ***pneumonia_Dec2015*** in clinical or referral files	[medcode] in ***pneumonia_THIN1505*** in medical file
	pneumonia_current_hes	count *(never missing in those eligible for analysis)*	≥0; . = missing	Number of episodes of pneumonia (inpatient admissions or records in primary care) following initiation and during follow-up classified as *currently* exposed to *UMEC or UMEC/VI* UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate_link])	[ICD_PRIMARY] in ***pneumonia_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***pneumonia_Dec2015*** in clinical or referral files	n/a
	pneumonia_prev_hes	count *(never missing in those eligible for analysis)*	≥0; . = missing	Number of episodes of pneumonia (inpatient admissions or records in primary care) following initiation and during follow-up classified as *currently and previously* exposed to UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate_link])	[ICD_PRIMARY] in ***pneumonia_icd*** in HES_primary_diag_hosp.txt and [medcode] in ***pneumonia_Dec2015*** in clinical or referral files	n/a
Date of first pneumonia after index date	d_pneumonia_current	date	date; . = missing	Date of first episode of pneumonia (recorded in primary care) following initiation and during follow-up classified as *currently* exposed to UMEC or	[eventdate] associated with [medcode] for ***pneumonia_Dec2015*** in clinical or referral files	[eventdate] associated with [medcode] in ***pneumonia_THI***

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
				UMEC/VI (i.e. [pneumonia_current]≥1)		***N1505*** in medical file
	d_pneumonia_prev	date	date; . = missing	Date of first episode of pneumonia (recorded in primary care) following initiation and during follow-up classified as *currently and previously* exposed to UMEC or UMEC/VI (i.e. [pneumonia_prev]≥1)	[eventdate] associated with [medcode] for ***pneumonia_Dec2015*** in clinical or referral files	[eventdate] associated with [medcode] in ***pneumonia_THIN1505*** in medical file
	d_pneumonia_current_hes	date	date; . = missing	Date of first episode of pneumonia (recorded in primary care or resulting in inpatient admission) following initiation and during follow-up classified as *currently* exposed to , UMEC or UMEC/VI (i.e. [pneumonia_current_hes]≥1)	[admidate] associated with [ICD_PRIMARY] for ***pneumonia_icd*** in HES_primary_diag_hosp.txt and [eventdate] associated with [medcode] for ***pneumonia_Dec2015*** in clinical or referral files	n/a
	d_pneumonia_prev_hes	date	date; . = missing	Date of first episode of pneumonia (recorded in primary care or resulting in inpatient admission) following initiation and during follow-up classified as *currently and previously* exposed to , UMEC or UMEC/VI (i.e. [pneumonia_prev_hes]≥1)	[admidate] associated with [ICD_PRIMARY] for ***pneumonia_icd*** in HES_primary_diag_hosp.txt and [eventdate] associated with [medcode] for ***pneumonia_Dec2015*** in clinical or referral files	n/a
Pneumonia on or prior to index date	pneumonia_base_cat1	categorical *(never missing)*	0 = no prior events; 1 = any prior events	Any episodes of pneumonia (recorded in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	[medcode] in ***pneumonia_Dec2015*** in clinical or referral files	[medcode] in ***pneumonia_THIN1505*** in medical file
	pneumonia_base_cat2	categorical *(never missing)*	0 = no prior events; 1 = 1 prior event; 2 = 2+ prior events	Number of episodes of pneumonia (recorded in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	[medcode] in ***pneumonia_Dec2015*** in clinical or referral files	[medcode] in ***pneumonia_THIN1505*** in medical file

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
	pneumonia_hesgold_base_cat1	categorical *(never missing in those eligible for analysis)*	0 = no prior events; 1 = any prior events	Any episode of pneumonia (inpatient admission or record in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	[ICD_PRIMARY] in ***pneumonia _icd*** in HES_primary_diag_hosp.txt and [medcode] in ***pneumonia _Dec2015*** in clinical or referral files	n/a
	pneumonia_hesgold_base_cat2	categorical *(never missing in those eligible for analysis)*	0 = no prior events; 1 = 1 prior event; 2 = 2+ prior events	Number of episodes of pneumonia (inpatient admissions or record in primary care) occurring on, or prior, to the index date (i.e. ≤[indexdate])	[ICD_PRIMARY] in ***pneumonia _icd*** in HES_primary_diag_hosp.txt and [medcode] in ***pneumonia _Dec2015*** in clinical or referral files	n/a
Acute exacerbation of COPD after index date	aecopd_current	count *(never missing)*	≥0	Number of acute COPD exacerbations (recorded in primary care) following initiation and during follow-up classified as *currently* exposed to, UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate])	*See full definition above.*	*See full definition above.*
	aecopd_prev	count *(never missing)*	≥0	Number of acute COPD exacerbations (recorded in primary care) following initiation and during follow-up classified as *currently and previously* exposed to UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate])	*See full definition above.*	*See full definition above.*
	aecopd_current_hes	count *(never missing in those eligible for analysis)*	≥0; . = missing	Number of acute exacerbations of COPD (recorded in primary care or resulting in hospital admission) following initiation and during follow-up classified as *currently* exposed to, UMEC or UMEC/VI (i.e.all periods of exposure >[indexdate] and ≤[censordate_link]).	[ICD_PRIMARY] in ***aecopd_icd*** in HES_primary_diag_hosp.txt and *see full definition above for defining exacerbations in primary care.*	n/a

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
	aecopd_prev_hes	count *(never missing in those eligible for analysis)*	≥0; . = missing	Number of acute exacerbations of COPD (recorded in primary care or resulting in hospital admission) following initiation and during follow-up classified as *currently and previously* exposed to UMEC or UMEC/VI (i.e.all periods of exposure >[indexdate] and ≤[censordate_link]).	[ICD_PRIMARY] in ***aecopd_icd*** in HES_primary_diag_hosp.txt and *see full definition above for defining exacerbations in primary care.*	n/a
Date of death	d_death	date	date; . = missing	Patient date of death as recorded in primary care	[deathdate] in patient file	[deathdate] in patient file if [deathdate] is not 00000000
	d_death_ons	date	date; . = missing	Patient date of death as recorded in ONS mortality register	[dod] in death_patient.txt file	n/a
All-cause mortality	death_current	binary *(never missing)*	0 = no; 1 = yes	Death (recorded in primary care) following initiation and during follow-up classified as *currently* exposed to, UMEC or UMEC/VI (i.e. all periods of exposure >[indexdate] and ≤[censordate])	[deathdate] in patient file	[deathdate] in patient file if [deathdate] is not 00000000
	death_current_ons	binary *(never missing in those eligible for analysis)*	0 = no; 1 = yes; . = missing	Death (as recorded in ONS mortality register) following initiation and during follow-up classified as *currently* exposed to, UMEC or UMEC/VI (i.e.all periods of exposure >[indexdate] and ≤[censordate_link])	[dod] in death_patient.txt file	n/a
Cardiovascular death	cv_death_current_ons	binary *(never missing in those eligible for analysis)*	0 = no; 1 = yes; . = missing	Cardiovascular death (as recorded in ONS mortality register) following initiation and during follow-up classified as *currently* exposed to, UMEC or UMEC/VI (i.e.all periods of exposure >[indexdate] and ≤[censordate_link])	[ICD] in ***cv_icd*** as underlying cause ([cause] in death_patient.txt	n/a
	cv_death_prev_ons	binary *(never missing in those*	0 = no; 1 = yes; . = missing	Cardiovascular death (as recorded in ONS mortality register) following initiation and during follow-up classified as	[ICD] in ***cv_icd*** as underlying cause [cause] in death_patient.txt	n/a

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
		eligible for analysis)		*currently and previously* exposed to UMEC or UMEC/VI (i.e.all periods of exposure >[indexdate] and ≤[censordate_link])		
Date of cardiovascular death	d_cv_death_current_ons	date	date; . = missing	Patient date of cardiovascular death (as recorded in ONS mortality register, [cv_death_onsgold]=1) following initiation and during follow-up classified as *currently* exposed to, UMEC or UMEC/VI	[dod] in death_patient.txt where [ICD] in ***cv_icd*** as underlying cause ([cause]	n/a

Objective 3 – Treatment patterns and adherence (UMEC & UMEC/VI ONLY)

This objective will use the combined CPRD+THIN cohort. For new users of UMEC/VI or UMEC defined during the identification period, treatment patterns and adherence measures will be considered only in patients with a **full 12 months' of follow-up** after their index treatment. It will not be possible to determine whether a patient discontinues UMEC or UMEC/VI if they are censored between 31 and 90 days after their last prescription. These patients will be flagged, and the primary analysis will take a conservative approach for these patients and assume they were only exposed for the 30 days period following their last prescription.

We will describe the first change within the 12 months' period following initiation.

For patients who are **not taking a concomitant COPD (inhalation) maintenance therapy** at the time of the index prescription, we will identify the following patterns:

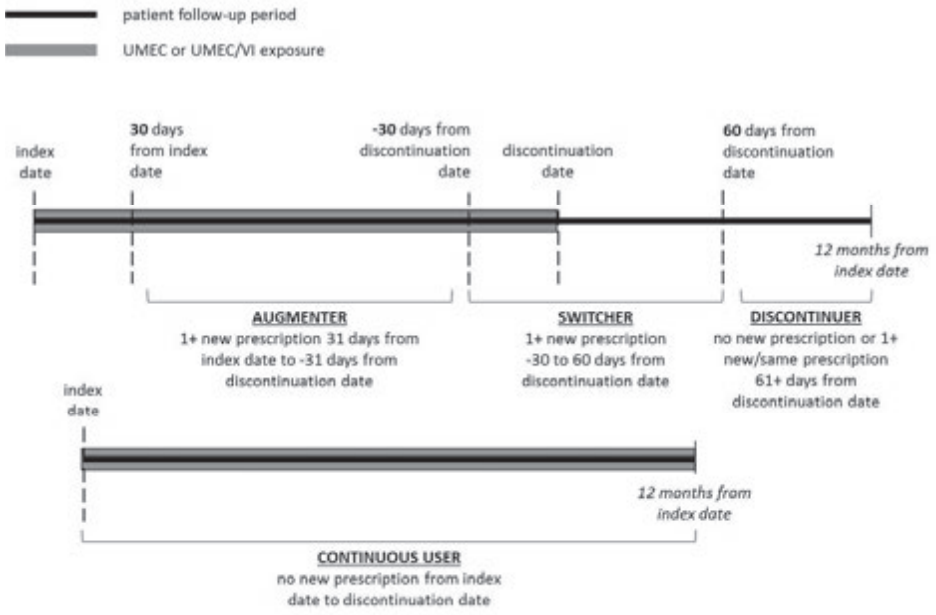
New users of UMEC:

- Continuous UMEC for the full 12 months
- Augment UMEC by adding LABA or ICS/LABA
- Immediate switch to another LAMA, LABA, ICS/LABA
- Discontinue UMEC (further broken down into (a) true discontinuer, (b) restart the index therapy after a break (drug hiatus) and (c) New maintenance therapy after a break (latent switch))

New users of UMEC/VI:

- Continuous UMEC/VI for the full 12 months
- Augment UMEC/VI by adding ICS or ICS/LABA
- Immediate switch to another LAMA, LABA, ICS/LABA or LAMA/LABA
- Discontinue UMEC (further broken down into (a) true discontinuer, (b) restart the index therapy after a break (drug hiatus) and (c) New maintenance therapy after a break (latent switch))

Full definitions of these treatment patterns are as follows:



1. *Continuous use:* Patient DOES NOT start taking another inhaled COPD maintenance therapy and continues to use index treatment (without a break of >91 days) through the 12 month after the index date.
2. *Augmentation:* Patient starts taking another inhaled COPD maintenance therapy (1 or more prescriptions) and the new treatment starts ≥31 days after the index date and ≥31 days before the discontinuation date for the index treatment or the end of 12 months following the index date. The augmentation date will be defined as the date of first prescription for the new COPD maintenance therapy.

   Note: for patients who qualify for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication will be considered a switch and not an augmentation. This is in line with the decision to allow patients to enter the study separately for UMEC and UMEC/VI (i.e. they are considered as separate products).

3. *Immediate switching:* Patient starts taking another inhaled COPD maintenance therapy (1 or more prescriptions) within 12 months of the index date, and the new treatment starts during an interval that is between ≤30 days before the discontinuation date for the index treatment and ≤60 days after the discontinuation date for the index treatment. The switching date will be defined as the date of first prescription for the new COPD maintenance therapy.

Note: for patients who qualify for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication will always be considered a switch.

4. *Discontinuation*: Patient meets the definition of discontinuation within 12 months of the index date and does not meet the definitions for continuous use, immediate switching and augmentation above. Discontinuation is defined as above in variable (disdate_N), in summary a patient has a gap of at least 91 days between consecutive prescriptions for an index medication, or between the last index medication prescription and the censoring date. The discontinuation date is set at 30 days after the prescription prior to the break

Discontinuers will be followed until 12 months after the index date and classified according to whether they:

a) True discontinuer: do not restart the index medication and do not start a new inhaled COPD maintenance treatment (i.e. true discontinuers)

b) Drug hiatus: restart the index medication

c) New maintenance therapy: start a new inhaled COPD maintenance treatment >60 days after discontinuation (i.e. latent switchers).

Note: for patients who qualify for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication will be considered a latent switch based on the rationale described earlier.

For patients who are taking a concomitant COPD (inhalation) maintenance therapy at the time of the index prescription the following treatment patterns will be considered:

In UMEC users taking a concomitant LABA/ICS, other LABA or concomitant other LAMA separately (numbers dependant):

- Continue both medications for the full 12 months, patients are allowed to change the exact type of LABA/ICS (or other LABA, other LAMA) and still be considered as continuing 'both medications'
- Discontinue both medications at the same time
- Discontinue UMEC and continue the LABA/ICS (or other LABA, other LAMA)
- Discontinue the LABA/ICS (or other LABA, other LAMA) and continue UMEC

In UMEC/VI users taking concomitant LABA/ICS, other LABA or other LAMA separately (numbers dependant):

- Continue both medications for the full 12 months, patients are allowed to change the exact type of LABA/ICS (or other LABA, other LAMA) and still be considered as continuing 'both medications'
- Discontinue both medications at the same time
- Discontinue UMEC/VI and continue the LABA/ICS (or other LABA, other LAMA)
- Discontinue the LABA/ICS (or other LABA, other LAMA) and continue UMEC

Full definitions of these treatment patterns are as follows:

1. *Continuous use of both drugs:* Patient continues to use both medications for 12 months from the date of index treatment until censoring.

2. *Discontinuation of index drug (*continue to use the concomitant medication*):* Patient discontinues the index drug within 12 months of the index date, but continues to use the concomitant therapy. The discontinuation date is therefore the date the index drug stopped.

3. *Discontinuation of concomitant drug (*continue to use the index medication*):* Patient discontinues the concomitant therapy within 12 months of the index date, but continues to use the index drug. The discontinuation date of the concomitant drug is therefore the date the concomitant drug stopped.

4. *Discontinuation of both drugs:* Patient meets the definition of discontinuation for both drugs (on the same day) and within 12 months from the index. Discontinuation is defined as gap of at least 91 days between consecutive prescriptions for the same medication, or between the last prescription for that medication and the censoring date.

We will only describe the first change within the 12 month period following initiation.

Treatment adherence

Treatment adherence will be assessed from the index UMEC/VI or UMEC prescription until the end of the 12 month after the index date. Treatment adherence will be measured in the first 12 months of follow-up, for **patients with at least 12 months of follow-up** after initiation of the index drug.

Medication possession ratio (MPR) will be calculated only in those with 12 complete months of follow-up from the index date and at least one additional UMEC or UMEC/VI prescription after the index prescription.

Calculated as follows:

$$\frac{\text{Number of days in possession of UMEC (or UMEC/VI) between last prescription date and index date}}{\text{Total number of days between index date and last prescription date}}$$

Where number of days in possession is calculated by multiplying the number of prescriptions in the period (minus the last prescription) by the assumed duration of 30 days and where last prescription date is the last prescription date recorded before the end of the follow-up period or discontinuation date, whichever occurs first. (*Note: each patient will have a unique denominator*). Additions to the index medication are allowed as long as the patient is still exposed to the index medication.

The MPR will be expressed as a percentage, with nonadherence defined as MPR <80% and adherence defined as MPR ≥80%.

Proportion of days covered (PDC) will be calculated in patients with 12 complete months of follow-up from the index date.

Calculated as follows:

$$\frac{\text{Number of days in possession of UMEC (or UMEC/VI) over 12 month follow-up period}}{\text{365 days}}$$

where number of days in possession is calculated by multiplying the number of prescriptions (at any dose) in the period (minus the last prescription) by the assumed duration of 30 days and where last prescription date is the last prescription date recorded before the end of the follow-up period or discontinuation date, whichever occurs first.

All eligible patients are included in the PDC calculation as only a single prescription of the index mediation is required.

The PDC will be expressed as a percentage. For the 0-12 month time period, PDC values will range from a minimum of 8% (only had one index prescription over 365 days) to a maximum of 100% (had medication available every day for the 365 day study period). The PDC will also be dichotomised, with nonadherence defined as PDC <80% and adherence defined as PDC ≥80%.

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
Treatment pattern for patients **with no** concomitant therapy	nocon_pattern	categorical *(never missing in those eligible for analysis)*	1 = continuous user; 2 = augmenter; 3 = immediate switcher; 4 = discontinuer; . = missing (if [laba_con]=1 or [icslaba_con=1 or [lama_con]=1)	Based on first change within one year of [indexdate]). *See full definitions above.*	derived [any_con] variable; [eventdate] in therapy file if [prodcode] in ***all_labd_June2018***	derived [any_con] variable; [prscdate] in therapy file if [drugcode] in ***all_labd_THIN1801***
	d_nocon_pattern	date	date; . = missing	Date of first change in treatment pattern within one year of [indexdate]	derived [any_con] variable; [eventdate] in therapy file if [prodcode] in ***all_labd_June2018***	derived [any_con] variable; [prscdate] in therapy file if [drugcode] in ***all_labd_THIN1801***
Type of discontinuation for discontinuers **with no** concomitant therapy	nocon_disc	categorical	1 = true discontinuer; 2 = drug hiatus; 3 = new maintenance therapy after a break; . = missing (if [nocon_pattern] not=4)	Based on first change within one year of [indexdate]). *See full definitions above.*	derived [nocon_pattern] variable; [eventdate] in therapy file if [prodcode] in ***all_labd_June2018***	derived [nocon_pattern] variable; [prscdate] in therapy file if [drugcode] in ***all_labd_THIN1801***
Treatment pattern for patients **with** concomitant therapy	con_pattern	categorical *(never missing in those eligible for analysis)*	1 = continuous use of both; 2 = discontinuation of both drugs; 3 = discontinuation of index only; 4 = discontinuation of concomitant only; . = missing	Based on first change within one year of [indexdate]). *See full definitions below.*	derived [con] variable; [eventdate] in therapy file if [prodcode] in ***all_labd_June2018***	derived [con] variable; [prscdate] in therapy file if [drugcode] in ***all_labd_THIN1801***
	d_con_pattern	date	date; . = missing	Date of first change in treatment pattern within one year of [indexdate]	derived [con] variable; [eventdate] in therapy file if [prodcode] in ***all_labd_June2018***	derived [con] variable; [prscdate] in therapy file if [drugcode] in ***all_labd_THIN1801***

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
Medication possession ratio	mpr	proportion	≥0.0 and ≤1.0; . = missing	Proportion of days in possession of medication between the index date and the last prescription date, for patients with ≥2 prescriptions of index medication.	***umeclidinium_June2018 & umeclidinium+vilanterol_June2018*** in therapy file	***umeclidinium_THIN1801*** and ***umeclidinium+vilanterol_THIN1801*** in therapy file
	mpr_cat	categorical	0 = non-adherent (<80%); 1 = adherent (≥80%); . = missing	Calculated when [mpr] is non missing	derived [mpr] variable	derived [mpr] variable
Proportion of days covered	pdc	proportion	≥0.08 and ≤1.0; . = missing	Proportion of days in possession of medication during the 365 day period starting from the index date.	***umeclidinium_June2018 & umeclidinium+vilanterol_June2018*** in therapy file	***umeclidinium_THIN1801*** and ***umeclidinium+vilanterol_THIN1801*** in therapy file
	pdc_cat	categorical	0 = non-adherent (<80%); 1 = adherent (≥80%); . = missing	Calculated when [pdc] is non missing	derived [pdc] variable	derived [pdc] variable

Additional variables

The following variables will be used to describe new users of UMEC/VI, UMEC, or other LABD in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use. Unless otherwise specified, timings will be based on the event date [eventdate] or prescription date [prscdate] variables in CPRD and THIN.

Demographic variables

Unless indicated otherwise, all the variables below will be defined using primary care data (i.e. CPRD-GOLD+THIN) only.

Description	Name	Type	Values	Definition and timing	CPRD sources	THIN sources
Age in years at index date	age	numerical *(never missing)*	≥0 and ≤115	year of index date [index_y] – year of birth [yob]	[yob] +1800 from patient file	first four characters of [yob] variable in patient file
	age_cat1	categorical *(never missing)*	1 = younger than 65 years (≥0 and <65); 2 = 65 years or older (≥65 and ≤115)			
	age_cat2	categorical *(never missing)*	1= younger than 18 years (≥0 and <18); 2 = 18-64 years (≥18 and <65); 3 = 65 years of older (≥65 and ≤115)			
Gender	gender	categorical *(never missing)*	1= male; 2 = female		[gender] in patient file	[sex] in patient file
Smoking status at cohort entry	smoking	categorical	1 = no/never smoke; 2 = ex smoker; 3 = (current) smoker; . = missing	Smoking status record that is most proximal to index date [indexdate] and that is on or after the start of registration (≥[regstart]) up to within 90 days of the index date (≤ [indexdate]+90). When duplicate records on the same day differ, '(current) smoker' will be chosen over 'ex smoker', which will be chosen over 'no/never smoker'.	[medcode] and [status] from ***smok 2018_05 v1.0 20180516*** code list in clinical or referral files and/or status described in additional clinical details file (entity type 4)	[medcode] and [status] code from ***smoking_THIN 2015*** code list in medical file and/or status described in AHD file (clinical [ahdcode] = 1003040000)

Description	Name	Type	Values	Definition and timing	CPRD sources	THIN sources
BMI at cohort entry in kg/m^2	bmi	numerical	≥10 and ≤70; . = missing	valid BMI (10-70 kg/m^2) record that is most proximal to index date [indexdate] and which is on or after the start of registration (≥[regstart]) and no more than 90 days after the index date.	calculated from most recent valid height (1.2-2.2m) recorded after age 18 years from [data1] with [enttype]=13 in additional file and valid weight (25-450kg) from [data1] from [enttype]=14 in additional file	calculated from most recent valid height (1.2-2.2m) recorded after age 18 years from clinical [ahdcode] = 1005010200 in AHD file and valid weight (25-450kg) from clinical [ahdcode] = 1005010200 in AHD file
	bmi_cat	categorical	1 = underweight (≥10 and <18.5); 2 = normal (≥18.5 and <25); 3 = overweight (≥25 and <30); 4 = obese (≥30 and <70); . = missing			
Area based deprivation quintile	abd	categorical	1 = Q1 (least deprived); 2 = Q2; 3 = Q3; 4 = Q4; 5 = Q5 (most deprived); . = missing	Townsend quintile of patient's postcode. In THIN where patients' can have multiple Townsend scores if they have moved, the most recent (i.e. current) record will be used to ensure consistency with CPRD data.	[townsend2001_5] in patient_townsend2001 .txt file	[townsend] in PVI file
Region of practice at index date	region	categorical	1 North East 2 North West 3 Yorkshire & The Humber 4 East Midlands 5 West Midlands 6 East of England 7 South West 8 South Central 9 London 10 South East Coast 11 Northern Ireland 12 Scotland 13 Wales	The Strategic Health Authority for practice postcode within England, and the country i.e. Wales, Scotland, or Northern Ireland for the rest	[region] from CPRD patient file	N\A

Description	Name	Type	Values	Definition and timing	CPRD sources	THIN sources
Country of practice at index date	country	categorical	1 = England 2 = Wales 3 = Scotland 4 = Northern Ireland	The country of the practice postcode	[region] from CPRD patient file	[country] from the practice file

Disease burden variables

Unless indicated otherwise, all the variables below will be defined using primary care data (i.e. CPRD-GOLD+THIN) only.

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
Number of COPD exacerbations at baseline (as recorded in primary care)	aecopd_base	count *(never missing)*	≥0	Number of acute exacerbations of COPD (recorded in primary care) in 12 months prior to (and including) the index date (within previous year (≥ [indexdate]-365	*See Outcomes for definition of acute exacerbation of COPD.*	*See Outcomes for definition of acute exacerbation of COPD.*
	aecopd_base_cat	categorical *(never missing)*	0 = none; 1 = one; 2 = two or more			
Number of COPD exacerbations at baseline (as recorded in primary and/or secondary care)	aecopd_base_hes	count	≥0; . = missing	Number of acute exacerbations of COPD (recorded in primary care and/or HES) in 12 months prior to (and including) the index date (within previous year (≥ [indexdate]-365)	*See Outcomes for definition of acute exacerbation of COPD.*	*See Outcomes for definition of acute exacerbation of COPD.*
	aecopd_base_hes_cat	categorical	0 = none; 1 = one; 2 = two or more; . = missing			
Dyspnoea at baseline	dyspnoea	categorical	1 = MRC Grade; 2 = MRC Grade 2; 3 = MRC Grade 3; 4 = MRC Grade 4; 5 = MRC Grade 5; . = missing	Recorded on index date [indexdate] or closest record to index date within previous 12 months (≥ [indexdate]-365)	[medcode] in ***dyspnoea_Dec2015*** code list (19432=1; 19427=2; 19426=3; 19430=4; 19429=5) in clinical or referral file	[medcode] in ***dyspnoea_THIN1505*** code list (173H.00=1; 173I.00=2; 173J.00=3; 173K.00=4;

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
						173L.00=5) in medical file
COPD severity at baseline	fev1	numerical	≥0 and ≤100; . = missing	Forced expiratory volume in 1 second, percent predicted, as recorded on index date [indexdate] or closest record to index date within previous 24 months (≥ [indexdate]-730)	[data2] associated with [enttype]=394 if units in percent ([data3=1] in additional file	from test [ahdcode] = 1001400260 in AHD file
	fev1_cat	categorical	1 = mild Grade 1 (≥80%); 2 = moderate Grade 2 (≥50% and <80%); 3 = severe Grade 3 (≥30% and <50%); 4 = very severe Grade 4 (≥0% and <30%); . = missing			from test [ahdcode] = 1001400260 in AHD file
	fev1_fvc	numerical	≥0 and ≤100; . = missing	FEV1/FVC ratio as recorded on index date [indexdate] or closest record to index date within previous 24 months (≥ [indexdate]-730)	[data2] associated with [enttype]=395 if units in percent ([data3=1] in additional file	from test [ahdcode] = 1001400261 in AHD file
	fev1_fvc_cat	categorical	1 = ≥70%; 2 = <70%; . = missing			from test [ahdcode] = 1001400261 in AHD file

* *Optional*

Comorbidity variables

Unless indicated otherwise, all the variables below will be defined using primary care data (i.e. CPRD-GOLD+THIN) only.

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
Cardio- and cerebro-vascular disease ever before	cardio_cvd	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. ≤[indexdate])	[medcode] in ***cardio_cvd_Dec2015*** code list in clinical or referral files	[medcode] in ***cardio_cvd_THIN1505*** code list in medical file
Beta-blocker prescribing in year prior to index date	beta_blocker_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in the 12 months prior to and including the index date (i.e. ≥ [indexdate]-365 and ≤[indexdate])	[prodcode] in ***beta_blocker_June2018*** code list in therapy file	[drugcode] in ***beta_blocker_THIN1801*** code list in therapy file
Pneumonia disease ever before	pneumonia_base	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. ≤[indexdate])	[medcode] in ***pneumonia_Dec2015*** code list in clinical or referral files	[medcode] in ***pneumonia_THIN1505*** code list in medical file
Gastroesophageal reflux disease ever before	gord	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. -≤[indexdate])	[medcode] in ***gord_Dec2015*** code list in clinical or referral files	[medcode] in ***gord_THIN1505*** code list in medical file
Diabetes ever before	diabetes	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. -≤[indexdate])	[medcode] in ***diabetes_Dec2015*** in code list n clinical or referral files	[medcode] in ***diabetes_THIN1505*** code list in medical file
Acute or chronic renal disease ever before	renal	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. ≤[indexdate])	[medcode] in ***renal_Dec2015*** code list in clinical or referral files	[medcode] in ***renal_THIN1505*** in medical file
Cancer (excluding non-melanoma skin cancer) ever before	cancer	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. ≤[indexdate])	[medcode] in ***cancer_Dec2015*** code list in clinical or referral files	[medcode] in ***cancer_THIN1505*** code list in medical file

Previous respiratory medication

Unless indicated otherwise, all the variables below will be defined using primary care data (i.e. CPRD-GOLD+THIN) only.

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
Short-acting bronchodilators (SABD*), in 12 months prior to index date	sabd_base1	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***sabd_June2018*** code list in therapy file	[drugcode] from ***sabd_THIN1801*** code list in therapy file
	n_sabd_base	count	≥0; . = missing	Number of prescriptions issued during the 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***sabd_June2018*** code list in therapy file	[drugcode] from ***sabd_THIN1801*** code list in therapy file
	sabd_base4	binary *(never missing)*	0 = no; 1 = yes	At least four records in the 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***sabd_June2018*** code list in therapy file	[drugcode] from ***sabd_THIN1801*** code list in therapy file
Inhaled corticosteroids (ICS) in a single device, in year prior to index date	ics_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***ics_June2018*** code list in therapy file	[drugcode] from ***ics_THIN1801*** code list in therapy file
	n_ics_base	count	≥0; . = missing	Number of prescriptions issued during the 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***ics_June2018*** code list in therapy file	[drugcode] from ***ics_THIN1801*** code list in therapy file
ICS/SABA in a single device, in year prior to index date	icssaba_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (≥	[prodcode] from ***ics+saba_June2018*** code list in therapy file	[drugcode] from ***ics+saba_THIN1801***code list in therapy file

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
				[indexdate]-365 and <[indexdate])		
	n_icssaba_base	count	≥0; . = missing	Number of prescriptions issued during the 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***ics+saba_June2018*** code list in therapy file	[drugcode] from ***ics+saba_THIN1801*** code list in therapy file
Long-acting beta1-agonist (LABA) in a single device, in year prior to index date	laba_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***all_laba_June2018*** code list in therapy file	[drugcode] from ***all_laba_THIN1801*** code list in therapy file
	n_laba_base	count	≥0; . = missing	Number of prescriptions issued during the 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***all_laba_June2018*** code list in therapy file	[drugcode] from ***all_laba_THIN1801*** code list in therapy file
ICS/LABA in a single device, in year prior to index date	icslaba_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***ics+laba_June2018*** code list in therapy file	[drugcode] from ***ics+laba_THIN1801*** code list in therapy file
	n_icslaba_base	count	≥0; . = missing	Number of prescriptions issued during the 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***ics+laba_June2018*** code list in therapy file	[drugcode] from ***ics+laba_THIN1801*** code list in therapy file
Long-acting anticholinergic (LAMA) in a single	lama_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (≥	[prodcode] from ***other_lama_June2018*** code list in therapy file	[drugcode] from ***other_lama_THIN1801*** code list in therapy file

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
device, in year prior to index date				[indexdate]-365 and <[indexdate])		
	n_ lama_base	count	≥0; . = missing	Number of prescriptions issued during the 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***other_lama_June2018*** code list in therapy file	[drugcode] from ***other_lama_THIN1802*** code list in therapy file
LABA/LAMA in a single device, in year prior to index date	labalama_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***other_labalama_June2018*** code list in therapy file	[drugcode] from ***other_labalama_THIN1801*** code list in therapy file
	n_labalama_base	count	≥0; . = missing	Number of prescriptions issued during the 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***other_labalama_June12018***code list in therapy file	[drugcode] from ***other_labalama_HTIN1801*** code list in therapy file
Theophylline or derivatives, in year prior to index date	theoph_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***theophylline_June2018*** code list in therapy file	[drugcode] from ***theophylline_THIN1801*** code list in therapy file
	n_theoph_base	count	≥0; . = missing	Number of prescriptions issued during the 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***theophylline_June2018*** code list in therapy file	[drugcode] from ***theophylline_THIN1801*** code list in therapy file
Roflumilast, in year prior to index date	roflum_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (≥	[prodcode] from ***roflumilast_June2018*** code list in therapy file	[drugcode] from ***roflumilast_THIN1801*** code list in therapy file

Description	Name	Type	Values	Definition and timing	CPRD source	THIN source
				[indexdate]-365 and <[indexdate])		
	n_roflum_base	count	≥0; . = missing	Number of prescriptions issued during the 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***roflumilast_June2018*** code list in therapy file	[drugcode] from ***roflumilast_THIN1801*** code list in therapy file
Oral corticosteroids (OCS) chronic** use, in year prior to index date	chronic_ocs_base4	binary *(never missing)*	0 = no; 1 = yes	At least 4 prescriptions with a maximum gap between prescriptions of 30 days, in 12 months prior to (and not including) index date (≥ [indexdate]-365 and <[indexdate])	[prodcode] from ***ocs_June2018*** code list in therapy file	[drugcode] from ***ocs_THIN1801*** code list in therapy file

** Includes the following "reliever" medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA.*
*** At least four prescription records with a maximum gap between two prescriptions equal to 30 days.*

6. Statistical analysis

All data management and analyses will be conducted by the CPRD Observational Research Team using the standard CPRD tools (Define, Refine and Extract), as well as the latest installed version of Stata SE (currently 14.1). Full logs will be kept for audit and quality assurance (QA) purposes. Quality assurance will include a review of all logs, analysis outputs, tables/figures and text in both the interim and final reports. CPRD disclosure rules for small cell counts will be adhered to in reports intended for publication and/or dissemination outside of GSK and CPRD.

The results of this study will be interpreted based on analyses using the combined CPRD-GOLD and THIN study population, and where appropriate, the CPRD-GOLD study population of patients eligible for linkage with CPRD-HES and CPRD-ONS. Exposure cohort and demographic descriptions will be replicated in all study cohorts (1] CPRD-GOLD+THIN, 2] CPRD-GOLD, 3] THIN and the 4] CPRD-GOLD cohort of patients eligible for linkage to CPRD-HES and CPRD-ONS) in order to explore potentially heterogeneity between databases. The main analyses and outputs (e.g. tables) will be presented for the combined CPRD-GOLD and THIN data and will be included reports to GSK.

Full analysis

Characteristics of the exposure cohorts

Characteristics of the exposure cohorts will be described separately for the all four study cohorts. All other baseline characteristics will be described using the CPRD+THIN cohort only. Dependent on numbers available the Other LABD group will be described split by Other LAMA, Other LABA and Other LABA/LAMA. All tables listed as (a) refer to UMEC and (b) to UMEC/VI, table numbers with decimal places indicate the same analysis has been duplicated in more than one cohort.

- E1 - Descriptive statistics (mean (SD); median (range)) on the calendar period of initiation, the duration of time until censoring and the reasons for censoring for the full cohort as well as by index medication group (UMEC, UMEC/VI or 'Other LABD') will be produced. [ExposureCohorts – T1.1 to T1.4]

- E2 - For new users of UMEC and UMEC/VI, descriptive statistics (mean (SD); median (range)) on the duration of time *currently exposed* will be described. The duration of current

exposure will include the sum of all time classified as currently exposed, from the index date until censoring or study end (inclusive). [ExposureCohorts – T1.1 to T1.4]

- E3 - The number and proportion of patients contributing more than one index drug will also be described. For these patients' the mean (SD) time in days between the discontinuation date of the first index medication and the index date of the subsequent medication (in cases where the two index medications do not overlap) or the mean (SD) time during which the two index medications overlap (in cases were the medication do overlap) will also be calculated. [ExposureCohorts – T1.1 to T1.4]

- E4 - The number and proportion of UMEC and UMEC/VI users that were flagged as taking concomitant maintenance therapy at the index date will be calculated and the type of concomitant drug described. [ExposureCohorts – T1.1 to T1.4]

- E5 - Descriptive analysis will be conducted using the demographic baseline characteristics and will be described separately for all four study cohorts [Baseline – T1.1 to T1.4]. The main CPRD+THIN cohort will be further stratified by any concomitant and no concomitant maintenance therapy at the index date [Baseline – T1.1(a) and T1.1(b)].

- E6 - Descriptive analysis will be conducted on the disease burden and comorbidity [Baseline – T2] for the main CPRD+THIN cohort which will be further stratified by any concomitant and no concomitant maintenance therapy at the index date [Baseline – T1.2(a) and T1.2(b)].

- E7 - Descriptive analysis will be conducted on respiratory medication variables (at baseline / cohort entry) for each of the three main exposure categories with count and percentage for categorical variables and mean (SD) for continuous variables for the CPRD+THIN cohort only [Baseline – T3].

- E8 - The total count of exacerbations (moderate or moderate/severe) will be categorised (for patients with COPD) and a summary per category tabulated. As well, the exacerbation rate (expressed per person-years) and 95% confidence interval will be calculated. For the rate calculations, the numerator will be the total number of exacerbations in the 12 months prior up to and including the prescription initiation date and the denominator will be all person time from 12 months prior to the prescription initiation date up to and including the prescription initiation date. This will be described in the CPRD+THIN cohort and the CPRD-HES-ONS cohort [Baseline – T4.1 & T4.2] with the main CPRD+THIN cohort further stratified by any concomitant and no concomitant maintenance therapy at the index date [Baseline – T4.1(a) and T4.1(b)].

- E9 - Respiratory conditions: For the Neither Asthma nor COPD diagnosis group only, common Respiratory READ codes (Chapter H: Respiratory System Codes) occurring in the 12 months prior to index date will be analysed to describe other respiratory conditions [Baseline – T5].

Objective 1 – Possible off-label prescribing

These analyses will be conducted among all patients who enter the study with an index prescription for UMEC, UMEC/VI or other LABD. Report the proportion of patients with possible off-label prescribing and characterize them, using information available prior to and at the time of index prescription initiation, in respect to patient demographics, disease burden, co-morbidity, and COPD or asthma medication use. ***Objective 1 will report results using the combined CPRD+THIN cohort only.***

Primary analyses

- O1.1 - Patients in each of the three main defined exposure category (UMEC/VI, UMEC, or 'Other LABD') will be split into the three pre-defined disease categories of 1) COPD, 2) asthma, and 3) neither COPD nor asthma. If sample size allows, patients in the other LABD cohort will be further stratified by type of index LABD (LAMA, LABA, LAMA/LABA). Frequencies will be tabulated. All three disease categories will be further stratified by concomitant prescription of ICS-containing medications at index date. For the COPD and asthma groups, we will describe what proportion had the diagnosis before and after their medication index date (as a binary variable (before/after) and by distinct time periods before and after). [Obj.1 - T1]

- O1.2 - Patients in each of the five defined exposure category (UMEC/VI, UMEC, 'Other LAMA', 'Other LABA', 'Other LABA/LAMA') will be split into the three pre-defined disease categories of 1) COPD, 2) asthma, and 3) neither COPD nor asthma and the three pre-defined off-label categories. Numbers and proportions of patients in the five exposure groups will be reported. [Obj.1 - T2]

- O1.3 - Descriptive analysis will be conducted using the demographic, disease burden, comorbidity and respiratory medication variables (at baseline / cohort entry) for each of the three main disease categories of COPD, asthma, and neither COPD nor asthma with count and percentage for categorical variables and mean (SD) for continuous variables. The total count of exacerbations will be categorised (for patients with COPD) and a summary per category tabulated. As well, the moderate exacerbation rate in primary care data only (expressed per person-years) and 95% confidence interval will be calculated. For the rate calculations, the numerator will be the total number of exacerbations in the 12 months prior

up to and including the prescription initiation date and the denominator will be all person time from 12 months prior to the prescription initiation date up to and including the prescription initiation date. This analysis will be presented overall [Obj.1 – T3] and stratified by new users of UMEC and UMEC/VI [Obj.1 – T3(a) & Obj.1 – T3(b)].

Objective 2 – Incidence of adverse events (*UMEC/VI and UMEC only)*

These analyses will be conducted only among patients who enter the study with an index prescription for UMEC or UMEC/VI in the CPRD+THIN cohort and the CPRD-HES-ONS cohort.

Primary analyses

- O2.1 - Counts and incidence (new events/person-time) rates will be enumerated for outcomes of interest occurring during follow-up within each of the new user cohorts of UMEC/VI and UMEC whilst **currently exposed** to UMEC/VI or UMEC with further stratification for patients with and without concomitant ICS therapy at index date in the CPRD+THIN cohort [Obj. 2 – T1.1 (a) & Obj. 2 – T1.1 (b)] and the CPRD-HES-ONS cohort only [Obj. 2 – T1.2 (a) & Obj. 2 – T1.2 (b)].
    - This analysis will consider all-cause mortality and cardiovascular death separately for the linked CPRD-HES-ONS (d) cohort. No attempt will be made to define cardiovascular death using primary care records.
- O2.2 - The time in days to (first) MI, stroke, CHF, pneumonia, and death event (all-cause mortality) will be visualised using Kaplan-Meier plots in the CPRD+THIN cohort. [Obj.2 – F1, Obj.2 – F2, Obj.2 – F3, Obj.2 – F4, Obj.2 – F5] and in the CPRD-HES-ONS cohort (with the addition of cardiovascular mortality) [Obj.2 – F6, Obj.2 – F7, Obj.2 – F8, Obj.2 – F9, Obj.2 – F10]

Secondary Analysis:

- O2.3 – Counts and incidence (new events/person-time) rates will be enumerated for outcomes of interest occurring during follow-up within each of the new user cohorts of UMEC/VI and UMEC whilst **currently exposed AND previously exposed** to UMEC/VI or UMEC with further stratification for patients with and without concomitant ICS therapy at index date in the CPRD+THIN cohort [Obj. 2 – T2.1 (a) & Obj. 2 – T2.1(b)] and CPRD-HES-ONS cohort [Obj. 2 – T2.2 (a) & Obj. 2 – T2.2 (b)].
- O2.4 - Counts and incidence (new events/person-time) rates will be enumerated for outcomes of interest occurring during follow-up within each of the new user cohorts of UMEC/VI and UMEC whilst **currently exposed** to UMEC/VI or UMEC patients **AND** stratified by patients with and without any concurrent treatment with other maintenance therapy in the CPRD+THIN cohort [Obj. 2 – T3.1 (a) & Obj. 2 – T3.1 (b)] and the CPRD-HES-ONS cohort [Obj. 2 – T3.2 (a) & Obj. 2 – T3.2 (b)].

Exploratory sensitivity analyses (of the primary analysis only)

- O2.5 - The primary analysis (O2.1, excluding stratification by concomitant ICS prescribing) will be further stratified by the primary definition of on-label and off-label use, using the [offlabel1] variable in the CPRD+THIN cohort [Obj. 2 – T4.1] and CPRD-HES-ONS cohort [Obj. 2 – T4.2].

Objective 3 – Treatment patterns and adherence (UMEC and UMEC/VI only)

These analyses will be conducted only among patients who enter the study with an index prescription for UMEC or UMEC/VI. Treatment patterns of inhalation therapies will be examined in the first 12 months following initiation and only among patients with at least 12 months of follow-up. Only prescriptions for inhaler therapies will be considered. Objective 3 will report results using the combined CPRD-GOLD+THIN cohort only.

Primary analyses

- O3.1 - Among eligible patients that ***do not have*** concomitant use of another ***inhaled*** maintenance therapy at index date, the count and percentage of patients falling into the four main mutually exclusive treatment pattern categories (continuous users, augmenters, switchers and discontinuers; defined using [nocon_pattern] variable) will be described. The count and percentage of discontinuers that (a) truly discontinue, (b) restart the index therapy after a break (drug hiatus), and (c) start a new maintenance therapy after a break (latent switch), will also be described (defined using [nocon_disc] variable). As well, the mean (SD) time (in days) from the index to the first change (among those with a change) will be reported. [Obj.3 – T1]

- O3.2 - For eligible patients who ***are*** taking a concomitant COPD ***inhalation*** maintenance therapy at index date, the count and percentage of patients falling into the mutually exclusive treatment pattern categories (Continuous use of both drugs, Discontinuation of index drug, Discontinuation of concomitant drug, Discontinuation of both drugs, defined with [con_pattern] variable) will be described. As well, the mean (SD) time (in days) from the index date to the first change (among those with a change) will be reported. [Obj.3 – T1]

- O3.3 - Among eligible patients that ***do not have*** concomitant use of another ***inhaled*** maintenance therapy at index date, Kaplan-Meier plots will be created to visualise time in days to first treatment change for UMEC and UMEC/VI users. [Obj.3 – F1 and Obj.3 – F3]

- O3.4 - For eligible patients who ***are*** taking a concomitant COPD ***inhalation*** maintenance therapy at index date, Kaplan-Meier plots will be created to visualise time in days to first treatment change for UMEC and UMEC/VI users. [Obj.3 – F2 and Obj.3 – F4]

- O3.5 - The count and percentage of patients who are adherent to the initially prescribed therapy during follow-up will be calculated using the MPR and PDC. As well as cut offs of >=80% for the MPR and PDC, the mean (SD) of these measures as continuous variables during follow-up will also be calculated. MPR will be calculated among patients who received at least two prescriptions during the first 12 months of follow-up; whilst the PDC will be

calculated among patients who received at least one prescription in the first 12 months of follow-up. Therefore the denominator and the numbers of patients eligible for these two measures will differ. [Obj.3 – T2]

- O3.6 - Patients will first be stratified as adherent or non-adherent to initial therapy with UMEC or UMEC/VI based on (a) MPR >=80% and MPR <80% during follow-up, and (b) PDC >=80% and PDC <80% during the first 12 months of follow-up. Descriptive analysis will be conducted using the demographic, disease burden, comorbidity and COPD and asthma medication variables at baseline / cohort entry for adherent and non-adherent patients using count and percentage for categorical variables and mean (SD) for continuous variables. [Obj.3 – T3]

Exploratory sensitivity analyses

- O3.7 - The primary analysis of treatment patterns (O3.1 and O3.3) will be further stratified by possible on-label and possible off-label use, using the [offlabel1] variable. [Obj.3 – T4]

- O3.8 - The primary analysis of adherence (O3.5) will be further stratified by possible on-label and possible off-label use, using the [offlabel1] variable. [Obj.3 – T5]

Interim analysis

The interim analysis will be conducted using CPRD-GOLD and THIN data and will include all patients meeting the inclusion and exclusion criteria during the exposure identification period. As CPRD-HES and CPRD-ONS data for the full study period will not be available at the time of the interim analysis; assessment of the number of patients in the CPRD-GOLD cohort of patients eligible for linkage to both CPRD-HES and CPRD-ONS, will not be possible. The following analyses will be included: basic description of the exposure cohorts (Tables [ExposureCohort – T1, Baseline – T1, T2, T3 & T4] and primary analyses of off-label use (Tables [Obj.1 – T2 & T3]).

Changes and deviations from study protocol

- UTS requirement removed for Comorbidities and prior medication variables
- Spirometry data collection period expanded from 1 to 2 years
- Asthma codelist updated
- COPD exacerbations definition updated

Annex 1. Data source documentation and dictionaries

The documents and data dictionaries embedded here are the latest versions available at the time of writing (July 2018). New versions will be added when and if there are significant changes to the data source documentation and/or dictionaries.

CPRD-GOLD data dictionary (v2.0)

THIN data dictionary (v2.5)

CPRD-Small area level data Set 16 (v2.4)

CPRD-HES documentation Set 16 (v2.1) and dictionary for basic HES (v2.1)

CPRD-ONS documentation (v1.8)

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CPRD GOLD Data Specification

Version 2.0

Date: 1st September 2017

Author:

PPD CPRD, UK.

NHS National Institute for Health Research

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Documentation Control Sheet
During the course of the project it may be necessary to issue amendments or clarifications to parts of this document. This form must be updated whenever changes are made and should be filed inside the front cover of the new or amended document.

Version	Summary of Change	Prepared By	Date	Reviewed By	Date
1.0	Initial Draft				
1.1	Modified	PPD	01/06/2009	PPD	22/07/2009
1.2	Modified		28/07/2009		30/07/2009
1.3	Modified		06/01/2011		07/01/2011
1.4	Modified		11/01/2013		11/01/2013
1.5	Modified		31/07/2013		03/08/2013
1.6	Formatted		11/12/2013		30/12/2013
1.7	Modified		19/11/2014		20/11/2014
1.8	Modified		06/05/2015		12/06/2015
1.9	Formatted		02/07/2015		03/07/2015
2.0	Modified		01/09/2017		01/09/2017

Summary of Changes

Version 1.1
- Refined wordings

Version 1.2
- Acceptable field in Patient file equals 1 if patient is acceptable, else 0 (Lookup reference incorrectly labelled as Y_N in previous versions)
- UTS field in Practice file has been derived using a CPRD algorithm that looks at death recording at the practice, and gaps in the data (prior to August 2009, this field was populated with the practice UTS date as was generated in the old FF-CPRD system)
- The ndd field in the Therapy file has been populated for the most common occurring dosage strings in the data (field was set to '0' prior to August 2009)
- Descriptions of all fields have been revised for clarity

Version 1.3
- Field name 'attendtype' in Referral table modified to 'attendance'

Version 1.4
- Reference to Multilex product code system has been changed to Gemscript

Version 1.5
- Added batch number as a field in immunisation
- Description and Mapping for 'data8' in Test file has been amended

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Version 1.6
- New CPRD branding and formatting

Version 1.7
- Mapping of 'data8' field in Test file has been amended to remove reference to GEN_SDC
- Description of date formatting has been updated to reflect new format
- Description of entity types has been updated to include date values

Version 1.8
- Merged information from Spec 1.5 and Spec 1.7
- All description tables now list Column Name, Field Name, Description, Mapping, Type, Format

Version 1.9
- Minor formatting of document

Version 2.0
- Removed textid fields from the clinical, immunisation, test and referral tables
- Removed textid and ndd fields, and added dosageid as a field in the therapy table
- Removed ses field from the patient table

Dataset Format

1. The **Patient** file (Patient*NNN*.txt) contains basic patient demographics and patient registration details for the patients.

2. The **Practice** file (Practice001.txt) contains details of each practice, including region and collection information.

3. The **Staff** file (Staff*NNN*.txt) contains practice staff details, with one record per member of staff.

4. The **Consultation** file (Consultation*NNN*.txt) contains information relating to the type of consultation as entered by the GP from a pre-determined list. Consultations can be linked to the events that occur as part of the consultation via the consultation identifier (consid).

5. The **Clinical** file (Clinical*NNN*.txt) contains medical history events. This file contains all the medical history data entered on the GP system, including symptoms, signs and diagnoses. This can be used to identify any clinical diagnoses, and deaths. Patients may have more than one row of data. The data is coded using Read codes, which allow linkage of codes to the medical terms provided.

6. The **Additional Clinical Details** file (Additional*NNN*.txt) contains information entered in the structured data areas in the GP's software. Patients may have more than one row of data. Data in this file is linked to events in the clinical file through the additional details identifier (adid).

7. The **Referral** file (Referral*NNN*.txt) contains referral details recorded on the GP system. These files contain information involving patient referrals to external care centres (normally to secondary care locations such as hospitals for inpatient or outpatient care), and include speciality and referral type.

8. The **Immunisation** file (Immunisation*NNN*.txt) contains details of immunisation records on the GP system.

9. The **Test** file (Test*NNN*.txt) contains records of test data on the GP system. The data is coded using a Read code, chosen by the GP, which will generally identify the type of test used. The test name is identified via the *Entity Type*, a numerical code, which is determined by the test result item chosen by the GP at source. There are three types of test records, involving 4, 7 or 8 data fields (data1 - data8). The data must be managed according to which sort of test record it is. Data can denote either qualitative text based results (for example 'Normal' or Abnormal') or quantitative results involving a numeric value.

10. The **Therapy** file (Therapy*NNN*.txt) contains details of all prescriptions on the GP system. This file contains data relating to all prescriptions (for drugs and appliances) issued by the GP. Patients may have more than one row of data. Drug products and appliances are recorded by the GP using the Gemscript product code system.

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Field descriptions

Full descriptions of fields in each file are provided in the tables below. All files can be linked using the encrypted patient identifier (patid). The last three digits of the patient identifier (patid) and staff identifier (staffid) denote the identifier of the practice (pracid) that the patient or staff belongs to. The mapping column references information relating to the use of data in the field. It specifies lookup references, linkages to other tables, and information on decoding numerical values. A mapping of 'None' indicates the existence of raw data in the field.

1. Patient

Column name	*Field name*	*Description*	*Mapping*	*Type*	*Format*
Patient Identifier	patid	Encrypted unique identifier given to a patient in CPRD GOLD	None	INTEGER	20
VAMP Identifier	vmid	Old VM id for the patient when the practice was using the VAMP system	None	INTEGER	20
Patient Gender	gender	Patient's gender	Lookup SEX	INTEGER	1
Birth Year	yob	Patient's year of birth	Value + 1800	INTEGER	4
Birth Month	mob	Patient's month of birth (for those aged under 16). 0 indicates no month set	None	INTEGER	2
Marital Status	marital	Patient's current marital status	Lookup MAR	INTEGER	3
Family Number	famnum	Family ID number	None	INTEGER	20
CHS Registered	chsreg	Value to indicate whether the patient is registered with Child Health Surveillance	Lookup Y_N	INTEGER	1
CHS Registration Date	chsdate	Date of registration with Child Health Surveillance	dd/mm/yyyy [1]	DATE	dd/mm/yyyy
Prescription Exemption	prescr	Type of prescribing exemption the patient has currently (e.g. medical / maternity)	Lookup PEX	INTEGER	3
Capitation Supplement	capsup	Level of capitation supplement the patient has currently (e.g. low, medium, high)	Lookup CAP	INTEGER	3
First Registration Date	frd	Date the patient first registered with the practice. If patient only has 'temporary' records, the date is the first encounter with the practice; if patient has	dd/mm/yyyy **1**	DATE	dd/mm/yyyy

[1] **dd/mm/yyyy**: Valid dates are in this format. Missing dates are NULL

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		'permanent' records it is the date of the first 'permanent' record (excluding preceding temporary records)			
Current Registration Date	crd	Date the patient's current period of registration with the practice began (date of the first 'permanent' record after the latest transferred out period). If there are no 'transferred out periods', the date is equal to 'frd'	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
Registration Status	regstat	Status of registration detailing gaps and temporary patients	PAT_STAT [2]	INTEGER	2
Registration Gaps	reggap	Number of days missing in the patients registration details	PAT_GAP [3]	INTEGER	5
Internal Transfer	internal	Number of internal transfer out periods, in the patient's registration details	None	INTEGER	2
Transfer Out Date	tod	Date the patient transferred out of the practice, if relevant. Empty for patients who have not transferred out	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
Transfer Out Reason	toreason	Reason the patient transferred out of the practice. Includes 'Death' as an option	Lookup TRA	INTEGER	3
Death Date	deathdate	Date of death of patient – derived using a CPRD algorithm	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
Acceptable Patient Flag	accept	Flag to indicate whether the patient has met certain quality standards: 1 = acceptable, 0 = unacceptable	Boolean	INTEGER	1

[2] **PAT_STAT:** Transferred out period is the time between a patient transferring out and re-registering at the same practice. If the patient has transferred out for a period of more than 1 day, and the transfer is not internal, this value is incremented. 0 means continuous registration, 1 means one 'transferred out period', 2 means two periods, etc. If the patient only has 'temporary' records then this value is set to 99.

[3] **PAT_GAP:** Number of days between patient's transferred out date and re-registration date for the patient's 'transferred out periods', regardless of whether the transfer was internal or not.

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CPRD More Dimensions to Data

2. Practice

Column name	*Field name*	*Description*	*Mapping*	*Type*	*Format*
Practice identifier	pracid	Encrypted unique identifier given to a specific practice in CPRD GOLD	None	INTEGER	3
Region	region	Value to indicate where in the UK the practice is based. The region denotes the Strategic Health Authority for practices within England, and the country i.e. Wales, Scotland, or Northern Ireland for the rest	Lookup PRG	INTEGER	3
Last Collection Date	lcd	Date of the last collection for the practice	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
Up To Standard Date	uts	Date at which the practice data is deemed to be of research quality. Derived using a CPRD algorithm that primarily looks at practice death recording and gaps in the data	dd/mm/yyyy **1**	DATE	dd/mm/yyyy

3. Staff

Column name	*Field name*	*Description*	*Mapping*	*Type*	*Format*
Staff Identifier	staffid	Encrypted unique identifier given to the practice staff member entering the data	None	INTEGER	20
Staff Gender	gender	Staff's gender	Lookup SEX	INTEGER	1
Staff Role	role	Role of the member of staff who created the event	Lookup ROL	INTEGER	3

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CPRD More Dimensions to Data

4. Consultation

Column name	*Field name*	*Description*	*Mapping*	*Type*	*Format*
Patient Identifier	patid	Encrypted unique identifier given to a patient in CPRD GOLD	None	INTEGER	20
Event Date	eventdate	Date associated with the event, as entered by the GP	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
System Date	sysdate	Date the event was entered into Vision	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
Consultation Type	constype	Type of consultation (e.g. Surgery Consultation, Night Visit, Emergency etc.)	Lookup COT	INTEGER	3
Consultation Identifier	consid	The consultation identifier linking events at the same consultation, when used in combination with pracid	Link **Event** tables	INTEGER	20
Staff Identifier	staffid	The identifier of the practice staff member entering the data. A value of 0 indicates that the staffid is unknown	Link **Staff** table	INTEGER	20
Duration	duration	The length of time (minutes) between the opening, and closing of the consultation record	None	INTEGER	10

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5. Clinical

Column name	*Field name*	*Description*	*Mapping*	*Type*	*Format*
Patient Identifier	patid	Encrypted unique identifier given to a patient in CPRD GOLD	None	INTEGER	20
Event Date	eventdate	Date associated with the event, as entered by the GP	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
System Date	sysdate	Date the event was entered into Vision	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
Consultation Type	constype	Code for the category of event recorded within the GP system (e.g. diagnosis or symptom)	Lookup SED	INTEGER	3
Consultation Identifier	consid	Identifier that allows information about the consultation to be retrieved, when used in combination with pracid	Link **Consultation** table	INTEGER	20
Medical Code	medcode	CPRD unique code for the medical term selected by the GP	Lookup Medical Dictionary	INTEGER	20
Staff Identifier	staffid	Identifier of the practice staff member entering the data. A value of 0 indicates that the staffid is unknown	Link **Staff** table	INTEGER	20
Episode	episode	Episode type for a specific clinical event	Lookup EPI	INTEGER	3
Entity Type	enttype	Identifier that represents the structured data area in Vision where the data was entered	Lookup Entity	INTEGER	5
Additional Details Identifier	adid	Identifier that allows additional information to be retrieved for this event, when used in combination with pracid. A value of 0 signifies that there is no additional information associated with the event.	Link **Additional Clinical Details** table	INTEGER	20

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CPRD More Dimensions to Data

6. Additional Clinical Details

Column name	*Field name*	*Description*	*Mapping*	*Type*	*Format*
Patient Identifier	patid	Encrypted unique identifier given to a patient in CPRD GOLD	None	INTEGER	20
Entity Type	enttype	Identifier that represents the structured data area in Vision where the data was entered	Lookup Entity	INTEGER	5
Additional Details Identifier	adid	Identifier that allows information about the original clinical event to be retrieved, when used in combination with pracid	Link **Clinical** table	INTEGER	20
Data 1	data1	Depends on Entity Type ♦	Lookup Entity	NUMERIC DATE	15.3 dd/mm/yyyy
Data 2	data2	Depends on Entity Type ♦	Lookup Entity	NUMERIC DATE	15.3 dd/mm/yyyy
Data 3	data3	Depends on Entity Type ♦	Lookup Entity	NUMERIC DATE	15.3 dd/mm/yyyy
Data 4	data4	Depends on Entity Type ♦	Lookup Entity	INTEGER DATE	12 dd/mm/yyyy
Data 5	data5	Depends on Entity Type ♦	Lookup Entity	INTEGER DATE	12 dd/mm/yyyy
Data 6	data6	Depends on Entity Type ♦	Lookup Entity	INTEGER DATE	12 dd/mm/yyyy
Data 7	data7	Depends on Entity Type ♦	Lookup Entity	INTEGER DATE	4 dd/mm/yyyy

♦ Each entity type may be associated with up to seven data fields. Content of each data field is dependent on the entity type – the fields may contain raw data values, dates in the form dd/mm/yyyy, or may be encoded values that represent read codes, text etc. The file Entity.xls contains information on all entity types, and provides the number of data fields associated with the entity, description of the data in each field, and details of the lookups needed to decode the data.

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7. Referral

Column name	*Field name*	*Description*	*Mapping*	*Type*	*Format*
Patient Identifier	patid	Encrypted unique identifier given to a patient in CPRD GOLD	None	INTEGER	20
Event Date	eventdate	Date associated with the event, as entered by the GP	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
System Date	sysdate	Date the event was entered into Vision	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
Consultation Type	constype	Code for the category of event recorded within the GP system (e.g. management or administration)	Lookup SED	INTEGER	3
Consultation Identifier	consid	Identifier that allows information about the consultation to be retrieved, when used in combination with pracid	Link **Consultation** table	INTEGER	20
Medical Code	medcode	CPRD unique code for the medical term selected by the GP	Lookup Medical Dictionary	INTEGER	20
Staff Identifier	staffid	Identifier of the practice staff member entering the data. A value of 0 indicates that the staffid is unknown	Link **Staff** table	INTEGER	20
Source	source	Classification of the source of the referral e.g. GP, Self	Lookup SOU	INTEGER	2
NHS Speciality	nhsspec	Referral speciality according to the National Health Service (NHS) classification	Lookup DEP	INTEGER	3
FHSA Speciality	fhsaspec	Referral speciality according to the Family Health Services Authority (FHSA) classification	Lookup SPE	INTEGER	3
In Patient	inpatient	Classification of the type of referral, e.g. Day case, In patient	Lookup RFT	INTEGER	2
Attendance Type	attendance	Category describing whether the referral event is the first visit, a follow-up etc.	Lookup ATT	INTEGER	2
Urgency	urgency	Classification of the urgency of the referral e.g. Routine, Urgent	Lookup URG	INTEGER	2

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CPRD More Dimensions to Data

8. Immunisation

Column name	*Field name*	*Description*	*Mapping*	*Type*	*Format*
Patient Identifier	patid	Encrypted unique identifier given to a patient in CPRD GOLD	None	INTEGER	20
Event Date	eventdate	Date associated with the event, as entered by the GP	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
System Date	sysdate	Date the event was entered into Vision	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
Consultation Type	constype	Code for the category of event recorded within the GP system (e.g. intervention)	Lookup SED	INTEGER	3
Consultation Identifier	consid	Identifier that allows information about the consultation to be retrieved, when used in combination with pracid	Link **Consultation** table	INTEGER	20
Medical Code	medcode	CPRD unique code for the medical term selected by the GP	Lookup Medical Dictionary	INTEGER	20
Staff Identifier	staffid	Identifier of the practice staff member entering the data. A value of 0 indicates that the staffid is unknown	Link **Staff** table	INTEGER	20
Type	immstype	Individual components of an immunisation, e.g. Mumps, Rubella, Measles	Lookup IMT	INTEGER	4
Stage	stage	Stage of the immunisation given, e.g. 1, 2, B2	Lookup IST	INTEGER	2
Status	status	Status of the immunisation e.g. Advised, Given, Refusal	Lookup IMM	INTEGER	3
Compound	compound	Immunisation compound administered – may be a single or multi-component preparation, e.g. MMR	Lookup IMC	INTEGER	4
Source	source	Location where the immunisation was administered, e.g. In this practice	Lookup INP	INTEGER	3
Reason	reason	Reason for administering the immunisation, e.g. Routine measure	Lookup RIN	INTEGER	3
Method	method	Route of administration for the immunisation, e.g. Oral, Intramuscular	Lookup IME	INTEGER	3
Batch Number	batch	Immunisation batch number	Lookup BatchNumber	INTEGER	20

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CPRD More Dimensions to Data

9. Test

Column name	*Field name*	*Description*	*Mapping*	*Type*	*Format*
Patient Identifier	patid	Encrypted unique identifier given to a patient in CPRD GOLD	None	INTEGER	20
Event Date	eventdate	Date associated with the event, as entered by the GP	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
System Date	sysdate	Date the event was entered into Vision	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
Consultation Type	constype	Code for the category of event recorded within the GP system (e.g. examination)	Lookup SED	INTEGER	3
Consultation Identifier	consid	Identifier that allows information about the consultation to be retrieved, when used in combination with pracid	Link **Consultation** table	INTEGER	20
Medical Code	medcode	CPRD unique code for the medical term selected by the GP	Lookup Medical Dictionary	INTEGER	20
Staff Identifier	staffid	Identifier of the practice staff member entering the data. A value of 0 indicates that the staffid is unknown	Link **Staff** table	INTEGER	20
Entity Type	enttype	Identifier that represents the structured data area in Vision where the data was entered	Lookup Entity	INTEGER	5

Depending on the Test Entity Type, tests have 4, 7, or 8 data fields:

4 fields:

Data 1	data1	Qualifier	Lookup TQU	INTEGER	3
Data 2	data2	Normal range from	None	NUMERIC	16.3
Data 3	data3	Normal range to	None	NUMERIC	16.3
Data 4	data4	Normal range basis	None	NUMERIC	16.3

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7 fields:

Data 1	data1	Operator	Lookup OPR	INTEGER	3
Data 2	data2	Value	None	NUMERIC	16.3
Data 3	data3	Unit of measure	Lookup SUM	INTEGER	4
Data 4	data4	Qualifier	Lookup TQU	INTEGER	3
Data 5	data5	Normal range from	None	NUMERIC	16.3
Data 6	data6	Normal range to	None	NUMERIC	16.3
Data 7	data7	Normal range basis (or peak flow device for entity type 311)	Lookup POP (or PFD)	INTEGER	2

8 fields:

Data 1	data1	Operator	Lookup OPR	INTEGER	3
Data 2	data2	Value	None	NUMERIC	16.3
Data 3	data3	Unit of measure	Lookup SUM	INTEGER	4
Data 4	data4	Qualifier	Lookup TQU	INTEGER	3
Data 5	data5	Normal range from	None	NUMERIC	16.3
Data 6	data6	Normal range to	None	NUMERIC	16.3
Data 7	data7	Normal range basis	Lookup POP	INTEGER	2
Data 8	data8	Expected delivery date (entity type 284) / Weeks (entity type 154)	dd/mm/yyyy None	DATE INTEGER	dd/mm/yyyy 10

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CPRD More Dimensions to Data

10. Therapy

Column name	*Field name*	*Description*	*Mapping*	*Type*	*Format*
Patient Identifier	patid	Encrypted unique identifier given to a patient in CPRD GOLD	None	INTEGER	20
Event Date	eventdate	Date associated with the event, as entered by the GP	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
System Date	sysdate	Date the event was entered into Vision	dd/mm/yyyy **1**	DATE	dd/mm/yyyy
Consultation Identifier	consid	Identifier that allows information about the consultation to be retrieved, when used in combination with pracid	Link **Consultation** table	INTEGER	20
Product Code	prodcode	CPRD unique code for the treatment selected by the GP	Lookup Product Dictionary	INTEGER	20
Staff Identifier	staffid	Identifier of the practice staff member entering the data. A value of 0 indicates that the staffid is unknown	Link **Staff** table	INTEGER	20
Dosage Identifier	dosageid	Identifier that allows dosage information on the event to be retrieved. Use the Common Dosages Lookup to obtain the anonymised dosage text, and extracted numerical information such as daily dose.	Lookup Common Dosages	CHAR	64
BNF Code	bnfcode	Code representing the chapter & section from the British National Formulary for the product selected by GP	Lookup BNFCodes	INTEGER	5
Total Quantity	qty	Total quantity entered by the GP for the prescribed product	None	INTEGER	20
Number of Days	numdays	Number of treatment days prescribed for a specific therapy event	None	INTEGER	20
Number of Packs	numpacks	Number of individual product packs prescribed for a specific therapy event	None	INTEGER	8
Pack Type	packtype	Pack size or type of the prescribed product	Lookup PackType	INTEGER	10
Issue Sequence Number	issueseq	Number to indicate whether the event is associated with a repeat schedule. Value of 0 implies the event is not part of a repeat prescription. A value ≥ 1 denotes the issue number for the prescription within a repeat schedule	None	INTEGER	20

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IMS Information Solutions Medical Research Limited

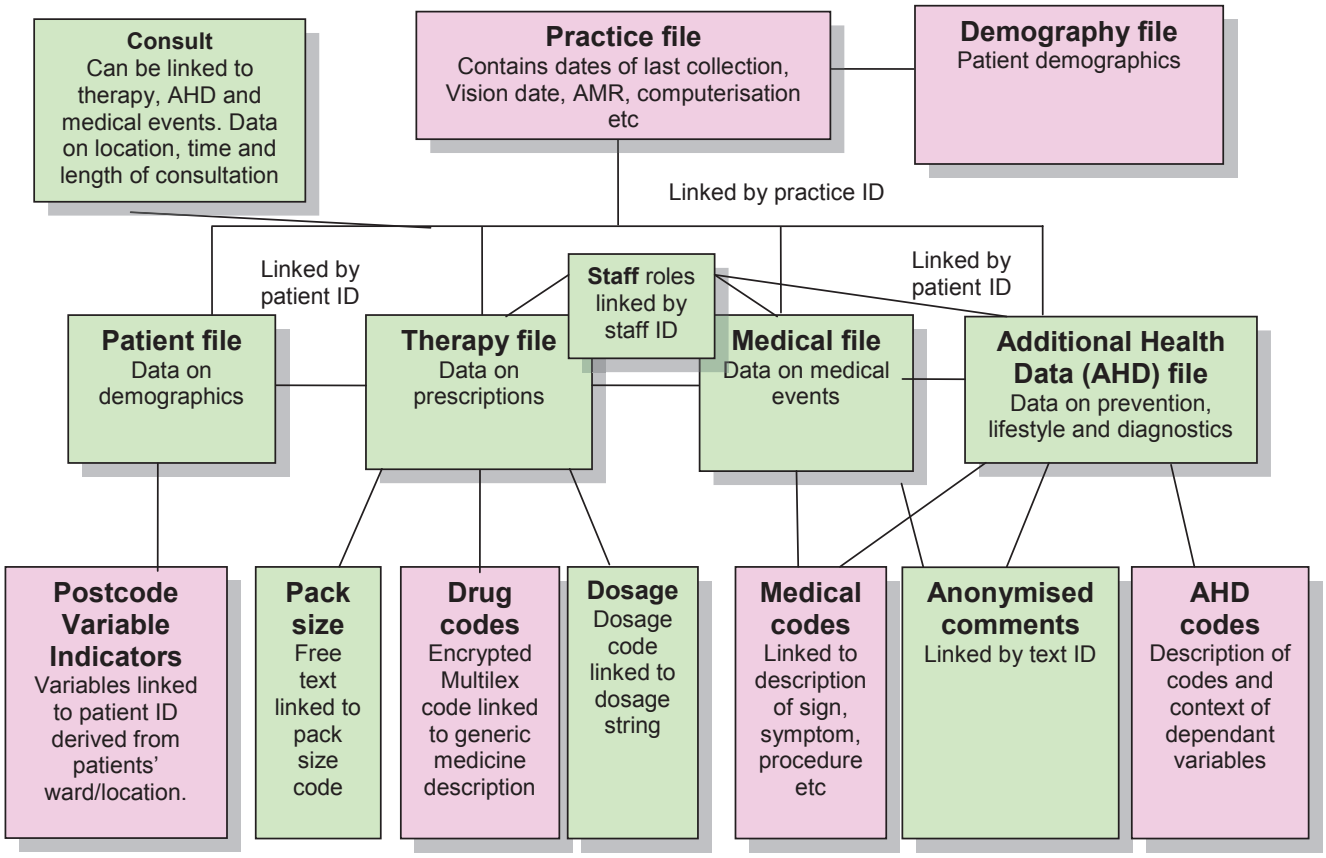
Research Format Selected Medical History THIN Data

Revised 2015

Version 2.5

Contents

1 Structure of THIN Data



The raw data files from THIN have been reorganised so that the data can be provided in a simplified, flexible structure. The data are organised by practice, then by patient, and followed by date so that all records relating to a single patient are stored together. Each practice's data are split into four standard ASCII fixed width text files and three linked files. These include: patient, medical, therapy and an additional health data (AHD) file which contains information on preventative healthcare, tests and immunisations. The linked files are: postcode variable indicators (PVI) consult and staff. In addition the THIN Data files are provided with a series of dictionaries and look-up tables which allow the coded information to be interpreted. This research format enables a great deal of flexibility in terms of querying and interrogating the data since they can be loaded and imported into virtually any database or statistical application. Alternatively the data can be stored as flat files and queried using any appropriate programming language.

2 PATIENT: Patient records

This file contains information on patient characteristics and registration details i.e. censoring dates for determining person-time in the database. Field values are updated so that there is only one record for each patient.

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
pracid	A9999	5	Practice id encrypted
patid	Any ASCII	4	Patient identifier - case sensitive and unique within practice
patflag	A	1	Flag which indicates the integrity of the data for that patient (see patflag)
yob	YYYYMM00 Or YYYY0000	8	Year of birth (month also included for children)
famnum	999999	6	Identifier shared by patients living at same address
sex	9	1	Sex of patient (see sex)
regdate	YYYYMMDD	8	Patients registration date with the practice
regstat	99	2	Registration status (see regstat)
xferdate	YYYYMMDD	8	Date of transfer out of practice (if applicable) 00000000 if not transferred out
regrea	99	2	Extended registration information (see regrea)
deathdate	YYYYMMDD	8	Patients date of death (derived by EPIC) 00000000 if no death date
deathinfo	A	1	Death information – cause of death (linked from death certificate or comment) (see deathinfo)
accept	9	1	Registration acceptance type (see accept)
institute	Y	1	Residential Institute Y = yes N = unknown
marital	99	2	Marital status (see marital)
dispensing	Y	1	Y indicates they are a dispensing patient, whose prescriptions can be dispensed by the practice. Blank if not a dispensing patient.
prscexempt	99	2	Prescription exemption (see prscexempt)
sysdate	YYYYMMDD	8	System date

Start-date	YYYYMMDD	8	Patient's start date computerisation or vision (if applicable)
End_date	YYYYMMDD	8	Patient's end date

2.1 Lookup tables for patient files

patflag	Description
A	Acceptable record
C	Acceptable: transferred out dead without additional death information
D	Not permanently registered
E	Out of sequence YOB. YOB greater than regdate
F	Out of sequence registration date. i.e. greater than xferdate
G	Regstat 5 and missing or invalid transfer out date
H	Missing or invalid registration date
I	Year of birth missing, invalid or over 115 years of age
J	Not male or female
K	Invalid transfer out date
N	Family number invalid
P	Invalid Regrea
Q	Out of sequence deathdate i.e before YOB or greater than last collection
R	No registration time i.e registration date = last collection or transfer out
S	Acceptable but no medical, therapy or AHD events recorded
M	Multiple problems. More than one of the above errors
X	Re-allocation of patid : 2 different patients with same patid

sex	Description
1	Male
2	Female
3	Indeterminate
4	Unknown
0	Null record

regstat	Description
01	Applied
02	Permanent
03	Temporary resident < 16 days
04	Temporary resident 16 days to 3 months
05	Transferred out
07	Immediately necessary treatment
08	Emergency treatment
09	Child Health Surveillance
10	Contraception
11	Maternity
12	Minor surgery
13	Private
14	Referred

regstat	Description
15	Walk in centre
16	GP with special Interest
17	Minor Injury Clinic
18	HMP inmate
19	Visitor (EC111)
99	Death
00	Null record

regrea	description
01	Death
02	Removal to new HA/HB/CSA
03	Internal transfer
04	Mental hospital
05	Embarkation
06	New HA/HB/CSA/Same GP
07	Adopted child
08	Services
09	Deduction at GP's request
10	Registration cancelled
11	Service Dependant
12	Deduction at patients request
13	Other Reason
14	Enlistment
15	Institution
16	Transfer within practice
17	Linkage
18	Ex-maternity only
19	Ex-child HS
20	Ex-minor operations
21	Ex-private
22	Other reasons
23	Registration cancelled
24	Institution
25	Intra-consortium transfer
26	Returned undelivered
27	Internal transfer- address change
28	Internal transfer within partnership
29	Correspondence states 'gone away'
30	Practice advise outside their area
31	Practice advise patient no longer resident
32	Practice advise removal via screening system.
33	Practice advise removal via vaccination data
34	Removal from Residential Institute
00	Null Record

deathinfo	description
A	Linked death certificate with cause of death
B	Death comment

accept	description
1	Birth
2	1st acceptance
3	Transfer-in
4	Immigrant
5	Ex-services
0	Null record

marital	description
01	Single
02	Married
03	Widowed
04	Divorced
05	Separated
06	Unknown
07	Engaged
08	Co-habiting
09	Remarried
10	Stable relationship
11	Civil partnership
00	Null record

prscexempt	description
01	Under 16 years of age
02	16, 17 or 18 and in full-time education
03	Woman aged 60 or over
04	Man aged 60 or over
05	Has a maternity/medical exemption certificate
06	Has a prescription prepayment certificate
07	Receives income support family credit et
08	Has a war pension exemption certificate
09	Not exempt
10	Gets disability working allowance
11	Receives income-based jobseeker's allowance
12	Is named on a current low income certificate (HC2) charges certificate
13	Was prescribed a free-of-charge contraceptive
14	Has a maternity exemption certificate
15	Has a medical exemption certificate
16	Receives income support
17	Has working family tax credit (WFTC) exemption or gets full or reduced WFTC

18	Has disabled person tax credit (DPTC) exemption or gets full or reduced DPTC
19	Aged 60 or over
20	Entitled to/has a valid NHS Tax Credit Exemption Certificate
21	Has a Partner who gets Pension Credit guarantee credit PCGC
00	Null record

3 MEDICAL: Medical records

This file contains a record of symptoms, diagnoses and interventions recorded by the GP and primary care team and information transcribed from discharge summaries following hospital stays or from letters sent by specialists. Each record is flagged to indicate its origin so that GP consultations can be distinguished from administrative and transcribed entries. There are many records per patient as a new record is generated with each new 'event' that is experienced by the patient.

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
pracid	A9999	5	Practice id encrypted
patid	Any ASCII	4	Patient identifier - case sensitive and unique within practice
eventdate	YYYYMMDD	8	Event date. Note for incomplete dates YYYYMM00, YYYY0000 or 00000000
enddate	YYYYMMDD	8	Event end date. Note 00000000 if no date recorded
datatype	99	2	Structured data type (see datatype)
medcode	Any ASCII (case sensitive)	7	Medical code (see READCODES)
medflag	A	1	Flag indicating integrity of the record (see medflag)
staffid	Any ASCII	4	Identifier of person entering record. 0000 = null record
source	A	1	Variable indicating origin of record (see source)
episode	A	1	Episode type (see episode)
nhsspec	AAA	3	Secondary care speciality (see nhsspeciality). 000 = null record
locate	AA	2	Location of consultation (see locate)
textid	Any ASCII	7	Link to free text comment (see THINComments)
category	9	1	Category of medical entry (see category)
priority	9	1	Priority 1 = life-threatening conditions (lookups not yet available)
medinfo	A	1	AIS extra information (see extrainfo)
inprac	Y/N	1	Event recorded in practice (Y/N)
private	Y/N	1	Private (Y) or NHS (N) treatment

medid	Any ASCII	4	Medical record identifier (unique ID for the data type)
consultid	Any ASCII	4	Consult link to same therapy AHD consultation
sysdate	YYYYMMDD	8	System date

4 Lookup tables for medical records

datatype	description
01	Medical History
02	Health Promotion - Smoking
03	Health Promotion - Alcohol
04	Health Promotion - Hypertension
05	Health Promotion - Overweight
06	Health Promotion - CHD
07	Health Promotion - Stroke/TIA
08	Health Promotion - FH of CVA/IHD
09	Hypertension register
10	Coronary heart disease register
11	Stroke/ TIA register
12	Diabetic register
13	Asthma register
14	Angina
15	Asthma consultation
16	CV/BP consultation
17	Diabetic consultation
18	HRT consultation
19	New registration consultation
20	Well person consultation
21	Allowances received - elderly
22	Ante-natal symptoms
23	Carers - elderly
24	Check next examination - CHS
25	FH Prevention comment
26	Diabetes concerns
27	Well person concerns
28	Foot care
29	Perinatal problems
30	Physical examination - CHS
31	Post-natal symptoms
32	Previous occupation - elderly
33	Ante natal risk factors
34	Ante natal social factors
35	Breast examination

datatype	description
36	Pelvic examination
37	Thyroid disease
38	Parental concerns
39	Epilepsy register
40	Continence - urinary
41	Continence - bowel
42	Occupation
43	Asthma concerns
44	Non linked referral
45	Non linked request
46	Thyroid disease not present
47	Angina not present

medflag	description
R	Acceptable record
S	Additional referral/request event
A	Event date missing or invalid
B	Medical Code (medcode) missing or invalid
D	Staffid invalid
E	Source invalid
F	Episode invalid
G	NHS speciality (speciality) invalid
L	Location (locate) invalid
M	Multiple problems. More than one of the above errors
N	Invalid category
O	Invalid priority

source	description
A	Doctor referral to inpatient, Accident & Emergency
C	Self referral to outpatient Accident & Emergency
D	Inpatient, hospital discharge summary
E	Doctor referral outpatient to Accident & Emergency
H	Doctor referral hospital admission inpatient
L	Hospital letter
B	Doctor referral to day case
O	Doctor referral to other
R	Doctor referral to outpatients
S	Patient requested referral to inpatient Accident & Emergency
F	Patient requested referral
G	Patient requested referral to inpatients
I	Patient requested referral to outpatients
J	3rd Party referral

source	description
K	3rd Party referral to outpatients
M	3rd Party referral to PCHT
N	PCHT referral
P	PCHT referral to outpatients
Q	Doctor referral to domiciliary
T	Doctor referral to direct access
U	To PHCT
V	Inpatient, unknown referral to Accident & Emergency
W	referral to day case
Y	referral to outpatient Accident & Emergency
Z	Referral to hospital admission inpatient
1	Referral to outpatients
2	Referral to other
3	Unknown referral
4	Doctor request from direct access Accident & Emergency
5	Doctor request from direct access
6	Doctor referral
7	3rd party referral to domiciliary
8	Referral to PHCT
9	Referral to domiciliary
a	PHCT referral to inpatient
b	3rd party referral to day case
c	Patient requested referral to direct access
e	Referral to direct access
f	Patient requested referral to domiciliary
g	3rd party referral to inpatient
j	3rd party referral to other
k	Patient requested referral to day case
m	Patient requested referral to PHCT
n	PHCT referral to other
o	Patient requested referral to other
p	PHCT referral to day case
q	PHCT referral to domiciliary
s	PHCT referral to direct access
t	3rd party referral to direct access
u	PHCT referral to PHCT
0	Null record

episode	description

1	First ever episode
2	New event
3	Continuing
4	Other
0	Null record

locate	description
A	Clinic
B	Night visit, Deputising service
C	Follow-up/routine visit
D	Night visit, Local rota
E	Mail from patient
F	Night visit , practice
G	Out of hours, Practice
H	Out of hours, Non Practice
I	Surgery consultation
J	Telephone call from a patient
K	Acute visit
L	Discharge details
M	Letter from Outpatients
N	Repeat Issue
O	Other
P	Results recording
Q	Mail to patient
R	Emergency Consultation
S	Administration
T	Casualty Attendance
U	Telephone call to a patient
V	Third Party Consultation
W	Hospital Admission
h	Children's Home Visit
Y	Day Case Report
n	GOS18 Report
X	Home Visit
i	Hotel Visit
o	NHS Direct Report
j	Nursing Home Visit
k	Residential Home Visit
l	Twilight Visit
u	Triage
Z	Walk-in Centre
f	Co-op Telephone advice

locate	description
d	Co-op Surgery Consultation
m	Co-op Home Visit
a	Minor Injury Service
1	Medicine Management
b	Community Clinic
p	Community Nursing Note
q	Community Nursing Report
2	Data Transferred from other system
e	Health Authority Entry
r	Health Visitor Note
s	Health Visitor Report
3	Hospital Inpatient Report
9	Initial Post Discharge Review
4	Laboratory Request
c	Night Visit
5	Radiology Request
6	Radiology Result
7	Referral Letter
t	Social Services Report
g	Telephone Consultation
8	Template Entry
w	GP to GP communication transaction
v	Non-consultation medication data
x	Non-consultation data
00	Null record

category	description
1	Symptom
2	Examination
3	Diagnosis
4	Intervention
5	Management
6	Administration
7	Presenting complaint

extrainfo	description
A	GP questionnaire
B	GP questionnaire & notes
C	Patient questionnaire
D	Discharge summary/ notes
E	Patient questionnaire & notes

5 Readcodes: Medical dictionary

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
medcode	Any ASCII (case sensitive)	7	Read code
description	Text	60	Description of the code

5.1 NHSpeciality: Hospital speciality and department code

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
nhsspec	AAA	3	Clinical speciality code
speciality	Text	variable	Speciality description
subspec	Text	variable	Sub-speciality description

6 THINcomments

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
textid	9999999	7	Textid code
description	Text	variable	Anonymised free text comment

7 THERAPY: Therapy records

This file contains details of prescriptions issued to patients. A new record is generated with each prescription, including each repeat prescription. Information recorded includes formulation, strength, dose and quantity prescribed. All items prescribed by GPs or nurses are captured.

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
pracid	A9999	5	Practice id encrypted
patid	Any ASCII	4	Patient identifier - case sensitive and unique within practice
prscdate	YYYYMMDD	8	Prescription date. Note for incomplete dates YYYYMM00, YYYY0000 or 00000000
drugcode	Any ASCII	8	Multilex drug code (see DRUGCODES)
therflag	A	1	Flag indicating integrity of the record (see therflag)
doscode	Any ASCII	7	Link to DOSAGE string
prscqty	9.999999	8	Quantity prescribed. Can also be number of packs. Note 0.000000 = null quantity
prscdays	999	3	Duration of the prescription in days. 000 = null days
private	Y/N	1	Private (Y) or NHS (N) prescriptions
staffid	Any ASCII	4	System assigned identifier of prescriber
prsctype	9	1	Acute or repeat prescription (see prsctype)
opno	99999,99	8	Number of original packs ordered. Note 00000000 or 00000.00 = null
bnf	Any ASCII	8	BNF1 chapter from DRUGCODES
seqnoiss	9999	4	Issue sequence number for repeat prescriptions. 0000 = null
maxnoiss	9999	4	Maximum number of issues for repeat prescriptions
packsize	9999999	7	Link to free text pack information (see packsize)
dosgval	9999.99	7	The calculated daily dosage (derived by EPIC)
locate	Any Ascii	2	Location of consultation (see locate)
drugsource	9	1	Source of drug (see drugsource)
inprac	Y/N	1	Event recorded in practice (Y/N)
therid	Any ascii	4	Unique therapy record identifier
consultid	Any ASCII	4	Consult link to same medical/AHD consultation
sysdate	YYYYMMDD	8	System date
dosage	Any ASCII	Variable – max 255 characters	Dosage as entered by doctor

7.1 Lookup tables for therapy files

therflag	description
Y	Acceptable record
A	Invalid prescription date
B	Invalid drug code
E	Invalid prescription quantity
F	Invalid number of days
G	Invalid private flag
H	Invalid staffid
K	Invalid OPNO
L	Invalid issue number
M	Multiple errors
N	Invalid max issue number
R	Invalid locate
U	Invalid inpractice
W	Invalid drugsource
X	Invalid system date

prsctype	description
1	Acute
0	Repeat

drugsource	description
1	By GP in another practice
2	By health carer in another practice
3	By hospital
4	Self prescribing
5	In practice
0	Null record

7.2 Drugcodes: Drug dictionary

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
multilexeid	Any ASCII	8	Encrypted Multilex Id
bnfcode1	99.99.99.99	11	BNF Hierarchy code 1
bnfcode2	99.99.99.99	11	BNF Hierarchy code 2
bnfcode3	99.99.99.99	11	BNF Hierarchy code 3
genericname	Text	120	Generic name of product
formulation	Text	50	Formulation
strength	Text	50	Abbreviated strength
units	Text	50	Units for Strength

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
status	Text	1	L=Live Formulation, D=Discontinued, G=Generic Only, S=Suppressed
hospitalonly	9	1	1=Yes, 0=No
nhsflag	9	1	1=Yes, 0=No
atc	Text	8	Anatomical Therapeutic Chemical Classification System code

7.3 Pack: pack dictionary

This file links to the drug dictionary and contains information at pack level. Price information is available on request

FIELD	TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
multilexeid	Any ASCII	8	Encrypted Multilex Product and Formulation ID
genericname	Text	120	Generic name
pack	Num	3	*Multilex* pack ID
packunit	Text	20	Units of pack
packsize	Num	7	Pack size
status	Text	1	L=Live, D=Discontinued, G=Generic Only, S=Suppressed, W=Withdrawn
legaltext	Text	30	Legal category – e.g. appliance, POM
divisible	Num	1	Pack divisibility 1= yes, 0 = no

7.4 Bnfcode: BNF code chapters

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
bnfcode	99.99.99.99	11	BNFcode 1 in drugcodes
description	Text	100	Description of BNF chapters

7.5 Packsize: look up table

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
packsize	Any ASCII	7	7 character packsize look-up code
description	Text	100	Description of packsize code as found in the raw data

7.6 Dosage: Prescribed dosage text

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
doscode	text	7	Records with a dosage code (see *doscode* field in the therapy record)
dosgval	9999.99	7	Dosage evaluations - prescribed number of units per day
description	Free text	Variable	Dosage text as entered by the GP

Dosage instructions that are recorded as free text in the THIN data have been split away from the therapy records into a global file called dosage. This file has an identifier linking it back to the therapy records.

8 AHD: Additional Health Data

This file contains multiple data types driven by the additional health data code. Essentially it contains information on preventative healthcare immunisations and test results.

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
pracid	A9999	5	Practice id encrypted
patid	Any ASCII	4	Patient identifier – case sensitive and unique within practice
eventdate	YYYYMMDD	8	Event date. Note for incomplete dates 00000000, YYYYMM00 or YYYY0000
ahdcode	999999999	10	AHD code (see AHDCODES)
ahdflag	A	1	Flag indicating integrity of the record (see ahdflag below)
data1	Any ASCII	13	AHD specific - Data1
data2	Any ASCII	13	AHD specific - Data2
data3	Any ASCII	13	AHD specific - Data3
data4	Any ASCII	13	AHD specific - Data4
data5	Any ASCII	13	AHD specific - Data5
data6	Any ASCII	13	AHD specific - Data6
medcode	Any ASCII (case sensitive)	7	Read medical code (see READCODES)
source	A	1	Variable indicating origin of record (see source)
nhsspec	AAA	3	Secondary care speciality (see nhsspeciality). 000 = null nhsspec
locate	Any ASCII	2	Location (see locate)
staffid	Any ASCII	4	Clinician ID. 0000 = null staffid
textid	Any ASCII	7	Link to anonymised free text comments
category	9	1	Category of medical entry (see category)
ahdinfo	A	1	AIS extra information (see extrainfo)
inprac	Y/N	1	Event recorded in practice (Y/N)
private	Y/N	1	Private (Y) or NHS (N) entries
ahdid	Any ASCII	4	AHD record identifier (unique with adhcode)
consultid	Any ASCII	4	Consult link to same medical/therapy consultation
sysdate	YYYYMMDD	8	System date

8.1 Lookup tables for AHD files

ahdflag	description
A	Invalid event date
B	Invalid medical code
C	Invalid source code
D	NHS speciality (speciality) invalid
E	Location (locate) contains invalid
H	Category invalid
L	Staffid invalid
M	Multiple errors
Y	Acceptable record

8.2 AHDcodes: AHD code information

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
datafile	Text	8	Data source type Clinical/Test/Imms
ahdcode	9999999999	10	AHD code
description	text	variable	Description of code
data1	text	variable	AHD value 1
data2	text	variable	AHD value 2
data3	text	variable	AHD value 3
data4	text	variable	AHD value 4
data5	text	variable	AHD value 5
data6	text	variable	AHD value 6

8.3 AHDlookups: lookup table for data values

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
dataname	Any ASCII	8	AHD lookup name
datadesc	text	variable	Description of AHD data value
lookup	text	variable	Value or Code in Data1 – Data6
lookupdesc	text	variable	Description of AHD qualifier

8.4 DeathAHDcomments: death comments linking to AHD

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
pracid	Any ASCII	5	Practice ID
patid	Any ASCII	4	Patient identifier – case sensitive and unique within practice
eventdate	YYYYMMDD	8	Event date. Note for incomplete dates 00000000, YYYYMM00 or YYYY0000
medcode	Any ASCII	7	Read Code

desc	text	variable	Free text comment

9 Consult: consultation information (on request)

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
pracid	A9999	5	Practice id encrypted
patid	Any ASCII	4	Patid - case sensitive and unique within practice
consultid	Any ASCII	4	Consultid
staffid	Any ASCII	4	Identifier of clinician
eventdate	YYYYMMDD	8	Event date
sysdate	YYYYMMDD	8	System date
systime	HHMMSS	6	System time
constype	999	3	type of consultation (see constype)
duration	999999	6	Duration of consultation record open

10 Lookup table for consult files

constype	description
001	Clinic
002	Night visit, deputising service
003	Follow-up/routine visit
004	Night visit, local rota
005	Mail from patient
006	Night visit , practice
007	Out of hours, practice
008	Out of hours, non practice
009	Surgery consultation
010	Telephone call from a patient
011	Acute visit
012	Discharge details
013	Letter from outpatients
014	Repeat issue
015	Other
016	Results recording
017	Mail to patient
018	Emergency consultation
019	Administration
020	Casualty attendance
021	Telephone call to a patient
022	Third Party consultation
023	Hospital admission
024	Children's home visit
025	Day Case Report
026	GOS18 report
027	Home visit

constype	description
028	Hotel visit
029	NHS Direct report
030	Nursing home visit
031	Residential home visit
032	Twilight visit
033	Triage
034	Walk-in Centre
035	Co-op telephone advice
036	Co-op surgery consultation
037	Co-op home visit
038	Minor Injury Service
039	Medicine management
100	Community clinic
101	Community nursing note
102	Community nursing report
103	Data transferred from other system
104	Health Authority entry
105	Health visitor note
106	Health visitor report
107	Hospital inpatient report
108	Initial post discharge review
109	Laboratory request
110	Night visit
111	Radiology request
112	Radiology result
113	Referral letter
114	Social services report
115	Telephone consultation
116	Template entry
117	GP to GP communication transaction
118	Non-consultation medication data
119	Non-consultation data

11 Staff: staff role

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
pracid	A9999	5	Practice id encrypted
staffid	Any ASCII	4	Link to diagnoser/clinician
sex	9	1	Sex of staff (see sex)
role	999	3	Role ID (see role)

11.1 Lookup tables for staff files

role	description
001	Senior partner
002	Partner
003	Assistant
004	Associate
005	Non-commercial local rota of less than 10 GPs
006	Commercial deputising service
007	Locum
008	GP registrar
009	Consultant
010	Sole practitioner
011	Practice nurse
012	Health visitor
013	Community nurse
014	Midwife
015	Community psychiatric nurse
016	Social worker
017	Pharmacist
018	Dispenser
019	Non-qualified dispenser
020	Practice manager
021	Fund manager
022	Business manager
023	Administrator
024	Secretary
025	Receptionist
026	Physiotherapist
027	Chiropodist
028	Dentist
029	Dietician
030	Counsellor
031	Osteopath
032	Maintenance staff
033	Other health care professional

role	description
034	Hospital nurse
035	Community medical officer
036	School nurse
037	Health education officer
038	Contact tracing nurse
039	Stomatherapist
040	Computer manager
041	Interpreter/link worker
042	Chiropractor
043	Acupuncturist
044	Homeopath
045	Mental handicap nurse
046	Carer
047	Salaried partner
048	Occupational therapist
049	Speech therapist
050	GP retainer
051	Phlebotomist
200	Other medical & dental
201	Other students
202	Other nursing & midwifery
203	Other allied health professionals
204	Other professional scientific & technical
205	Other healthcare scientists
206	Other additional clinical services
207	Other admin & clerical

12 PVI: Postcode linked variables

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
pracid	A9999	5	Practice id encrypted
patid	Any ASCII	4	Patient identifier - Case sensitive and unique within practice
urbanrural	Numeric	1	Rural Urban classification of wards 1 = Urban >10k – Sparse, 2 = Town & Fringe – Sparse, 3 = Village, Hamlet & Isolated dwellings – Sparse, 4 = Urban >10k - Less sparse, 5 = Town & Fringe – Less sparse 6 = Village, Hamlet & Isolated dwelling – Less sparse. 0 = no record
eth_percw	Numeric	1	Quintile of proportion of ward population who define themselves as 'White'. 1 = lowest, 5 = highest 0 = no record
eth_percm	Numeric	1	Quintile of proportion of ward population who define themselves as 'Mixed'. 1 = lowest, 5 = highest 0 = no record
eth_percas	Numeric	1	Quintile of proportion of ward population who define themselves as 'Asian or Asian British'. 1 = lowest, 5 = highest 0 = no record
eth_percb	Numeric	1	Quintile of proportion of ward population who define themselves as 'Black or Black British'. 1 = lowest, 5 = highest 0 = no record
eth_perco	Numeric	1	Quintile of proportion of ward population who define themselves as

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
			'Other'. 1 = lowest, 5 = highest 0 = no record
prop_llti	Numeric	1	Proportion of ward population with limiting long-term illness. 1 = lowest, 5 = highest 0 = no record
no2	Numeric	1	Quintile of estimated mean level of Nitrogen Dioxide, 2001. 1 = lowest, 5 = highest 0 = no record
pm10	Numeric	1	Quintile of estimated mean level of Particulate Matter, 2001. 1 = lowest, 5 = highest 0 = no record
so2	Numeric	1	Quintile of estimated mean level of Sulphur Dioxide, 2001. 1 = lowest, 5 = highest 0 = no record
nox	Numeric	1	Quintile of estimated level of Nitrogen Oxides, 2001. 1 = lowest, 5 = highest 0 = no record
townsend	AlphaNumeric	1	Quintile of Townsend score 1 = lowest, 5 = highest 0 = no record X = Townsend score is unavailable or the calculation deemed inappropriate
date	Numeric	8	Date of collection and change of quintile score (if any)

If the postcode is missing or not found in the lookup table then a record will be still be output for that patient but this record will contain only the patient id (e.g. ." PPD ,0,0,0,0,0,0,0,0,0,0,0,19900101")

The only variable available for Scotland & Northern Ireland are the Townsend scores.

13 THINprac: practice file

The THIN practice file is created for each update and provides a summary of information for each practice.

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
prac	A9999	5	Encrypted practice Id (file extension)
compdate	DD/MM/YYYY	10	Date of Computerisation
visiondate	DD/MM/YYYY	10	Date for Vision
amr	DD/MM/YYYY	10	Date of AMR
collectdate	DD/MM/YYYY	10	Date of last collection
country	A	1	E = England, W = Wales S = Scotland, I = Northern Ireland
dataflag	Any Ascii	2	Flag to indicate data issue (see dataflag)
description	Any Ascii	255	Description of data issue
status	A	1	Practice status A = active, W = Withdrawn, S = Suspended

Data flag lookup

dataflag	description
1	One gap of 14 -30 days in therapy before conversion to Vision
2	Gap of over 30 days or more than one gap of over 14 days in therapy before conversion to Vision
3	One gap of 14 – 30 days in Medical records before conversion to Vision
4	More than one gap of over 14 days in Medical records before conversion to Vision
5	Gaps of over 14 days in Medical & therapy before conversion to Vision
0	Missing consultation in Medical and AHD files therefore missing locate & source flags
6	Low numbers of records in therapy records before conversion to Vision
7	Low numbers of records in medical records before conversion to Vision
8	Low numbers of records in medical and therapy before conversion to Vision
9	Low number of records in therapy records and a gap of over 14 days before conversion to Vision
A	One gap of over 14 days after conversion to Vision
*	Limited therapy data (zero drugcodes) prior to Vision date
S	Practice has split
M	Practice has merged

C	Practice has changed user number

14 THINResearchFiles:

We are reviewing the content and format of the research file. This has not yet been completed for the new data format.

15 MidYearCounts: THIN Data denominators

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
year	9999	4	Years from 1986 - 2009
age	9999	4	Ages from 0 – 100+
male	99999	5	Number of males registered on the 1/7
female	99999	5	Number of females registered on the 1/7
total	99999	5	Total number of patients registered on the 1/7

16 PatientStats: Counts of patients by practice

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
prac	Any ASCII	5	Practice
totalpatients	99999	5	Total number of patients in the practice
acceptable	99999	5	Total acceptable patients for research A or C
active	99999	5	Total active patients, still registered with the practice
transferredout	99999	5	Total number of patients with regstat 5
died	99999	5	Total number of patients who have died regstat 99
female	99999	5	Active female patients
male	99999	5	Active male patients

17 THINFirstAndLast: Details of THIN Data fields

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
filename	Text	8	Multilex Product and Formulation ID encrypted
recordcount	999999	8	Number of record in file
recordsize	99999	5	Number of characters in record
filesize	999999999	9	Size of file in Kb

firstrecord	Text	80	First record in file
lastrecord	Text	80	Last record in file

18 THIN Lookup Tables

This ancil file provides an electronic copy of all the lookups for the THIN data files.

FIELD	CHARACTER TYPE	MAX NO. OF CHARACTERS	DESCRIPTION
tablename	Any ASCII	10	Description of table
lookupval	Any ASCII	3	Table lookup value
description	Text	255	Value description

19 Demography file

The demography file provides researchers with summary demographic information for all patients in THIN Data. In addition to basic demographic information such as age/sex and registration status, the file includes patients' start and end dates, last recorded weight and height and most recent smoking and alcohol status (with dates).

Field name	Format	Description
combid	Text	Combined practice & patid
pracid	Text (A1234)	THIN practice id
patid	Text	Patient id
patflag	Text (A)	patflag
active	Text (Y/N)	Calculated Y/N Y = regstat 1 or 2 and prac status = A, N = any other regstat
age	Number (999)	Calculated age at last date of collection
dob	Date (DD/MM/YYYY)	Date of Birth where month and day is missing 01/01 is used
sex	Text (M)	M = male or F = female
regstat	Number (01)	Patient registration status
startdate	Date (DD/MM/YYYY)	Calculated – later of regdate or AMR date
enddate	Date (DD/MM/YYYY)	Calculated – earlier of transferout date or last collection date
regdate	Date (DD/MM/YYYY)	Patient registration date from patient file
compdate	Date (DD/MM/YYYY)	Practice computerisation date
visdate	Date (DD/MM/YYYY)	Date practice converted to Vision
amrdate	Date (DD/MM/YYYY)	Practice AMR date
Collection date	Date (DD/MM/YYYY)	Practice last collection date
xferdate	Date (DD/MM/YYYY)	Patient transfer out date
deathdte	Date (DD/MM/YYYY)	Patient death date
smoking	Text	Smoking status - Calculated C/X/N/U (see

Field name	Format	Description
		below)
smokedate	Date (DD/MM/YYYY)	Date of last smoking record
alcohol	Text	Alcohol status - Calculated C/T/X/U (see below)
alcoholunits	Number (999)	Alcohol units/week
alcoholdate	Date (DD/MM/YYYY)	Date of last alcohol record
height	Decimal (1,3)	Most recent height in M
heightdate	Date (DD/MM/YYYY)	Date of last height
weight	Decimal (2,3)	Most recent Weight in KG
bmi	Decimal (2,1)	Most recent BMI from Vision
weightdate	Date (DD/MM/YYYY)	Most recent weight date

19.1 Smoking status

Smoking Status Flag	Description	How this is calculated
C	Current	If the closest record prior to last date is current smoker and there are no subsequent records of ex-smoker or non-smoker
X	Ex	If the closest record prior to last date is non-smoker but previous records are current smoker or ex-smoker
N	Non	If there are no records with current smoker or ex-smoker at any time and a record of non- smoker
U	Unknown	If there are no records found for current smoker, ex-smoker or non-smoker

19.2 Alcohol status

Alcohol Status Flag	Description	How this is calculated
C	Current	If the closest record prior to last date is current alcohol and there are no subsequent records of ex-alcohol or non-alcohol
X	Ex	If the closest record prior to last date is non- alcohol but previous records are current alcohol or ex-alcohol, or last record is ex-alcohol
T	Non	If there are no records with current alcohol or ex-alcohol at any time and a record of non- alcohol
U	Unknown	If there are no records found for current alcohol, ex-alcohol or non-alcohol

For some patients the last record for smoking\alcohol maybe some time before the last collection date. In this case we assume that the patient's status has not changed during the time period between last smoking record and last collection date.

Medicines & Healthcare products Regulatory Agency

CPRD

Small area level data based on patient postcode

Documentation and Data Dictionary (Set 16)

Version 2.4

Date: 05 June 2018

NHS National Institute for Health Research

Medicines & Healthcare products Regulatory Agency

CPRD

Documentation Control Sheet

Over time, it may be necessary to issue amendments or clarifications to parts of this document. This form must be updated whenever changes are made.

Version	Affected Areas: Summary of Change	Prepared By	Reviewed By
0.9	Initial Draft	PPD	
1.0	Modified		
1.1	Modified		
1.2	Formatted		
1.3	Modified		
2.0	Modified		
2.1	Modified		
2.2	Modified		
2.3	Modified and formatted		
2.4	Modified		

Summary of Changes

Version 1.0
- Release version
- Incorporated changes to ordering of deprivation quintiles\deciles (1=least deprived) and corrections to dataset description for Townsend scores
- Added section on choosing which classification to use for a single study

Version 1.1
- Updated for set 10

Version 1.2
- Formatted document with new agency branding

Version 1.3
- Updated for set 11
- Amended description of eligibility criteria, missing values, and hyperlinks

Version 2.0
- Updated for set 12
- Addition of 2015 English Index of Multiple Deprivation references and data updated

Version 2.1
- Updated for set 13
- NHS postcode directory updated to May 2016
- Linkage summary results updated

Version 2.2
- Updated for set 14
- Linkage summary results and quintile methodology updated

NHS National Institute for Health Research

Medicines & Healthcare products Regulatory Agency

CPRD

Version 2.3
- Updated for set 15
- Updated header and footer with new agency branding

Version 2.4
- Updated for set 16

Background

Classifications based on the population characteristics of small areas or neighbourhoods (and the individuals who live there) have been in use for several decades. In health research they have many applications, including: as a proxy for individual level measures of socioeconomic status; for planning and targeting of health and social care services; for ecological studies of environmental effects on health; and for individual level studies where characteristics of place of residence are of particular interest.[1] There are a wide range on small area data available from many sources. CPRD has linked the GP practice postcode for both CPRD GOLD and CPRD Aurum to some of the most commonly requested area level data. This includes several measures of area level deprivation and a rural-urban classification.

Census geography [2]**:**

The small area data provided is based on census geography which is the main geography directly associated with the UK Census in England, Wales and Northern Ireland. The base unit of this geography is the Output Areas (OA) which are built from clusters of adjacent postcode units [3]. Output areas usually contain around 110-140 households and are designed to be similar in population size and social characteristics based on tenure of household and dwelling type. Output Areas can be aggregated into Super Output Areas (SOA) which can be sub-divided into lower layer super output areas (LSOA) and middle layer super output areas (MSOA) in England and Wales [2].

The small area data provided by CPRD is at LSOA level which are typically built up from 4-6 COAs and have a notional minimum size of 1,000 residents and 300 households, and an average of 1,600 residents [4]. In Northern Ireland data Super Output Area (SOA) are used which have a population of 2,100 people [5]. In Scotland a similar geography known as data zones (DZ) are used which are slightly smaller than LSOAs, with the majority having a population of 500-1,000 residents.

Area level measures of deprivation:

There are a number of well-known area-based measures of deprivation, of which two are available at the LSOA level for linkage to CPRD primary care data through the patient postcode. Additional measures are linked through the practice postcode. The measures linked through the patient postcode are:

The English Index of Multiple Deprivation (IMD):

One of the most commonly used measures is the Index of Multiple Deprivation (IMD). This is a composite measure derived from of a number of indicators covering different aspects ('domains') of material deprivation: housing, employment, income, access to services, education and skills, crime, and living environment. Each domain index can itself be a composite score derived from two or more sub-domain indicators. In addition, a composite index - often referred to as the Index of Multiple Deprivation (IMD) - is calculated as a weighted sum of the domain indices.

The first official 'Indices of Deprivation' for England [6] were produced by the UK Department for Communities and Local Government in 2000, replacing the 1998 Index of Local Deprivation. Updates for 2004, 2007, 2010 and 2015 were calculated at lower layer super output area (LSOA) level [7]. Similar indices exist for Wales [8], Scotland [9] and Northern Ireland [5], [10] but are not currently linked to CPRD primary care data at the patient postcode level. It is important to note that differences in methodology and source data mean that the indices are not directly comparable between different countries. Note also that all the indices measure relative rather than absolute deprivation. As such it is the ranking of areas provided by the IMD score, rather than the actual score itself, which is of primary interest.

Townsend Score: [11], [12]

This indicator was devised by Townsend *et al* in 1988 as an index of material deprivation and disadvantage. Originally calculated at ward level, it was based on 4 measures from the 1981 census:

- Unemployment: proportion of the economically active population aged 16-59/64 who are unemployed.
- Car ownership: proportion of households with no car.
- Home ownership: proportion of households not owning their own home.
- Household overcrowding: proportion of private households with >=1 resident per room.

The index is created as the sum of scores for each standardised measure. Townsend scores have been recalculated using data from the 1991 and 2001 census, and for different geographies – for example census output areas (OA) and LSOA. As with IMD scores, it is the ranking of areas provided by the Townsend score, rather than the actual score itself, which is of primary interest.

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What data are available through this linkage?

For practices in England that have consented to participate in the linkage scheme, the patient postcode of residence is mapped to the 2001 and 2011 LSOA boundaries using a postcode lookup file. The LSOA of residence then allows linkage to the following LSOA-level deprivation measures [6]:

- 2004 English Index of Multiple Deprivation (2001 LSOA boundaries)
- 2007 English Index of Multiple Deprivation (2001 LSOA boundaries)
- 2010 English Index of Multiple Deprivation (2001 LSOA boundaries)
- 2015 English Index of Multiple Deprivation (2011 LSOA boundaries)
- Townsend score: calculated at LSOA level using unadjusted 2001 census data[12]

Linkages at the practice postcode level are available separately. This uses the practice postcode which is linked via LSOA, SOA (Northern Ireland) or datazone (DZ) (Scotland), to several measures of area level deprivation and a rural-urban classification. These data are described in the documentation on small area data for practices.

Which area-based classification should I use?

Only one patient level classification will be provided for a single study (see section on disclosure control). In deciding which classification is most appropriate, there are a number of things to consider:

- theoretical considerations: the four IMD classifications summarise a larger range of 'domains' of deprivation than Townsend which is intended to focus on material deprivation. It may be helpful to review the literature on the derivation of the different classifications.
- data coverage period: you may want to select a measure derived from data collected during a period which most closely coincides with your study period.
- external validity: you may wish to select a classification that allows your results to be most comparable with other published work.

Aside from these issues, it is worth noting that all of the available measures are very highly correlated. Spearman's rank correlation coefficients are between 0.94-0.98 for deciles of the 4 different IMD classifications, and between 0.87-0.89 for deciles of Townsend vs the 4 IMD classifications. This means that for many applications, the choice of area-based deprivation measure is unlikely to have a significant impact on the results or interpretation.

Disclosure control

IMD scores and rankings are in the public domain and can be used to identify individual LSOAs. Therefore CPRD will normally only provide the quintile, decile or 'twentile' groupings based on the ranking. These quantiles are calculated by ranking all national LSOAs from most deprived to least deprived and dividing them into equal groups. This ranking is not restricted to the CPRD population, no further processing is done on the data and the quantiles are not weighted.

Technical note: different approaches are available for assigning quantile membership (quintile, deciles etc) when the number of units to be grouped is not an exact multiple of the number of groups. The quintile, decile and 'twentile' groupings were created with the –xtile– command in Stata version [13], with the –nquantile()– option to specify the number of equal sized groups to be created (quintiles=5 groups; deciles=10 groups; 'twentiles'=20 groups).

By cross-tabulating two or more classifications it is possible to identify very small groups of lower super output areas (LSOA). In order to minimise the possibility of deductive disclosure of a patients' area of residence, CPRD will only supply one of the area-based deprivation measures for any one study. If you feel you have a compelling justification for using two or more classifications in the same study you should contact CPRD to discuss your requirements.

Eligibility for inclusion in patient-level postcode linkage

Patients are eligible for inclusion if ALL the following criteria are satisfied:

- they are registered with a practice which has consented to participate in the CPRD patient-level linkage scheme. Currently the linkage scheme is restricted to practices in England.
- the patient has no record indicating dissent from the transmission of personal confidential data to NHS Digital, formerly known as the Health and Social Care Information Centre (HSCIC).
- a full postcode of residence is recorded at the general practice, and has a valid format.

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Related files

- **Linkage eligibility file** (linkage_eligibility.txt) - this file contains a record for every patient registered with a linked practice prior to transmission of identifiers to the trusted third party, along with flags to indicate the patients' eligibility for inclusion in each of the available linkages. Note that eligibility for linkage does not necessarily mean that the patient will appear in the linked dataset. For patient level deprivation measures, the relevant columns are:
  - [patid]: the unique CPRD patient identifier
  - [lsoa_e]: this flag is set to 1 if the patient if eligible for inclusion in linkages based on patient postcode of residence (based on eligibility criteria above), and 0 otherwise.

NHS Postcode Directory (NHSPD) [14]
The Office for National Statistics (ONS) supplies postcode-related data to the Organisation Data Service (ODS). The Organisation Data Service (ODS) is provided by NHS Digital and is responsible for the publication of all organisation and practitioner codes and NHS data standards. NHSPD is updated on a quarterly basis and can be downloaded from:
https://digital.nhs.uk/organisation-data-service/data-downloads/national-statistics

Linkage summary results - set 16

- *Coverage period for linkage*: undefined. The patient postcode is available only for the last recorded address, and is valid up to the time of the data extract used for the linkage i.e. the linkage date. The date from which the patient first resided at that postcode is not recorded.
- *Postcode lookup file version* (maps unit postcodes to LSOA): NHSPD, November 2017

CPRD GOLD
- *Number of practices in linkage* (see linkage_eligibility.txt file): 411
- *Number of patients in linked practices* (see linkage_eligibility.txt file): 10,553,586
- *Number of patients eligible for postcode linkage* (lsoa_e=1 in linkage_eligibility.txt): 10,052,096
- *Number of records in each IMD/Townsend data file*: 10,052,096
- *Number of patients with valid area-based deprivation score data*: 10,010,384
- *Number of patients with a postcode having a valid format, but which could **not** be linked to a English LSOA based on the 2001 and 2011 LSOA classifications:* 41,712 (IMD and Townsend score quantiles are set to missing for these patients).

CPRD Aurum
- *Number of practices in linkage* (see linkage_eligibility.txt file): 232
- *Number of patients in linked practices* (see linkage_eligibility.txt file): 6,566,869
- *Number of patients eligible for postcode linkage* (lsoa_e=1 in linkage_eligibility.txt): 6,528,544
- *Number of records in each IMD/Townsend data file*: 6,528,544
- *Number of patients with valid area-based deprivation score data*: 6,515,166
- *Number of patients with a postcode having a valid format, but which could **not** be linked to a English LSOA based on the 2001 and 2011 LSOA classifications:* 13,378 (IMD and Townsend score quantiles are set to missing for these patients).

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Dataset specification - set 16

Missing values for IMD and Townsend quantiles
Where a postcode appears in a valid format but cannot be linked to an English LSOA (2001 / 2011 classification as appropriate), the IMD and Townsend score quantiles are set to missing. This may occur for a number of reasons:

- a non-geographic postcode
- a new postcode which is not included in the version of the NHS postcode directory used at the time of the linkage processing
- a postcode which is not in England
- an invalid postcode (but having the correct format)

Index of Multiple Deprivation:

File name: patient_imd2004.txt

Column name	*Description*	*Format*
patid	The encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	integer: 20
pracid	The encrypted unique key given to a practice in CPRD GOLD or CPRD Aurum	integer: 5
imd2004_5	IMD 2004 quintile (1=LEAST deprived,…, 5=MOST deprived)	integer: 5
imd2004_10	IMD 2004 decile (1=LEAST deprived,…, 10=MOST deprived)	integer: 10
imd2004_20	IMD 2004 'twentile' (1=LEAST deprived,…, 20=MOST deprived)	integer: 20

File name: patient_imd2007.txt

Column name	*Description*	*Format*
patid	The encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	integer: 20
pracid	The encrypted unique key given to a practice in CPRD GOLD or CPRD Aurum	integer: 5
imd2007_5	IMD 2007 quintile (1=LEAST deprived,…, 5=MOST deprived)	integer: 5
imd2007_10	IMD 2007 decile (1=LEAST deprived,…, 10=MOST deprived)	integer: 10
imd2007_20	IMD 2007 'twentile' (1=LEAST deprived,…, 20=MOST deprived)	integer: 20

File name: patient_imd2010.txt

Column name	*Description*	*Format*
patid	The encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	integer: 20
pracid	The encrypted unique key given to a practice in CPRD GOLD or CPRD Aurum	integer: 5
imd2010_5	IMD 2010 quintile (1=LEAST deprived,…, 5=MOST deprived)	integer: 5
imd2010_10	IMD 2010 decile (1=LEAST deprived,…, 10=MOST deprived)	integer: 10
imd2010_20	IMD 2010 'twentile' (1=LEAST deprived,…, 20=MOST deprived)	integer: 20

File name: patient_imd2015.txt

Column name	*Description*	*Format*
patid	The encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	integer: 20
pracid	The encrypted unique key given to a practice in CPRD GOLD or CPRD Aurum	integer: 5
imd2015_5	IMD 2015 quintile (1=LEAST deprived,…, 5=MOST deprived)	integer: 5
imd2015_10	IMD 2015 decile (1=LEAST deprived,…, 10=MOST deprived)	integer: 10
imd2015_20	IMD 2015 'twentile' (1=LEAST deprived,…, 20=MOST deprived)	integer: 20

Townsend:

File name: patient_townsend2001.txt

Column name	*Description*	*Format*
patid	The encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	integer: 20
pracid	The encrypted unique key given to a practice in CPRD GOLD or CPRD Aurum	integer: 5
townsend2001_5	Townsend 2001 quintile (1=LEAST deprived,…, 5=MOST deprived)	integer: 5
townsend2001_10	Townsend 2001 decile (1=LEAST deprived,…, 10=MOST deprived)	integer: 10
townsend2001_20	Townsend 2001 'twentile' (1=LEAST deprived,…, 20=MOST deprived)	integer: 20

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Reference list

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NHS National Institute for Health Research

Hospital Episode Statistics (HES)

Admitted Patient Care (APC)

Data Dictionary

Basic HES (Set 16)

Version 2.1

Date: 06 June 2018

Medicines & Healthcare products Regulatory Agency

CPRD

Documentation Control Sheet

Over time, it may be necessary to issue amendments or clarifications to parts of this document. This form must be updated whenever changes are made.

Version	Affected Areas Summary of Change	Prepared By	Reviewed By
1.0	Initial Draft		
1.1	Modified	PPD	
1.2	Modified		
1.3	Modified		
1.4	Modified		
1.5	Modified		
1.6	Formatted		
1.7	Modified		
1.8	Modified		
1.9	Modified		
1.10	Modified		
2.0	Modified and Formatted		
2.1	Modified		

Summary of changes

Version 1.1
- Refined wordings

Version 1.2
- Added new field (HESid) in source file
- Formatted all diagnosis ICD codes into XXX, or XXX.X format
- Added new field (ICDx) in diagnoses tables

Version 1.3
- Prefixed all files with HES_
- Removed source table – make use of linkage_eligibility.txt to define cohort of linked patients
- Removed birthyear and gender fields from patient file (hes_patient.txt)
- Added new fields (gen_hesid, n_patid_hes) to patient file (hes_patient.txt)
- Removed primary field from diagnoses by episode table (hes_diagnosis_epi.txt)
- Added new field (d_order) in diagnoses by episode table (hes_diagnosis_epi.txt)
- Added new field (p_order) in procedures by episode table (hes_procedures_epi.txt)

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Version 1.4
- Added description of the 'match rank' variable now included in HES patients table (hes_patient.txt)
- Added guidance relating to the variable 'admimeth' found in the hospitalisation (hes_hospital.txt) and episodes table (hes_episodes.txt)
- Added description relating to handling of unfinished consultant episodes
- Added HES Health Resource Group (HRG) table (hes_hrg.txt)

Version 1.5
- Corrected 'Type' value for field 'admimeth' in hospitalisations and episodes tables

Version 1.6
- Formatted with new agency branding and updated document title
- Included version of HES on front page

Version 1.7
- Updated the document version number, date and HES set
- Changed variable order in the HES Patient table (hes_patient.txt)
- Included the variable 'gen_ethnicity' in the HES Patient table (hes_patient.txt)
- Included the variable 'ethnos' in the HES Episodes table (hes_episodes.txt)

Version 1.8
- Updated the document version number, date and HES set
- Added a footnote to the HES hospital table (hes_hospital.txt) about changes to 'duration'
- Added a footnote to the HES episodes table (hes_episodes.txt) about changes to 'epidur'
- Added a footnote to the HES primary diagnosis table (hes_primary_diag_hosp.txt) to clarify the reference to 'primary'

Version 1.9
- Updated the document version number, date and HES set

Version 1.10
- Updated the document version number, date and HES set

Version 2.0
- Updated the document version number, date and HES set
- Removed the variable 'hrglate' in the Health Resource Group table (hes_hrg.txt). See HES APC Set 15 documentation for further details.
- Updated header and footer with new agency branding

Version 2.1
- Updated the document version number, date and HES set
- Updated to include CPRD Aurum

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HES APC: Data dictionary (Basic)

1. Patient (hes_patient.txt)

Column name	*Description*	*Type*	*Format*
patid	Encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	INTEGER	20
pracid	Encrypted unique key given to a practice in CPRD GOLD or CPRD Aurum	INTEGER	5
gen_hesid[1]	A generated unique key assigned to a patient in the HES data. An individual that has contributed data to more than one CPRD practice has the same gen_hesid.	INTEGER	20
n_patid_hes[1]	Number of individuals in CPRD GOLD or CPRD Aurum assigned the same gen_hesid (unique patient identifier generated in HES)	INTEGER	3
gen_ethnicity[1]	Patient's ethnicity derived from all HES data (including HES outpatient, HES admitted patient care and HES A&E)	CHAR	10
match_rank[2]	Indicates the quality of matching between a record in HES and CPRD primary care data and gives the level of confidence that an HES record has been correctly matched to a patient in CPRD GOLD or CPRD Aurum.	INTEGER	1

[1] Variable generated by CPRD.
[2] An eight-step process is used to match patients in CPRD primary care data (CPRD GOLD or CPRD Aurum) and HES using some or all of the following: NHS number, date of birth, sex and postcode. Only data for patients matched using steps 1-5 has been provided. This variable was first available with HES set 10.

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2. Hospitalisations (hes_hospital.txt)

Column name	*Description*	*Type*	*Format*
patid	Encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	INTEGER	20
spno	Spell number uniquely identifying a hospitalisation	INTEGER	20
admidate	Date of admission	DATE	dd/mm/yyyy
discharged	Date of discharge	DATE	dd/mm/yyyy
admimeth[3]	Method of admission	CHAR	2
admisorc	Source of admission	INTEGER	2
disdest	Destination on discharge	INTEGER	2
dismeth	Method of discharge	INTEGER	1
duration[4]	Duration of hospitalisation spell in days	INTEGER	5
elecdate	Date of decision to admit patient	DATE	dd/mm/yyyy
elecdur	Waiting time (difference in days between elecdate and admidate)	INTEGER	5

[3] From April 2013, National Codes 2A, 2B, 2C and 2D have been introduced to replace National Code 28 *'Other means'*. Records containing these codes prior to April 2013 will U group and will consequently not attract tariff. Further information on the attributes of HES variables including 'admimeth' can be found here http://www.datadictionary.nhs.uk/items_index_a_child.asp?shownav=1

[4] Values of the 'duration' variable are now provided as generated by HES. These were previously recalculated by the CPRD by incrementing the original values by 1.

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3. Episodes (hes_episodes.txt)

Column name	*Description*	*Type*	*Format*
patid	Encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	INTEGER	20
spno	Spell number uniquely identifying a hospitalisation	INTEGER	20
epikey[5]	Episode key uniquely identifying an episode of care	INTEGER	20
admidate	Date of admission	DATE	dd/mm/yyyy
epistart	Date of start of episode	DATE	dd/mm/yyyy
epiend	Date of end of episode	DATE	dd/mm/yyyy
discharged	Date of discharge	DATE	dd/mm/yyyy
eorder	Order of episode within spell	INTEGER	3
epidur[6]	Duration of episode in days	INTEGER	5
epitype	Type of episode (general, delivery, birth, psychiatric etc.)	INTEGER	1
admimeth[3]	Method of admission	CHAR	2
admisorc	Source of admission	INTEGER	2
disdest	Destination on discharge	INTEGER	2
dismeth	Method of discharge	INTEGER	1
mainspef	Speciality under which consultant is contracted	CHAR	3
tretspef	Speciality under which consultant is working in period of care	CHAR	3
pconsult	Consultant code (pseudonymised)	CHAR	16
intmanig	Intended management	INTEGER	1
classpat	Patient classification: (Actual Management) 1=Ordinary admission; 2=Day case admission; 3=Regular day attendee; 4=Regular night attendee; 5=Mothers and babies using only delivery facilities; 8=Not applicable (other maternity event)	INTEGER	1
firstreg	First regular day or night admission?	CHAR	2
ethnos	Patient ethnicity as recorded with the HES Admitted Patient Care episode	CHAR	10

[5] Only finished consultant episodes occurring within the financial year (up to midnight on 31Mar) are included. Patients with an unfinished consultant episode in the current financial year will have their record represented as a finished episode in the next financial year of HES data. The discharge date of patients with both finished and unfinished consultant episodes in the same spell in the financial year have been set to missing (.)

[6] Values of the epidur variable are now provided as generated by HES. These were previously recalculated by the CPRD by incrementing the original values by 1.

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4. Diagnoses

- **By episode (hes_diagnosis_epi.txt):** ICD10 codes across an episode

Column name	*Description*	*Type*	*Format*
patid	Encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	INTEGER	20
spno	Number uniquely identifying a hospitalisation	INTEGER	20
epikey	Episode key uniquely identifying an episode of care	INTEGER	20
epistart	Start date of episode of care	DATE	dd/mm/yyyy
epiend	Date of end of episode	DATE	dd/mm/yyyy
ICD	An ICD10 diagnosis code in XXX or XXX.X format	CHAR	5
ICDx	5th/6th characters of the ICD code (if available)	CHAR	2
d_order	Ordering of diagnosis code in episode, within range 1-20	INTEGER	2

- **By hospitalisation (hes_diagnosis_hosp.txt):** Unique ICD10 codes across a hospitalisation

Column name	*Description*	*Type*	*Format*
patid	Encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	INTEGER	20
spno	Spell number uniquely identifying a hospitalisation	INTEGER	20
admidate	Date of admission	DATE	dd/mm/yyyy
discharged	Date of discharge	DATE	dd/mm/yyyy
ICD	An ICD10 diagnosis code in XXX or XXX.X format	CHAR	5
ICDx	5th/6th characters of the ICD code (if available)	CHAR	2

- **Primary¥ diagnoses across a hospitalisation (hes_primary_diag_hosp.txt)**

Column name	*Description*	*Type*	*Format*
patid	Encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	INTEGER	20
spno	Spell number uniquely identifying a hospitalisation	INTEGER	20
admidate	Date of admission	DATE	dd/mm/yyyy
discharged	Date of discharge	DATE	dd/mm/yyyy
ICD_PRIMARY	Primary ICD10 diagnosis code in XXX or XXX.X format	CHAR	5
ICDx	5th/6th characters of the ICD code (if available)	CHAR	2

¥ The first diagnosis recorded during each episode of care in a spell

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5. Procedures (hes_procedures_epi.txt)

Column name	*Description*	*Type*	*Format*
patid	Encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	INTEGER	20
spno	Spell number uniquely identifying a hospitalisation	INTEGER	20
epikey	Episode key uniquely identifying an episode of care	INTEGER	20
admidate	Date of admission	DATE	dd/mm/yyyy
epistart	Start date of episode of care	DATE	dd/mm/yyyy
epiend	Date of end of episode	DATE	dd/mm/yyyy
discharged	Date of discharge	DATE	dd/mm/yyyy
OPCS	An OPCS 4 procedure code	CHAR	4
evdate	Date of operation / procedure	DATE	dd/mm/yyyy
p_order	Ordering of OPCS code in episode, within range 1-24	INTEGER	2

6. Health Resource Group (hes_hrg.txt)

Column name	*Description*	*Type*	*Format*
patid	Encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	INTEGER	20
spno	Spell number uniquely identifying a hospitalisation	INTEGER	20
epikey	Episode key uniquely identifying an episode of care	INTEGER	20
domproc	NHS Trust derived dominant procedure	CHAR	5
hrglate35	HRG version 3.5 derived by HES	CHAR	4
hrgnhs	NHS Trust derived HRG value	CHAR	4
hrgnhsvn	Version number of Trust derived HRG	CHAR	3
suscorehrg	SUS¥ generated Core Spell HRG	CHAR	3-5
sushrg	SUS¥ generated HRG	CHAR	3-5
sushrgvers	SUS¥ generated HRG version number	NUMERIC	3
hes_yr	Year of HES record (generated by CPRD)	NUMERIC	4

¥The Secondary Uses Service (SUS) supports the NHS and its partners by providing a single source of comprehensive data for 'secondary uses'; purposes other than primary clinical care.

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CPRD

Hospital Episode Statistics (HES) Admitted Patient Care and CPRD primary care data Documentation (Set 16)

Version 2.1

Date : 06 June 2018

Medicines & Healthcare products Regulatory Agency

CPRD

Documentation Control Sheet

Over time, it may be necessary to issue amendments or clarifications to parts of this document. This form must be updated whenever changes are made.

Version	Affected Areas Summary of Change	Prepared By	Reviewed By
1.0	Initial Draft		
1.1	Modified	PPD	
1.2	Modified		
1.3	Modified		
1.4	Modified		
1.5	Formatted		
1.6	Modified		
1.7	Modified		
1.8	Modified		
1.9	Modified		
2.0	Modified and Formatted		
2.1	Modified		

Summary of Changes

Version 1.1
- Refined wordings

Version 1.2
- Created separate data dictionary/specification for Integrated, Basic and Full HES
- Amended section on HES data and CPRD GOLD to reflect what linked data represents

Version 1.3
- Amended 'What are the HES?' section, including information on the HSCIC

Version 1.4
- Updated the document title to change the focus to Admitted Patient Care data
- Updated 'HES data and CPRD GOLD' to 'HES Admitted Patient Care data and CPRD GOLD'
- Removed reference to linked HES inpatient data being the only HES data source currently available in CPRD
- Added information about the match_rank variable which is newly available for set 10
- Removed reference to HES Outpatient (OP) data under 'Future plans' as OP data is now available as an additional data module and has its own documentation

Version 1.5
- Formatted with new agency branding and updated document title
- Included version of HES on front page

Version 1.6

- Updated document version number, date and HES set
- Clarified the information relating to the 'match_rank' variable under 'HES Admitted Patient Care data and CPRD GOLD'
- Updated section on ethnicity data derived by CPRD as recorded under 'Data structure and formatting'
- Updated the last year of collection of augmented care period data as recorded under 'Data structure and formatting'

Version 1.7

- Updated document version number, date and HES set
- Added the HES APC coverage dates for this release
- Removed reference to HES Outpatient and Accident & Emergency data
- Added table of proportion of patients linked by match_rank
- Added details about availability of records with match_rank values of 6 to 8
- Added details about availability of records with multiple HESIDs
- Added changes introduced in set 12
- Added information under 'Known issues' relating to provisional release of HES data

Version 1.8

- Updated document version number, date and HES set
- Added the HES APC coverage dates for this release
- Added explanation of changed definition of the derived ethnicity variable
- Added changes introduced in set 13
- Updated references to reflect change of name from HSCIC to NHS Digital

Version 1.9

- Updated document version number, date and HES set
- Added the HES APC coverage dates for this release
- Added changes introduced in set 14
- Updated web links

Version 2.0

- Updated document version number, date and HES set
- Updated header and footer with new agency branding
- HRG variable changes detailed

Version 2.1

- Updated document version number, date and HES set
- Updated link address for NHS Digital HES data dictionary
- Updated to include CPRD Aurum
- Updated table numbers

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CPRD

HES Admitted Patient Care (APC) data linked to CPRD primary care data

This document provides an overview of the HES Admitted Patient Care (HES APC) data, and the available subset that is linked to CPRD GOLD and CPRD Aurum.

What are the HES Admitted Patient Care data?

The Hospital Episode Statistics (HES) represent a data warehouse of English NHS data related to health care provider activity across three main patient groups:

- Admitted patient care – inpatient and day case admissions to hospital
- Outpatient appointments and attendances
- Accident and Emergency attendances

The HES data are managed by NHS Digital (http://content.digital.nhs.uk/hes), formerly known as the Health and Social Care Information Centre. The data are extracted from a data warehouse on a monthly basis. At the end of the fiscal year there is a "month 13" annual refresh which corrects known data quality issues prior to locking the annual published data.

The HES APC data contains details of all admissions to *English* NHS health care providers. The patients include private patients and residents outside of England, who were treated by NHS health care providers, including treatment by the independent sector, if funded by the NHS. All NHS health care providers in England, including acute hospital trusts, primary care trusts and mental health trusts provide data. The data is available at the person level as a consultant episode for admitted patients.

There are extensions to the admitted patient care data that cover maternity and adult critical care (referred to as either Augmented Care Periods or as the Critical Care Minimum Data Set; as the underlying data standards have changed over time).

Data have been collected for admitted patient care data from 1989 onwards. CPRD only links data from 1997 due to the introduction of the NHS number which is an important element in the linkage of the data. More than 17 million consultant episodes are added each year. The data are recorded for episodes ending from April 1st to the following March 31st each year, corresponding to NHS fiscal years.

Before requesting HES APC data, users are encouraged to familiarise themselves with the content of HES APC data. Details on the fields available and changes to field definitions over time can be found at: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/hospital-episode-statistics-data-dictionary. Details of HES APC activity statistics can be found at: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-episode-statistics-for-admitted-patient-care-outpatient-and-accident-and-emergency-data

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Accessing HES Admitted Patient Care data linked to CPRD GOLD and CPRD Aurum

HES APC data can only be accessed as part of a data extract linked to CPRD primary care data (CPRD GOLD or CPRD Aurum). Access is provided by CPRD subject to MHRA Independent Scientific Advisory Committee (ISAC) approval. Key items of HES APC data, notably the hospitalisation discharge date, and all ICD10 codes, can be provided with CPRD primary care data at no extra charge (see documentation for Integrated HES). Please note that these data cannot be used reliably to identify outcomes in a study. Alternatively, more extensive data can be provided at a cost. The cost of access depends upon the volume of data required.

Not all patients in CPRD GOLD or CPRD Aurum are eligible to be linked to HES, for example, due to the region in which they reside (outside England), or the lack of a valid NHS identifier. Source files (linkage_eligibility.txt) are provided to allow researchers to identify the subset of patients who are eligible to have linked HES data.

Linkage coverage period

The latest release of HES APC data linked to CPRD primary care data (set 16) covers the period **April 1997 – December 2017**. Please note that the data for 2017/2018 (April 2017 – December 2017) are provisional HES data, up to Month 9.

Linkage algorithm and the match_rank variable

The linkage between HES APC and CPRD primary care data uses an eight-step deterministic linkage algorithm based on four identifiers, shown in Table 1 below. The linkage is undertaken by NHS Digital, acting as a trusted-third-party, on behalf of CPRD. No personal identifiers are held by CPRD, or included in the CPRD GOLD, CPRD Aurum, or linked HES APC data.

Table 1: NHS Digital 8 step linkage algorithm

Step	Match
1	Exact NHS number, sex, date of birth (DOB), postcode
2	Exact NHS number, sex, DOB
3	Exact NHS number, sex, postcode, partial DOB
4	Exact NHS number, sex, partial DOB
5	Exact NHS number, postcode
6	Exact sex, DOB and postcode (where NHS number does not contradict the match, the DOB is not 1st of January & the postcode not on the communal establishment list)
7	Exact sex, DOB and postcode (where the NHS number does not contradict the match and the DOB is not 1st of January)
8	Exact NHS number

The matching steps are applied sequentially. If a CPRD GOLD or CPRD Aurum patient record is matched in one step, it is no longer available for matching in subsequent steps. Matching results are summarised in Table 2A and 2B below.

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Table 2A: Number and proportion of **CPRD GOLD** patients matched to a HES patient* at each step of the linkage algorithm in set 16.

Linkage step (match_rank)	Frequency	Percent
1	5241901	67.6
2	2227150	28.7
3	13344	0.2
4	17528	0.2
5	3567	0.1
6	232007	3.0
7	13992	0.2
8	5396	0.1

*includes patients in all HES datasets (Admitted patient care, Outpatient, and A&E)

Table 2B: Number and proportion of **CPRD Aurum** patients matched to a HES patient* at each step of the linkage algorithm in set 16.

Linkage step (match_rank)	Frequency	Percent
1	3627901	64.0
2	1962286	34.6
3	8269	0.2
4	13136	0.2
5	1934	0.0
6	45633	0.8
7	2832	0.1
8	4330	0.1

* includes patients in all HES datasets (Admitted patient care, Outpatient, and A&E)

CPRD provides users with a match_rank variable which corresponds to the step at which a match was established. In general, a lower value for the match_rank is considered stronger evidence for a positive match. Note that only patients with a match_rank of 5 or less are considered definitive matches and are included in the linked HES APC dataset. Patients matched on steps 6-8 have been retained in separate files. We envisage that the retained records will primarily be of interest to methodological researchers. If you are interested in these data, please speak to a member of the CPRD Observational Research team prior to submission of your protocol to the ISAC.

A minority of patients are linked to multiple HESIDs. These patients are removed from the HES APC dataset. However, the data have been retained and are available on request. If you are interested in these data, please speak to a member of the CPRD Observational Research team prior to submission of your protocol to the ISAC.

As far as possible, the linked HES APC data is supplied “as is”, without any modification or cleaning during processing by CPRD. Where CPRD has modified the HES data, these are detailed below.

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Data structure and formatting

The data has been arranged into files relating to hospitalisations (alternatively known as spells in HES), episodes, and files for events that are linked to specific episodes.

Hospitalisations refer to the total period of inpatient hospital stay from admission to discharge. When a hospitalisation spans the end of the HES year, it is artificially modelled as two hospitalisations, from admission to end of HES year (in the first year's HES data) and from start of the HES year to final discharge (in the second HES year).

An episode is a time-period within a hospitalisation, which corresponds to the period where the patient is in the continuous care of one consultant using the beds of one health care provider. Note that this is not always the same as a single stay in hospital, because a patient may be transferred from one consultant to another during their stay. In these cases, there will be two or more-episode records for the hospitalisation. Consultant episodes will also terminate when a patient is transferred between health care provider organisations, even though their inpatient care may be continuous.

Each patient may have one or more HES hospitalisations. Each hospitalisation can consist of one or more episodes. For each episode, up to 20 diagnoses and 24 procedures may be recorded. Additionally, each episode can have up to nine periods of augmented care. If the HES hospitalisation is related to pregnancy, each episode can additionally have information on up to nine babies to accommodate multiple births.

For each patient cohort, HES APC data will be provided as separate text tab delimited files. These files can be linked to the corresponding CPRD GOLD or CPRD Aurum patient cohort file using the CPRD generated encrypted patient key (patid). Files can be imported into statistical software such as Stata or SAS, or into data management packages such as Microsoft Access, for further data processing and analysis.

The format of the HES data has been modified for linked patients in the following ways:

- **Unique HES patient key (gen_hesid):** A patient key has been generated to identify a unique patient in the HES data. This is unique across all CPRD-linked HES datasets including HES admitted patient care, HES outpatient and HES accident and emergency (A&E) data. An individual that has contributed data to more than one CPRD practice will have the same patient key (gen_hesid) in the HES_patient file. Researchers will need to consider how this may impact their study.

- **Ethnicity:** Ethnicity (ethnos) is recorded in each episode of the original HES data and these are recoded (see Table 3 below) and provided in the HES episodes table (hes_episodes.txt). Most patients have the same ethnicity grouping for each episode. However, for a minority of patients, recording of ethnicity varies between episodes, both within and across hospitalisations. CPRD use the following stepwise process to derive a single ethnicity variable (gen_ethnicity) for each subject in the patient file:

    1. The variable is set to the most frequently recorded ethnicity value across episodes and hospitalisations in the HES Admitted Patient Care, HES Outpatient and HES A&E data.
    2. Where the most frequently recorded ethnicity is "Unknown", "Unknown" values are removed, and the value is reset to the most commonly recorded ethnicity.
    3. Where there is no majority, the derived ethnicity is recorded as "Unknown".

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Recoded Ethnicity	*Original Ethnicities*
White	0 = White, A = British (White), B = Irish (White), C = Any other White background
Black_Caribbean	1 = Black – Caribbean, M = Caribbean (Black or Black British)
Black_African	2 = Black – African, N = African (Black or Black British)
Black_Other	3 = Black – Other, P = Any other Black background
Indian	4 = Indian, H = Indian (Asian or Asian British)
Pakistani	5 = Pakistani, J = Pakistani (Asian or Asian British)
Bangladeshi	6 = Bangladeshi, K = Bangladeshi (Asian or Asian British)
Other_Asian	L = Any other Asian background
Chinese	7 = Chinese, R = Chinese (other ethnic group)
Mixed	D = White and Black Caribbean (Mixed), E = White and Black African (Mixed), F = White and Asian (Mixed), G = Any other Mixed background
Other	8 = Any other ethnic group, S = Any other ethnic group
Unknown	9 = Not given, X = Not known, Z = Not stated

Table 3: Ethnicity recoding by CPRD

- **Hospitalisations (within a health care provider):** A hospitalisation level file was created, containing the spell number (uniquely identifying a hospitalisation), dates of admission and discharge, and duration of hospitalisation (in days).

- **Augmented Care Data**: This area has been noted by HES as having some data quality issues. We have included the data mostly "as is" except structuring it into a separate file. The limitations reflect that some hospitals record augmented care periods using systems which may not show up as augmented care in the HES data. There can be up to nine augmented care periods during a single episode. Since augmented care focuses on keeping patients alive, there can be overlapping episodes (where multiple 'teams' have a role at the same time). This means the numbers of days in augmented care do not always correspond to the number of days within an episode. The variable 'numacp' determines the number of augmented care records per episode. Augmented care data is available until the year 2007/2008, after which it has been replaced by the Critical Care Data set.

- **Critical Care Data**: The source of HES critical care data is the CCMDS (Critical Care Minimum Data Set), which includes records for critical care periods in adult designated wards. Any one

patient can have multiple critical care stays, which may be in the same or different time period for the same or different condition. Critical care data is available from HES years 2008 onwards.

- **Maternity data:** This area has also been noted by the HES as having some data quality issues. As with the augmented care data, these data are restructured into a separate file in an array format. There can be information recorded on up to nine births within a single episode (six births for years prior to 2003). Otherwise, the data has not been altered. Several quality issues may be readily obvious. Two variables, 'numbaby' and 'numtailb', were used in a hierarchical algorithm to determine the number of births per episode. 'numtailb', if not missing, was used. Where 'numtailb' was missing, 'numbaby' (where not missing) was used. Where 'numtailb' was missing and 'numbaby' was not missing but had a filled value of "X" (unknown), the number of births in the episode was assumed to be nine.

Changes introduced in HES APC sets

Set 12

Licensing obligations require that no attempts are made to re-identify patients in CPRD data sets. The epikey variable has been encoded by CPRD to minimise the risk of breaching licensing conditions through linkage of these data to other HES data sources containing patient identifiable information. What this means is that from set 12, the epikey variable is different from that of previous sets and will differ in each future release of HES APC linkage sets.

Values of the variables 'duration', 'epidur' and 'acpdur' are now provided as generated by HES. These were previously recalculated by CPRD by adding one day to all durations where hospital admission and discharge occurred on the same day. Values are being retained as generated by HES to provide users with greater flexibility in analysis.

Set 13

The definition of the derived ethnicity variable in the patient file has been changed so that ethnicity is specified where at least one episode has a specific ethnicity recorded but the majority of values are "unknown". This is the second recent change to the ethnicity data provided. Since set 11, the original ethnicity value for each episode has been included in the hospital episodes file (hes_episodes.txt), and derived patient ethnicity (gen_ethnicity) data is based on data recorded in HES Outpatient and HES A&E data in addition to HES Admitted Patient Care.

Set 15

Health Resource Group file (hes_hrg.txt): the hrglate variable has been retired and is no longer supplied by NHS Digital. It has therefore been removed from the Set 15 dataset. NHS Digital have updated the hrglate35 variable, and this data is now complete and available for the HES years 2003-2011.

Known issues

During the development process, we conferred with the HES team regarding some issues identified, in small numbers, in the data. These known issues include:

- Invalid/missing dates depicted as 15/10/1582 or 01/01/1600
- Episodes where admission date precedes the epistart date
- Unfinished episodes
- Explicit duplicate records which vary only by unique episode identifier (epikey)
- Maternity records may have inconsistencies which need to be considered when using the data

- Provisional HES data are monthly publications of HES data. These data may be incomplete or contain errors for which no adjustments have yet been made by HES. Counts produced from provisional data are likely to be lower than those generated for the same period in the final dataset. It is also probable that clinical data are not complete, which may affect the last two months of any given period. There may also be errors due to coding inconsistencies that have not yet been investigated and corrected. At the end of the fiscal year ("month 13"), the annual data is refreshed and known data quality issues are corrected, prior to locking the annual published data.

Look-up files

CPRD do not provide ICD-10 or OPCS dictionaries.

The ICD-10 codes have been slightly modified from those provided by the WHO. We recommend acquiring lookup tables for ICD-10 codes from the NHS Digital Clinical Classifications Service by emailing them at PPD or by telephoning PPD Note that a license is required.

It is likely that the lookup table that will be of most use to you is the ICD-10 Metadata file. This file contains all valid ICD codes, their titles, and category titles. You will be able to find out further information, including details of the licence you will need to obtain at:
https://digital.nhs.uk/article/1117/Clinical-Classifications

The Office of Population Censuses and Surveys (OPCS) Classification of Interventions and Procedures codes are also available from the NHS Digital Clinical Classifications Service:
https://digital.nhs.uk/article/1117/Clinical-Classifications

As with ICD10 codes, a license may be required to access OPCS data.

Future plans

Additional administrative years of HES data will be incorporated as they become available. Additional practices will also be added as they consent to the linkage.

Plans have been made to include data from Scotland, Wales and Northern Ireland, but there is no timescale set on when this might happen. The HES-CPRD link is part of the total linkage programme that will enable more comprehensive anonymised longitudinal patient journeys to be tracked.

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CPRD

ONS death registration data and CPRD primary care data Documentation (Set 16)

Version 1.8

Date: 1 June 2018

NHS National Institute for Health Research

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CPRD

Documentation Control Sheet

Over time, it may be necessary to issue amendments or clarifications to parts of this document. This form must be updated whenever changes are made.

Version	Affected Areas Summary of Change	Prepared By	Reviewed By
1.0	Initial	PPD	
1.1	Modified		
1.2	Modified		
1.3	Formatted		
1.4	Modified		
1.5	Modified		
1.6	Modified		
1.7	Modified and formatted		
1.8	Modified		

Summary of Changes

Version 1.1
- Corrected errors in and added information to the description of the death_matchrank variable
- Incorporated information about lags in registration and potential implications for research use
- Incorporated updated details on the ICD-10 version used by ONS
- Corrected errors in the descriptions of variables cause_neonatal1 through cause_neonatal8

Version 1.2
- Updated for set 10
  - Added information on match rank variable
  - Removed outdated information on multiple matches
  - Updated details of linkage coverage period
  - Added match_rank and dod_partial variables to data dictionary table

Version 1.3
- Updated header and footer to new agency branding

Version 1.4
- Updated for set 12 and with further information on:
  - The linkage coverage period
  - The proportion of patients linked by match_rank
  - The change from ICD-9 to ICD-10 as of 2001 and selection of underlying cause of death
  - The change in causal sequencing from January 2011

Version 1.5
- Updated for set 13 with information on the coverage period

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Version 1.6

- Updated for set 14 with information on the coverage period

Version 1.7

- Updated for set 15 with information on coverage period and addition of date of registration (dor), gen_death_id, and n_patid_death variables
- Updated header and footer with new agency branding

Version 1.8

- Updated for set 16
- Updated to include CPRD Aurum
- Updated to include the place of death category indicators

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CPRD

ONS death registration data linked to CPRD primary care data

This document provides an overview of the Office for National Statistics (ONS) death registration data, and the available subset that is linked to CPRD GOLD and CPRD Aurum.

What are death registration data?

The legal requirement to certify and register all deaths occurring in England and Wales means that death registrations provide the most complete data source for mortality statistics. Official mortality statistics for England and Wales are based on the details collected from death registrations.

The registration of deaths occurring in England and Wales is carried out by the Local Registration Service in partnership with the General Register Office (GRO). Information collected at death registration is recorded on the Registration Online (RON) system by registrars. Most of the information is normally supplied by the informant (usually a close relative of the deceased) while the cause of death is usually obtained from the Medical Certificate of Cause of Death (MCCD) completed by a medical practitioner when the death is certified. Deaths should be registered within five days of the date of death and on average 78% of deaths are registered within this time frame [1]. There are a number of situations when the registration of a death will be delayed (for example, deaths referred to coroners) for weeks, months or years until the cause is established although most deaths are registered within one month (94%). Those deaths which have delays in recording are not random but differential by age at death and/or cause of death. The median delay is longer than 5 days for deaths caused by: sudden infant death syndrome (149 days), ill-defined and unspecified causes (148 days), external causes (139 days), mesothelioma (94 days), mental and behavioural disorders due to psychoactive substance abuse (83 days) and pregnancy, childbirth and the puerperium (39 days) [1].

When data are entered into RON, there are validation checks to help ensure the details entered are correct. The registrar will also ask the informant to check that the information entered is correct, before the registration is submitted. Regular receipt and diagnostic tests are performed by ONS resulting in weekly contact with the identified registrars to resolve any issues. Once on the ONS database, data are passed through a series of automatic validation processes which highlight any inconsistencies.

For the majority of deaths, the underlying cause is now coded automatically using the Automated Cause Coding System (ACCS); the remainder are coded manually by experienced coders. The ACCS coding makes the selection of the underlying and secondary causes of death based on ICD rules and from the condition or conditions reported by the certifier, as recorded on the certificate. The information can come both parts of the certificate. ONS provide further details on how this coding is done in section 9 on the ONS website:
https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetomortalitystatisticsjuly2017

The accuracy of the automated coding is checked regularly. Cause coding of deaths certified after inquest is performed manually since the ACCS cannot readily cope with the free text format used by coroners when describing the circumstances of the death. Completeness checks are conducted to ensure all death registrations have been received. Further checks are also carried out before the annual mortality data set is finalised.

Since January 2001, information on cause of death in England and Wales has been coded using the 10th revision of the “International classification of diseases” (ICD-10). ICD-10 was implemented on the recommendation of the World Health Organization (WHO) and replaced ICD-9, which had been in use since 1979 [2]. The Office for National Statistics has carried out a comprehensive study to analyse the

changes in mortality statistics that are a result of the change in classification. In ICD-10, the first character of each code is alphabetic rather than numeric. This has enabled the expansion of the number of codes to provide for recently recognised conditions and more detail about common diseases. Some diseases and groups of conditions have been moved between broad groups (ICD chapters), from one to another, to reflect current ideas of aetiology and pathology. These changes mean that data cannot easily be compared across ICD-9 and ICD-10. Some changes in the numbers of deaths attributed to diseases are due to artefacts in the coding system.

In addition to the changes in the coding used there have been several changes to the rules governing selection of the underlying cause of death, reducing the number from 9 to 5. The changes in the application of Rule 3 have the biggest impact. This rule allows a condition that is reported in either Part I or II of the death certificate to take precedence over the condition selected using the other coding rules if it is obviously a direct consequence of that condition. In ICD-10 the list of conditions affected by Rule 3 is more clearly defined than in ICD-9 and is also broader in scope [3]. The impact of this is to reduce the number of deaths assigned to conditions such as pneumonia and to increase the number of deaths assigned to chronic debilitating diseases. In England and Wales, about 20% of deaths mention pneumonia, so the effect of this rule change is large. Examples of determining sequences and the application of the General Principle and Rules 1, 2 and 3 are available from the WHO [4].

In January 2011, the software used for cause of death coding was updated from ICD-10 v2001.2 to v2010. The ONS conducted a bridge coding study [5]. According to the ONS, the main changes in ICD-10 v2010 were amendments to the modification tables and selection rules used to ascertain a causal sequence and consistently assign underlying cause of death from the conditions recorded on the death certificate.

Accessing death registration data linked to CPRD GOLD and CPRD Aurum

ONS death registration data can only be accessed as part of a data extract linked to CPRD primary care data (CPRD GOLD or CPRD Aurum). Access is provided by CPRD subject to MHRA Independent Scientific Advisory Committee (ISAC) approval.

Not all patients in CPRD GOLD or CPRD Aurum are eligible to be linked to death data, for example, due to the region in which they usually resided (outside England), or the lack of a valid NHS number. Source files (linkage_eligibility.txt) are provided to allow researchers to select the subset of patients who are eligible to have a record in the death registration data.

Linkage coverage period

The death registration data includes all deaths *registered* during the coverage period. The latest release (set 16) covers the period from **2nd January 1998 to 13th February 2018**. From set 15 onwards the date of registration for each death has been included in addition to the date of death. Late registration for some deaths means that the proportion of deaths captured is lower for the last year of the coverage period, and this proportion is likely to differ by age at death and cause of death. This is especially pronounced for the last 1-2 weeks of available death data which shows an under count of the total number of deaths as these data do not capture those where the registration of a death has been delayed (e.g. deaths referred to coroners).

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CPRD

Linkage algorithm and the match rank variable

Linkage between ONS death registration data and CPRD primary care data uses an eight-step deterministic linkage algorithm based on four identifiers, shown in Table 1 below. Postcode in the ONS data is based on the usual residence of the deceased as recorded in the death registration data. The linkage is undertaken by NHS Digital, acting as a trusted-third-party, on behalf of CPRD. No personal identifiers are held by CPRD, or included in the CPRD GOLD, CPRD Aurum, or linked death registration data.

Table 1: NHS Digital 8 step linkage algorithm

Step	Match
1	Exact NHS number, sex, date of birth (DOB), postcode
2	Exact NHS number, sex, DOB
3	Exact NHS number, sex, postcode, partial DOB
4	Exact NHS number, sex, partial DOB
5	Exact NHS number, postcode
6	Exact sex, DOB and postcode (where the NHS number does not contradict the match, the DOB is not 1st of January and the postcode is not on the communal establishment list)
7	Exact sex, DOB and postcode (where the NHS number does not contradict the match and the DOB is not 1st of January)
8	Exact NHS number

The matching steps are applied sequentially. If a CPRD GOLD or CPRD Aurum patient record is matched in one step, it is no longer available for matching in subsequent steps. Matching results are summarised in Table 2A and 2B below.

Table 2A: Number and proportion of **CPRD GOLD** patients matched to a patient in death registration data at each step of the linkage algorithm in set 16.

Linkage step (match_rank)	Frequency	Percent
1	572,896	59.87
2	340,989	35.63
3	13,494	1.41
4	12,027	1.26
5	1,967	0.21
6	11,852	1.24
7	2,123	0.22
8	1,615	0.17

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CPRD

Table 2B: Number and proportion of **CPRD Aurum** patients matched to a patient in death registration data at each step of the linkage algorithm in set 16. Please note the low numbers of patients with match ranks 6 to 8 is due to the processing of the CPRD Aurum dataset with CPRD only being provided linkage information for patients with complete NHS numbers.

Linkage step (match_rank)	Frequency	Percent
1	344,976	59.44
2	216,644	37.33
3	8,338	1.44
4	7,814	1.35
5	1,379	0.24
6	70	0.01
7	11	0
8	1,152	0.2

CPRD provides users with a match_rank variable which corresponds to the step at which the match was established. In general, a lower value for the match_rank is considered stronger evidence for a positive match. Note that only patients with a match_rank of 5 or less are considered definitive matches and are included in the linked death registration data. Patients matched on steps 6-8 have been retained in separate files. We envisage that the retained records will primarily be of interest to methodological researchers. If you are interested in these data, please speak to a member of the CPRD Observational Research team prior to submission of your protocol to the ISAC.

A minority of patients are linked to multiple death records. These patients are removed from the linked death registration data. However, the data have been retained and are available on request. If you are interested in these data, please speak to a member of the CPRD Observational Research team prior to submission of your protocol to the ISAC.

Modified linkage eligibility files are available upon request for patients matched on steps 6-8 and for patients linked to multiple death records.

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CPRD

Data structure and formatting
As far as possible, the linked death registration data is supplied "as is" without any modification or cleaning during processing by CPRD. Where CPRD has modified the data, these are detailed below.

Modification of the coded data: All ICD codes have been normalized into a standard format.

ICD-9 codes: the 1st character of an ICD-9 code is either a number, the letter V, or the letter E (External Causes of Injury and Poisoning). ICD-9 codes will appear in the data with:

- 3 characters (formatted as XXX)
- 4 characters (formatted as XXX.X or EXXX)
- 5 characters (formatted as EXXX.X)

ICD-10 codes: the 1st character of an ICD-10 code is always a letter. ICD-10 codes will appear in the data with:

- 3 characters (formatted as XXX)
- 4 characters (formatted as XXX.X)

All codes associated with a death dated from January 2001 have been formatted as ICD-10.

Place of Death: From set 16 onwards CPRD has expanded the information included in the linked ONS death registration data to include a variation of the communal establishment code to differentiate between deaths at home and in hospital. The place of death variable (pod_category) has ten categories that provide information on whether the place where death occurred was the home, an establishment (and whether this was local authority or NHS) or elsewhere. An additional three category variable (nhs_indicator) indicates whether the death occurred within an NHS establishment, a non-NHS establishment or elsewhere/home.

Known issues
Before requesting a data extract, you should familiarise yourself with the contents of the ONS death registration data by reviewing the data dictionary as outlined below. Some fields, which are of great potential interest, are/were not mandatory.

- **Date of death (DOD)**: There are some DOD before the start of data collection (1995-1997) and for a small number of records this field is incomplete and only a partial data is provided.
- **Date or registration (DOR)**: This field is complete; users may want to consider including information from the DOR when the DOD is missing, and the partial date only offers the year.
- **Cause of death**: This field is not always complete.

Look-up files
CPRD do not provide ICD-10 or ICD-9 dictionaries.

CPRD recommend acquiring lookup tables for ICD-10 codes from the NHS Digital Technology Reference data Update Distribution (TRUD) Clinical Classifications Service [6] by creating an account, logging in, subscribing to items of interest and downloading the associated files once a subscription is accepted. They can also be contacted via PPD

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ONS death registration data: Data dictionary

1. Patient file (death_patient.txt)

Column name	*Description*	*Type*	*Format*
patid	Encrypted unique key given to a patient in CPRD GOLD or CPRD Aurum	INTEGER	20
pracid	Encrypted unique key given to a practice in CPRD GOLD or CPRD Aurum	INTEGER	5
gen_death_id[1]	A generated unique key assigned to a patient in the death registration data. An individual that has contributed data to more than one CPRD practice has the same gen_death_id	INTEGER	20
n_patid_death[1]	Number of individuals in CPRD GOLD or CPRD Aurum assigned the same gen_death_id	INTEGER	3
match_rank[2]	Indicates the quality of matching between a record in death registration data and CPRD primary care data and gives the level of confidence that an ONS death registration record has been correctly matched to a patient in CPRD GOLD or CPRD Aurum.	INTEGER	1
dor	Date of registration of death	DATE	dd/mm/yyyy
dod	Date of death	DATE	dd/mm/yyyy
dod_partial	Partial date of death: where exact date of death is not known, a missing month or day is represented as "00". This field is empty when exact date of death is recorded.	CHAR	YYYY-MM-DD
pod_category	Indicates a category for the place of death	INTEGER	2
nhs_indicator	Indicates whether place of death occurred in an NHS establishment, non-NHS establishment or elsewhere/home	INTEGER	1
cause	Underlying cause of death	CHAR	6
cause1	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause2	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause3	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause4	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause5	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause6	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause7	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause8	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause9	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause10	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause11	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause12	Recorded cause of death (non-neonatal deaths only)	CHAR	6

[1] Variable generated by CPRD.
[2] An eight-step process is used to match patients in CPRD primary care data (CPRD GOLD or CPRD Aurum) and ONS death registration data using some or all of the following: NHS number, date of birth, sex and postcode. Only data for patients matched using steps 1-5 has been provided.

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cause13	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause14	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause15	Recorded cause of death (non-neonatal deaths only)	CHAR	6
cause_neonatal1	Cause of death mentions for neonatal deaths (deaths occurring within 28 days of life)	CHAR	6
cause_neonatal2	Cause of death mentions for neonatal deaths (deaths occurring within 28 days of life)	CHAR	6
cause_neonatal3	Cause of death mentions for neonatal deaths (deaths occurring within 28 days of life)	CHAR	6
cause_neonatal4	Cause of death mentions for neonatal deaths (deaths occurring within 28 days of life)	CHAR	6
cause_neonatal5	Cause of death mentions for neonatal deaths (deaths occurring within 28 days of life)	CHAR	6
cause_neonatal6	Cause of death mentions for neonatal deaths (deaths occurring within 28 days of life)	CHAR	6
cause_neonatal7	Cause of death mentions for neonatal deaths (deaths occurring within 28 days of life)	CHAR	6
cause_neonatal8	Cause of death mentions for neonatal deaths (deaths occurring within 28 days of life)	CHAR	6

References

[1] Office for National Statistics, “Impact of registration delays on mortality statistics, 2011,” *Natl. Arch.*, no. table 2, pp. 94–95, 2011.

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[3] Office of National Statistics, “Comparison of ICD9 and ICD10 rules for selection of underlying cause of death.” [Online]. Available: http://www.statcan.gc.ca/pub/84-548-x/2005001/t/4078902-eng.htm.

[4] World Health Organisation, “Rules and guidelines for mortality and morbidity coding,” *Int. Classif. Dis. Relat. Heal. Probl. Tenth Revis. Vol. 2*, pp. 31–92, 2004.

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[6] NHS Digital, “Technology Reference data Update Distribution (TRUD).” [Online]. Available: https://isd.digital.nhs.uk/trud3/user/guest/group/0/home. [Accessed: 23-May-2017].

Annex 2. Glossary of terms

Acceptable patients [CPRD-GOLD]

In CPRD, patients are labelled as 'acceptable' for use in research by a process that identifies and excludes patients with non-continuous follow up or patients with poor data recording that raises suspicion as to the validity of the that patients record. Patient data is checked, for the following issues:

- An empty or invalid first registration date
- An empty or invalid current registration date
- Absence of a record for a year of birth
- A first registration date prior to their birth year
- A current registration date prior to their birth year
- A transferred out reason with no transferred out date
- A transferred out date with no transferred out reason
- A transferred out date prior to their first registration date
- A transferred out date prior to their current registration date
- A current registration date prior to their first registration date
- A gender other than Female/Male/Indeterminate
- An age of greater than 115 at end of follow-up
- Recorded health care episodes in years prior to birth year
- All recorded health care episodes have empty or invalid event dates
- Registration status of temporary patients

If any of these conditions are true then the patient is labelled unacceptable, and is not recommended for use in research.

Acceptable quality patients [THIN]

The THIN database uses patient flags 17 to describe the quality of individual patient records. For the purposes of this SAP, we define acceptable quality records as those with a patient flag [patflag] of A or C.

- A Acceptable record
- C Acceptable: transferred out dead without additional death information
- D Not permanently registered
- E Out of sequence YOB. YOB greater than regdate
- F Out of sequence registration date. i.e. greater than xferdate
- G Regstat 5 and missing or invalid transfer out date
- H Missing or invalid registration date
- I Year of birth missing, invalid or over 115 years of age
- J Not male or female
- K Invalid transfer out date
- N Family number invalid
- P Invalid Regrea
- Q Out of sequence deathdate i.e before YOB or greater than last collection
- R No registration time i.e registration date = last collection or transfer out
- S Acceptable but no medical, therapy or AHD events recorded
- M Multiple problems. More than one of the above errors
- X Re-allocation of patid: 2 different patients with same patid

Acceptable Mortality Recording (AMR) date [THIN]

AMR is a quality marker which is used to exclude periods of follow-up where deaths were not recorded at an acceptable level and thus avoid periods of immortal time. The AMR date has been assigned internally by IMS Health and is generated by reviewing trends in death reporting for each individual THIN practice against the predicted numbers of deaths derived from national statistics given the practice's demographics. The AMR is the year from which the practice is deemed to be reporting all-cause mortality proportionally in line with these statistics.

Derived date of death [CPRD-GOLD]

The CPRD derived death date combines information from the patient registration, death administration and clinical Read codes.

Derived date of death [THIN]

This is the best estimate of a patient's date of death, based on coded information in their electronic medical record. The variable is created by IMS Health to give researchers a guide to the patient's date of death. A study found that whilst records of death and the date of death are reliable, the transfer out date of the practice is often later. They therefore recommend, where possible, using 'deathdate' rather than 'transfer out date' for the most reliable estimation of the date of death.

Read codes [CPRD-GOLD and THIN]

Read codes are a standard vocabulary of coded clinical terms that have been in use in the NHS since 1985. GPs use Read codes to enter medical terms into their system in the practice. Specifically, the GP software system (Vision) from which CPRD collects data uses a modified version of the unified 5-byte Read version 2. In addition to the 5-digit Read Code, the system is designed to accommodate synonyms using an additional 2 digits in codes.

Up-to-standard (UTS) date [CPRD-GOLD]

The overall quality of data in CPRD practices is mediated by use of an 'up to standard' (UTS) date, which is deemed as the date at which data in the practice is considered to have continuous high quality data fit for use in research. This is mediated by an analysis on the total data in the practice, which is refreshed every time a new collection for a practice is processed into the database. It is based on two central concepts: assurance of continuity in data recording (gap analysis), and avoidance of use of data for which transferred out and dead patients have been removed (death recording).

Gap Analysis

To detect whether there is any meaningful gaps in the data it is necessary to look in more detail at single day gaps as well as longer gaps. A single day alone may reflect a situation where nothing was recorded that day at the practice, i.e. the practice was not open, such as

on a bank holiday. A longer gap may reflect a situation where the practice did not offer a service and patients may have been treated elsewhere. If a meaningful gap is found, the earliest date after which there is no significant gap is identified.

Death Recording

It is expected that a standard number of deaths will be recorded at a practice over time. Assessment of gaps in death recording is performed taking the size of the practice into account. A safety margin is built in to account for both geographical and seasonal variation in death rates. If a meaningful gap is found, the earliest date after which there is no significant gap is identified.

The UTS date is set to the latest of these dates for each practice. The CPRD recommend that analyses are performed on data following the practice UTS date.

UTS follow-up [CPRD-GOLD]

In CPRD, UTS follow-up begins from the latest of the patient's registration date and the practice up-to-standard date. UTS follow-up ends at the earliest of the patient's death[11], transfer out of the practice, or practice last collection date.

[11] This may be defined using the CPRD algorithm for identifying dates of death, or from using the ONS death certificate data.

Annex 3. Code lists

Read medical code lists for CPRD and THIN

All code lists for the final report were compiled using the June 2018 version of the CPRD medical dictionary and the 1801 version of the THIN medical dictionary. With the exception of the gord and renal code lists, all Read code lists are based on those provided by Dr PPD (Imperial College London). Additionally, the pneumonia and mi code lists were cross-checked with externally published code lists (DeSantostefano 2014 and Herrett 2013). The asthma and copd code lists were also cross-checked with code lists supplied by GSK (sent July 2015). All CPRD product code lists for copd products were cross-checked with code lists supplied by GSK (sent April 2016). Where changes were required to the CPRD product code lists, these changes were applied to the THIN product code lists as well.

Medical code lists for CV outcomes in CPRD and THIN

Interim code lists were created using the December 2015 version of the CPRD product dictionary and the 1505 version of the THIN dictionary.

The final code lists were created using the June 2018 version of the CPRD product dictionary and the 1801 version of the THIN dictionary.

Code lists for the CV outcomes used in the final report in CPRD and THIN:

CARDIO_CVD

medcode	readcode	desc
16085	1442	H/O: raised blood lipids
6434	1736	Paroxysmal nocturnal dyspnoea
26670	2432	O/E - pulse irregularly irreg.
3757	3272	ECG: atrial fibrillation
6771	3273	ECG: atrial flutter
16565	6627	Good hypertension control
27511	6628	Poor hypertension control
30776	6629	Hypertension:follow-up default
18249	7920	Saphenous vein graft replacement of coronary artery
8312	7920.11	Saphenous vein graft bypass of coronary artery
9414	7921	Other autograft replacement of coronary artery
7134	7921.11	Other autograft bypass of coronary artery
31556	7922	Allograft replacement of coronary artery
32651	7922.11	Allograft bypass of coronary artery
19402	7923	Prosthetic replacement of coronary artery
36011	7923.11	Prosthetic bypass of coronary artery
33461	7924	Revision of bypass for coronary artery
37682	7925	Connection of mammary artery to coronary artery
28837	7925.11	Creation of bypass from mammary artery to coronary artery
96804	7926	Connection of other thoracic artery to coronary artery
32976	6146200	Hypertension induced by oral contraceptive pill
8679	7920000	Saphenous vein graft replacement of one coronary artery
7634	7920100	Saphenous vein graft replacement of two coronary arteries
7442	7920200	Saphenous vein graft replacement of three coronary arteries
11610	7920300	Saphenous vein graft replacement of four+ coronary arteries
44561	7921000	Autograft replacement of one coronary artery NEC
19413	7921100	Autograft replacement of two coronary arteries NEC
10209	7921200	Autograft replacement of three coronary arteries NEC
42708	7921300	Autograft replacement of four of more coronary arteries NEC
70111	7922000	Allograft replacement of one coronary artery
57241	7922100	Allograft replacement of two coronary arteries
45886	7922200	Allograft replacement of three coronary arteries
45370	7922300	Allograft replacement of four or more coronary arteries
92419	7923000	Prosthetic replacement of one coronary artery
66664	7923100	Prosthetic replacement of two coronary arteries
66236	7923200	Prosthetic replacement of three coronary arteries
67761	7923300	Prosthetic replacement of four or more coronary arteries
52938	7924000	Revision of bypass for one coronary artery
67554	7924100	Revision of bypass for two coronary arteries
31540	7924200	Revision of bypass for three coronary arteries
33718	7925000	Double anastomosis of mammary arteries to coronary arteries
31519	7925100	Double implant of mammary arteries into coronary arteries
51507	7925300	Single anastomosis of mammary artery to coronary artery NEC
22647	7925311	LIMA single anastomosis
68123	7925312	RIMA single anastomosis
68139	7925400	Single implantation of mammary artery into coronary artery
62608	7926000	Double anastom thoracic arteries to coronary arteries NEC
67591	7926200	Single anastomosis of thoracic artery to coronary artery NEC
60753	7926300	Single implantation thoracic artery into coronary artery NEC
5744	7927500	Open angioplasty of coronary artery
8762	13B3.00	Low cholesterol diet
52246	13YA.00	Stroke group member
2666	14A2.00	H/O: hypertension
35674	14A3.00	H/O: myocardial infarct <60

40399	14A4.00	H/O: myocardial infarct >60
6336	14A5.00	H/O: angina pectoris
15058	14A6.00	H/O: heart failure
34135	14A7.00	H/O: CVA/stroke
6305	14A7.11	H/O: CVA
5871	14A7.12	H/O: stroke
13567	14AB.00	H/O: TIA
50372	14AH.00	H/O: Myocardial infarction in last year
57062	14AJ.00	H/O: Angina in last year
66873	14AK.00	H/O: Stroke in last year
46912	14AM.00	H/O: Heart failure in last year
6345	14AN.00	H/O: atrial fibrillation
93460	14AR.00	History of atrial flutter
21235	1J60.00	Suspected heart failure
22356	1JD..00	Suspected hypertension
9913	1O1..00	Heart failure confirmed
28994	212R.00	Atrial fibrillation resolved
5155	23E1.00	O/E - pulmonary oedema
2550	243..11	O/E - irregular pulse
46672	388D.00	New York Heart Assoc classification heart failure symptoms
4444	662..12	Hypertension monitoring
18590	662b.00	Moderate hypertension control
18482	662c.00	Hypertension six month review
19070	662d.00	Hypertension annual review
18686	662e.00	Stroke/CVA annual review
107886	662e.11	Stroke annual review
18853	662f.00	New York Heart Association classification - class I
21826	662F.00	Hypertension treatm. started
13188	662G.00	Hypertensive treatm.changed
13189	662g.00	New York Heart Association classification - class II
12948	662H.00	Hypertension treatm.stopped
19066	662h.00	New York Heart Association classification - class III
51214	662i.00	New York Heart Association classification - class IV
13185	662K.00	Angina control
19542	662K000	Angina control - good
15373	662K100	Angina control - poor
14782	662K200	Angina control - improving
29300	662K300	Angina control - worsening
15349	662Kz00	Angina control NOS
10792	662M.00	Stroke monitoring
3425	662O.00	On treatment for hypertension
28914	662o.00	Haemorrhagic stroke monitoring
13186	662P.00	Hypertension monitoring
109771	662P100	Telehealth hypertension monitoring
83502	662p.00	Heart failure 6 month review
95359	662r.00	Trial withdrawal of antihypertensive therapy
18746	662S.00	Atrial fibrillation monitoring
12366	662T.00	Congestive heart failure monitoring
30779	662W.00	Heart failure annual review
9936	66X..00	Lipid disorder monitoring
95835	679X.00	Heart failure education
45773	6A9..00	Atrial fibrillation annual review
737	792..11	Coronary artery bypass graft operations
7137	7920y00	Saphenous vein graft replacement of coronary artery OS
51515	7920z00	Saphenous vein graft replacement coronary artery NOS
61310	7921y00	Other autograft replacement of coronary artery OS

7609	7921z00	Other autograft replacement of coronary artery NOS
59423	7922y00	Other specified allograft replacement of coronary artery
48767	7922z00	Allograft replacement of coronary artery NOS
19193	7923z00	Prosthetic replacement of coronary artery NOS
97953	7924y00	Other specified revision of bypass for coronary artery
57634	7924z00	Revision of bypass for coronary artery NOS
37719	7925y00	Connection of mammary artery to coronary artery OS
56990	7925z00	Connection of mammary artery to coronary artery NOS
72780	7926z00	Connection of other thoracic artery to coronary artery NOS
55598	792C.00	Other replacement of coronary artery
55092	792C000	Replacement of coronary arteries using multiple methods
93828	792Cy00	Other specified replacement of coronary artery
70755	792Cz00	Replacement of coronary artery NOS
34963	792D.00	Other bypass of coronary artery
3159	792Dy00	Other specified other bypass of coronary artery
33471	792Dz00	Other bypass of coronary artery NOS
84152	793M100	Perc transluminal ablation of atrial wall for atrial flutter
86416	793M300	Perc translum ablat conduct sys heart for atrial flutter NEC
55351	7P24200	Delivery of rehabilitation for stroke
85944	7Q01.00	High cost hypertension drugs
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
18057	8B26.00	Antihypertensive therapy
45960	8B27.00	Antianginal therapy
24503	8B29.00	Cardiac failure therapy
10783	8BAG.00	Cholesterol reduction programme
39147	8BAG000	Cholesterol reduction programme - invited
51023	8BAG100	Cholesterol reduction program - attended
10899	8BAG200	Cholesterol reduction program - declined
32244	8BG2.00	Lipid lowering therapy indicated
11056	8BL0.00	Patient on maximal tolerated antihypertensive therapy
6243	8CA4700	Patient advised re low cholesterol diet
32945	8CL3.00	Heart failure care plan discussed with patient
71747	8CR3.00	Hyperlipidaemia clinical management plan
12680	8CR4.00	Hypertension clinical management plan
32898	8H2S.00	Admit heart failure emergency
17851	8HBE.00	Heart failure follow-up
13707	8HBJ.00	Stroke / transient ischaemic attack referral
91288	8Hg8.00	Discharge from practice nurse heart failure clinic
56458	8HHM.00	Ref to multidisciplinary stroke function improvement service
70619	8HHz.00	Referral to heart failure exercise programme
71235	8Hk0.00	Referred to heart failure education group
18804	8HTQ.00	Referral to stroke clinic
22333	8I3N.00	Hypertension treatment refused
34213	9h1..00	Exception reporting: LVD quality indicators
11613	9h11.00	Excepted from LVD quality indicators: Patient unsuitable
28649	9h12.00	Excepted from LVD quality indicators: Informed dissent
10962	9h2..00	Exception reporting: stroke quality indicators
11039	9h21.00	Excepted from stroke quality indicators: Patient unsuitable
11074	9h22.00	Excepted from stroke quality indicators: Informed dissent
34108	9h3..00	Exception reporting: hypertension quality indicators
10961	9h31.00	Excepted from hypertension qual indicators: Patient unsuit
10976	9h32.00	Excepted from hypertension qual indicators: Informed dissent
63350	9hF..00	Exception reporting: atrial fibrillation quality indicators
39114	9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
90935	9hH..00	Exception reporting: heart failure quality indicators
30749	9hH0.00	Excepted heart failure quality indicators: Patient unsuitabl

64062	9hH1.00	Excepted heart failure quality indicators: Informed dissent
4344	9N03.00	Seen in hypertension clinic
340	9N0I.00	Seen in lipid clinic
2091	9N0J.00	Seen in cholesterol clinic
12627	9N0k.00	Seen in heart failure clinic
27634	9N1y200	Seen in hypertension clinic
19002	9N2p.00	Seen by community heart failure nurse
30335	9N4K.00	DNA - Did not attend cholesterol clinic
95021	9N4s.00	Did not attend practice nurse heart failure clinic
83481	9N4w.00	Did not attend heart failure clinic
69062	9N6T.00	Referred by heart failure nurse specialist
36806	9Oc..00	Lipid disorder monitoring administration
97166	9Oc0.00	Attends lipid disorder monitoring
93761	9Oc2.00	Lipid disorder monitoring first letter
5215	9OI..00	Hypertension monitoring admin.
27525	9OI..11	Hypertension clinic admin.
45149	9OI1.00	Attends hypertension monitor.
31117	9OI4.00	Hypertens.monitor.1st letter
31127	9OI5.00	Hypertens.monitor 2nd letter
31175	9OI6.00	Hypertens.monitor 3rd letter
41634	9OI7.00	Hypertens.monitor verbal inv.
28874	9OI8.00	Hypertens.monitor phone invite
36305	9OIA.00	Hypertension monitor.chck done
24127	9OIA.11	Hypertension monitored
34192	9OIZ.00	Hypertens.monitoring admin.NOS
31218	9Om..00	Stroke/transient ischaemic attack monitoring administration
28753	9Om0.00	Stroke/transient ischaemic attack monitoring first letter
34245	9Om1.00	Stroke/transient ischaemic attack monitoring second letter
34375	9Om2.00	Stroke/transient ischaemic attack monitoring third letter
51465	9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati
89913	9Om4.00	Stroke/transient ischaemic attack monitoring telephone invte
18793	9On..00	Left ventricular dysfunction monitoring administration
60710	9On0.00	Left ventricular dysfunction monitoring first letter
60721	9On1.00	Left ventricular dysfunction monitoring second letter
72341	9On2.00	Left ventricular dysfunction monitoring third letter
92305	9On3.00	Left ventricular dysfunction monitoring verbal invite
96484	9On4.00	Left ventricular dysfunction monitoring telephone invite
32911	9Or..00	Heart failure monitoring administration
19380	9Or0.00	Heart failure review completed
90193	9Or1.00	Heart failure monitoring telephone invite
90192	9Or2.00	Heart failure monitoring verbal invite
72965	9Or3.00	Heart failure monitoring first letter
72386	9Or4.00	Heart failure monitoring second letter
89650	9Or5.00	Heart failure monitoring third letter
57832	9Os..00	Atrial fibrillation monitoring administration
90187	9Os0.00	Atrial fibrillation monitoring first letter
90188	9Os1.00	Atrial fibrillation monitoring second letter
90189	9Os2.00	Atrial fibrillation monitoring third letter
90190	9Os3.00	Atrial fibrillation monitoring verbal invite
90191	9Os4.00	Atrial fibrillation monitoring telephone invite
13228	C32..00	Disorders of lipoid metabolism
18708	C32..11	Disorder of cholesterol metabolism
339	C320.00	Pure hypercholesterolaemia
3484	C320.11	Familial hypercholesterolaemia
55855	C320.12	Fredrickson type IIa lipidaemia
59095	C320.13	Low density lipoproteinaemia

3386	C320000	Familial hypercholesterolaemia
34825	C320100	Hyperbetalipoproteinaemia
26019	C320200	Hyperlipidaemia, group A
34224	C320300	Low-density-lipoprotein-type (LDL) hyperlipoproteinaemia
37273	C320400	Fredrickson's hyperlipoproteinaemia, type IIa
97989	C320500	Familial defective apolipoprotein B-100
53091	C320y00	Other specified pure hypercholesterolaemia
7447	C320z00	Pure hypercholesterolaemia NOS
54499	C321.11	Fredrickson type IV lipidaemia
12439	C321000	Hypertriglyceridaemia
5791	C322.00	Mixed hyperlipidaemia
52992	C322.11	Fredrickson type IIb lipidaemia
59564	C322.12	Fredrickson type III lipidaemia
637	C324.00	Hyperlipidaemia NOS
16306	C325.00	Lipoprotein deficiencies
34146	C325100	Hypo-alpha-lipoproteinaemia
70793	C325200	Hypo-beta-lipoproteinaemia
16290	C325300	A-beta-lipoproteinaemia
95952	C328.00	Dyslipidaemia
68741	C32y.00	Other disorders of lipoid metabolism
67948	C32y200	Lipoid dermatoarthritis
16534	C32yz00	Other disorder of lipoid metabolism NOS
39783	C32z.00	Disorder of lipoid metabolism NOS
66240	Cyu8D00	[X]Other hyperlipidaemia
97890	Cyu8E00	[X]Other disorders of lipoprotein metabolism
8634	E004.11	Multi infarct dementia
36568	F050.00	Embolism of central nervous system venous sinus
55885	F050000	Embolism cavernous sinus
64467	F050100	Embolism superior longitudinal sinus
84404	F050300	Embolism transverse sinus
31390	F051.00	Thrombosis of central nervous system venous sinuses
22006	F051000	Thrombosis cavernous sinus
20161	F051100	Thrombosis of superior longitudinal sinus
3585	F051200	Thrombosis lateral sinus
28309	F051300	Thrombosis transverse sinus
61366	F051z00	Thrombosis of central nervous system venous sinus NOS
37086	F404200	Blind hypertensive eye
6702	F421300	Hypertensive retinopathy
63746	Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms
93459	Fyu5600	[X]Other lacunar syndromes
22262	G1yz100	Rheumatic left ventricular failure
204	G2...00	Hypertensive disease
8732	G2...11	BP - hypertensive disease
799	G20..00	Essential hypertension
107704	G20..12	Primary hypertension
15377	G200.00	Malignant essential hypertension
1894	G201.00	Benign essential hypertension
4372	G202.00	Systolic hypertension
83473	G203.00	Diastolic hypertension
10818	G20z.00	Essential hypertension NOS
3712	G20z.11	Hypertension NOS
16292	G21..00	Hypertensive heart disease
50157	G210.00	Malignant hypertensive heart disease
95334	G210000	Malignant hypertensive heart disease without CCF
72668	G210100	Malignant hypertensive heart disease with CCF
52427	G211.00	Benign hypertensive heart disease

61660	G211000	Benign hypertensive heart disease without CCF
52127	G211100	Benign hypertensive heart disease with CCF
31464	G21z.00	Hypertensive heart disease NOS
61166	G21z000	Hypertensive heart disease NOS without CCF
8857	G21z011	Cardiomegaly - hypertensive
62718	G21z100	Hypertensive heart disease NOS with CCF
16173	G21zz00	Hypertensive heart disease NOS
4668	G22..00	Hypertensive renal disease
39649	G220.00	Malignant hypertensive renal disease
43935	G221.00	Benign hypertensive renal disease
32423	G222.00	Hypertensive renal disease with renal failure
15106	G22z.00	Hypertensive renal disease NOS
29310	G22z.11	Renal hypertension
63466	G23..00	Hypertensive heart and renal disease
67232	G230.00	Malignant hypertensive heart and renal disease
63000	G231.00	Benign hypertensive heart and renal disease
21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
28684	G233.00	Hypertensive heart and renal disease with renal failure
57987	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
68659	G23z.00	Hypertensive heart and renal disease NOS
7329	G24..00	Secondary hypertension
31755	G240.00	Secondary malignant hypertension
59383	G240000	Secondary malignant renovascular hypertension
73293	G240z00	Secondary malignant hypertension NOS
57288	G241.00	Secondary benign hypertension
25371	G241000	Secondary benign renovascular hypertension
51635	G241z00	Secondary benign hypertension NOS
34744	G244.00	Hypertension secondary to endocrine disorders
16059	G24z.00	Secondary hypertension NOS
31387	G24z000	Secondary renovascular hypertension NOS
31341	G24z100	Hypertension secondary to drug
42229	G24zz00	Secondary hypertension NOS
18765	G2y..00	Other specified hypertensive disease
7057	G2z..00	Hypertensive disease NOS
241	G30..00	Acute myocardial infarction
13566	G30..11	Attack - heart
2491	G30..12	Coronary thrombosis
30421	G30..13	Cardiac rupture following myocardial infarction (MI)
1204	G30..14	Heart attack
1677	G30..15	MI - acute myocardial infarction
13571	G30..16	Thrombosis - coronary
17689	G30..17	Silent myocardial infarction
12139	G300.00	Acute anterolateral infarction
5387	G301.00	Other specified anterior myocardial infarction
40429	G301000	Acute anteroapical infarction
17872	G301100	Acute anteroseptal infarction
14897	G301z00	Anterior myocardial infarction NOS
8935	G302.00	Acute inferolateral infarction
29643	G303.00	Acute inferoposterior infarction
23892	G304.00	Posterior myocardial infarction NOS
14898	G305.00	Lateral myocardial infarction NOS
63467	G306.00	True posterior myocardial infarction
3704	G307.00	Acute subendocardial infarction
9507	G307000	Acute non-Q wave infarction
10562	G307100	Acute non-ST segment elevation myocardial infarction
1678	G308.00	Inferior myocardial infarction NOS

30330	G309.00	Acute Q-wave infarct
17133	G30A.00	Mural thrombosis
32854	G30B.00	Acute posterolateral myocardial infarction
29758	G30X.00	Acute transmural myocardial infarction of unspecif site
12229	G30X000	Acute ST segment elevation myocardial infarction
34803	G30y.00	Other acute myocardial infarction
28736	G30y000	Acute atrial infarction
62626	G30y100	Acute papillary muscle infarction
41221	G30y200	Acute septal infarction
46017	G30yz00	Other acute myocardial infarction NOS
14658	G30z.00	Acute myocardial infarction NOS
23579	G310.00	Postmyocardial infarction syndrome
15661	G310.11	Dressler's syndrome
36523	G311.00	Preinfarction syndrome
4656	G311.11	Crescendo angina
39655	G311.12	Impending infarction
1431	G311.13	Unstable angina
19655	G311.14	Angina at rest
7347	G311100	Unstable angina
17307	G311200	Angina at rest
34328	G311300	Refractory angina
18118	G311400	Worsening angina
11983	G311500	Acute coronary syndrome
54251	G311z00	Preinfarction syndrome NOS
39449	G312.00	Coronary thrombosis not resulting in myocardial infarction
9276	G31y000	Acute coronary insufficiency
68357	G31y100	Microinfarction of heart
4017	G32..00	Old myocardial infarction
16408	G32..11	Healed myocardial infarction
17464	G32..12	Personal history of myocardial infarction
1430	G33..00	Angina pectoris
20095	G330.00	Angina decubitus
18125	G330000	Nocturnal angina
29902	G330z00	Angina decubitus NOS
12986	G331.00	Prinzmetal's angina
11048	G331.11	Variant angina pectoris
36854	G332.00	Coronary artery spasm
25842	G33z.00	Angina pectoris NOS
66388	G33z000	Status anginosus
54535	G33z100	Stenocardia
7696	G33z200	Syncope anginosa
1414	G33z300	Angina on effort
9555	G33z500	Post infarct angina
26863	G33z600	New onset angina
12804	G33z700	Stable angina
28554	G33zz00	Angina pectoris NOS
24540	G34y000	Chronic coronary insufficiency
18842	G35..00	Subsequent myocardial infarction
45809	G350.00	Subsequent myocardial infarction of anterior wall
38609	G351.00	Subsequent myocardial infarction of inferior wall
72562	G353.00	Subsequent myocardial infarction of other sites
46166	G35X.00	Subsequent myocardial infarction of unspecified site
36423	G36..00	Certain current complication follow acute myocardial infarct
24126	G360.00	Haemopericardium/current comp folow acut myocard infarct
23708	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
37657	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn

59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
8568	G37..00	Cardiac syndrome X
32272	G38..00	Postoperative myocardial infarction
46112	G380.00	Postoperative transmural myocardial infarction anterior wall
46276	G381.00	Postoperative transmural myocardial infarction inferior wall
41835	G384.00	Postoperative subendocardial myocardial infarction
68748	G38z.00	Postoperative myocardial infarction, unspecified
8464	G400.00	Acute cor pulmonale
5695	G41z.11	Chronic cor pulmonale
5141	G554000	Congestive cardiomyopathy
68766	G554011	Congestive obstructive cardiomyopathy
2212	G573.00	Atrial fibrillation and flutter
1664	G573000	Atrial fibrillation
1757	G573100	Atrial flutter
1268	G573200	Paroxysmal atrial fibrillation
35127	G573300	Non-rheumatic atrial fibrillation
96277	G573400	Permanent atrial fibrillation
96076	G573500	Persistent atrial fibrillation
23437	G573z00	Atrial fibrillation and flutter NOS
2062	G58..00	Heart failure
1223	G58..11	Cardiac failure
398	G580.00	Congestive heart failure
2906	G580.11	Congestive cardiac failure
10079	G580.12	Right heart failure
10154	G580.13	Right ventricular failure
9524	G580.14	Biventricular failure
23707	G580000	Acute congestive heart failure
32671	G580100	Chronic congestive heart failure
27884	G580200	Decompensated cardiac failure
11424	G580300	Compensated cardiac failure
94870	G580400	Congestive heart failure due to valvular disease
884	G581.00	Left ventricular failure
23481	G581.11	Asthma - cardiac
43618	G581.12	Pulmonary oedema - acute
5942	G581.13	Impaired left ventricular function
5255	G581000	Acute left ventricular failure
27964	G582.00	Acute heart failure
4024	G58z.00	Heart failure NOS
12590	G58z.11	Weak heart
17278	G58z.12	Cardiac failure NOS
8966	G5yy900	Left ventricular systolic dysfunction
12550	G5yyA00	Left ventricular diastolic dysfunction
5051	G61..00	Intracerebral haemorrhage
6960	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
18604	G61..12	Stroke due to intracerebral haemorrhage
31595	G610.00	Cortical haemorrhage
40338	G611.00	Internal capsule haemorrhage
46316	G612.00	Basal nucleus haemorrhage
13564	G613.00	Cerebellar haemorrhage
7912	G614.00	Pontine haemorrhage
62342	G615.00	Bulbar haemorrhage
30045	G616.00	External capsule haemorrhage
30202	G617.00	Intracerebral haemorrhage, intraventricular

57315	G618.00	Intracerebral haemorrhage, multiple localized
31060	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
28314	G61X000	Left sided intracerebral haemorrhage, unspecified
19201	G61X100	Right sided intracerebral haemorrhage, unspecified
3535	G61z.00	Intracerebral haemorrhage NOS
31805	G62..00	Other and unspecified intracranial haemorrhage
20284	G62z.00	Intracranial haemorrhage NOS
45781	G63..00	Precerebral arterial occlusion
57495	G63..11	Infarction - precerebral
32447	G630.00	Basilar artery occlusion
4240	G631.00	Carotid artery occlusion
4152	G631.12	Thrombosis, carotid artery
40847	G632.00	Vertebral artery occlusion
98642	G633.00	Multiple and bilateral precerebral arterial occlusion
51326	G63y.00	Other precerebral artery occlusion
23671	G63y000	Cerebral infarct due to thrombosis of precerebral arteries
24446	G63y100	Cerebral infarction due to embolism of precerebral arteries
71585	G63z.00	Precerebral artery occlusion NOS
8837	G64..00	Cerebral arterial occlusion
5363	G64..11	CVA - cerebral artery occlusion
569	G64..12	Infarction - cerebral
6155	G64..13	Stroke due to cerebral arterial occlusion
16517	G640.00	Cerebral thrombosis
36717	G640000	Cerebral infarction due to thrombosis of cerebral arteries
15019	G641.00	Cerebral embolism
34758	G641.11	Cerebral embolus
27975	G641000	Cerebral infarction due to embolism of cerebral arteries
3149	G64z.00	Cerebral infarction NOS
15252	G64z.11	Brainstem infarction NOS
5602	G64z.12	Cerebellar infarction
25615	G64z000	Brainstem infarction
47642	G64z100	Wallenberg syndrome
5185	G64z111	Lateral medullary syndrome
9985	G64z200	Left sided cerebral infarction
10504	G64z300	Right sided cerebral infarction
26424	G64z400	Infarction of basal ganglia
504	G65..00	Transient cerebral ischaemia
1433	G65..12	Transient ischaemic attack
23942	G650.00	Basilar artery syndrome
33377	G651.00	Vertebral artery syndrome
21118	G651000	Vertebro-basilar artery syndrome
44765	G653.00	Carotid artery syndrome hemispheric
50594	G654.00	Multiple and bilateral precerebral artery syndromes
19354	G65y.00	Other transient cerebral ischaemia
1895	G65z.00	Transient cerebral ischaemia NOS
55247	G65z000	Impending cerebral ischaemia
16507	G65z100	Intermittent cerebral ischaemia
15788	G65zz00	Transient cerebral ischaemia NOS
1469	G66..00	Stroke and cerebrovascular accident unspecified
1298	G66..11	CVA unspecified
6253	G66..12	Stroke unspecified
6116	G66..13	CVA - Cerebrovascular accident unspecified
18689	G660.00	Middle cerebral artery syndrome
19280	G661.00	Anterior cerebral artery syndrome
19260	G662.00	Posterior cerebral artery syndrome
8443	G663.00	Brain stem stroke syndrome

17322	G664.00	Cerebellar stroke syndrome
33499	G665.00	Pure motor lacunar syndrome
51767	G666.00	Pure sensory lacunar syndrome
7780	G667.00	Left sided CVA
12833	G668.00	Right sided CVA
16956	G669.00	Cerebral palsy, not congenital or infantile, acute
70536	G671000	Acute cerebrovascular insufficiency NOS
3979	G672.00	Hypertensive encephalopathy
31816	G672.11	Hypertensive crisis
37947	G676.00	Nonpyogenic venous sinus thrombosis
39344	G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
51759	G677000	Occlusion and stenosis of middle cerebral artery
57527	G677100	Occlusion and stenosis of anterior cerebral artery
65770	G677200	Occlusion and stenosis of posterior cerebral artery
55602	G677300	Occlusion and stenosis of cerebellar arteries
71274	G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
101733	G67A.00	Cerebral vein thrombosis
48149	G681.00	Sequelae of intracerebral haemorrhage
43451	G682.00	Sequelae of other nontraumatic intracranial haemorrhage
39403	G683.00	Sequelae of cerebral infarction
6228	G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
40758	G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
33543	G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
69753	Gyu2.00	[X]Hypertensive diseases
97533	Gyu2100	[X]Hypertension secondary to other renal disorders
39546	Gyu3000	[X]Other forms of angina pectoris
96838	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
109035	Gyu3500	[X]Subsequent myocardial infarction of other sites
53810	Gyu6200	[X]Other intracerebral haemorrhage
91627	Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
53745	Gyu6400	[X]Other cerebral infarction
90572	Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
92036	Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
96630	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
94482	Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
62227	H461.00	Acute pulmonary oedema due to chemical fumes
30214	H54..00	Pulmonary congestion and hypostasis
1585	H541.00	Pulmonary congestion
26082	H541000	Chronic pulmonary oedema
7321	H541z00	Pulmonary oedema NOS
61229	H54z.00	Pulmonary congestion and hypostasis NOS
558	H584.00	Acute pulmonary oedema unspecified
5293	H584z00	Acute pulmonary oedema NOS
52679	L417.00	Obstetric cerebral venous thrombosis
69686	L417000	Cerebral venous thrombosis in pregnancy
55974	L417100	Cerebral venous thrombosis in the puerperium
47607	L440.11	CVA - cerebrovascular accident in the puerperium
56279	L440.12	Stroke in the puerperium
20822	Q48y100	Congenital cardiac failure
20324	R2y1000	[D]Cardiorespiratory failure
69776	SP00300	Mechanical complication of coronary bypass
12734	SP07600	Coronary artery bypass graft occlusion
21660	TJC7.00	Adverse reaction to other antihypertensives
20497	TJC7z00	Adverse reaction to antihypertensives NOS
63164	U60C500	[X]Oth antihyperten drug caus advers eff in therap use, NEC
30770	U60C511	[X] Adverse reaction to other antihypertensives

44350	U60C51A	[X] Adverse reaction to antihypertensives NOS
50923	U60C600	[X]Antihyperlipidaem/antiarterioscl drg caus adv ef ther use
42765	ZC2CI00	Dietary advice for lipid disorder
33694	ZC2CJ00	Dietary advice for hyperlipidaemia
42248	ZLEP.00	Discharge from stroke serv
26242	ZRad.00	New York Heart Assoc classification heart failure symptoms
19348	ZV12511	[V]Personal history of stroke
7138	ZV12512	[V]Personal history of cerebrovascular accident (CVA)
101251	ZV12D00	[V]Personal history of transient ischaemic attack
18913	ZV45700	[V]Presence of aortocoronary bypass graft
5030	ZV45K00	[V]Presence of coronary artery bypass graft
5674	ZV45K11	[V]Presence of coronary artery bypass graft - CABG
12569	ZV65317	[V]Dietary surveillance in hypercholesterolaemia

CHF

medcode	readcode	desc
6434	1736	Paroxysmal nocturnal dyspnoea
15058	14A6.00	H/O: heart failure
46912	14AM.00	H/O: Heart failure in last year
21235	1J60.00	Suspected heart failure
9913	1O1..00	Heart failure confirmed
5155	23E1.00	O/E - pulmonary oedema
46672	388D.00	New York Heart Assoc classification heart failure symptoms
18853	662f.00	New York Heart Association classification - class I
13189	662g.00	New York Heart Association classification - class II
19066	662h.00	New York Heart Association classification - class III
51214	662i.00	New York Heart Association classification - class IV
83502	662p.00	Heart failure 6 month review
12366	662T.00	Congestive heart failure monitoring
30779	662W.00	Heart failure annual review
95835	679X.00	Heart failure education
24503	8B29.00	Cardiac failure therapy
32945	8CL3.00	Heart failure care plan discussed with patient
32898	8H2S.00	Admit heart failure emergency
17851	8HBE.00	Heart failure follow-up
91288	8Hg8.00	Discharge from practice nurse heart failure clinic
70619	8HHz.00	Referral to heart failure exercise programme
71235	8Hk0.00	Referred to heart failure education group
34213	9h1..00	Exception reporting: LVD quality indicators
11613	9h11.00	Excepted from LVD quality indicators: Patient unsuitable
28649	9h12.00	Excepted from LVD quality indicators: Informed dissent
90935	9hH..00	Exception reporting: heart failure quality indicators
30749	9hH0.00	Excepted heart failure quality indicators: Patient unsuitabl
64062	9hH1.00	Excepted heart failure quality indicators: Informed dissent
12627	9N0k.00	Seen in heart failure clinic
19002	9N2p.00	Seen by community heart failure nurse
95021	9N4s.00	Did not attend practice nurse heart failure clinic
83481	9N4w.00	Did not attend heart failure clinic
69062	9N6T.00	Referred by heart failure nurse specialist
18793	9On..00	Left ventricular dysfunction monitoring administration
60710	9On0.00	Left ventricular dysfunction monitoring first letter
60721	9On1.00	Left ventricular dysfunction monitoring second letter
72341	9On2.00	Left ventricular dysfunction monitoring third letter
92305	9On3.00	Left ventricular dysfunction monitoring verbal invite
96484	9On4.00	Left ventricular dysfunction monitoring telephone invite
32911	9Or..00	Heart failure monitoring administration
19380	9Or0.00	Heart failure review completed
90193	9Or1.00	Heart failure monitoring telephone invite
90192	9Or2.00	Heart failure monitoring verbal invite
72965	9Or3.00	Heart failure monitoring first letter
72386	9Or4.00	Heart failure monitoring second letter
89650	9Or5.00	Heart failure monitoring third letter
22262	G1yz100	Rheumatic left ventricular failure
50157	G210.00	Malignant hypertensive heart disease
95334	G210000	Malignant hypertensive heart disease without CCF
72668	G210100	Malignant hypertensive heart disease with CCF
52127	G211100	Benign hypertensive heart disease with CCF
62718	G21z100	Hypertensive heart disease NOS with CCF
67232	G230.00	Malignant hypertensive heart and renal disease
21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure

57987	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
8464	G400.00	Acute cor pulmonale
5695	G41z.11	Chronic cor pulmonale
5141	G554000	Congestive cardiomyopathy
68766	G554011	Congestive obstructive cardiomyopathy
2062	G58..00	Heart failure
1223	G58..11	cardiac
398	G580.00	Congestive heart failure
2906	G580.11	Congestive cardiac failure
10079	G580.12	Right heart failure
10154	G580.13	Right ventricular failure
9524	G580.14	Biventricular failure
23707	G580000	Acute congestive heart failure
32671	G580100	Chronic congestive heart failure
27884	G580200	Decompensated cardiac failure
11424	G580300	Compensated cardiac failure
94870	G580400	Congestive heart failure due to valvular disease
884	G581.00	Left ventricular failure
23481	G581.11	Asthma - cardiac
43618	G581.12	Pulmonary oedema - acute
5942	G581.13	Impaired left ventricular function
5255	G581000	Acute left ventricular failure
27964	G582.00	Acute heart failure
4024	G58z.00	Heart failure NOS
12590	G58z.11	Weak heart
17278	G58z.12	Cardiac failure NOS
8966	G5yy900	Left ventricular systolic dysfunction
12550	G5yyA00	Left ventricular diastolic dysfunction
62227	H461.00	Acute pulmonary oedema due to chemical fumes
30214	H54..00	Pulmonary congestion and hypostasis
1585	H541.00	Pulmonary congestion
26082	H541000	Chronic pulmonary oedema
7321	H541z00	Pulmonary oedema NOS
61229	H54z.00	Pulmonary congestion and hypostasis NOS
558	H584.00	Acute pulmonary oedema unspecified
5293	H584z00	Acute pulmonary oedema NOS
20822	Q48y100	Congenital cardiac failure
20324	R2y1000	[D]Cardiorespiratory failure
26242	ZRad.00	New York Heart Assoc classification heart failure symptoms

MI

medcode	readcode	desc
35674	14A3.00	H/O: myocardial infarct <60
40399	14A4.00	H/O: myocardial infarct >60
50372	14AH.00	H/O: Myocardial infarction in last year
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
241	G30..00	Acute myocardial infarction
13566	G30..11	Attack - heart
2491	G30..12	Coronary thrombosis
30421	G30..13	Cardiac rupture following myocardial infarction (MI)
1204	G30..14	Heart attack
1677	G30..15	MI - acute myocardial infarction
13571	G30..16	Thrombosis - coronary
17689	G30..17	Silent myocardial infarction
12139	G300.00	Acute anterolateral infarction
5387	G301.00	Other specified anterior myocardial infarction
40429	G301000	Acute anteroapical infarction
17872	G301100	Acute anteroseptal infarction
14897	G301z00	Anterior myocardial infarction NOS
8935	G302.00	Acute inferolateral infarction
29643	G303.00	Acute inferoposterior infarction
23892	G304.00	Posterior myocardial infarction NOS
14898	G305.00	Lateral myocardial infarction NOS
63467	G306.00	True posterior myocardial infarction
3704	G307.00	Acute subendocardial infarction
9507	G307000	Acute non-Q wave infarction
10562	G307100	Acute non-ST segment elevation myocardial infarction
1678	G308.00	Inferior myocardial infarction NOS
30330	G309.00	Acute Q-wave infarct
17133	G30A.00	Mural thrombosis
32854	G30B.00	Acute posterolateral myocardial infarction
29758	G30X.00	Acute transmural myocardial infarction of unspecif site
12229	G30X000	Acute ST segment elevation myocardial infarction
34803	G30y.00	Other acute myocardial infarction
28736	G30y000	Acute atrial infarction
62626	G30y100	Acute papillary muscle infarction
41221	G30y200	Acute septal infarction
46017	G30yz00	Other acute myocardial infarction NOS
14658	G30z.00	Acute myocardial infarction NOS
23579	G310.00	Postmyocardial infarction syndrome
15661	G310.11	Dressler's syndrome
68357	G31y100	Microinfarction of heart
4017	G32..00	Old myocardial infarction
16408	G32..11	Healed myocardial infarction
17464	G32..12	Personal history of myocardial infarction
9555	G33z500	Post infarct angina
18842	G35..00	Subsequent myocardial infarction
45809	G350.00	Subsequent myocardial infarction of anterior wall
38609	G351.00	Subsequent myocardial infarction of inferior wall
72562	G353.00	Subsequent myocardial infarction of other sites
46166	G35X.00	Subsequent myocardial infarction of unspecified site
36423	G36..00	Certain current complication follow acute myocardial infarct
24126	G360.00	Haemopericardium/current comp folow acut myocard infarct
23708	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
37657	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI

59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
32272	G38..00	Postoperative myocardial infarction
46112	G380.00	Postoperative transmural myocardial infarction anterior wall
46276	G381.00	Postoperative transmural myocardial infarction inferior wall
41835	G384.00	Postoperative subendocardial myocardial infarction
68748	G38z.00	Postoperative myocardial infarction, unspecified
96838	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
109035	Gyu3500	[X]Subsequent myocardial infarction of other sites

STROKE

medcode	readcode	desc
52246	13YA.00	Stroke group member
34135	14A7.00	H/O: CVA/stroke
6305	14A7.11	H/O: CVA
5871	14A7.12	H/O: stroke
13567	14AB.00	H/O: TIA
66873	14AK.00	H/O: Stroke in last year
18686	662e.00	Stroke/CVA annual review
107886	662e.11	Stroke annual review
10792	662M.00	Stroke monitoring
28914	662o.00	Haemorrhagic stroke monitoring
55351	7P24200	Delivery of rehabilitation for stroke
13707	8HBJ.00	Stroke / transient ischaemic attack referral
56458	8HHM.00	Ref to multidisciplinary stroke function improvement service
18804	8HTQ.00	Referral to stroke clinic
10962	9h2..00	Exception reporting: stroke quality indicators
11039	9h21.00	Excepted from stroke quality indicators: Patient unsuitable
11074	9h22.00	Excepted from stroke quality indicators: Informed dissent
31218	9Om..00	Stroke/transient ischaemic attack monitoring administration
28753	9Om0.00	Stroke/transient ischaemic attack monitoring first letter
34245	9Om1.00	Stroke/transient ischaemic attack monitoring second letter
34375	9Om2.00	Stroke/transient ischaemic attack monitoring third letter
51465	9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati
89913	9Om4.00	Stroke/transient ischaemic attack monitoring telephone invte
8634	E004.11	Multi infarct dementia
36568	F050.00	Embolism of central nervous system venous sinus
55885	F050000	Embolism cavernous sinus
64467	F050100	Embolism superior longitudinal sinus
84404	F050300	Embolism transverse sinus
31390	F051.00	Thrombosis of central nervous system venous sinuses
22006	F051000	Thrombosis cavernous sinus
20161	F051100	Thrombosis of superior longitudinal sinus
3585	F051200	Thrombosis lateral sinus
28309	F051300	Thrombosis transverse sinus
61366	F051z00	Thrombosis of central nervous system venous sinus NOS
63746	Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms
93459	Fyu5600	[X]Other lacunar syndromes
5051	G61..00	Intracerebral haemorrhage
6960	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
18604	G61..12	Stroke due to intracerebral haemorrhage
31595	G610.00	Cortical haemorrhage
40338	G611.00	Internal capsule haemorrhage
46316	G612.00	Basal nucleus haemorrhage
13564	G613.00	Cerebellar haemorrhage
7912	G614.00	Pontine haemorrhage
62342	G615.00	Bulbar haemorrhage
30045	G616.00	External capsule haemorrhage
30202	G617.00	Intracerebral haemorrhage, intraventricular
57315	G618.00	Intracerebral haemorrhage, multiple localized
31060	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
28314	G61X000	Left sided intracerebral haemorrhage, unspecified
19201	G61X100	Right sided intracerebral haemorrhage, unspecified
3535	G61z.00	Intracerebral haemorrhage NOS
31805	G62..00	Other and unspecified intracranial haemorrhage
20284	G62z.00	Intracranial haemorrhage NOS

45781	G63..00	Precerebral arterial occlusion
57495	G63..11	Infarction - precerebral
32447	G630.00	Basilar artery occlusion
4240	G631.00	Carotid artery occlusion
4152	G631.12	Thrombosis, carotid artery
40847	G632.00	Vertebral artery occlusion
98642	G633.00	Multiple and bilateral precerebral arterial occlusion
51326	G63y.00	Other precerebral artery occlusion
23671	G63y000	Cerebral infarct due to thrombosis of precerebral arteries
24446	G63y100	Cerebral infarction due to embolism of precerebral arteries
71585	G63z.00	Precerebral artery occlusion NOS
8837	G64..00	Cerebral arterial occlusion
5363	G64..11	CVA - cerebral artery occlusion
569	G64..12	Infarction - cerebral
6155	G64..13	Stroke due to cerebral arterial occlusion
16517	G640.00	Cerebral thrombosis
36717	G640000	Cerebral infarction due to thrombosis of cerebral arteries
15019	G641.00	Cerebral embolism
34758	G641.11	Cerebral embolus
27975	G641000	Cerebral infarction due to embolism of cerebral arteries
3149	G64z.00	Cerebral infarction NOS
15252	G64z.11	Brainstem infarction NOS
5602	G64z.12	Cerebellar infarction
25615	G64z000	Brainstem infarction
47642	G64z100	Wallenberg syndrome
5185	G64z111	Lateral medullary syndrome
9985	G64z200	Left sided cerebral infarction
10504	G64z300	Right sided cerebral infarction
26424	G64z400	Infarction of basal ganglia
504	G65..00	Transient cerebral ischaemia
1433	G65..12	Transient ischaemic attack
23942	G650.00	Basilar artery syndrome
33377	G651.00	Vertebral artery syndrome
21118	G651000	Vertebro-basilar artery syndrome
44765	G653.00	Carotid artery syndrome hemispheric
50594	G654.00	Multiple and bilateral precerebral artery syndromes
19354	G65y.00	Other transient cerebral ischaemia
1895	G65z.00	Transient cerebral ischaemia NOS
55247	G65z000	Impending cerebral ischaemia
16507	G65z100	Intermittent cerebral ischaemia
15788	G65zz00	Transient cerebral ischaemia NOS
1469	G66..00	Stroke and cerebrovascular accident unspecified
1298	G66..11	CVA unspecified
6253	G66..12	Stroke unspecified
6116	G66..13	CVA - Cerebrovascular accident unspecified
18689	G660.00	Middle cerebral artery syndrome
19280	G661.00	Anterior cerebral artery syndrome
19260	G662.00	Posterior cerebral artery syndrome
8443	G663.00	Brain stem stroke syndrome
17322	G664.00	Cerebellar stroke syndrome
33499	G665.00	Pure motor lacunar syndrome
51767	G666.00	Pure sensory lacunar syndrome
7780	G667.00	Left sided CVA
12833	G668.00	Right sided CVA
16956	G669.00	Cerebral palsy, not congenital or infantile, acute
70536	G671000	Acute cerebrovascular insufficiency NOS

37947	G676.00	Nonpyogenic venous sinus thrombosis
39344	G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
51759	G677000	Occlusion and stenosis of middle cerebral artery
57527	G677100	Occlusion and stenosis of anterior cerebral artery
65770	G677200	Occlusion and stenosis of posterior cerebral artery
55602	G677300	Occlusion and stenosis of cerebellar arteries
71274	G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
101733	G67A.00	Cerebral vein thrombosis
48149	G681.00	Sequelae of intracerebral haemorrhage
43451	G682.00	Sequelae of other nontraumatic intracranial haemorrhage
39403	G683.00	Sequelae of cerebral infarction
6228	G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
40758	G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
33543	G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
53810	Gyu6200	[X]Other intracerebral haemorrhage
91627	Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
53745	Gyu6400	[X]Other cerebral infarction
90572	Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
92036	Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
96630	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
94482	Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
52679	L417.00	Obstetric cerebral venous thrombosis
69686	L417000	Cerebral venous thrombosis in pregnancy
55974	L417100	Cerebral venous thrombosis in the puerperium
47607	L440.11	CVA - cerebrovascular accident in the puerperium
56279	L440.12	Stroke in the puerperium
42248	ZLEP.00	Discharge from stroke serv
19348	ZV12511	[V]Personal history of stroke
7138	ZV12512	[V]Personal history of cerebrovascular accident (CVA)
101251	ZV12D00	[V]Personal history of transient ischaemic attack

CV_DEATH

medcoc	readco	desc
i10	i10x	essentialprimaryhypertension
I11	I11	Hypertensive heart disease
I11.0	I110	Hypertensive heart disease with (congestive) heart failure
I11.9	I119	Hypertensive heart disease without (congestive) heart failure
I12	I12	Hypertensive renal disease
I12.0	I120	Hypertensive renal disease with renal failure
I12.9	I129	Hypertensive renal disease without renal failure
I13	I13	Hypertensive heart and renal disease
I13.0	I130	Hypertensive heart and renal disease with (congestive) heart failure
I13.1	I131	Hypertensive heart and renal disease with renal failure
I13.2	I132	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
I13.9	I139	Hypertensive heart and renal disease, unspecified
I15	I15	Secondary hypertension
I15.0	I150	Renovascular hypertension
I15.1	I151	Hypertension secondary to other renal disorders
I15.2	I152	Hypertension secondary to endocrine disorders
I15.8	I158	Other secondary hypertension
I15.9	I159	Secondary hypertension, unspecified
I20	I20	Angina pectoris
I20.0	I200	Unstable angina
I20.1	I201	Angina pectoris with documented spasm
I20.8	I208	Other forms of angina pectoris
I20.9	I209	Angina pectoris, unspecified
I21	I21	Acute myocardial infarction
I21.0	I210	Acute transmural myocardial infarction of anterior wall
I21.1	I211	Acute transmural myocardial infarction of inferior wall
I21.2	I212	Acute transmural myocardial infarction of other sites
I21.3	I213	Acute transmural myocardial infarction of unspecified site
I21.4	I214	Acute subendocardial myocardial infarction
I21.9	I219	Acute myocardial infarction, unspecified
I22	I22	Subsequent myocardial infarction
I22.0	I220	Subsequent myocardial infarction of anterior wall
I22.1	I221	Subsequent myocardial infarction of inferior wall
I22.8	I228	Subsequent myocardial infarction of other sites
I22.9	I229	Subsequent myocardial infarction of unspecified site
I23	I23	Certain current complications following acute myocardial infarction
I23.0	I230	Haemopericardium as current complication following acute myocardial infarction
I23.1	I231	Atrial septal defect as current complication following acute myocardial infarction
I23.2	I232	Ventricular septal defect as current complication following acute myocardial infarction
I23.3	I233	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction
I23.4	I234	Rupture of chordae tendineae as current complication following acute myocardial infarction
I23.5	I235	Rupture of papillary muscle as current complication following acute myocardial infarction
I23.6	I236	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
I23.8	I238	Other current complications following acute myocardial infarction
I24	I24	Other acute ischaemic heart diseases
I24.0	I240	Coronary thrombosis not resulting in myocardial infarction
I24.1	I241	Dressler's syndrome
I24.8	I248	Other forms of acute ischaemic heart disease
I24.9	I249	Acute ischaemic heart disease, unspecified
I25	I25	Chronic ischaemic heart disease
I25.0	I250	Atherosclerotic cardiovascular disease, so described
I25.1	I251	Atherosclerotic heart disease
I25.2	I252	Old myocardial infarction
I25.3	I253	Aneurysm of heart
I25.4	I254	Coronary artery aneurysm
I25.5	I255	Ischaemic cardiomyopathy
I25.6	I256	Silent myocardial ischaemia
I25.8	I258	Other forms of chronic ischaemic heart disease
I25.9	I259	Chronic ischaemic heart disease, unspecified
I26	I26	Pulmonary embolism
I26.0	I260	Pulmonary embolism with mention of acute cor pulmonale
I26.9	I269	Pulmonary embolism without mention of acute cor pulmonale
I27	I27	Other pulmonary heart diseases
I27.0	I270	Primary pulmonary hypertension
I27.1	I271	Kyphoscoliotic heart disease
I27.2	I272	Other secondary pulmonary hypertension
I27.8	I278	Other specified pulmonary heart diseases
I27.9	I279	Pulmonary heart disease, unspecified
I28	I28	Other diseases of pulmonary vessels
I28.0	I280	Arteriovenous fistula of pulmonary vessels
I28.1	I281	Aneurysm of pulmonary artery
I28.8	I288	Other specified diseases of pulmonary vessels
I28.9	I289	Disease of pulmonary vessels, unspecified
I30	I30	Acute pericarditis
I30.0	I300	Acute nonspecific idiopathic pericarditis

I30.1	I301	Infective pericarditis
I30.8	I308	Other forms of acute pericarditis
I30.9	I309	Acute pericarditis, unspecified
I31	I31	Other diseases of pericardium
I31.0	I310	Chronic adhesive pericarditis
I31.1	I311	Chronic constrictive pericarditis
I31.2	I312	Haemopericardium, not elsewhere classified
I31.3	I313	Pericardial effusion (noninflammatory)
I31.8	I318	Other specified diseases of pericardium
I31.9	I319	Disease of pericardium, unspecified
I32	I32	Pericarditis in diseases classified elsewhere
I32.0	I320	Pericarditis in bacterial diseases classified elsewhere
I32.1	I321	Pericarditis in other infectious and parasitic diseases classified elsewhere
I32.8	I328	Pericarditis in other diseases classified elsewhere
I33	I33	Acute and subacute endocarditis
I33.0	I330	Acute and subacute infective endocarditis
I33.9	I339	Acute endocarditis, unspecified
I34	I34	Nonrheumatic mitral valve disorders
I34.0	I340	Mitral (valve) insufficiency
I34.1	I341	Mitral (valve) prolapse
I34.2	I342	Nonrheumatic mitral (valve) stenosis
I34.8	I348	Other nonrheumatic mitral valve disorders
I34.9	I349	Nonrheumatic mitral valve disorder, unspecified
I35	I35	Nonrheumatic aortic valve disorders
I35.0	I350	Aortic (valve) stenosis
I35.1	I351	Aortic (valve) insufficiency
I35.2	I352	Aortic (valve) stenosis with insufficiency
I35.8	I358	Other aortic valve disorders
I35.9	I359	Aortic valve disorder, unspecified
I36	I36	Nonrheumatic tricuspid valve disorders
I36.0	I360	Nonrheumatic tricuspid (valve) stenosis
I36.1	I361	Nonrheumatic tricuspid (valve) insufficiency
I36.2	I362	Nonrheumatic tricuspid (valve) stenosis with insufficiency
I36.8	I368	Other nonrheumatic tricuspid valve disorders
I36.9	I369	Nonrheumatic tricuspid valve disorder, unspecified
I37	I37	Pulmonary valve disorders
I37.0	I370	Pulmonary valve stenosis
I37.1	I371	Pulmonary valve insufficiency
I37.2	I372	Pulmonary valve stenosis with insufficiency
I37.8	I378	Other pulmonary valve disorders
I37.9	I379	Pulmonary valve disorder, unspecified
I38	I38X	Endocarditis, valve unspecified
I39	I39	Endocarditis and heart valve disorders in diseases classified elsewhere
I39.0	I390	Mitral valve disorders in diseases classified elsewhere
I39.1	I391	Aortic valve disorders in diseases classified elsewhere
I39.2	I392	Tricuspid valve disorders in diseases classified elsewhere
I39.3	I393	Pulmonary valve disorders in diseases classified elsewhere
I39.4	I394	Multiple valve disorders in diseases classified elsewhere
I39.8	I398	Endocarditis, valve unspecified, in diseases classified elsewhere
I40	I40	Acute myocarditis
I40.0	I400	Infective myocarditis
I40.1	I401	Isolated myocarditis
I40.8	I408	Other acute myocarditis
I40.9	I409	Acute myocarditis, unspecified
I41	I41	Myocarditis in diseases classified elsewhere
I41.0	I410	Myocarditis in bacterial diseases classified elsewhere
I41.1	I411	Myocarditis in viral diseases classified elsewhere
I41.2	I412	Myocarditis in other infectious and parasitic diseases classified elsewhere
I41.8	I418	Myocarditis in other diseases classified elsewhere
I42	I42	Cardiomyopathy
I42.0	I420	Dilated cardiomyopathy
I42.1	I421	Obstructive hypertrophic cardiomyopathy
I42.2	I422	Other hypertrophic cardiomyopathy
I42.3	I423	Endomyocardial (eosinophilic) disease
I42.4	I424	Endocardial fibroelastosis
I42.5	I425	Other restrictive cardiomyopathy
I42.6	I426	Alcoholic cardiomyopathy
I42.7	I427	Cardiomyopathy due to drugs and other external agents
I42.8	I428	Other cardiomyopathies
I42.9	I429	Cardiomyopathy, unspecified
I43	I43	Cardiomyopathy in diseases classified elsewhere
I43.0	I430	Cardiomyopathy in infectious and parasitic diseases classified elsewhere
I43.1	I431	Cardiomyopathy in metabolic diseases
I43.2	I432	Cardiomyopathy in nutritional diseases
I43.8	I438	Cardiomyopathy in other diseases classified elsewhere
I44	I44	Atrioventricular and left bundle-branch block
I44.0	I440	Atrioventricular block, first degree

I44.1	I441	Atrioventricular block, second degree
I44.2	I442	Atrioventricular block, complete
I44.3	I443	Other and unspecified atrioventricular block
I44.4	I444	Left anterior fascicular block
I44.5	I445	Left posterior fascicular block
I44.6	I446	Other and unspecified fascicular block
I44.7	I447	Left bundle-branch block, unspecified
I45	I45	Other conduction disorders
I45.0	I450	Right fascicular block
I45.1	I451	Other and unspecified right bundle-branch block
I45.2	I452	Bifascicular block
I45.3	I453	Trifascicular block
I45.4	I454	Nonspecific intraventricular block
I45.5	I455	Other specified heart block
I45.6	I456	Pre-excitation syndrome
I45.8	I458	Other specified conduction disorders
I45.9	I459	Conduction disorder, unspecified
I46	I46	Cardiac arrest
I46.0	I460	Cardiac arrest with successful resuscitation
I46.1	I461	Sudden cardiac death, so described
I46.9	I469	Cardiac arrest, unspecified
I47	I47	Paroxysmal tachycardia
I47.0	I470	Re-entry ventricular arrhythmia
I47.1	I471	Supraventricular tachycardia
I47.2	I472	Ventricular tachycardia
I47.9	I479	Paroxysmal tachycardia, unspecified
I48	I48X	Atrial fibrillation and flutter
I49	I49	Other cardiac arrhythmias
I49.0	I490	Ventricular fibrillation and flutter
I49.1	I491	Atrial premature depolarization
I49.2	I492	Junctional premature depolarization
I49.3	I493	Ventricular premature depolarization
I49.4	I494	Other and unspecified premature depolarization
I49.5	I495	Sick sinus syndrome
I49.8	I498	Other specified cardiac arrhythmias
I49.9	I499	Cardiac arrhythmia, unspecified
I50	I50	Heart failure
I50.0	I500	Congestive heart failure
I50.1	I501	Left ventricular failure
I50.9	I509	Heart failure, unspecified
I51	I51	Complications and ill-defined descriptions of heart disease
I51.0	I510	Cardiac septal defect, acquired
I51.1	I511	Rupture of chordae tendineae, not elsewhere classified
I51.2	I512	Rupture of papillary muscle, not elsewhere classified
I51.3	I513	Intracardiac thrombosis, not elsewhere classified
I51.4	I514	Myocarditis, unspecified
I51.5	I515	Myocardial degeneration
I51.6	I516	Cardiovascular disease, unspecified
I51.7	I517	Cardiomegaly
I51.8	I518	Other ill-defined heart diseases
I51.9	I519	Heart disease, unspecified
I60	I60	Subarachnoid haemorrhage
I60.0	I600	Subarachnoid haemorrhage from carotid siphon and bifurcation
I60.1	I601	Subarachnoid haemorrhage from middle cerebral artery
I60.2	I602	Subarachnoid haemorrhage from anterior communicating artery
I60.3	I603	Subarachnoid haemorrhage from posterior communicating artery
I60.4	I604	Subarachnoid haemorrhage from basilar artery
I60.5	I605	Subarachnoid haemorrhage from vertebral artery
I60.6	I606	Subarachnoid haemorrhage from other intracranial arteries
I60.7	I607	Subarachnoid haemorrhage from intracranial artery, unspecified
I60.8	I608	Other subarachnoid haemorrhage
I60.9	I609	Subarachnoid haemorrhage, unspecified
I61	I61	Intracerebral haemorrhage
I61.0	I610	Intracerebral haemorrhage in hemisphere, subcortical
I61.1	I611	Intracerebral haemorrhage in hemisphere, cortical
I61.2	I612	Intracerebral haemorrhage in hemisphere, unspecified
I61.3	I613	Intracerebral haemorrhage in brain stem
I61.4	I614	Intracerebral haemorrhage in cerebellum
I61.5	I615	Intracerebral haemorrhage, intraventricular
I61.6	I616	Intracerebral haemorrhage, multiple localized
I61.8	I618	Other intracerebral haemorrhage
I61.9	I619	Intracerebral haemorrhage, unspecified
I62	I62	Other nontraumatic intracranial haemorrhage
I62.0	I620	Subdural haemorrhage (acute)(nontraumatic)
I62.1	I621	Nontraumatic extradural haemorrhage
I62.9	I629	Intracranial haemorrhage (nontraumatic), unspecified
I63	I63	Cerebral infarction

I63.0	I630	Cerebral infarction due to thrombosis of precerebral arteries
I63.1	I631	Cerebral infarction due to embolism of precerebral arteries
I63.2	I632	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	I633	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	I634	Cerebral infarction due to embolism of cerebral arteries
I63.5	I635	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	I636	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	I638	Other cerebral infarction
I63.9	I639	Cerebral infarction, unspecified
I64	I64X	Stroke, not specified as haemorrhage or infarction
I65	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I65.0	I650	Occlusion and stenosis of vertebral artery
I65.1	I651	Occlusion and stenosis of basilar artery
I65.2	I652	Occlusion and stenosis of carotid artery
I65.3	I653	Occlusion and stenosis of multiple and bilateral precerebral arteries
I65.8	I658	Occlusion and stenosis of other precerebral artery
I65.9	I659	Occlusion and stenosis of unspecified precerebral artery
I66	I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I66.0	I660	Occlusion and stenosis of middle cerebral artery
I66.1	I661	Occlusion and stenosis of anterior cerebral artery
I66.2	I662	Occlusion and stenosis of posterior cerebral artery
I66.3	I663	Occlusion and stenosis of cerebellar arteries
I66.4	I664	Occlusion and stenosis of multiple and bilateral cerebral arteries
I66.8	I668	Occlusion and stenosis of other cerebral artery
I66.9	I669	Occlusion and stenosis of unspecified cerebral artery
I67	I67	Other cerebrovascular diseases
I67.0	I670	Dissection of cerebral arteries, nonruptured
I67.1	I671	Cerebral aneurysm, nonruptured
I67.2	I672	Cerebral atherosclerosis
I67.3	I673	Progressive vascular leukoencephalopathy
I67.4	I674	Hypertensive encephalopathy
I67.5	I675	Moyamoya disease
I67.6	I676	Nonpyogenic thrombosis of intracranial venous system
I67.7	I677	Cerebral arteritis, not elsewhere classified
I67.8	I678	Other specified cerebrovascular diseases
I67.9	I679	Cerebrovascular disease, unspecified
I68	I68	Cerebrovascular disorders in diseases classified elsewhere
I68.0	I680	Cerebral amyloid angiopathy
I68.1	I681	Cerebral arteritis in infectious and parasitic diseases classified elsewhere
I68.2	I682	Cerebral arteritis in other diseases classified elsewhere
I68.8	I688	Other cerebrovascular disorders in diseases classified elsewhere
I69	I69	Sequelae of cerebrovascular disease
I69.0	I690	Sequelae of subarachnoid haemorrhage
I69.1	I691	Sequelae of intracerebral haemorrhage
I69.2	I692	Sequelae of other nontraumatic intracranial haemorrhage
I69.3	I693	Sequelae of cerebral infarction
I69.4	I694	Sequelae of stroke, not specified as haemorrhage or infarction
I69.8	I698	Sequelae of other and unspecified cerebrovascular diseases
I70	I70	Atherosclerosis
I70.0	I700	Atherosclerosis of aorta
I70.00	I7000	Atherosclerosis of aorta
I70.01	I7001	Atherosclerosis of aorta
I70.1	I701	Atherosclerosis of renal artery
I70.10	I7010	Atherosclerosis of renal artery
I70.11	I7011	Atherosclerosis of renal artery
I70.2	I702	Atherosclerosis of arteries of extremities
I70.20	I7020	Atherosclerosis of arteries of extremities
I70.21	I7021	Atherosclerosis of arteries of extremities
I70.8	I708	Atherosclerosis of other arteries
I70.80	I7080	Atherosclerosis of other arteries
I70.81	I7081	Atherosclerosis of other arteries
I70.9	I709	Generalized and unspecified atherosclerosis
I70.90	I7090	Generalized and unspecified atherosclerosis
I70.91	I7091	Generalized and unspecified atherosclerosis
I71	I71	Aortic aneurysm and dissection
I71.0	I710	Dissection of aorta [any part]
I71.1	I711	Thoracic aortic aneurysm, ruptured
I71.2	I712	Thoracic aortic aneurysm, without mention of rupture
I71.3	I713	Abdominal aortic aneurysm, ruptured
I71.4	I714	Abdominal aortic aneurysm, without mention of rupture
I71.5	I715	Thoracoabdominal aortic aneurysm, ruptured
I71.6	I716	Thoracoabdominal aortic aneurysm, without mention of rupture
I71.8	I718	Aortic aneurysm of unspecified site, ruptured
I71.9	I719	Aortic aneurysm of unspecified site, without mention of rupture
icdcode	id	description

CARDIO_CVD

v1	v2	v3
readcode	desc	medcode
13B3.00	Low cholesterol diet	13B3.00
13YA.00	Stroke group member	13YA.00
1442.00	H/O: raised blood lipids	1442.00
14A2.00	H/O: hypertension	14A2.00
14A3.00	H/O: myocardial infarct <60	14A3.00
14A4.00	H/O: myocardial infarct >60	14A4.00
14A5.00	H/O: angina pectoris	14A5.00
14A6.00	H/O: heart failure	14A6.00
14A7.00	H/O: CVA/stroke	14A7.00
14A7.11	H/O: CVA	14A7.11
14A7.12	H/O: stroke	14A7.12
14AB.00	H/O: TIA	14AB.00
14AH.00	H/O: Myocardial infarction in last year	14AH.00
14AJ.00	H/O: Angina in last year	14AJ.00
14AK.00	H/O: Stroke in last year	14AK.00
14AM.00	H/O: Heart failure in last year	14AM.00
14AN.00	H/O: atrial fibrillation	14AN.00
14AR.00	History of atrial flutter	14AR.00
1736.00	Paroxysmal nocturnal dyspnoea	1736.00
1J60.00	Suspected heart failure	1J60.00
1JD..00	Suspected hypertension	1JD..00
1O1..00	Heart failure confirmed	1O1..00
212R.00	Atrial fibrillation resolved	212R.00
23E1.00	O/E - pulmonary oedema	23E1.00
243..11	O/E - irregular pulse	243..11
2432.00	O/E - pulse irregularly irreg.	2432.00
3272.00	ECG: atrial fibrillation	3272.00
3273.00	ECG: atrial flutter	3273.00
388D.00	New York Heart Assoc classification heart failure symptoms	388D.00
6146200	Hypertension induced by oral contraceptive pill	6146200
662..12	Hypertension monitoring	662..12
6627.00	Good hypertension control	6627.00
6628.00	Poor hypertension control	6628.00
6629.00	Hypertension:follow-up default	6629.00
662F.00	Hypertension treatm. started	662F.00
662G.00	Hypertensive treatm.changed	662G.00
662H.00	Hypertension treatm.stopped	662H.00
662K.00	Angina control	662K.00
662K000	Angina control - good	662K000
662K100	Angina control - poor	662K100
662K200	Angina control - improving	662K200
662K300	Angina control - worsening	662K300
662Kz00	Angina control NOS	662Kz00
662M.00	Stroke monitoring	662M.00
662O.00	On treatment for hypertension	662O.00
662P.00	Hypertension monitoring	662P.00
662S.00	Atrial fibrillation monitoring	662S.00

662T.00	Congestive heart failure monitoring	662T.00
662W.00	Heart failure annual review	662W.00
662b.00	Moderate hypertension control	662b.00
662c.00	Hypertension six month review	662c.00
662d.00	Hypertension annual review	662d.00
662e.00	Stroke/CVA annual review	662e.00
662f.00	New York Heart Association classification - class I	662f.00
662g.00	New York Heart Association classification - class II	662g.00
662h.00	New York Heart Association classification - class III	662h.00
662i.00	New York Heart Association classification - class IV	662i.00
662o.00	Haemorrhagic stroke monitoring	662o.00
662p.00	Heart failure 6 month review	662p.00
662r.00	Trial withdrawal of antihypertensive therapy	662r.00
66X..00	Lipid disorder monitoring	66X..00
679X.00	Heart failure education	679X.00
6A9..00	Atrial fibrillation annual review	6A9..00
792..11	Coronary artery bypass graft operations	792..11
7920.00	Saphenous vein graft replacement of coronary artery	7920.00
7920.11	Saphenous vein graft bypass of coronary artery	7920.11
7920000	Saphenous vein graft replacement of one coronary artery	7920000
7920100	Saphenous vein graft replacement of two coronary arteries	7920100
7920200	Saphenous vein graft replacement of three coronary arteries	7920200
7920300	Saphenous vein graft replacement of four+ coronary arteries	7920300
7920y00	Saphenous vein graft replacement of coronary artery OS	7920y00
7920z00	Saphenous vein graft replacement coronary artery NOS	7920z00
7921.00	Other autograft replacement of coronary artery	7921.00
7921.11	Other autograft bypass of coronary artery	7921.11
7921000	Autograft replacement of one coronary artery NEC	7921000
7921100	Autograft replacement of two coronary arteries NEC	7921100
7921200	Autograft replacement of three coronary arteries NEC	7921200
7921300	Autograft replacement of four of more coronary arteries NEC	7921300
7921y00	Other autograft replacement of coronary artery OS	7921y00
7921z00	Other autograft replacement of coronary artery NOS	7921z00
7922.00	Allograft replacement of coronary artery	7922.00
7922.11	Allograft bypass of coronary artery	7922.11
7922000	Allograft replacement of one coronary artery	7922000
7922100	Allograft replacement of two coronary arteries	7922100
7922200	Allograft replacement of three coronary arteries	7922200
7922300	Allograft replacement of four or more coronary arteries	7922300
7922y00	Other specified allograft replacement of coronary artery	7922y00
7922z00	Allograft replacement of coronary artery NOS	7922z00
7923.00	Prosthetic replacement of coronary artery	7923.00
7923.11	Prosthetic bypass of coronary artery	7923.11
7923000	Prosthetic replacement of one coronary artery	7923000
7923100	Prosthetic replacement of two coronary arteries	7923100
7923200	Prosthetic replacement of three coronary arteries	7923200
7923300	Prosthetic replacement of four or more coronary arteries	7923300
7923z00	Prosthetic replacement of coronary artery NOS	7923z00
7924.00	Revision of bypass for coronary artery	7924.00
7924000	Revision of bypass for one coronary artery	7924000

7924100	Revision of bypass for two coronary arteries	7924100
7924200	Revision of bypass for three coronary arteries	7924200
7924y00	Other specified revision of bypass for coronary artery	7924y00
7924z00	Revision of bypass for coronary artery NOS	7924z00
7925.00	Connection of mammary artery to coronary artery	7925.00
7925.11	Creation of bypass from mammary artery to coronary artery	7925.11
7925000	Double anastomosis of mammary arteries to coronary arteries	7925000
7925100	Double implant of mammary arteries into coronary arteries	7925100
7925300	Single anastomosis of mammary artery to coronary artery NEC	7925300
7925311	LIMA single anastomosis	7925311
7925312	RIMA single anastomosis	7925312
7925400	Single implantation of mammary artery into coronary artery	7925400
7925y00	Connection of mammary artery to coronary artery OS	7925y00
7925z00	Connection of mammary artery to coronary artery NOS	7925z00
7926.00	Connection of other thoracic artery to coronary artery	7926.00
7926000	Double anastom thoracic arteries to coronary arteries NEC	7926000
7926200	Single anastomosis of thoracic artery to coronary artery NEC	7926200
7926300	Single implantation thoracic artery into coronary artery NEC	7926300
7926z00	Connection of other thoracic artery to coronary artery NOS	7926z00
7927500	Open angioplasty of coronary artery	7927500
792C.00	Other replacement of coronary artery	792C.00
792C000	Replacement of coronary arteries using multiple methods	792C000
792Cy00	Other specified replacement of coronary artery	792Cy00
792Cz00	Replacement of coronary artery NOS	792Cz00
792D.00	Other bypass of coronary artery	792D.00
792Dy00	Other specified other bypass of coronary artery	792Dy00
792Dz00	Other bypass of coronary artery NOS	792Dz00
793M100	Perc transluminal ablation of atrial wall for atrial flutter	793M100
793M300	Perc translum ablat conduct sys heart for atrial flutter NEC	793M300
7P24200	Delivery of rehabilitation for stroke	7P24200
7Q01.00	High cost hypertension drugs	7Q01.00
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct	889A.00
8B26.00	Antihypertensive therapy	8B26.00
8B27.00	Antianginal therapy	8B27.00
8B29.00	Cardiac failure therapy	8B29.00
8BAG.00	Cholesterol reduction programme	8BAG.00
8BAG000	Cholesterol reduction programme - invited	8BAG000
8BAG100	Cholesterol reduction program - attended	8BAG100
8BAG200	Cholesterol reduction program - declined	8BAG200
8BG2.00	Lipid lowering therapy indicated	8BG2.00
8BL0.00	Patient on maximal tolerated antihypertensive therapy	8BL0.00
8CA4700	Patient advised re low cholesterol diet	8CA4700
8CL3.00	Heart failure care plan discussed with patient	8CL3.00
8CR3.00	Hyperlipidaemia clinical management plan	8CR3.00
8CR4.00	Hypertension clinical management plan	8CR4.00
8H2S.00	Admit heart failure emergency	8H2S.00
8HBE.00	Heart failure follow-up	8HBE.00
8HBJ.00	Stroke / transient ischaemic attack referral	8HBJ.00
8HHM.00	Ref to multidisciplinary stroke function improvement service	8HHM.00
8HHz.00	Referral to heart failure exercise programme	8HHz.00

8HTQ.00	Referral to stroke clinic	8HTQ.00
8Hg8.00	Discharge from practice nurse heart failure clinic	8Hg8.00
8Hk0.00	Referred to heart failure education group	8Hk0.00
8I3N.00	Hypertension treatment refused	8I3N.00
9N03.00	Seen in hypertension clinic	9N03.00
9N0I.00	Seen in lipid clinic	9N0I.00
9N0J.00	Seen in cholesterol clinic	9N0J.00
9N0k.00	Seen in heart failure clinic	9N0k.00
9N1y200	Seen in hypertension clinic	9N1y200
9N2p.00	Seen by community heart failure nurse	9N2p.00
9N4K.00	DNA - Did not attend cholesterol clinic	9N4K.00
9N4s.00	Did not attend practice nurse heart failure clinic	9N4s.00
9N4w.00	Did not attend heart failure clinic	9N4w.00
9N6T.00	Referred by heart failure nurse specialist	9N6T.00
9OI..00	Hypertension monitoring admin.	9OI..00
9OI..11	Hypertension clinic admin.	9OI..11
9OI1.00	Attends hypertension monitor.	9OI1.00
9OI4.00	Hypertens.monitor.1st letter	9OI4.00
9OI5.00	Hypertens.monitor 2nd letter	9OI5.00
9OI6.00	Hypertens.monitor 3rd letter	9OI6.00
9OI7.00	Hypertens.monitor verbal inv.	9OI7.00
9OI8.00	Hypertens.monitor phone invite	9OI8.00
9OIA.00	Hypertension monitor.chck done	9OIA.00
9OIA.11	Hypertension monitored	9OIA.11
9OIZ.00	Hypertens.monitoring admin.NOS	9OIZ.00
9Oc..00	Lipid disorder monitoring administration	9Oc..00
9Oc0.00	Attends lipid disorder monitoring	9Oc0.00
9Oc2.00	Lipid disorder monitoring first letter	9Oc2.00
9Om..00	Stroke/transient ischaemic attack monitoring administration	9Om..00
9Om0.00	Stroke/transient ischaemic attack monitoring first letter	9Om0.00
9Om1.00	Stroke/transient ischaemic attack monitoring second letter	9Om1.00
9Om2.00	Stroke/transient ischaemic attack monitoring third letter	9Om2.00
9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati	9Om3.00
9Om4.00	Stroke/transient ischaemic attack monitoring telephone invte	9Om4.00
9On..00	Left ventricular dysfunction monitoring administration	9On..00
9On0.00	Left ventricular dysfunction monitoring first letter	9On0.00
9On1.00	Left ventricular dysfunction monitoring second letter	9On1.00
9On2.00	Left ventricular dysfunction monitoring third letter	9On2.00
9On3.00	Left ventricular dysfunction monitoring verbal invite	9On3.00
9On4.00	Left ventricular dysfunction monitoring telephone invite	9On4.00
9Or..00	Heart failure monitoring administration	9Or..00
9Or0.00	Heart failure review completed	9Or0.00
9Or1.00	Heart failure monitoring telephone invite	9Or1.00
9Or2.00	Heart failure monitoring verbal invite	9Or2.00
9Or3.00	Heart failure monitoring first letter	9Or3.00
9Or4.00	Heart failure monitoring second letter	9Or4.00
9Or5.00	Heart failure monitoring third letter	9Or5.00
9Os..00	Atrial fibrillation monitoring administration	9Os..00
9Os0.00	Atrial fibrillation monitoring first letter	9Os0.00
9Os1.00	Atrial fibrillation monitoring second letter	9Os1.00

9Os2.00	Atrial fibrillation monitoring third letter	9Os2.00
9Os3.00	Atrial fibrillation monitoring verbal invite	9Os3.00
9Os4.00	Atrial fibrillation monitoring telephone invite	9Os4.00
9h1..00	Exception reporting: LVD quality indicators	9h1..00
9h11.00	Excepted from LVD quality indicators: Patient unsuitable	9h11.00
9h12.00	Excepted from LVD quality indicators: Informed dissent	9h12.00
9h2..00	Exception reporting: stroke quality indicators	9h2..00
9h21.00	Excepted from stroke quality indicators: Patient unsuitable	9h21.00
9h22.00	Excepted from stroke quality indicators: Informed dissent	9h22.00
9h3..00	Exception reporting: hypertension quality indicators	9h3..00
9h31.00	Excepted from hypertension qual indicators: Patient unsuit	9h31.00
9h32.00	Excepted from hypertension qual indicators: Informed dissent	9h32.00
9hF..00	Exception reporting: atrial fibrillation quality indicators	9hF..00
9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent	9hF1.00
9hH..00	Exception reporting: heart failure quality indicators	9hH..00
9hH0.00	Excepted heart failure quality indicators: Patient unsuitabl	9hH0.00
9hH1.00	Excepted heart failure quality indicators: Informed dissent	9hH1.00
C32..00	Disorders of lipoid metabolism	C32..00
C32..11	Disorder of cholesterol metabolism	C32..11
C320.00	Pure hypercholesterolaemia	C320.00
C320.11	Familial hypercholesterolaemia	C320.11
C320.12	Fredrickson type IIa lipidaemia	C320.12
C320.13	Low density lipoproteinaemia	C320.13
C320000	Familial hypercholesterolaemia	C320000
C320100	Hyperbetalipoproteinaemia	C320100
C320200	Hyperlipidaemia, group A	C320200
C320300	Low-density-lipoprotein-type (LDL) hyperlipoproteinaemia	C320300
C320400	Fredrickson's hyperlipoproteinaemia, type IIa	C320400
C320500	Familial defective apolipoprotein B-100	C320500
C320y00	Other specified pure hypercholesterolaemia	C320y00
C320z00	Pure hypercholesterolaemia NOS	C320z00
C321.11	Fredrickson type IV lipidaemia	C321.11
C321000	Hypertriglyceridaemia	C321000
C322.00	Mixed hyperlipidaemia	C322.00
C322.11	Fredrickson type IIb lipidaemia	C322.11
C322.12	Fredrickson type III lipidaemia	C322.12
C324.00	Hyperlipidaemia NOS	C324.00
C325.00	Lipoprotein deficiencies	C325.00
C325100	Hypo-alpha-lipoproteinaemia	C325100
C325200	Hypo-beta-lipoproteinaemia	C325200
C325300	A-beta-lipoproteinaemia	C325300
C328.00	Dyslipidaemia	C328.00
C32y.00	Other disorders of lipoid metabolism	C32y.00
C32y200	Lipoid dermatoarthritis	C32y200
C32yz00	Other disorder of lipoid metabolism NOS	C32yz00
C32z.00	Disorder of lipoid metabolism NOS	C32z.00
Cyu8D00	[X]Other hyperlipidaemia	Cyu8D00
Cyu8E00	[X]Other disorders of lipoprotein metabolism	Cyu8E00
E004.11	Multi infarct dementia	E004.11
F050.00	Embolism of central nervous system venous sinus	F050.00

F050000	Embolism cavernous sinus	F050000
F050100	Embolism superior longitudinal sinus	F050100
F050300	Embolism transverse sinus	F050300
F051.00	Thrombosis of central nervous system venous sinuses	F051.00
F051000	Thrombosis cavernous sinus	F051000
F051100	Thrombosis of superior longitudinal sinus	F051100
F051200	Thrombosis lateral sinus	F051200
F051300	Thrombosis transverse sinus	F051300
F051z00	Thrombosis of central nervous system venous sinus NOS	F051z00
F404200	Blind hypertensive eye	F404200
F421300	Hypertensive retinopathy	F421300
Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms	Fyu5500
Fyu5600	[X]Other lacunar syndromes	Fyu5600
G1yz100	Rheumatic left ventricular failure	G1yz100
G2...00	Hypertensive disease	G2...00
G2...11	BP - hypertensive disease	G2...11
G20..00	Essential hypertension	G20..00
G200.00	Malignant essential hypertension	G200.00
G201.00	Benign essential hypertension	G201.00
G202.00	Systolic hypertension	G202.00
G203.00	Diastolic hypertension	G203.00
G20z.00	Essential hypertension NOS	G20z.00
G20z.11	Hypertension NOS	G20z.11
G21..00	Hypertensive heart disease	G21..00
G210.00	Malignant hypertensive heart disease	G210.00
G210000	Malignant hypertensive heart disease without CCF	G210000
G210100	Malignant hypertensive heart disease with CCF	G210100
G211.00	Benign hypertensive heart disease	G211.00
G211000	Benign hypertensive heart disease without CCF	G211000
G211100	Benign hypertensive heart disease with CCF	G211100
G21z.00	Hypertensive heart disease NOS	G21z.00
G21z000	Hypertensive heart disease NOS without CCF	G21z000
G21z011	Cardiomegaly - hypertensive	G21z011
G21z100	Hypertensive heart disease NOS with CCF	G21z100
G21zz00	Hypertensive heart disease NOS	G21zz00
G22..00	Hypertensive renal disease	G22..00
G220.00	Malignant hypertensive renal disease	G220.00
G221.00	Benign hypertensive renal disease	G221.00
G222.00	Hypertensive renal disease with renal failure	G222.00
G22z.00	Hypertensive renal disease NOS	G22z.00
G22z.11	Renal hypertension	G22z.11
G23..00	Hypertensive heart and renal disease	G23..00
G230.00	Malignant hypertensive heart and renal disease	G230.00
G231.00	Benign hypertensive heart and renal disease	G231.00
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure	G232.00
G233.00	Hypertensive heart and renal disease with renal failure	G233.00
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail	G234.00
G23z.00	Hypertensive heart and renal disease NOS	G23z.00
G24..00	Secondary hypertension	G24..00
G240.00	Secondary malignant hypertension	G240.00

G240000	Secondary malignant renovascular hypertension	G240000
G240z00	Secondary malignant hypertension NOS	G240z00
G241.00	Secondary benign hypertension	G241.00
G241000	Secondary benign renovascular hypertension	G241000
G241z00	Secondary benign hypertension NOS	G241z00
G244.00	Hypertension secondary to endocrine disorders	G244.00
G24z.00	Secondary hypertension NOS	G24z.00
G24z000	Secondary renovascular hypertension NOS	G24z000
G24z100	Hypertension secondary to drug	G24z100
G24zz00	Secondary hypertension NOS	G24zz00
G2y..00	Other specified hypertensive disease	G2y..00
G2z..00	Hypertensive disease NOS	G2z..00
G30..00	Acute myocardial infarction	G30..00
G30..11	Attack - heart	G30..11
G30..12	Coronary thrombosis	G30..12
G30..13	Cardiac rupture following myocardial infarction (MI)	G30..13
G30..14	Heart attack	G30..14
G30..15	MI - acute myocardial infarction	G30..15
G30..16	Thrombosis - coronary	G30..16
G30..17	Silent myocardial infarction	G30..17
G300.00	Acute anterolateral infarction	G300.00
G301.00	Other specified anterior myocardial infarction	G301.00
G301000	Acute anteroapical infarction	G301000
G301100	Acute anteroseptal infarction	G301100
G301z00	Anterior myocardial infarction NOS	G301z00
G302.00	Acute inferolateral infarction	G302.00
G303.00	Acute inferoposterior infarction	G303.00
G304.00	Posterior myocardial infarction NOS	G304.00
G305.00	Lateral myocardial infarction NOS	G305.00
G306.00	True posterior myocardial infarction	G306.00
G307.00	Acute subendocardial infarction	G307.00
G307000	Acute non-Q wave infarction	G307000
G307100	Acute non-ST segment elevation myocardial infarction	G307100
G308.00	Inferior myocardial infarction NOS	G308.00
G309.00	Acute Q-wave infarct	G309.00
G30A.00	Mural thrombosis	G30A.00
G30B.00	Acute posterolateral myocardial infarction	G30B.00
G30X.00	Acute transmural myocardial infarction of unspecif site	G30X.00
G30X000	Acute ST segment elevation myocardial infarction	G30X000
G30y.00	Other acute myocardial infarction	G30y.00
G30y000	Acute atrial infarction	G30y000
G30y100	Acute papillary muscle infarction	G30y100
G30y200	Acute septal infarction	G30y200
G30yz00	Other acute myocardial infarction NOS	G30yz00
G30z.00	Acute myocardial infarction NOS	G30z.00
G310.00	Postmyocardial infarction syndrome	G310.00
G310.11	Dressler's syndrome	G310.11
G311.00	Preinfarction syndrome	G311.00
G311.11	Crescendo angina	G311.11
G311.12	Impending infarction	G311.12

G311.13	Unstable angina	G311.13
G311.14	Angina at rest	G311.14
G311100	Unstable angina	G311100
G311200	Angina at rest	G311200
G311300	Refractory angina	G311300
G311400	Worsening angina	G311400
G311500	Acute coronary syndrome	G311500
G311z00	Preinfarction syndrome NOS	G311z00
G312.00	Coronary thrombosis not resulting in myocardial infarction	G312.00
G31y000	Acute coronary insufficiency	G31y000
G31y100	Microinfarction of heart	G31y100
G32..00	Old myocardial infarction	G32..00
G32..11	Healed myocardial infarction	G32..11
G32..12	Personal history of myocardial infarction	G32..12
G33..00	Angina pectoris	G33..00
G330.00	Angina decubitus	G330.00
G330000	Nocturnal angina	G330000
G330z00	Angina decubitus NOS	G330z00
G331.00	Prinzmetal's angina	G331.00
G331.11	Variant angina pectoris	G331.11
G332.00	Coronary artery spasm	G332.00
G33z.00	Angina pectoris NOS	G33z.00
G33z000	Status anginosus	G33z000
G33z100	Stenocardia	G33z100
G33z200	Syncope anginosa	G33z200
G33z300	Angina on effort	G33z300
G33z500	Post infarct angina	G33z500
G33z600	New onset angina	G33z600
G33z700	Stable angina	G33z700
G33zz00	Angina pectoris NOS	G33zz00
G34y000	Chronic coronary insufficiency	G34y000
G35..00	Subsequent myocardial infarction	G35..00
G350.00	Subsequent myocardial infarction of anterior wall	G350.00
G351.00	Subsequent myocardial infarction of inferior wall	G351.00
G353.00	Subsequent myocardial infarction of other sites	G353.00
G35X.00	Subsequent myocardial infarction of unspecified site	G35X.00
G36..00	Certain current complication follow acute myocardial infarct	G36..00
G360.00	Haemopericardium/current comp folow acut myocard infarct	G360.00
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct	G361.00
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn	G362.00
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI	G363.00
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct	G364.00
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct	G365.00
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI	G366.00
G37..00	Cardiac syndrome X	G37..00
G38..00	Postoperative myocardial infarction	G38..00
G380.00	Postoperative transmural myocardial infarction anterior wall	G380.00
G381.00	Postoperative transmural myocardial infarction inferior wall	G381.00
G384.00	Postoperative subendocardial myocardial infarction	G384.00
G38z.00	Postoperative myocardial infarction, unspecified	G38z.00

G400.00	Acute cor pulmonale	G400.00
G41z.11	Chronic cor pulmonale	G41z.11
G554000	Congestive cardiomyopathy	G554000
G554011	Congestive obstructive cardiomyopathy	G554011
G573.00	Atrial fibrillation and flutter	G573.00
G573000	Atrial fibrillation	G573000
G573100	Atrial flutter	G573100
G573200	Paroxysmal atrial fibrillation	G573200
G573300	Non-rheumatic atrial fibrillation	G573300
G573400	Permanent atrial fibrillation	G573400
G573500	Persistent atrial fibrillation	G573500
G573z00	Atrial fibrillation and flutter NOS	G573z00
G58..00	Heart failure	G58..00
G58..11	Cardiac failure	G58..11
G580.00	Congestive heart failure	G580.00
G580.11	Congestive cardiac failure	G580.11
G580.12	Right heart failure	G580.12
G580.13	Right ventricular failure	G580.13
G580.14	Biventricular failure	G580.14
G580000	Acute congestive heart failure	G580000
G580100	Chronic congestive heart failure	G580100
G580200	Decompensated cardiac failure	G580200
G580300	Compensated cardiac failure	G580300
G580400	Congestive heart failure due to valvular disease	G580400
G581.00	Left ventricular failure	G581.00
G581.11	Asthma - cardiac	G581.11
G581.12	Pulmonary oedema - acute	G581.12
G581.13	Impaired left ventricular function	G581.13
G581000	Acute left ventricular failure	G581000
G582.00	Acute heart failure	G582.00
G58z.00	Heart failure NOS	G58z.00
G58z.11	Weak heart	G58z.11
G58z.12	Cardiac failure NOS	G58z.12
G5yy900	Left ventricular systolic dysfunction	G5yy900
G5yyA00	Left ventricular diastolic dysfunction	G5yyA00
G61..00	Intracerebral haemorrhage	G61..00
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage	G61..11
G61..12	Stroke due to intracerebral haemorrhage	G61..12
G610.00	Cortical haemorrhage	G610.00
G611.00	Internal capsule haemorrhage	G611.00
G612.00	Basal nucleus haemorrhage	G612.00
G613.00	Cerebellar haemorrhage	G613.00
G614.00	Pontine haemorrhage	G614.00
G615.00	Bulbar haemorrhage	G615.00
G616.00	External capsule haemorrhage	G616.00
G617.00	Intracerebral haemorrhage, intraventricular	G617.00
G618.00	Intracerebral haemorrhage, multiple localized	G618.00
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified	G61X.00
G61X000	Left sided intracerebral haemorrhage, unspecified	G61X000
G61X100	Right sided intracerebral haemorrhage, unspecified	G61X100

G61z.00	Intracerebral haemorrhage NOS	G61z.00
G62..00	Other and unspecified intracranial haemorrhage	G62..00
G62z.00	Intracranial haemorrhage NOS	G62z.00
G63..00	Precerebral arterial occlusion	G63..00
G63..11	Infarction - precerebral	G63..11
G630.00	Basilar artery occlusion	G630.00
G631.00	Carotid artery occlusion	G631.00
G631.12	Thrombosis, carotid artery	G631.12
G632.00	Vertebral artery occlusion	G632.00
G633.00	Multiple and bilateral precerebral arterial occlusion	G633.00
G63y.00	Other precerebral artery occlusion	G63y.00
G63y000	Cerebral infarct due to thrombosis of precerebral arteries	G63y000
G63y100	Cerebral infarction due to embolism of precerebral arteries	G63y100
G63z.00	Precerebral artery occlusion NOS	G63z.00
G64..00	Cerebral arterial occlusion	G64..00
G64..11	CVA - cerebral artery occlusion	G64..11
G64..12	Infarction - cerebral	G64..12
G64..13	Stroke due to cerebral arterial occlusion	G64..13
G640.00	Cerebral thrombosis	G640.00
G640000	Cerebral infarction due to thrombosis of cerebral arteries	G640000
G641.00	Cerebral embolism	G641.00
G641.11	Cerebral embolus	G641.11
G641000	Cerebral infarction due to embolism of cerebral arteries	G641000
G64z.00	Cerebral infarction NOS	G64z.00
G64z.11	Brainstem infarction NOS	G64z.11
G64z.12	Cerebellar infarction	G64z.12
G64z000	Brainstem infarction	G64z000
G64z100	Wallenberg syndrome	G64z100
G64z111	Lateral medullary syndrome	G64z111
G64z200	Left sided cerebral infarction	G64z200
G64z300	Right sided cerebral infarction	G64z300
G64z400	Infarction of basal ganglia	G64z400
G65..00	Transient cerebral ischaemia	G65..00
G65..12	Transient ischaemic attack	G65..12
G650.00	Basilar artery syndrome	G650.00
G651.00	Vertebral artery syndrome	G651.00
G651000	Vertebro-basilar artery syndrome	G651000
G653.00	Carotid artery syndrome hemispheric	G653.00
G654.00	Multiple and bilateral precerebral artery syndromes	G654.00
G65y.00	Other transient cerebral ischaemia	G65y.00
G65z.00	Transient cerebral ischaemia NOS	G65z.00
G65z000	Impending cerebral ischaemia	G65z000
G65z100	Intermittent cerebral ischaemia	G65z100
G65zz00	Transient cerebral ischaemia NOS	G65zz00
G66..00	Stroke and cerebrovascular accident unspecified	G66..00
G66..11	CVA unspecified	G66..11
G66..12	Stroke unspecified	G66..12
G66..13	CVA - Cerebrovascular accident unspecified	G66..13
G660.00	Middle cerebral artery syndrome	G660.00
G661.00	Anterior cerebral artery syndrome	G661.00

G662.00	Posterior cerebral artery syndrome	G662.00
G663.00	Brain stem stroke syndrome	G663.00
G664.00	Cerebellar stroke syndrome	G664.00
G665.00	Pure motor lacunar syndrome	G665.00
G666.00	Pure sensory lacunar syndrome	G666.00
G667.00	Left sided CVA	G667.00
G668.00	Right sided CVA	G668.00
G669.00	Cerebral palsy, not congenital or infantile, acute	G669.00
G671000	Acute cerebrovascular insufficiency NOS	G671000
G672.00	Hypertensive encephalopathy	G672.00
G672.11	Hypertensive crisis	G672.11
G676.00	Nonpyogenic venous sinus thrombosis	G676.00
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic	G676000
G677000	Occlusion and stenosis of middle cerebral artery	G677000
G677100	Occlusion and stenosis of anterior cerebral artery	G677100
G677200	Occlusion and stenosis of posterior cerebral artery	G677200
G677300	Occlusion and stenosis of cerebellar arteries	G677300
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries	G677400
G67A.00	Cerebral vein thrombosis	G67A.00
G681.00	Sequelae of intracerebral haemorrhage	G681.00
G682.00	Sequelae of other nontraumatic intracranial haemorrhage	G682.00
G683.00	Sequelae of cerebral infarction	G683.00
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction	G68X.00
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries	G6W..00
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	G6X..00
Gyu2.00	[X]Hypertensive diseases	Gyu2.00
Gyu2100	[X]Hypertension secondary to other renal disorders	Gyu2100
Gyu3000	[X]Other forms of angina pectoris	Gyu3000
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site	Gyu3400
Gyu6200	[X]Other intracerebral haemorrhage	Gyu6200
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	Gyu6300
Gyu6400	[X]Other cerebral infarction	Gyu6400
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries	Gyu6500
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries	Gyu6600
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified	Gyu6F00
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries	Gyu6G00
H461.00	Acute pulmonary oedema due to chemical fumes	H461.00
H54..00	Pulmonary congestion and hypostasis	H54..00
H541.00	Pulmonary congestion	H541.00
H541000	Chronic pulmonary oedema	H541000
H541z00	Pulmonary oedema NOS	H541z00
H54z.00	Pulmonary congestion and hypostasis NOS	H54z.00
H584.00	Acute pulmonary oedema unspecified	H584.00
H584z00	Acute pulmonary oedema NOS	H584z00
L417.00	Obstetric cerebral venous thrombosis	L417.00
L417000	Cerebral venous thrombosis in pregnancy	L417000
L417100	Cerebral venous thrombosis in the puerperium	L417100
L440.11	CVA - cerebrovascular accident in the puerperium	L440.11
L440.12	Stroke in the puerperium	L440.12
Q48y100	Congenital cardiac failure	Q48y100

R2y1000	[D]Cardiorespiratory failure	R2y1000
SP00300	Mechanical complication of coronary bypass	SP00300
SP07600	Coronary artery bypass graft occlusion	SP07600
TJC7.00	Adverse reaction to other antihypertensives	TJC7.00
TJC7z00	Adverse reaction to antihypertensives NOS	TJC7z00
U60C500	[X]Oth antihyperten drug caus advers eff in therap use, NEC	U60C500
U60C511	[X] Adverse reaction to other antihypertensives	U60C511
U60C51A	[X] Adverse reaction to antihypertensives NOS	U60C51A
U60C600	[X]Antihyperlipidaem/antiarterioscl drg caus adv ef ther use	U60C600
ZC2CI00	Dietary advice for lipid disorder	ZC2CI00
ZC2CJ00	Dietary advice for hyperlipidaemia	ZC2CJ00
ZLEP.00	Discharge from stroke serv	ZLEP.00
ZRad.00	New York Heart Assoc classification heart failure symptoms	ZRad.00
ZV12511	[V]Personal history of stroke	ZV12511
ZV12512	[V]Personal history of cerebrovascular accident (CVA)	ZV12512
ZV12D00	[V]Personal history of transient ischaemic attack	ZV12D00
ZV45700	[V]Presence of aortocoronary bypass graft	ZV45700
ZV45K00	[V]Presence of coronary artery bypass graft	ZV45K00
ZV45K11	[V]Presence of coronary artery bypass graft - CABG	ZV45K11
ZV65317	[V]Dietary surveillance in hypercholesterolaemia	ZV65317

CHF

v1	v2	v3
readcode	desc	medcode
14A6.00	H/O: heart failure	14A6.00
14AM.00	H/O: Heart failure in last year	14AM.00
1736.00	Paroxysmal nocturnal dyspnoea	1736.00
1J60.00	Suspected heart failure	1J60.00
1O1..00	Heart failure confirmed	1O1..00
23E1.00	O/E - pulmonary oedema	23E1.00
388D.00	New York Heart Assoc classification heart failure symptoms	388D.00
662T.00	Congestive heart failure monitoring	662T.00
662W.00	Heart failure annual review	662W.00
662f.00	New York Heart Association classification - class I	662f.00
662g.00	New York Heart Association classification - class II	662g.00
662h.00	New York Heart Association classification - class III	662h.00
662i.00	New York Heart Association classification - class IV	662i.00
662p.00	Heart failure 6 month review	662p.00
679X.00	Heart failure education	679X.00
8B29.00	Cardiac failure therapy	8B29.00
8CL3.00	Heart failure care plan discussed with patient	8CL3.00
8H2S.00	Admit heart failure emergency	8H2S.00
8HBE.00	Heart failure follow-up	8HBE.00
8HHz.00	Referral to heart failure exercise programme	8HHz.00
8Hg8.00	Discharge from practice nurse heart failure clinic	8Hg8.00
8Hk0.00	Referred to heart failure education group	8Hk0.00
9N0k.00	Seen in heart failure clinic	9N0k.00
9N2p.00	Seen by community heart failure nurse	9N2p.00
9N4s.00	Did not attend practice nurse heart failure clinic	9N4s.00
9N4w.00	Did not attend heart failure clinic	9N4w.00
9N6T.00	Referred by heart failure nurse specialist	9N6T.00
9On..00	Left ventricular dysfunction monitoring administration	9On..00
9On0.00	Left ventricular dysfunction monitoring first letter	9On0.00
9On1.00	Left ventricular dysfunction monitoring second letter	9On1.00
9On2.00	Left ventricular dysfunction monitoring third letter	9On2.00
9On3.00	Left ventricular dysfunction monitoring verbal invite	9On3.00
9On4.00	Left ventricular dysfunction monitoring telephone invite	9On4.00
9Or..00	Heart failure monitoring administration	9Or..00
9Or0.00	Heart failure review completed	9Or0.00
9Or1.00	Heart failure monitoring telephone invite	9Or1.00
9Or2.00	Heart failure monitoring verbal invite	9Or2.00
9Or3.00	Heart failure monitoring first letter	9Or3.00
9Or4.00	Heart failure monitoring second letter	9Or4.00
9Or5.00	Heart failure monitoring third letter	9Or5.00
9h1..00	Exception reporting: LVD quality indicators	9h1..00
9h11.00	Excepted from LVD quality indicators: Patient unsuitable	9h11.00
9h12.00	Excepted from LVD quality indicators: Informed dissent	9h12.00
9hH..00	Exception reporting: heart failure quality indicators	9hH..00
9hH0.00	Excepted heart failure quality indicators: Patient unsuitabl	9hH0.00
9hH1.00	Excepted heart failure quality indicators: Informed dissent	9hH1.00
G1yz100	Rheumatic left ventricular failure	G1yz100

G210.00	Malignant hypertensive heart disease	G210.00
G210000	Malignant hypertensive heart disease without CCF	G210000
G210100	Malignant hypertensive heart disease with CCF	G210100
G211100	Benign hypertensive heart disease with CCF	G211100
G21z100	Hypertensive heart disease NOS with CCF	G21z100
G230.00	Malignant hypertensive heart and renal disease	G230.00
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure	G232.00
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail	G234.00
G400.00	Acute cor pulmonale	G400.00
G41z.11	Chronic cor pulmonale	G41z.11
G554000	Congestive cardiomyopathy	G554000
G554011	Congestive obstructive cardiomyopathy	G554011
G58..00	Heart failure	G58..00
G58..11	Cardiac failure	G58..11
G580.00	Congestive heart failure	G580.00
G580.11	Congestive cardiac failure	G580.11
G580.12	Right heart failure	G580.12
G580.13	Right ventricular failure	G580.13
G580.14	Biventricular failure	G580.14
G580000	Acute congestive heart failure	G580000
G580100	Chronic congestive heart failure	G580100
G580200	Decompensated cardiac failure	G580200
G580300	Compensated cardiac failure	G580300
G580400	Congestive heart failure due to valvular disease	G580400
G581.00	Left ventricular failure	G581.00
G581.11	Asthma - cardiac	G581.11
G581.12	Pulmonary oedema - acute	G581.12
G581.13	Impaired left ventricular function	G581.13
G581000	Acute left ventricular failure	G581000
G582.00	Acute heart failure	G582.00
G58z.00	Heart failure NOS	G58z.00
G58z.11	Weak heart	G58z.11
G58z.12	Cardiac failure NOS	G58z.12
G5yy900	Left ventricular systolic dysfunction	G5yy900
G5yyA00	Left ventricular diastolic dysfunction	G5yyA00
H461.00	Acute pulmonary oedema due to chemical fumes	H461.00
H54..00	Pulmonary congestion and hypostasis	H54..00
H541.00	Pulmonary congestion	H541.00
H541000	Chronic pulmonary oedema	H541000
H541z00	Pulmonary oedema NOS	H541z00
H54z.00	Pulmonary congestion and hypostasis NOS	H54z.00
H584.00	Acute pulmonary oedema unspecified	H584.00
H584z00	Acute pulmonary oedema NOS	H584z00
Q48y100	Congenital cardiac failure	Q48y100
R2y1000	[D]Cardiorespiratory failure	R2y1000
ZRad.00	New York Heart Assoc classification heart failure symptoms	ZRad.00

MI

v1	v2	v3
readcode	desc	medcode
14A3.00	H/O: myocardial infarct <60	14A3.00
14A4.00	H/O: myocardial infarct >60	14A4.00
14AH.00	H/O: Myocardial infarction in last year	14AH.00
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct	889A.00
G30..00	Acute myocardial infarction	G30..00
G30..11	Attack - heart	G30..11
G30..12	Coronary thrombosis	G30..12
G30..13	Cardiac rupture following myocardial infarction (MI)	G30..13
G30..14	Heart attack	G30..14
G30..15	MI - acute myocardial infarction	G30..15
G30..16	Thrombosis - coronary	G30..16
G30..17	Silent myocardial infarction	G30..17
G300.00	Acute anterolateral infarction	G300.00
G301.00	Other specified anterior myocardial infarction	G301.00
G301000	Acute anteroapical infarction	G301000
G301100	Acute anteroseptal infarction	G301100
G301z00	Anterior myocardial infarction NOS	G301z00
G302.00	Acute inferolateral infarction	G302.00
G303.00	Acute inferoposterior infarction	G303.00
G304.00	Posterior myocardial infarction NOS	G304.00
G305.00	Lateral myocardial infarction NOS	G305.00
G306.00	True posterior myocardial infarction	G306.00
G307.00	Acute subendocardial infarction	G307.00
G307000	Acute non-Q wave infarction	G307000
G307100	Acute non-ST segment elevation myocardial infarction	G307100
G308.00	Inferior myocardial infarction NOS	G308.00
G309.00	Acute Q-wave infarct	G309.00
G30A.00	Mural thrombosis	G30A.00
G30B.00	Acute posterolateral myocardial infarction	G30B.00
G30X.00	Acute transmural myocardial infarction of unspecif site	G30X.00
G30X000	Acute ST segment elevation myocardial infarction	G30X000
G30y.00	Other acute myocardial infarction	G30y.00
G30y000	Acute atrial infarction	G30y000
G30y100	Acute papillary muscle infarction	G30y100
G30y200	Acute septal infarction	G30y200
G30yz00	Other acute myocardial infarction NOS	G30yz00
G30z.00	Acute myocardial infarction NOS	G30z.00
G310.00	Postmyocardial infarction syndrome	G310.00
G310.11	Dressler's syndrome	G310.11
G31y100	Microinfarction of heart	G31y100
G32..00	Old myocardial infarction	G32..00
G32..11	Healed myocardial infarction	G32..11
G32..12	Personal history of myocardial infarction	G32..12
G33z500	Post infarct angina	G33z500
G35..00	Subsequent myocardial infarction	G35..00
G350.00	Subsequent myocardial infarction of anterior wall	G350.00
G351.00	Subsequent myocardial infarction of inferior wall	G351.00

G353.00	Subsequent myocardial infarction of other sites	G353.00
G35X.00	Subsequent myocardial infarction of unspecified site	G35X.00
G36..00	Certain current complication follow acute myocardial infarct	G36..00
G360.00	Haemopericardium/current comp folow acut myocard infarct	G360.00
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct	G361.00
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn	G362.00
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI	G363.00
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct	G364.00
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct	G365.00
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI	G366.00
G38..00	Postoperative myocardial infarction	G38..00
G380.00	Postoperative transmural myocardial infarction anterior wall	G380.00
G381.00	Postoperative transmural myocardial infarction inferior wall	G381.00
G384.00	Postoperative subendocardial myocardial infarction	G384.00
G38z.00	Postoperative myocardial infarction, unspecified	G38z.00
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site	Gyu3400

STROKE

v1	v2	v3
readcode	desc	medcode
13YA.00	Stroke group member	13YA.00
14A7.00	H/O: CVA/stroke	14A7.00
14A7.11	H/O: CVA	14A7.11
14A7.12	H/O: stroke	14A7.12
14AB.00	H/O: TIA	14AB.00
14AK.00	H/O: Stroke in last year	14AK.00
662M.00	Stroke monitoring	662M.00
662e.00	Stroke/CVA annual review	662e.00
662o.00	Haemorrhagic stroke monitoring	662o.00
7P24200	Delivery of rehabilitation for stroke	7P24200
8HBJ.00	Stroke / transient ischaemic attack referral	8HBJ.00
8HHM.00	Ref to multidisciplinary stroke function improvement service	8HHM.00
8HTQ.00	Referral to stroke clinic	8HTQ.00
9Om..00	Stroke/transient ischaemic attack monitoring administration	9Om..00
9Om0.00	Stroke/transient ischaemic attack monitoring first letter	9Om0.00
9Om1.00	Stroke/transient ischaemic attack monitoring second letter	9Om1.00
9Om2.00	Stroke/transient ischaemic attack monitoring third letter	9Om2.00
9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati	9Om3.00
9Om4.00	Stroke/transient ischaemic attack monitoring telephone invte	9Om4.00
9h2..00	Exception reporting: stroke quality indicators	9h2..00
9h21.00	Excepted from stroke quality indicators: Patient unsuitable	9h21.00
9h22.00	Excepted from stroke quality indicators: Informed dissent	9h22.00
E004.11	Multi infarct dementia	E004.11
F050.00	Embolism of central nervous system venous sinus	F050.00
F050000	Embolism cavernous sinus	F050000
F050100	Embolism superior longitudinal sinus	F050100
F050300	Embolism transverse sinus	F050300
F051.00	Thrombosis of central nervous system venous sinuses	F051.00
F051000	Thrombosis cavernous sinus	F051000
F051100	Thrombosis of superior longitudinal sinus	F051100
F051200	Thrombosis lateral sinus	F051200
F051300	Thrombosis transverse sinus	F051300
F051z00	Thrombosis of central nervous system venous sinus NOS	F051z00
Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms	Fyu5500
Fyu5600	[X]Other lacunar syndromes	Fyu5600
G61..00	Intracerebral haemorrhage	G61..00
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage	G61..11
G61..12	Stroke due to intracerebral haemorrhage	G61..12
G610.00	Cortical haemorrhage	G610.00
G611.00	Internal capsule haemorrhage	G611.00
G612.00	Basal nucleus haemorrhage	G612.00
G613.00	Cerebellar haemorrhage	G613.00
G614.00	Pontine haemorrhage	G614.00
G615.00	Bulbar haemorrhage	G615.00
G616.00	External capsule haemorrhage	G616.00
G617.00	Intracerebral haemorrhage, intraventricular	G617.00
G618.00	Intracerebral haemorrhage, multiple localized	G618.00

G61X.00	Intracerebral haemorrhage in hemisphere, unspecified	G61X.00
G61X000	Left sided intracerebral haemorrhage, unspecified	G61X000
G61X100	Right sided intracerebral haemorrhage, unspecified	G61X100
G61z.00	Intracerebral haemorrhage NOS	G61z.00
G62..00	Other and unspecified intracranial haemorrhage	G62..00
G62z.00	Intracranial haemorrhage NOS	G62z.00
G63..00	Precerebral arterial occlusion	G63..00
G63..11	Infarction - precerebral	G63..11
G630.00	Basilar artery occlusion	G630.00
G631.00	Carotid artery occlusion	G631.00
G631.12	Thrombosis, carotid artery	G631.12
G632.00	Vertebral artery occlusion	G632.00
G633.00	Multiple and bilateral precerebral arterial occlusion	G633.00
G63y.00	Other precerebral artery occlusion	G63y.00
G63y000	Cerebral infarct due to thrombosis of precerebral arteries	G63y000
G63y100	Cerebral infarction due to embolism of precerebral arteries	G63y100
G63z.00	Precerebral artery occlusion NOS	G63z.00
G64..00	Cerebral arterial occlusion	G64..00
G64..11	CVA - cerebral artery occlusion	G64..11
G64..12	Infarction - cerebral	G64..12
G64..13	Stroke due to cerebral arterial occlusion	G64..13
G640.00	Cerebral thrombosis	G640.00
G640000	Cerebral infarction due to thrombosis of cerebral arteries	G640000
G641.00	Cerebral embolism	G641.00
G641.11	Cerebral embolus	G641.11
G641000	Cerebral infarction due to embolism of cerebral arteries	G641000
G64z.00	Cerebral infarction NOS	G64z.00
G64z.11	Brainstem infarction NOS	G64z.11
G64z.12	Cerebellar infarction	G64z.12
G64z000	Brainstem infarction	G64z000
G64z100	Wallenberg syndrome	G64z100
G64z111	Lateral medullary syndrome	G64z111
G64z200	Left sided cerebral infarction	G64z200
G64z300	Right sided cerebral infarction	G64z300
G64z400	Infarction of basal ganglia	G64z400
G65..00	Transient cerebral ischaemia	G65..00
G65..12	Transient ischaemic attack	G65..12
G650.00	Basilar artery syndrome	G650.00
G651.00	Vertebral artery syndrome	G651.00
G651000	Vertebro-basilar artery syndrome	G651000
G653.00	Carotid artery syndrome hemispheric	G653.00
G654.00	Multiple and bilateral precerebral artery syndromes	G654.00
G65y.00	Other transient cerebral ischaemia	G65y.00
G65z.00	Transient cerebral ischaemia NOS	G65z.00
G65z000	Impending cerebral ischaemia	G65z000
G65z100	Intermittent cerebral ischaemia	G65z100
G65zz00	Transient cerebral ischaemia NOS	G65zz00
G66..00	Stroke and cerebrovascular accident unspecified	G66..00
G66..11	CVA unspecified	G66..11
G66..12	Stroke unspecified	G66..12

G66..13	CVA - Cerebrovascular accident unspecified	G66..13
G660.00	Middle cerebral artery syndrome	G660.00
G661.00	Anterior cerebral artery syndrome	G661.00
G662.00	Posterior cerebral artery syndrome	G662.00
G663.00	Brain stem stroke syndrome	G663.00
G664.00	Cerebellar stroke syndrome	G664.00
G665.00	Pure motor lacunar syndrome	G665.00
G666.00	Pure sensory lacunar syndrome	G666.00
G667.00	Left sided CVA	G667.00
G668.00	Right sided CVA	G668.00
G669.00	Cerebral palsy, not congenital or infantile, acute	G669.00
G671000	Acute cerebrovascular insufficiency NOS	G671000
G676.00	Nonpyogenic venous sinus thrombosis	G676.00
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic	G676000
G677000	Occlusion and stenosis of middle cerebral artery	G677000
G677100	Occlusion and stenosis of anterior cerebral artery	G677100
G677200	Occlusion and stenosis of posterior cerebral artery	G677200
G677300	Occlusion and stenosis of cerebellar arteries	G677300
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries	G677400
G67A.00	Cerebral vein thrombosis	G67A.00
G681.00	Sequelae of intracerebral haemorrhage	G681.00
G682.00	Sequelae of other nontraumatic intracranial haemorrhage	G682.00
G683.00	Sequelae of cerebral infarction	G683.00
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction	G68X.00
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries	G6W..00
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	G6X..00
Gyu6200	[X]Other intracerebral haemorrhage	Gyu6200
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	Gyu6300
Gyu6400	[X]Other cerebral infarction	Gyu6400
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries	Gyu6500
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries	Gyu6600
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified	Gyu6F00
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries	Gyu6G00
L417.00	Obstetric cerebral venous thrombosis	L417.00
L417000	Cerebral venous thrombosis in pregnancy	L417000
L417100	Cerebral venous thrombosis in the puerperium	L417100
L440.11	CVA - cerebrovascular accident in the puerperium	L440.11
L440.12	Stroke in the puerperium	L440.12
ZLEP.00	Discharge from stroke serv	ZLEP.00
ZV12511	[V]Personal history of stroke	ZV12511
ZV12512	[V]Personal history of cerebrovascular accident (CVA)	ZV12512
ZV12D00	[V]Personal history of transient ischaemic attack	ZV12D00

Some product code lists are grouped together. These are listed below.

Grouped Code List Name	Code Lists Included
all_labd	salmeterol, salmeterol+fluticasone, formoterol, formoterol+budesonide, formoterol+aclidinium, formoterol+beclometasone, formoterol+fluticasone, tiotropium, glycopyrronium, glycopyrronium+indacaterol, aclidinium, indacaterol, olodaterol, umeclidinium, umeclidinium+vilanterol, vilanterol+fluticasone, tiotropium+olodaterol
lama	tiotropium, glycopyrronium, aclidinium, umeclidinium
laba	salmeterol, formoterol, indacaterol, olodaterol
laba+lama	formoterol+aclidinium, glycopyrronium+indacaterol, umeclidinium+vilanterol, tiotriopium+olodaterol
ics+laba	salmeterol+fluticasone, formoterol+budesonide, formoterol+beclometasone, formoterol+fluticasone, vilanterol+fluticasone
ics+lama	[none]
all_ics	saba+ics, ics, salmeterol+fluticasone, formoterol+budesonide, formoterol+beclometasone, formoterol+fluticasone, vilanterol+fluticasone
all_other_labd	salmeterol, salmeterol+fluticasone, formoterol, formoterol+budesonide, formoterol+aclidinium, formoterol+beclometasone, formoterol+fluticasone, tiotropium, glycopyrronium, glycopyrronium+indacaterol, aclidinium, indacaterol, olodaterol, vilanterol+fluticasone, tiotropium+olodaterol
all_other_labd_lama	tiotropium, glycopyrronium, aclidinium
all_other_labd_labalama	formoterol+aclidinium, glycopyrronium+indacterol, tiotropium+olodaterol
all_other_labd_laba	salmeterol, salmaterol+fluticasone, formoterol, formoterol+budesonide, formoterol+beclometasone, formoterol+fluticasone, indacaterol, olodaterol, vilanterol+fluticasone
all_sabd	saba, sama, saba+sama, saba+cromoglycate

Annex 4. Algorithms for identification of moderate and severe exacerbations of COPD

COPD EXACERBATION ALGORITHM

This algorithm aims to determine recorded events and episodes of AECOPD in the CPRD; it is based on a GSK supported validation study (WEUSKOP5893) conducted by the team led by Dr. PPD from Imperial College [2]. It was adapted by PPD and PPD Respiratory Epidemiology and RWD Analytics, respectively, in December 2015.

Primary care derived AECOPD, i.e. GP recording of COPD exacerbation, is defined as the presence of an event, i.e. record, for one of the four following events:

(1) Prescriptions for antibiotics (ATB) AND oral corticosteroids (OCS) for a length of 5 to 14 days each (both prescriptions must have the same start date but each can last for a different number of days);

(2) Presence of respiratory symptoms (codes suggesting an increase in two or more of: breathlessness, cough, or sputum volume and/or purulence recorded on the same date) and a prescription for ATB or OCS (or both) on the same day;

(3) Lower Respiratory Tract Infection (LRTI) medical code;

(4) AECOPD specific medical code.

Points to consider:

1. Exacerbation events associated with LRTI or AECOPD medical codes recorded on the day of an annual review visit for COPD or asthma are not flagged ***(see Read/medcodes list Appendix 2, Table 1.)*** as it's thought the GP might register the AECOPD event as part of the annual review (not due to the underlying illness)
2. The exacerbation events involving ATB & OCS are not flagged if there was a record for OCS rescue packs or deferred/advanced ATB on the same day ***(see Read/medcodes list Appendix 2, Table 1).***
3. Number of days issued is missing for the majority of OCS & ATB prescriptions. The following imputation rules were applied based on the results from a test COPD cohort of 10,000 patients using CPRD data over all years:

   (A) Only 7% of the ATB/OCS scripts had a valid record for script duration (var: numdays). Of those values, only those between 1 and 100 are considered valid.
   (B) After exploring other dosing variables, it was realized that QTY ('Quantity prescribed') / NDD ('Numeric Daily Dose') can sometimes produce script duration values. As before, only values between 1 and 100 are considered valid. This leaves around 15% of scripts with missing values.
   (C) Using the patient's own data in the year before the script with missing duration, valid values from these ever-coarsening strata are applied. The strata are:-
   - Product
   - Substance / Strength / Formulation
   - Substance / Strength
   - Substance / Formulation
   - Substance
     a. If there are multiple valid values within the strata, the one closest to the date of the script with missing duration is used. If there were no scripts with valid duration values, the routine is repeated using the patient's data in the 6m after the script with missing duration In all, these rules imputed a further 6% of the scripts.

   (D) The final imputation uses data from the whole cohort. The most common value from the strata above is applied (in the ever-coarsening order given). Generally, the 'Product' strata imputes the remaining therapies with a handful imputed using the 'Substance' strata.

When all four code sets are used together to identify GP-recorded AECOPD events, a ***PPV of about 86% and sensitivity of around 63%*** can be expected.[2] COPD epidemiology studies and clinical trials typically report moderate-severe AECOPD as a composite trait based on health-care utilization for moderate events (primary

care or GP-managed) and severe events (hospital admissions). Emergency contacts (ie A&E or ED) not requiring overnight stay have been classified ambiguously as either moderate or severe events by various studies, The validation study showed that it was not possible to discriminate between moderate and severe exacerbation events using exclusively CPRD; the PPV was about 50%. Moreover, sensitivity of capturing severe events was extremely poor (maximum=10%). Hence, the GP data can be used to ascertain mainly moderate COPD exacerbations Due to a relatively low expected incidence rate of hospitalized AECOPD (ECLIPSE study incidence rate: 0.26 AECOPD requiring hospital admission per person-year), we would expect most of the events recorded by GPs to be moderate.

Events of AECOPD requiring hospital admission, also called severe exacerbations, *must* be identified in the Hospital Episodes Statistics (HES), because the validation study showed that GP records lack sufficient sensitivity AND PPV to ascertain hospitalized exacerbation events reliably (3). N.B. This finding also applies to specific Read code labelled as hospital admission for COPD.

The ascertainment of hospitalized AECOPD from HES is achieved using ICD-10 codes. If the hospitalisation spell contains a diagnosis code listed in Appendix 2, Table 2. and the position within the spell is satisfied, then it is counted as an AECOPD requiring hospital admission. N.B. Full HES database contains Finished Consultant Episode (FCE) flag variable (table: Admitted Patient Care), which is not available in the linked CPRD-HES database. Hence, our algorithm refers to spells rather than FCEs.

AECOPD diagnosis in the HES should be ascertained based on ICD-10 codes as follows ***see code list Appendix 2, Table 2.***:

- Use codes J44.0, J44.1 ("definite" codes) in any position within a spell or J44.9 ("possible" code) in the first position within a spell (as proposed by Dr. PPD and colleagues in their validation study). This definition can be used even when there is no link to primary care data and no further confirmation of COPD diagnosis;
- Additionally, use codes J22 in any position within a spell, J44, J44.8, J41, J42, J43 ("possible" codes) in the first position of any HES spell in a cohort of patients diagnosed with COPD, e.g. using CPRD-GOLD;
- Further, if high sensitivity is required, consider adding codes: for asthma (J45, J45.0, J45.1, J45.8, J45.9, and J.46), J47.0, J47.1 and J47.9 for bronchiectasis or for respiratory failure (J96.0, J96.2) in the first position of any HES spell if COPD diagnosis is confirmed in primary care data

In terms of the J22 code (Lower respiratory tract infections), a misclassification with pneumonia is a concern; however, J22 code recorded for patients diagnosed with COPD is essentially the same as the J44.0 code (COPD with acute LRTI). As remuneration for an inpatient episode of pneumonia is higher, it is assumed both codes, J22 and J44 will be predominantly used for AECOPD.

Further, it is possible to limit the hospital admission events only to those flagged as emergency admissions using the HES variable "admimeth" (see Appendix 2, Table 3). But, using this flag, only a limited number of events are eliminated (provided the ICD-10 COPD codes are used as described) and hence it is advised not to use the 'admimeth' variable.

Once events have been identified, they are grouped into episodes. **An AECOPD episode** is composed of one or more of the five exacerbation events described above, i.e. hospitalization exacerbation or primary care derived exacerbation. The start of an episode is the date of the first exacerbation event. The episode length is initially 14 days. Subsequently, from the start date +14 days, a 14-day rolling window is applied to identify a period of at least 2 weeks free of exacerbation events. This is to ensure that a relapse was not categorised as a separate episode. Algorithmically, the routine can be described thus:-

1. Following an exacerbation event, project forwards 14 days and use as a potential end date (exacerbations in this period are ignored, assumed related to the initial exacerbation).
2. If there are no exacerbation events in the 14 days after the potential end date, halt the algorithm; the episode has been fully identified.
3. If there is an exacerbation in this period, move the potential end date to the exacerbation + 14 days.

4a. If there are no further exacerbations between exacerbation and potential end date (14 days later), the episode is complete.

4b. If there is another exacerbation in this 14 day period, repeat from 4a with the new, later exacerbation event.

Each episode has two variables describing exacerbation type; the first describes the exacerbation type for the first event in the episode, the second records the severest exacerbation type in the episode.

NOTE:

- It is acceptable for the length of prescription for OCS or ATB to exceed the exacerbation episode END DATE.
- When keeping exacerbation episodes within a specific time period, episodes that have already started are included. For example, 'where start < epi_start < end or start < epi_end < end'.

The initial minimal length of the episode, the 14 days window, is based on evidence on median recovery time published by PPD and colleagues [4] and PPD and colleagues [5]. The additional 14 day exacerbation event free window is a time window between two exacerbation episodes that are distinctively separate from each other and are indicative of recurrent events as opposed to relapse of the initial episode. As many as 23% of exacerbations do not recover by 35 days from the start,[6]. Therefore, it is customary in clinical trials and observational studies to apply a window consisting of several days where symptoms are expected to return to pre-exacerbation level. The objective of this exacerbation free window is to discriminate between a relapse of the existing episode and a recurrence.

Relapse can be flagged in a specific study, if required, where the episode length is longer than 14 days.

Appendix 2, Table 1. Code list for Annual review of asthma or COPD, rescue packs of OCS and deferred ATB

medcode	read_code v7	Label
9520	66YB.00	Chronic obstructive pulmonary disease monitoring
10043	66YJ.00	Asthma annual review
11287	66YM.00	Chronic obstructive pulmonary disease annual review
25997	8BP0.00	Deferred antibiotic therapy
28743	66Yf.00	Number of COPD exacerbations in past year
100459	8B32.00	Advance supply of steroid medication
101042	8BMW.00	Issue of chronic obstructive pulmonary disease rescue pack

Appendix 2, Table 2. ICD-10 codes to ascertain AECOPD in the HES

ICD-10	Description	Disease/ Category	Use to ascertain AECOPD usage
J22	Lower respiratory tract infection	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J41	Simple and mucopurulent chronic bronchitis	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J41.0	Simple chronic bronchitis	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J41.1	Mucopurulent chronic bronchitis	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J41.8	Mixed simple and mucopurulent chronic bronchitis	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J42	Unspecified chronic bronchitis	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J43	Emphysema	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J43.0	MacLeod's syndrome	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J43.1	Panlobular emphysema	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J43.2	Centrilobular emphysema	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J43.8	Other emphysema	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J43.9	Emphysema, unspecified	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J44	Other chronic obstructive pulmonary disease	Possible	Use if COPD diagnosed in primary care data in First position of any finished consultant episode
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection	Definite	Any position of any finished consultant episode as per validation study
J44.1	Chronic obstructive pulmonary disease with acute exacerbation, unspecified	Definite	Any position of any finished consultant episode as per validation study
J44.8	Other specified chronic obstructive pulmonary disease	Possible	Dtto
J44.9	Chronic obstructive pulmonary disease, unspecified	Possible	First position of any finished consultant episode as per validation study
J45	Asthma	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode
J45.0	Predominantly allergic asthma	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode
J45.1	Nonallergic asthma	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode
J45.8	Mixed asthma	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode
J45.9	Asthma, unspecified	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode
J46	Status asthmaticus	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode
J47.0	Bronchiectasis with acute lower respiratory infection	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode
J47.1	Bronchiectasis with (acute) exacerbation	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode
J47.9	Bronchiectasis, uncomplicated	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode
J96.0	Acute respiratory failure	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode
J96.2	Acute and chronic respiratory failure	Potential (not a part of the current algorithm)	If increased sensitivity required, use if COPD diagnosed in primary care data in First position of any finished consultant episode

Appendix 2, Table 3. Emergency Admissions flag in HES

<admimeth> (12, 22, 23, 24, and 28):
21 = Emergency: via Accident and Emergency (A&E) services, including the casualty department of the provider

22 = Emergency: via general practitioner (GP)

23 = Emergency: via Bed Bureau, including the Central Bureau

24 = Emergency: via consultant outpatient clinic

28 = Emergency: other means, including patients who arrive via the A&E department of another healthcare provider

ANNEX 3: Treatment pattern definitions

For patients **not taking a concomitant COPD (inhalation) maintenance therapy** at the time of the index prescription, the following patterns were defined:

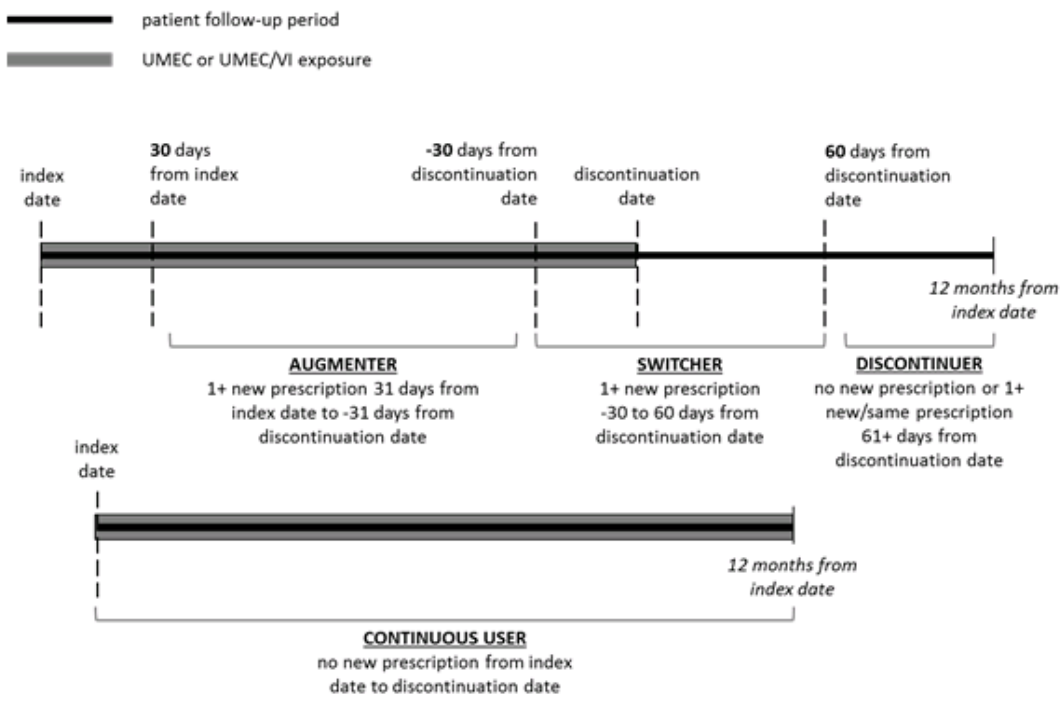
New users of UMEC:

- Continuous UMEC for the full 12 months
- Augment UMEC by adding LABA or ICS/LABA
- Immediate switch to another LAMA, LABA, ICS/LABA
- Discontinue UMEC (further broken down into (a) true discontinuer, (b) restart the index therapy after a break (drug hiatus) and (c) New maintenance therapy after a break (latent switch))

New users of UMEC/VI:

- Continuous UMEC/VI for the full 12 months
- Augment UMEC/VI by adding ICS or ICS/LABA
- Immediate switch to another LAMA, LABA, ICS/LABA or LAMA/LABA
- Discontinue UMEC (further broken down into (a) true discontinuer, (b) restart the index therapy after a break (drug hiatus) and (c) New maintenance therapy after a break (latent switch))

Full definitions of these treatment patterns were as follows:



1. *Continuous use:* Patient DID NOT start taking another inhaled COPD maintenance therapy and continued to use index treatment (without a break of >91 days) through the 12 month after the index date.
2. *Augmentation:* Patient started taking another inhaled COPD maintenance therapy (1 or more prescriptions) and the new treatment started ≥31 days after the index date and ≥31 days before the discontinuation date for the index treatment or the end of 12 months following the index date. The augmentation date was defined as the date of first prescription for the new COPD maintenance therapy.

   Note: for patients who qualified for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication was considered a switch and not an augmentation. This is in line with the decision to allow patients to enter the study separately for UMEC and UMEC/VI (i.e. they were considered as separate products).

3. *Immediate switching:* Patient started taking another inhaled COPD maintenance therapy (1 or more prescriptions) within 12 months of the index date, and the new treatment started during an interval that was between ≤30 days before the discontinuation date for the index treatment and ≤60 days after the discontinuation date for the index treatment. The switching date was defined as the date of first prescription for the new COPD maintenance therapy.

   Note: for patients who qualified for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication was always considered a switch.

4. *Discontinuation*: Patient met the definition of discontinuation within 12 months of the index date and did meet the definitions for continuous use, immediate switching and augmentation above. Discontinuation was defined as a gap of at least 91 days between consecutive prescriptions for an index medication, or between the last index medication prescription and the censoring date. The discontinuation date was set at 30 days after the prescription prior to the break

Discontinuers were followed until 12 months after the index date and classified according to whether they were:

- True discontinuer: did not restart the index medication and did not start a new inhaled COPD maintenance treatment (i.e. true discontinuers)

- Drug hiatus: restarted the index medication
- New maintenance therapy: started a new inhaled COPD maintenance treatment >60 days after discontinuation (i.e. latent switchers).

Note: for patients who qualified for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication was considered a latent switch based on the rationale described earlier.

For patients who were taking a concomitant COPD (inhalation) maintenance therapy at the time of the index prescription the following treatment patterns will be considered:

- In UMEC users taking a concomitant LABA/ICS, other LABA or other LAMA separately (numbers dependent):
- Continued both medications for the full 12 months, patients were allowed to change the exact type of LABA/ICS (or other LABA, other LAMA) and still be considered as continuing 'both medications'
- Discontinued both medications at the same time
- Discontinued UMEC and continued the LABA/ICS (or other LABA, other LAMA)
- Discontinued the LABA/ICS (or other LABA, other LAMA) and continued UMEC

In UMEC/VI users taking concomitant LABA/ICS, other LABA or other LAMA separately (numbers dependent):

- Continue both medications for the full 12 months, patients are allowed to change the exact type of LABA/ICS (or other LABA, other LAMA) and still be considered as continuing 'both medications'
- Discontinue both medications at the same time
- Discontinue UMEC/VI and continue the LABA/ICS (or other LABA, other LAMA)
- Discontinue the LABA/ICS (or other LABA, other LAMA) and continue UMEC

Full definitions of these treatment patterns were as follows:

1. *Continuous use of both drugs:* Patient continued to use both medications for 12 months from the date of index treatment until censoring.

2. *Discontinuation of index drug (*continued to use the concomitant medication*):* Patient discontinued the index drug within 12 months of the index date, but continued to use the concomitant therapy. The discontinuation date was therefore the date the index drug stopped.

3. *Discontinuation of concomitant drug (*continued to use the index medication*):* Patient discontinued the concomitant therapy within 12 months of the index date, but continued to use the index drug. The discontinuation date of the concomitant drug was therefore the date the concomitant drug stopped.

4. *Discontinuation of both drugs:* Patient met the definition of discontinuation for both drugs (on the same day) and within 12 months from the index. Discontinuation was defined as gap of at least 91 days between consecutive prescriptions for the same medication, or between the last prescription for that medication and the censoring date.

Only the first change within the 12 month period following initiation was described.

ANNEX 4. ADDITIONAL INFORMATION

Annex 4.1 COPD Diagnosis Codes

medcode	readterm
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
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
93568	Very severe chronic obstructive pulmonary disease
108586	Chronic obstruct pulmonary disease management plan declined
109774	Telehealth chronic obstructive pulmonary disease monitoring

Annex 4.2 Asthma Diagnosis Codes

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

medcode	readterm
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
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

medcode	readterm
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