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.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

TITLE PAGE

Division: Worldwide Development
Document Number: 2017N341352_00
Information Type: Worldwide Epidemiology Final Study Report
Control: Non-Interventional

Title:	PRJ2282/201491: CHESS: CPRD-COPD Hawthorne Effect Study in Salford: A UK cohort study to characterise patients enrolled in the Salford Lung Study and to evaluate a potential Hawthorne effect

Development phase:	IV
Compound number:	Fluticasone furorate/vilanterol (GSK2285997)
Effective date:	28-SEP-2017
Description:	Final report of a Category 4 Post-Authorisation Study commitment made in the European Union for fluticasone furorate/vilanterol (FF/VI) to evaluate the representativeness of the usual care (UC) arm of the Salford Lung Study (SLS) for Chronic Obstructive Pulmonary Disease (COPD) compared with the COPD population in the rest of England, to assess if there was presence of a Hawthorne effect and to provide additional data on rates of hospitalised pneumonia in the COPD population.

Subject: COPD in the general population of England and comparison with the Salford Lung Study.

Author(s): University of Manchester: PPD
PPD
GlaxoSmithKline: PPD
Medical writers: PPD and PPD Complete Regulatory, a division of McCann Complete Medical.

Indication Studied: COPD

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

PASS INFORMATION

Title	CHESS - CPRD-COPD Hawthorne Effect Study in Salford: A UK cohort study to characterise patients enrolled in the Salford Lung Study and to evaluate a potential Hawthorne effect.
Version identifier of the final study report	1.0
Date of last version of the final study report.	25 September 2017
EU PAS register number	EUPAS10376
Active substance	Fluticasone furoate/ vilanterol (FF/VI) ATC: R03AK10. Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics
Medicinal product	**Relvar Ellipta®** **Revinty Ellipta®**
Product reference	EU/1/13/886/001-006 EU/1/14/929/001-006
Procedure number	EMEA/H/C/002673 EMEA/H/C/002745
Marketing authorisation holder(s)	Glaxo Group Limited 980 Great West Road Brentford Middlesex TW8 9GS UK
Joint PASS	No
Research question and objectives	The SLS evaluated the effectiveness and safety of initiating treatment with a once daily inhaled combination of fluticasone furoate and vilanterol (FF/VI) compared with continuing usual care (UC) among patients with Chronic obstructive pulmonary disease (COPD) in Salford and surrounding areas of England. There are two main concerns with the trial methodology: 1) The trial population may not be representative of the wider English COPD population eligible for FF/VI, and 2) there may be differences in or changes to local practice or patient behaviour caused by conducting a study (a 'Hawthorne effect'). The aims of this study were therefore to: • Evaluate the representativeness of the SLS-COPD UC arm in terms of the wider patient population targeted for FF/VI,

	using comparisons with COPD patients in CPRD who fulfil the SLS-COPD protocol inclusion/exclusion criteria. • Compare the rate of COPD exacerbations in the SLS-COPD UC arm with COPD patients in CPRD over the 12-month study period, to detect a potential Hawthorne effect. • Compare the rate of hospitalised pneumonia in the SLS-COPD UC arm with COPD patients in CPRD over the 12-month study period.
Country(-ies) of study	England
Author	Dr PPD PPD Email: PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Glaxo Group Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK
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1. LIST OF ABBREVIATIONS

AECOPD	Acute exacerbations of chronic obstructive pulmonary disease
AIC	Akaike Information Criterion
BMI	Body mass index
CHESS	CPRD-COPD Hawthorne Effect Study in Salford
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
CPRD-GOLD	Clinical Practice Research Datalink
CPRD-GM-IC cohort	CPRD patients recorded as residing in Greater Manchester who would have met SLS inclusion criteria during the timeframe of the SLS-COPD trial
CPRD-xGM-IC cohort	CPRD patients recorded as not residing in Greater Manchester who would have met SLS inclusion criteria during the timeframe of the SLS-COPD trial
eCRF	Electronic case report form
EHR	Electronic Health Record
FEV_1	Forced expiratory volume in 1 second
FF	Fluticasone furoate
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPRD	General Practice Research Database
GP	General practice/practitioner
GSK	GlaxoSmithKline
HCU	Health care utilisation
HES	Hospital Episode Statistics
HR_{adj}	Adjusted hazard ratio
ICD	International Classification of Diseases
ICS	Inhaled corticosteroid
IMD	Index of Multiple Deprivation
ISAC	CPRD Independent Scientific Advisory Committee
LA	Local authority(ies)
LABA	Long-acting bronchodilator(s)

LAMA	Long-acting muscarinic antagonist(s)
LSOA	Lower layer super output area
MHRA	Medicines and Healthcare Products Regulatory Agency
MPR	Medication possession ratio
MRC	Medical Research Council
NHS	National Health Service
NWeH	North West eHealth
OCS	Oral corticosteroid(s)
ONS	Office for National Statistics
PDC	Percent days covered
PO1	Primary objective 1
PO2	Primary objective 2
PO3	Primary objective 3
QC	Quality control
RR	Relative rate
RR_{adj}	Adjusted relative rate
SES	Socio-economic status
SIS	Salford Integrated System
SLS	Salford Lung Study
SLS-UC	The UC arm of SLS-COPD
SO1	Secondary objective 1
SO2	Secondary objective 2
SO3	Secondary objective 3
UC	Usual care
UK	United Kingdom
UoM	University of Manchester
VI	Vilanterol

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None

2. RESPONSIBLE PARTIES

PPD (Principal Investigator); PPD

GlaxoSmithKline: PPD

Clinical Practice Research Datalink: PPD

Medical writers: PPD and PPD from Complete Regulatory, a division of McCann Complete Medical.

STUDY ADVISORY COMMITTEE

The role of the Scientific Committee was to review and provide feedback on the study design and major study documents.

Members of the Scientific Committee included:

Name	Role
External members	
Professor PPD	Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester
Professor PPD	Clinical Professor in Public Health Informatics, Health eResearch Centre, Farr Institute for Health Informatics Research, University of Manchester
Professor PPD	Professor of Health eResearch, Health eResearch Centre, Farr Institute for Health Informatics Research, University of Manchester
Dr PPD	Chief Clinical Officer, North West eHealth, Salford Royal Hospital
Professor PPD	Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine
Professor PPD	Professor, Consultant in Respiratory Medicine, Department of Public Health, Section of Social Medicine, University of Copenhagen
PPD	Research Statistician, Clinical Practice Research Datalink
Dr PPD	Head of Interventional Research, Clinical Practice Research Datalink
GSK members	
Dr PPD	Head, Real World Data and Analytics, Real World Evidence and Epidemiology
Dr PPD	Global Medical Advisory Lead, Respiratory Franchise
PPD	Director, Clinical Statistics

Key milestones for the Scientific Committee were:

Milestone	Date
Project overview meeting	13-JUN-2014
Protocol and analysis discussions	03-OCT-2016
Preliminary results discussions	20-JUN-2016
Final results reviewed	25-AUG-2017

3. ABSTRACT

Title

PRJ2282/201491: CHESS: CPRD-COPD Hawthorne Effect Study in Salford: A UK cohort study to characterise patients enrolled in the Salford Lung Study and to evaluate a potential Hawthorne effect

Keywords

Salford Lung Study, CPRD, COPD, Hawthorne effect.

Rationale and background

The Salford Lung Study (SLS) was a unique randomised trial evaluating the effectiveness and safety of initiating once daily inhaled combination of fluticasone furoate and vilanterol (FF/VI), compared with continuing on usual care (UC) among patients with chronic obstructive pulmonary disease (COPD). The trial took place in Salford and surrounding areas in England. While the pragmatic nature of the trial was designed to test effectiveness in routine care, two potential concerns had been raised:

1. The trial population may not be representative of the wider population in which FF/VI may be used, and;
2. There may be differences in or changes to local practice or patient behaviour induced by the act of participation in a study (a 'Hawthorne effect'), which have the potential to bias assessments of effectiveness of both FF/VI and UC.

Research questions and objectives

The objective of the study was to evaluate the representativeness of Salford, and the potential Hawthorne effect, to place the SLS-COPD in wider context by assessing differences in demographics, COPD exacerbation rate and pneumonia rate between the UC arm of the SLS and the wider England COPD population using the Clinical Practice Research Datalink (CPRD-GOLD) [hereafter referred to as CPRD].

Study design

This was a retrospective observational COPD cohort study, comparing selected cohorts of COPD patients in the broader, non-trial population of England with the UC arm of the SLS-COPD over a 12-month period.

Setting

This study was conducted using data from England, United Kingdom (UK). The SLS-COPD was conducted in Salford and surrounding areas in Greater Manchester, England. The CPRD is a UK-wide database of primary care data, provided by the UK's Medicines and Healthcare products Regulatory Agency. Additional datasets used included Hospital

Episode Statistics (HES; England only), and the UK-wide Office of National Statistics (ONS) and Index of Multiple Deprivation 2010 (IMD 2010).

Subjects and study size, including dropouts

The UC arm of the COPD SLS comprised 1,403 subjects. Approximately 16,700 patients from the CPRD database matched the inclusion criteria for this study.

Variables and data sources

The datasets included the following patient characteristics: sex, age, socio-economic status (SES), forced expiratory volume in 1 second expressed as the percent predicted (FEV_1%), ratio of FEV_1 to forced vital capacity (FEV_1/FVC), Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, smoking status, body mass index (BMI), historical comorbidities, Charlson comorbidity score, Medical Research Council (MRC) dyspnoea score and current COPD medication group, and local authority (LA).

There were two data sources for the UC arm of the SLS; the SLS raw primary care electronic medical record ('SLS-EMR') and SLS-COPD study database ('SLS-database').

The data sources for the comparator cohorts were derived from the CPRD, linked to secondary care data via HES, death records from the ONS and postcode-derived IMD 2010 data, creating a cohort of COPD patients from England only.

We compared COPD participants in the SLS-UC arm with patient from the CPRD and examined whether the SLS-UC population was unusual in the context of regional variation across England in terms of: 1) baseline demographic, clinical and treatment variables, 2) outcomes, including acute COPD exacerbation episodes, in models adjusted for baseline variables, and 3) outcomes in patients before and during the trial.

Results

Characteristics of study participants (PO1): The SLS-UC and CPRD cohorts were broadly comparable; trial participants were younger (median age 66.7 vs 71.4 years, respectively), more deprived (percentage in most deprived quintile: 51.5% vs 21.4%), more likely to smoke (47.5% vs. 19.7%), had higher GOLD stage but were less comorbid (lower Charlson scores) and there were small but significant differences in COPD usual care medication.

Number of COPD exacerbation episodes during the SLS study period (PO2): Adjusted Poisson models indicated that rates of COPD exacerbation were significantly higher in the SLS-UC arm compared with the average in England (adjusted relative rate [RR_{adj}]=1.12, 95% CI 1.05-1.19, p=0.0010), and correspondingly, in the context of local authority variation, SLS-UC rates were unusually high, placing at the 98.4th percentile.

Number of hospitalised pneumonia episodes during the SLS study period (PO3): Rates of hospitalised pneumonia (as defined by International Classification of Diseases [ICD]-10 codes) in the SLS-UC arm did not differ significantly from the rest of England

after adjustment for population characteristics (RR_{adj}=0.95, 95% CI 0.72-1.31, p=0.86). In addition, there were no differences between cohorts in the time to first hospitalisation for pneumonia (adjusted hazard ratio [HR_{adj}]=0.87, 95% CI 0.69-1.12, p=0.30).

Discussion

This observational cohort study provides a framework in which to place trials such as the SLS-COPD into wider context with respect to generalizability and to obtain evidence about a potential Hawthorne effect. In terms of most demographic and clinical characteristics, the SLS-UC cohort was broadly similar to the COPD patient population of England. There was some evidence supporting a Hawthorne effect on the primary outcome of COPD exacerbations; exacerbations were unusually high in the SLS-UC population, however additional secondary analyses revealed they were also unusually high for this population before the trial commenced. Further evidence of a Hawthorne effect was seen in the secondary outcomes, through behavioural changes such as coding practices of general practitioners (GPs) and the number of COPD medications prescribed. There was no evidence of differences in rates of hospitalised pneumonia (as defined by ICD-10 codes) in the SLS-UC cohort compared with the rest of England.

This study provided a provided a novel set of methods for assessing the generalisability of a trial set in routine care and to our knowledge, is the first of its kind. Given trials set in routine care are becoming more feasible, studies such as this will become increasing important.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	5-APR-2009	5-APR-2009	Index dates for patients were determined by randomisation dates for SLS (5th April 2012 to 24th October 2014). Data were required for 3 years prior to this date to meet inclusion criteria.
End of data collection	25-OCT-2015	25-OCT-2015	Date of Last Subject Last Visit within the SLS
Registration in the EU PAS register	10-NOV-2015	10-NOV-2015	
Final report of study results	29-AUG-2017	25-SEPT-2017	The report and study results were delivered by the University of Manchester to GSK on 29-AUG-2017 but the report required review and finalisation within GSK, hence the delay between planned and actual dates.

6. RATIONALE AND BACKGROUND

6.1. Background

Chronic obstructive pulmonary disease (COPD) is a chronic obstructive disease of the airways associated with a significant social and healthcare burden (Lopez, 2006; Vestbo, 2013). Most patients with COPD are managed in primary care, as reflected in recent United Kingdom (UK) guidelines, which are specifically targeted at primary care physicians (Bellamy, 2006). The major goals of treatment are to relieve symptoms, improve activity/exercise tolerance, prevent and treat exacerbations, reduce mortality risk and improve health status. However, despite such guidelines, COPD remains under-diagnosed and under-treated; variations in treatments, standards of care and adherence to guidelines have been reported across different geographical regions (Aisanov, 2012; Corrado, 2012; Sobradillo-Peña, 2000).

Large computerised patient databases provide a useful source of real life observational data, and the General Practice Research Database (GPRD) has been successfully used to generate descriptive epidemiology data in COPD (Hansell, 1999; Hansell, 2004; Soriano, 2000; van Staa, 2012) from a large group of UK primary care practices. Historically, the limitations of the GPRD were a time gap between data capture and availability for the researcher and limited links to other healthcare databases, although these are currently being addressed with the development of the Clinical Practice Research Datalink (CPRD) and in recent Phase 4 pragmatic clinical trials (van Staa, 2012). The use of electronic health record (EHR) data in health research is a key objective in the UK Department of Health's national research strategy (Department of Health, 2006).

The SLS was designed to evaluate the effectiveness and safety of initiating treatment with the once daily inhaled combination of fluticasone furoate and vilanterol (FF/VI) compared to continuing with existing maintenance therapy (usual care [UC]) in a broad population of subjects with COPD. The trial was initiated in 2012 and was conducted in and around Salford, England, a community served mainly by a single hospital with an established electronic health record system linking primary and secondary care.

Participants were recruited at their own general practice (GP) and were followed up for 12 months (referred to hereafter as 12-month study period); for full methods, see Bakerly, 2015. This setting permitted minimally unobtrusive observation of subjects for effectiveness and safety monitoring, blended into routine clinical care. A separate SLS study evaluated the use of FF/VI compared to UC in subjects with asthma, but this report only includes analysis and results for the COPD arm. The primary results of the SLS-COPD study have been presented elsewhere (Vestbo, 2016).

6.2. Rationale

The primary strength of the SLS is its broad inclusion criteria and minimal interference in the subjects' normal care, enabling assessment of the effectiveness of FF/VI in clinical practice, as opposed to demonstrating its efficacy in the context of a highly controlled

clinical trial. While the real world nature of the trial was designed to test effectiveness in routine care, two potential concerns had been raised:

1. The trial population may not be representative of the wider population in which the medicine may be used, and;
2. There may be differences in or changes to local practice or patient behaviour caused by conducting a study (a 'Hawthorne effect'), which have the potential to bias assessments of effectiveness of both FF/VI and UC.

The Hawthorne effect (also referred to as the observer effect) is a type of reactivity in which individuals improve or modify an aspect of their behaviour in response to their awareness of being observed (French, 1953). In the context of this study, a potential Hawthorne effect may manifest as differences in or changes to behaviours and decision making of GPs and nurses in their care of subjects with COPD enrolled in SLS, or differences in or changes to the subjects' behaviour during the study period.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Co-primary objectives

This study aimed to determine whether the population in the SLS-COPD study was representative of the wider population of COPD patients in England potentially eligible for treatment with FF/VI, and whether SLS participants were subject to the Hawthorne effect.

The co-primary objectives of this study were:

- Primary objective 1 (PO1): To characterise the participants enrolled in the usual care arm of SLS-COPD compared with COPD patients in England (using the CPRD) who fulfil the protocol inclusion/exclusion criteria to evaluate the representativeness of SLS-COPD participants in terms of the wider patient population targeted for FF/VI.
- Primary objective 2 (PO2): To compare the rate of COPD exacerbations in the SLS-COPD usual care arm with that of COPD patients in CPRD over the 12-month study period, to assess a potential Hawthorne effect.
- Primary objective 3 (PO3): To compare the rate of hospitalised pneumonia in the SLS-COPD usual care arm with that of COPD patients in CPRD over the 12-month study period.

7.2. Secondary objectives

The secondary objectives of this study were:

- Secondary objective 1 (SO1): To compare healthcare utilisation (HCU), mortality and prescription counts for COPD therapies between the SLS-COPD usual care arm and the CPRD cohort.
- Secondary objective 2 (SO2): To evaluate how alternate definitions of COPD exacerbations and pneumonia may affect estimations of outcome rates.

- Secondary objective 3 (SO3): To compare rate of COPD exacerbations and HCU endpoints in SLS-COPD usual care arm before and after SLS-COPD commenced.

8. RESEARCH METHODS

8.1. Study design

The CPRD-COPD Hawthorne Effect Study in Salford (CHESS) was a retrospective, observational study designed to compare certain characteristics of, and outcomes experienced by, participants enrolled in the SLS-COPD trial who were randomised to the UC arm (SLS-UC) and COPD patients in the general population of England (as captured in the CPRD) The codes used to define COPD are given in ANNEX 2.

Participants in the SLS-UC arm were followed for 12 months from randomisation (12-month study period). Each SLS-UC participant was matched to >1 subject from the CPRD database who fulfilled the SLS-COPD inclusion/exclusion criteria by index date which was defined as the randomisation date of the SLS-UC participant. The CPRD matched cohort was also followed for up to 12 months, unless censored earlier at lost to follow up (i.e. left the contributing GP practice) or death.

8.2. Study Population and Setting

The SLS-UC cohort comprised 1,403 participants from Salford and the surrounding areas of Greater Manchester, England.

In the CPRD database there were approximately 16,700 subjects located in England who fulfilled the inclusion/exclusion criteria and were matched to SLS-UC participants by index date.

8.2.1. Exposure definitions

Exposure definitions are described in Section 8.3.5.1.

8.2.2. Outcome definitions

Outcome definitions are described in Section 8.3.5.2 (primary) and Section 8.3.5.3 (secondary).

8.2.3. Confounders and effect modifiers

All confounders were calculated at index dates only, unless otherwise specified.

- Sex
- Age
- Socio-economic status (SES): This used Index of Multiple Deprivation (IMD) 2010 quintiles, based on the lower layer super-output area (LSOA) of the patient.
- Current COPD medication group. There are three medication groups of interest: long-acting muscarinic antagonists (LAMA), long-acting bronchodilators (LABA)

and inhaled corticosteroids (ICS). As reliable prescription duration was unavailable in CPRD, exact combinations that involved overlap of prescriptions could not be calculated. Instead any prescriptions for these in the previous three months were identified, and 8 groups were created:

- No medication in the last three months
- LABA only
- LAMA only
- ICS only
- LAMA/LABA
- LAMA/ICS
- LABA/ICS
- LAMA/LABA/ICS

- Comorbidities (at any time in patient history prior to index date):
  - Cardio-and cerebrovascular diseases (specifically heart failure, myocardial infarction, stroke)
  - Depression
  - Anxiety
  - Asthma
  - Pneumonia
  - Gastro-oesophageal reflux and peptic ulcer disease
  - Charlson score (Quan, 2011), with COPD excluded from the score: Co-morbidities were treated as 'history of' at index date if they were recorded at any time prior to the index date.
- Markers of COPD severity:
  - Previous COPD exacerbation: The number (i.e. count) of COPD exacerbation episodes observed in 12 months prior to index date where exacerbations were defined using primary care data only or a combination of primary care and secondary data, depending on whether hospital data was used to calculate the outcome variable. This value was divided by the time available to have an episode. This may have been less than 12 months, because patients were not at risk of another episode during, or shortly after, a previous episode.
  - Forced expiratory volume in 1 second (FEV1) % predicted: Most recent value from within 36 months prior to index date (otherwise missing)
  - FEV_1/forced vital capacity (FVC) ratio: Most recent value from within 36 months prior to index date (otherwise missing)
  - Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage: Most recent value from within 36 months prior to index date (otherwise missing)

- Medical Research Council (MRC) dyspnoea score: Most recent value from within 36 months prior to index date (otherwise missing)

Interaction terms (i.e. effect modifiers) were not considered.

8.3. Data Sources

8.3.1. SLS-UC Cohort

Two data sources were available for the SLS-UC participants for the purposes of this study;

1. Data collected in the SLS-COPD study database, UC arm only. This dataset was the final, compiled and cleaned data used for the statistical analysis of the SLS-COPD trial. Data were from numerous sources including study electronic case report forms (eCRF), hospital records, patient questionnaires, imaging data and other sources.
2. Data collected using the raw primary care EHR for SLS-COPD UC participants

Variables were compared between these two data sources and a 'core' SLS dataset created for this study; decisions as to which source to select for the core SLS dataset were based on data availability or what was seen to be the more appropriate comparator to the CPRD.

The core dataset included the following variables sourced from the **SLS database**:

- Sex
- Age
- SES (using IMD 2010 scores)
- FEV_1%
- Ratio of FEV_1 to FVC (FEV_1/FVC)
- GOLD stage
- Smoking status
- Body mass index (BMI)

The core dataset included the following variables sourced from the **SLS-EHR database.**

- Historical comorbidities (not available in the SLS-study database)
- Charlson co-morbidity score (with COPD removed) (not available in the SLS-study database)
- Medical Research Council (MRC) dyspnoea score (not available in the SLS-study database)
- Current asthma and current COPD medication groups (for improved comparability with the CPRD).

- This core dataset was linked with additional study outcome variables from either the SLS COPD study database or SLS-EHR database to create two analytic cohorts, hereafter referred to 'SLS-database cohort' or 'SLS-EHR cohort', respectively.
    - In the SLS-database cohort, COPD exacerbations (in the 12-months prior to and during the study period), immunisation history for influenza/pneumococcal disease and hospitalised pneumonia (defined in Section 8.3.5.2) were sourced from the SLS-database. Critically for PO2, COPD exacerbations were taken directly as entered into the eCRF by SLS investigators as part of the trial, which included medical verification of the events.
    - In the SLS-EHR cohort, COPD exacerbations (in the 12-months prior to and during the study period) and immunisation history for influenza/pneumococcal disease were derived using the primary care EHR data. Importantly, this means that COPD exacerbations were derived using a validated algorithm for use in primary care data (Rothnie, 2016) and were not verified in the same way as they were in the SLS-database cohort.

8.3.2. CPRD

Comparator cohorts were derived from the CPRD-GOLD; CPRD-GOLD is a source of primary care data, provided as a commercial product by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) from a broadly representative sample of UK general practices. **Only practices that were able to link to secondary care data via Hospital Episode Statistics (HES) were included in this study.** As HES data is only available for NHS hospitals based in England, this effectively excluded patients registered at GPs located in Scotland, Wales and Northern Ireland. CPRD data was also linked to death records from the Office for National Statistics (ONS), and postcode-derived Index of Multiple Deprivation 2010 data (IMD 2010 scores), a metric of SES in England. All data linkage of CPRD to additional datasets was undertaken by the MHRA, the provider of the CPRD dataset. As regional data are anonymised in CPRD datasets available for research purposes, the MHRA created a data flag to indicate patients resident in Greater Manchester for the purposes of this study.

Cohorts from the CPRD were generated as follows:

- CPRD: CPRD database; all practices eligible for HES linkage, all COPD patients. Codes for COPD are provided in ANNEX 2.
- CPRD-GM: CPRD database; practices/patients eligible for linkage, in Greater Manchester only, COPD patients.
- CPRD-xGM: CPRD database; excluding practices/patients in Greater Manchester, COPD patients. This was created to minimise the risk of patients having care records in both the SLS and CPRD cohorts.
- CPRD-GM-IC: CPRD COPD patients recorded as residing in Greater Manchester who would have met SLS inclusion/exclusion criteria during the timeframe of the SLS-COPD trial.

- CPRD-xGM-IC: CPRD COPD patients recorded as not residing in Greater Manchester who would have met SLS inclusion/exclusion criteria during the timeframe of the SLS-COPD trial.

The latter two cohorts were used in the main analyses of the study, with the CPRD-xGM-IC cohort being the main comparator population of interest.

8.3.3. Cohort generation (matching process)

The SLS cohorts were used as provided with no additional modification.

For the CPRD, comparator cohorts were generated by matching on the randomisation dates of the participants in SLS-UC arm, which ranged from 5 April 2012 to 24 October 2014. Outcomes were assessed over a 12-month period to match the study period of the trial.

The process for generating the index date-matched cohorts were as follows:

CPRD patients that fulfilled the following criteria:

i. Diagnosis code of COPD

ii. Aged ≥40 years

iii. At least one day of 'up to standard' registration in CPRD.

iv. Restriction to patients that would have been potentially eligible for recruitment at some point during the SLS trial (alive, currently treated COPD for a period of at least one day between 5 April 2012 and 24 October 2014).

v. The matching algorithm then simulated index dates for the CPRD cohort from the distribution of randomisation dates of the SLS UC patients and tested their eligibility on this date.

After these steps, the following steps were applied for each potentially SLS eligible patient in CPRD:

- A participant from the SLS-UC arm was randomly sampled (with replacement); the index date of this SLS participant was assigned to the CPRD patient;
- The SLS inclusion and exclusion criteria (see Section 8.3.4) were applied to the CPRD patient on the index date.

Eligible patients in the CPRD comparator cohort were followed for a maximum of 12 months. Patients not eligible on the index date were discarded unless the reason for ineligibility was an extant COPD exacerbation, in which case eligibility was reassessed after resolution. Patients were then flagged depending on whether they were registered to a practice in Greater Manchester (CPRD-GM) or not (CPRD-xGM).

8.3.4. Inclusion/exclusion criteria

8.3.4.1. SLS-UC cohort

Inclusion and exclusion criteria for the SLS-UC cohort were per the SLS protocol, reproduced here for clarity.

The SLS inclusion criteria were:

- Male or female participants aged ≥40 years
- Had received a documented diagnosis of COPD from a general practitioner
- Patients who had a history of treatment with oral glucocorticoids, antibiotics (in association with GP contact) and/or hospitalisation for at least one COPD exacerbation in the three years prior to index date.
- Receiving current COPD usual care therapy, defined as:
    - ICS alone or in combination with a LABA (a fixed dose combination or an ICS and LABA provided in two separate inhalers, or ICS and LAMA);
    - or long-acting bronchodilator therapy alone or the use of two bronchodilators (i.e. LABA and LAMA);
    - or 'triple therapy' i.e. ICS and LABA plus a long acting muscarinic antagonist (LAMA)

The SLS exclusion criteria for the SLS-UC cohort were:

- COPD exacerbation within two weeks of index date
- Chronic users of oral glucocorticoids
- Participants with life-threatening conditions or uncontrolled/clinically significant disease, as determined by the GP

8.3.4.2. CPRD cohort

Specific inclusion and exclusion criteria were applied to the CPRD cohorts (in addition to any such criteria placed on this population by the MHRA at source).

CPRD cohort inclusion criteria were:

- Age ≥40 years
- Recorded diagnosis of COPD prior to their assigned index date (see Section 8.3.5.2 for further information)
- Alive on their assigned index date
- History of treatment with systemic corticosteroids, antibiotics (in association with GP contact) and/or hospitalisation for the treatment of ≥1 COPD exacerbation in the three years prior to their index date

CPRD cohort exclusion criteria were:

- Registered with a GP surgery located in the Greater Manchester area
- Less than 12 months of follow-up prior to their assigned index date (i.e. registered at a contributing practice < 12 months ago)
- Unstable COPD, defined as a COPD exacerbation in the two weeks prior to their index date. Note that this was not an absolute exclusion; for these patients, their index date was delayed for a minimum two weeks after the onset of any such exacerbation and until the exacerbation had resolved (see Section 8.3.5.2)
- A chronic user of systemic corticosteroids: Prescribed for respiratory or other indications; chronic use defined as at least four prescription records over a 12-month period with a maximum gap between two prescriptions equal to 30 days.

Although the SLS-COPD additionally excluded participants with life threatening conditions or uncontrolled/clinically significant disease, as determined by the GP, this definition could not be matched exactly within the CPRD, as this decision was down to the clinician's discretion. For this reason, this criterion was not applied to the CPRD cohort.

8.3.5. Definitions

8.3.5.1. Exposure definitions

The primary exposure of interest was whether a patient was enrolled in SLS (yes/no), hence SLS-UC was compared with CPRD-xGM-IC (main comparator) or CPRD-GM-IC. The CPRD-GM was also examined and compared with CPRD-xGM.

8.3.5.2. Primary outcome definitions

Moderate/severe COPD exacerbation (PO2):

SLS-UC

SLS-EHR: Moderate/severe COPD exacerbations were defined algorithmically (Rothnie, 2016) as described below for CPRD.

SLS-Database: Moderate/severe COPD exacerbations were defined as recorded as in the SLS-COPD eCRF.

CPRD

Within the CPRD cohorts, the number of moderate/severe exacerbations of COPD was defined using a previously validated algorithm (Rothnie, 2016). In general, moderate exacerbations are those managed in primary care, whereas severe events are those resulting in a hospitalisation. The algorithm was based on diagnostic and treatment codes for COPD/respiratory infections (see ANNEX 2) and is summarised below:

1. Prescription of pre-specified antibiotics and oral corticosteroids for 5-14 days, both on the same day

2. Exacerbation symptom definition (exacerbation symptoms are codes suggesting increases in two or more of: breathlessness, cough, or sputum volume and/or purulence) and antibiotics, where the medical code is recorded on the same day as a prescription for antibiotics or oral corticosteroids
3. Lower respiratory tract infection code (not including pneumonia codes, but including acute bronchitis and other lower respiratory tract infection diagnosis codes)
4. A definite acute exacerbation of COPD (AECOPD) medical diagnosis code

After determining all the events for COPD exacerbations (i.e. any of the definitions listed above), they were combined to produce exacerbation episodes. The definition of an exacerbation episode was as follows:

1. Following an exacerbation event, the date of the event was projected forwards 14 days and used as a potential end-of-episode date. Exacerbations within this period were assumed to be related to the initial exacerbation.
2. If there were no exacerbations in the 14 days after the potential end-of-episode date, the algorithm was halted; the episode was fully identified.
3. If there were exacerbations in the 14 days after the potential end-of-episode date, the potential end-of-episode date was moved 14 days forward of the start of the last exacerbation in these 14 days.
4. The process was repeated from step 2 until there were 14 days after the end-of-episode date clear of exacerbations.

Within the CPRD, all analyses involving COPD exacerbations were based on COPD exacerbation episodes, not COPD exacerbations *per se*.

There were two definitions for COPD exacerbation episodes as an outcome used in the final analysis:

1. The number of COPD exacerbation episodes recorded as a ‘count’ variable were used to derive the rate of COPD exacerbation episodes observed over the 12-month period.

As a consequence of the way in which exacerbation episodes are defined, a subject was not at risk of an episode at all times (i.e. they were not at risk during, or immediately after, an extant episode). Therefore, the time at risk for episodes may have been less than the total follow-up available for the patient. The exact period of follow-up whilst at risk of an episode was derived and used as an offset term in modelling where appropriate (i,e. excluding the interval from the day after the start of the episode until 14 days after the last note of an exacerbation within an episode from the time at risk).

2. The time until first COPD exacerbation episode. If a subject had no recorded episodes, the time until the censoring event (e.g. lost to follow up, end of study, etc) was recorded.

Analysing time to event data provided a complimentary analysis to the count data, where the assumption of independent events could be violated. Also, the impact of records with

multiple false positives (episodes) was reduced when considering time to event, as only the first false positive impacted the analysis.

As COPD exacerbations were derived differently in the two SLS cohorts, the data source for the COPD exacerbation episodes in the CPRD differed, in an attempt to match how exacerbation events were recorded in the SLS. Specifically,

- In comparison with the SLS-database cohort, exacerbations were derived using the exacerbation algorithm defined in Section 8.3.5.2, and used both primary and secondary care data.
- In comparison with the SLS-EHR cohort, exacerbations were derived algorithmically (as per Section 8.3.5.2, with Condition 1 of the algorithm relaxed to 'prescription of pre-specified antibiotics and oral corticosteroid on the same day only', dropping the additional requirement of a prescribing period of 5-14 days), and used primary care data only. This comparison provides a 'like-for-like' comparison of COPD exacerbations between the SLS and CPRD.

Hospitalised pneumonia (PO3):

For the SLS-UC, the SLS-database cohort was used and pneumonia was defined as a hospitalisation where a pneumonia ICD-10 code (see ANNEX 2) was present as either a main or secondary diagnosis (up to 13 secondary diagnosis fields).

In the CPRD cohorts, pneumonia was defined as hospitalisation where a pneumonia International Classification of Diseases (ICD)-10 code (see ANNEX 2) was recorded in any diagnosis position at any point during the hospitalisation.

Similar to COPD exacerbations, two aspects of this outcome were recorded:

1. The number of pneumonia episodes in the year after index date, recorded as a count variable.
2. The time until the first pneumonia episode.

8.3.5.3. Secondary outcome definitions

Healthcare utilisation (SO1):

All contact with primary care and all hospital admissions during the 12-month study period were recorded as counts. The number of days the subject had contact with the primary care services and the number of days spent in hospital were counted as separate variables. Any contact with the GP (including phone calls etc.) was included and defined by any medical code recorded. Any code(s) recorded on the same day as a code indicating participation in a trial was not counted.

Medication adherence (SO1):

Medication possession ratio (MPR) and percent days covered (PDC) were not calculated due to insufficient recording of required data in the CPRD, which would necessitate numerous assumptions to be made. Instead, the number of distinct COPD prescriptions

prescribed by the GP over the course of the 12-month study period was calculated. This provided a more appropriate estimate of medication adherence that the study team were confident could reliably be derived from both CPRD and the SLS data.

Treatment switching (SO1):

Four consecutive 3-month periods were defined across the 12-month study period. In each 3-month period, a subject may have been in one of eight groups, defined by the medications they received in the period; No medication, LAMA, LABA, ICS, LAMA/LABA, LAMA/ICS, LABA/ICS, LAMA/LABA/ICS.

Between each period, switching was defined as:

- Step up (addition of one or more extra medications)
- Step down (removal of one or more extra medications)
- Switching (addition or removal of a medication class)
- None (same medication group as previous 3-month interval)

Mortality (SO1):

Mortality was defined as all causes of death during the 12-month study period. For the SLS-UC cohort, this data was provided as a field in the SLS-database. For the CPRD cohort, deaths were determined using ONS linked mortality data.

Other definitions of COPD exacerbation (SO2):

Other definitions of COPD exacerbation were described per the outputs of the study by Rothnie (2016). Exacerbations were defined through different subsets of the types of events which count towards an episode. The subsets chosen are defined below (see Section 8.3.5.2 for the COPD exacerbation episode definitions 1-4):

- Definition A: COPD exacerbation episodes matching definitions 1 OR 2 OR 3 OR 4. This definition was similar to the original definition but did not include secondary care events.
- Definition B: COPD exacerbation episodes matching definitions 2 OR 3 OR 4. This definition excluded events defined by prescription of oral corticosteroids (OCS) and ATB on the same day.
- Definition C: COPD exacerbation episodes matching definitions 3 OR 4. This defined COPD exacerbation episodes by lower respiratory tract infection and AECOPD codes only.
- Definition D: COPD exacerbation episodes matching definition 4. This defined COPD exacerbation episodes by AECOPD codes only.

Pneumonia as primary diagnosis of hospitalisation (SO2)

This represents hospitalisations where the primary diagnosis of the first episode of a hospitalisation event was a pneumonia code.

For the SLS-UC cohort the SLS-database was used and pneumonia was defined as a hospitalisation where a pneumonia ICD-10 code (see ANNEX 2) was present as either a main or secondary diagnosis (up to 13 secondary diagnosis fields).

In the CPRD cohort, pneumonia was defined as hospitalisation where a pneumonia ICD-10 code (see ANNEX 2) was recorded in any diagnosis position at any point during the hospitalisation.

Rate of COPD exacerbations and HCU outcomes in SLS-UC before and after the SLS trial (SO3)

For this analysis, the SLS-EHR dataset for the SLS-UC cohort was compared to the CPRD primary care only dataset. For the purposes of this objective, the additional 12 months immediately prior to the index date were also analysed. The rate of COPD exacerbations was derived algorithmically (Rothnie, 2016) using the definitions as stated above in SO2; number of primary care contacts, COPD medication prescribing and treatment switching were assessed (as defined in SO1).

8.3.6. Missing data

To handle missing data, a single stochastic regression imputation was applied. Each cohort was imputed separately, with each imputation model comprising all covariates and the main outcome variable (See Section 8.6.1.2 for further detail). Variables necessary to impute were IMD 2010, FEV_1%, FEV_1/FVC ratio, GOLD stage, MRC dyspnoea score, BMI and smoking status. A complete case analysis was also conducted as a sensitivity analysis.

8.4. Study size

The SLS-UC cohort comprised 1403 patients. Within CPRD, there were 164,400 COPD patients eligible for HES linkage. From this population, study analytic populations were determined:

- CPRD-xGM-IC (with COPD exacerbations defined from primary care data only); n=16,758. This cohort was compared to SLS-EHR cohort data for PO1 and PO2.
- CPRD-xGM-IC (with COPD exacerbation defined from primary care+secondary care): n=16,745 patients. This cohort was compared to SLS-database cohort data, due to the availability of secondary care data in both cohorts, and used for PO3.

No formal assessment of statistical power was undertaken; however, the sample size for this study was very large, hence implying considerable statistical power.

8.5. Data Management

8.5.1. Data transformations (data handling conventions)

8.5.1.1. Covariates included in statistical modelling

Covariates considered for inclusion in statistical modelling were:

- Sex
- Age
- SES (using IMD-2010 quintiles)
- Current COPD medication group (defined from the prior 3 months to index date)
- History of specific comorbidities (defined as a record at any point in the past i.e. ever the EHR):
    - Cardio- and cerebrovascular diseases
    - Depression
    - Anxiety
    - Asthma
    - Pneumonia
    - Gastro-oesophageal reflux/peptic ulcer disease
    - Charlson co-morbidity score (with COPD removed)
- Number of COPD exacerbations in previous 12 months
- FEV_1%
- FEV_1/FVC
- GOLD stage
- MRC dyspnoea score
- Smoking status
- BMI
- Immunisation for influenza and pneumococcal disease

8.5.2. Resourcing needs

The study was led by the principal investigator, a senior lecturer, at University of Manchester (UoM), in collaboration with North West eHealth (NWeH), CPRD and PhD-level epidemiologists at GlaxoSmithKline (GSK). A Scientific Committee was assembled and were required to review and input into study design and major study documents.

The protocol was developed between UoM, GSK and CPRD and protocol finalisation was carried out by responsible parties at the UoM. The specifications for the data sets

were developed by the UoM, GSK, CPRD and NWeH. NWeH were responsible for the data extraction from the COPD SLS database and the CPRD cohort dataset was created by responsible parties at the UoM and CPRD. Data analyses were conducted by analysts at the UoM, under guidance of senior statistician/epidemiologists, and and quality control/assurance of the analyses was carried out by GSK. The final study report was drafted by researchers at the UoM and GSK and was reviewed by the Scientific Committee. GSK were responsible for reporting to regulatory agencies.

8.6. Data analyses

Due to the differences in data field availability between SLS-UC study database records and SLS-UC EHR records, different analyses utilised different data sources depending on the information required in order to maintain comparability. Table 1 presents a summary of the data sources utilised by analyses.

Table 1 Data sources utilised by objective

Objective	Source tables and figures	SLS data source	CPRD data source
PO1/PO2	Table 1– Table 18 Figure 1- Figure 13	SLS-Database	CPRD primary care +secondary care
PO1/PO2	Table 19– Table 36 Figure 14- Figure 26	SLS-EHR	CPRD primary care
PO3	Table 37– Table 46	SLS-Database	CPRD primary care +secondary care
SO1 (EMIS-Vision comparison, primary care use, COPD prescriptions and treatment switching)	Table 47.1- Table 50, Table 52- Table 53, Table 55- Table 56, Table 59- Table 62	SLS-EHR	CPRD primary care
SO1 (mortality and secondary care use)	Table 48, Table 51, Table 54, Table 57- Table 58, Table 63- Table 64	SLS-Database	CPRD primary care
SO2 (alternative COPD definitions)	Table 65– Table 81	SLS-EHR	CPRD primary care
SO2 (alternative pneumonia definition)	Table 82– Table 85	SLS-Database	CPRD primary care +secondary care
SO3	Table 86.1– Table 107	SLS-EHR	CPRD primary care
Sensitivity analyses, using complete cases only (PO1/PO2)	Table 108– Table 111	SLS-Database	CPRD primary care +secondary care
Sensitivity analyses, using complete cases only (PO1/PO2)	Table 112– Table 115	SLS-EHR	CPRD primary care
Summary of missing data	Table 116	SLS-EHR, SLS-Database	N/A

8.6.1. Essential analyses

8.6.1.1. Characterisation of study participants (PO1)

The overall aim of the primary comparison was to determine whether the SLS-UC cohort was representative of the population of COPD patients in England who would be eligible for treatment with FF/VI. The CPRD-xGM-IC cohort was selected as the main comparison, however data are also presented for the CPRD-GM-IC cohort for completeness. To assess the representativeness of the SLS-UC population compared with the CPRD-xGM-IC, distributions of all covariates and outcomes were summarised for each cohort as proportions for binary and categorical variables, rates (with standard deviation) for count variables, and means (with standard deviation) and medians (with 2.5 to 97.5 percentile ranges) for continuous variables.

Descriptive modelling was also used to ascertain whether the characteristics observed within SLS-UC were unusual by comparison with regional variations observed within CPRD-xGM-IC cohort, as follows.

Within the CPRD, there were 148 anonymised local authorities (LA); for the purposes of the comparisons in this study, the SLS-UC cohort was deemed as a comparable population unit. Where appropriate, mean values of variables were calculated for each LA in CPRD and the distribution of these values was used to generate an empirical 2.5 to 97.5 percentile range for each given variable. If the mean value (or other appropriate summary statistic) for the SLS-UC cohort lay outside of this distribution for a given variable, the SLS-UC cohort was considered to be unusual.

Similarly, for categorical variables, a 'reference distribution' was constructed as the distribution in the entire CPRD-xGM-IC cohort. For each LA and for the SLS-UC cohort, a Chi-squared statistic was calculated comparing the LA to the reference distribution (with the LA removed). In this case, the test statistics from each LA compared to CPRD-xGM-IC were used to construct a 0 to 95 percentile range; if the SLS-UC cohort's Chi-squared test statistic was above the empirical 95th percentile, it was considered unusual.

8.6.1.2. Regression imputation on CPRD-xGM-IC, CPRD-GM-IC and SLS-UC

A single stochastic regression imputation was performed across CPRD-xGM-IC, CPRD-GM-IC and SLS-UC cohorts separately. The process was also separate for the coded data (SLS-database) and the raw data (SLS-EHR). The imputation model comprised all confounders and outcomes available and imputed a single dataset. The imputation was performed on all variables where 'missing' did not represent absence of a condition or use of medication. (i.e. age, sex, BMI, GOLD stage, SES, $FEV\%_1$ predicted, FEV_1/FVC ratio and MRC dyspnoea score; see Section 8.3.6). Imputed datasets were compared with the complete data (by variable; Source Data: Results Table 5.1, Table 6.1, and Table 7.1 and Source Data: Results Table 24.1, Table 25.1, and Table 26.1 for SLS-database and SLS-EHR, respectively). As more than 10% of the patients within cohorts had missing data, all subsequent analysis were run using imputed datasets. Sensitivity analyses that repeated the main analysis from PO2 using complete case datasets were also performed (Table 108 to Table 115).

8.6.1.3. Comparison of the rate of COPD exacerbations between SLS-UC and CPRD-xGM-IC (PO2)

Rates of COPD exacerbations (event rates calculated as the number of events per person year) were reported for the CRPD-xGM-IC and SLS-UC cohorts. Regional variation was assessed in the same way as representativeness (see Section 8.6.1.1) in that an empirical 2.5 to 97.5 percentile distribution of event rates by LA was constructed and this was used to evaluate whether the event rates for SLS-UC cohort were 'unusual' (i.e. fell outside the 2.5 to 97.5 percentile). Multi-level Poisson models were fitted to the data; the models combined both datasets and used two levels, patient and LA, with random intercepts included at the LA level.

A fixed set of covariates was used across all models as opposed to model selection criteria (e.g. Akaike Information Criterion [AIC] backwards selection) for consistency of predictors across different analyses. The covariates selected were those which were significant on fitting univariate models and had a significant likelihood ratio test. Covariates included were sex; age; SES; current COPD medication group; history of: Depression, anxiety, asthma, pneumonia and gastroesophageal/ peptic ulcer disease; COPD exacerbation history; MRC dyspnoea score; pneumococcal immunisation status; FEV_1%; FEV_1/FVC and smoking status.

All confounders were included as covariates with outcomes corresponding to the primary and secondary study outcomes, using a separate model for each. Continuous variables were treated as linear, with a quadratic term (e.g. age^2) also included to allow for any simple deviations from linearity. For parsimony purposes, interactions between confounders (i.e. effect modification) were not considered. For the primary model, membership of SLS-UC cohort was not included as a covariate, because doing so would correspond to testing whether SLS-UC rates of exacerbation deviated from the population average rather than ascertaining whether the SLS-UC rates were unusual in the context of regional variation.

Point estimates for the random effects were then reported and examined in context of the SLS region. Per PO1, if the random effect of the SLS region fell outside the 2.5 to 97.5 percentile range, it was concluded that SLS-UC cohort is unusual compared with the rest of the England. Cox proportional hazard models were used for time to event analyses.

As a further descriptive study, simple regression models of each outcome were produced. For the count outcomes, Poisson models were used after assessment for over-dispersion was checked. The actual period of follow-up for each patient (which could be greater than or less than 12 months) was included as an offset. The SLS-UC and CPRD-xGM-IC cohorts were combined into one dataset, and included an indicator of SLS membership. The SLS indicator's rate ratio and confidence interval (CI) was evaluated in three models:

1. A model including SLS indicator as the only covariate.
2. A model including SLS indicator, age, and gender as covariates.
3. A model including the SLS indicator, plus all confounders as potential covariates. Continuous variables were treated as linear, with a quadratic term (e.g. age^2) also

included to allow for any simple deviations from linearity. For parsimony purposes, interactions between confounders were not considered.

Cox proportional hazard models were used for time to event analyses. The SLS indicator was included as a covariate to determine its hazard ratio (HR) and associated CIs and the three models described above were fitted. The results of these models are descriptive only and did not account for the regional variation in CPRD.

8.6.1.4. Comparison of the rate of pneumonia hospitalisations between SLS-UC and CPRD-xGM-IC (PO3)

Rates of pneumonia hospitalisation events were reported for both the SLS-UC and CPRD-xGM-IC cohorts. Analyses for PO3 were carried out using the same approach as for PO2 (see Section 8.6.1.3) but the SLS-database data was used for the SLS-UC and was compared to the CPRD cohort using primary care+secondary care as these datasets contained hospitalisation data which were required to define pneumonia events, as per the definitions of this study.

8.6.1.5. Healthcare utilisation, mortality, and prescription counts for COPD therapies endpoints (SO1)

Analyses for SO1 included comparisons of SLS-UC and CPRD-xGM-IC cohorts with respect to healthcare utilisation by assessing primary care visits, hospital admissions, mortality (all causes) and prescription counts.

Descriptive summaries for all SO1 outcome variables were produced. All subsequent analysis of the treatment switching variable, utilized the 'any switch' variable; a yes/no (or 1/0) to denote whether a patient did or did not switch treatment over the course of the 12-month study period. This was offset by the number of full periods in which a patient could possibly switch. A descriptive comparison of the number of each of the outcomes variables with respect to the regional variation in CPRD was also performed. For each of the outcomes, a test statistic was used to calculate a 2.5 to 97.5 percentile range and the SLS was placed within this interval. The test statistics used were rate (number of contacts/prescriptions per 1000 person years) for the healthcare utilisation and medication adherence outcomes; rate (number of deaths per 1000 person years) for the death outcome; and the proportion of treatment switchers for the treatment switching outcome.

Multi-level models were fitted to the data for each of the outcomes, using an empirical percentile range for the random effects. Cox proportional hazards models were used for mortality, Poisson models were used for the healthcare utilisation and medication adherence outcomes, and a logistic regression model was used for the treatment switching outcome. For the healthcare utilisation variables assessing contact with primary care, the time at risk was adjusted to account for number of days where a trial related code is present. For treatment switching, the offset used, was the number of full periods a patient had valid follow-up for, minus one.

In addition, a comparison of EMIS and Vision EHR data systems was conducted; these are commonly used EHR systems in UK primary care. To determine whether there were systematic differences between the EMIS and Vision data systems in the SLS-UC cohort (e.g. potential problems with code lists, using differing recording practices etc.), subjects

were flagged according to whether they were enrolled at a practice using the EMIS or Vision recording systems and a Poisson model was fitted to the SLS-UC cohort only, with the outcome equalling the number of medical codes in the 12-month study period.

8.6.1.6. Sensitivity analysis to assess the impact of different definitions of COPD and pneumonia exacerbation (SO2)

For each sub-definition of the COPD and pneumonia outcomes, descriptive summaries of rates were produced and were assessed with respect to regional variation. A series of sensitivity analyses exploring alternate definitions of COPD and pneumonia outcomes were also performed. The alternate definitions are COPD definitions given as a variation of the Rothnie definitions (Rothnie, 2016; see Table 2).

Table 2 Alternate definitions of COPD exacerbation criteria

	COPD Exacerbation Episode Criteria	Definition			
		A	B	C	D
1	Prescription of pre-specified antibiotics (ABx) and oral corticosteroid (OCS) both on the same day, where OCS prescribed for 5-14 days	Y			
2	Exacerbation symptom(s)[a] and antibiotics, where medical code is on the same day as prescription OR,	Y	Y		
	Exacerbation symptom definition and oral corticosteroids, where medical code is on the same day as prescription	Y	Y		
3	Lower respiratory tract infection code (not including pneumonia codes, but including acute bronchitis and other lower respiratory tract infection diagnosis codes)	Y	Y	Y	
4	Definite AECOPD medical diagnosis code	Y	Y	Y	Y
5	Code denoting COPD hospitalisation (possible) [if secondary care data available][b]	Y	Y	Y	Y
6	Code denoting COPD hospitalisation (definite) [if secondary care data available][b]	Y	Y	Y	Y

[a] Exacerbation symptoms are codes suggesting an increase in 2 or more of: Breathlessness, cough, sputum volume or purulence.
[b] Only used when secondary care data was available.
Note: for analyses using primary care data only (i.e. CPRD primary care only vs. SLS-EHR, the criteria 5-14 days was dropped from Condition 1 and criteria 5 and 6 could not be implemented.

For pneumonia, the following alternative definition was implemented using the SLS-database and CPRD primary care+secondary care, due to the requirement for

hospitalisation data, whereby pneumonia was classed as the primary or main diagnosis of the hospitalisation:

- SLS-UC: Pneumonia was defined as a hospitalisation where a pneumonia ICD-10 code (see ANNEX 2) was present as the main diagnosis only.
- CPRD: Pneumonia was defined as hospitalisation where a pneumonia ICD-10 code (see ANNEX 2) was recorded as primary diagnoses of the first episode of the hospitalisation.

For both COPD and pneumonia, Poisson/Cox multi-level models were fitted to the outcome variables. The results are presented in Source Data: Results Table 70 to Table 73 (COPD sub definition B), Source Data: Results Table 74 to Table 77 (COPD sub definition C), Source Data: Results Table 78 to Table 81 (COPD sub definition D) and Source Data: Results Table 82 to Table 85 (pneumonia as primary admission diagnosis of hospitalisation).

8.6.1.7. Comparison of COPD exacerbation rates and HCU in SLS-UC prior to and during the study (SO3)

Rates of COPD exacerbations and HCU outcomes (number of primary care contacts, COPD medication prescribing and treatment switching) among the SLS-UC cohort during the 12-month study period (or matched 12-month follow-up in CPRD) were compared, at a patient level, with the period 12 months before the SLS started. A 'difference-in-difference' design was used and addressed the question of whether the change in rates before to during trial in SLS-UC was unusual in the context of the corresponding distribution of changes in event rates by LA observed in CPRD-xGM-IC. As in the other analyses, 'unusual' was defined as being outside the 2.5 to 97.5 percentile distribution of changes in event rates by LA. To explore this further, multilevel models were fitted to the data. The model combined both datasets and had 3 levels: observation period, patient, and LA. Specifically, each patient had 2 observation periods: before and during the trial.

Point estimates for the random effects in context of the SLS region were interpreted in a similar way to those in PO2; however, in this analysis the primary interest is in the LA-level random effect describing the change in rates between the pre- and peri-trial observation periods. If the random effect associated with the SLS region fell outside the 2.5 to 97.5 percentile range, it was concluded that SLS-UC was unusual compared with the rest of England. As a further interpretation, the random effects multiplied by the fixed effect for the change in rate between pre- and peri-trial were presented, which gives the relative change in rates for SLS-UC, and for context, the corresponding distribution of changes for the other LAs as derived from CPRD.

As described in Section 8.3.3, index-date matched CPRD and SLS-EHR cohorts were created using a criterion that required that an ongoing COPD exacerbation episode must have ended before an index date was assigned. For this objective, a new cohorts were created with this criterion removed so bias was not introduced from the year before the trial to during the trial period. The number of events in the 365 days before and after the index date were counted, making relevant adjustments for immortal time (defined as time period during where the outcome could not occur because of the exposure definition).

8.6.2. General considerations for data analyses

Analyses for PO1 and PO2 were replicated using both SLS-UC data sources (SLS-database and SLS-EHR, see Section 8.3); however, results from analyses based on SLS-EHR data are the focus of this report. This is because data in the CPRD and SLS-EHR datasets were recorded more consistently compared with that in the SLS-database and therefore provided a more accurate comparison (see Section 8.3.1).

8.6.3. Exploratory analyses

8.6.3.1. Comparison of COPD populations registered with CPRD between Greater Manchester and rest of England

Demographics, confounders and outcomes between CPRD-GM and CPRD-xGM were compared. As these subjects did not have an index date, we selected to impose an index date which represented the median entry date of participants in the SLS-UC and then applied a fixed follow-up of 12 months for these comparisons.

Data were summarised as proportions in each category for binary and categorical variables, means (95% confidence interval) and medians (2.5 to 97.5 percentile range) for continuous variables, and rates (95% confidence interval) for count variables. For time to event variables, Kaplan-Meier curves of each group were plotted together on one axis for comparison.

8.6.3.2. Power calculation

No formal power calculations were carried out for the study. However, power was not considered to be an issue as the number of patients in the CPRD cohort was >16,000, producing a ratio of approximately 11:1 patients to SLS.

8.6.3.3. Initial data cleaning

A number of data cleaning steps were undertaken prior to cohort generation and analyses. These included the following:

- Patient age: The number of patients with ages greater than 115 years old at index date were reported, and age set to missing.
- Height: Measurements among participants aged 18 years or older, outside the range 0.4 to 2.36 m were considered implausible and set to missing.
- Weight: Measurements among participants aged 18 years or older, outside the range 35 to 350 kg were considered implausible and set to missing.
- BMI: BMI values were derived on dates when either weight or BMI itself were recorded. When only weight had been recorded, BMI was derived from the recorded weight and the most recent measurement of height provided it was taken when the patient was aged 18 years or older. The number of BMIs (kg/m^2) less than 13, and the number of BMIs greater than 60, were reported and set to missing.
- Smoking: In assessing smoking status at baseline all records of status up to and including the index date were considered. Whenever there had been evidence of

smoking in the past (status of either "current" or "ex") status was set to "ex" if the latest record of status up to and including the index date was either "never" or "ex"; otherwise status was as last recorded ("current", "ex", "never").

- FEV_1 and FVC: FEV_1 and FVC measures were converted to standard units and implausible values were set to missing.

8.6.4. Amendments to the statistical analysis plan

1. Comparator cohorts. The protocol made reference to a comparison with data obtained directly from the Salford HER for a within-Salford comparison of those eligible to receive FF/VI with those entered into SLS. However, SLS recruited across Greater Manchester making this comparison less relevant, and an unnecessary level of complexity to the study. This comparison was replaced with a comparison of CPRD data from contributing practices across Greater Manchester to the data collected in SLS for the UC arm.
2. Although the protocol described the use of an UK cohort, the requirement for linkage to HES restricted the patients selected from the CPRD to those registered at English practices only. As such, comparisons between the SLS-UC and the English (not UK) CPRD population were made.
3. The exclusion criteria 'Patients with any life-threatening condition or uncontrolled/clinically significant disease, i.e. diagnosis codes in any preceding period' was removed as this could not be matched exactly to the SLS. Initially, a sensitivity analysis, investigating the propensity for death was proposed. Analyses for primary objectives were to be repeated excluding patients with the highest propensity for death. However, although it was technically possible to calculate a propensity score for the CPRD cohort, there was no information available – be it the number of patients excluded or the reasons for their exclusion – regarding patients who were either not approached for the trial or were not advanced past their initial screening visit based on the pattern or severity of their co-morbidities (i.e. fitting the criteria of life-threatening condition). As such, any metric describing propensity for death generated for the CPRD cohort could not be calibrated against Salford patients who may have been considered for SLS, thereby rendering such a score meaningless in the context of deciding upon a cut-off for cohort selection. Therefore, this analysis was not carried out.
4. For the CPRD, an exclusion criteria of less than 12 months of prior data before index date was added in order to calculate baseline variables.
5. An extra endpoint was defined, which was time until first COPD exacerbation episode. This was to provide an analysis which accounted for a lack of independence between events and also the miscoding of multiple events (multiple false positives).
6. Extra analyses regarding intermediate models for endpoints based on baseline covariates were added. These were to bridge the gap between comparison of event rates and the full multilevel models (main analysis) that also investigated outcome rated within individual local authorities.
7. A propensity for membership in SLS was created and densities for SLS and non-SLS members were compared.

8. For the SLS-UC, two alternative measures of exacerbations were available, as reported in the SLS-database and as detected from the SLS-EHR. Since those reported in the SLS-COPD study database include events occurring in primary and secondary care, these were compared to exacerbations detected within the linked primary and secondary care data on CPRD (Source Data: results Table 1 to Table 18). Unfortunately, the linkage from SLS-EHR to secondary care was not available for this study, so exacerbations detected through the SLS-EHR for SLS-UC were compared to exacerbations detected from CPRD primary care data alone (Source Data: Results Table 19 to Table 36).
9. Within PO2, the fitted exacerbation rates vs. actual exacerbation rates plot was replaced by a visualization of the random effects. This better fulfilled the aim of gaining a visual interpretation of where SLS-UC lies in comparison to the other LAs.
10. It was not possible to use AIC backward selection to arrive at the final set of models. Not all the models were converging for every set of variables tested in the AIC selection procedure. Furthermore, for the algorithms that did converge there were a wide variety of variables in the models. For consistency across analyses, a single set of predictor variables across all the models were used. The variables selected were based on significance in univariate models of the main outcome (PO2) and likelihood ratio tests for those univariate models.
11. In addition to history of asthma, current asthma was also derived at the index date and reported. This was defined as a medical code representing asthma (same definition as used for history of asthma) in the 12 months prior to index date without any recording of a medical code for resolved asthma in the same 12-month interval. The medical codes representing resolution were as follows:

Medcode	Read code	Description
10996	2126200#	Asthma resolved
11839	212G.00#	Asthma resolved

12. Changes to HCU endpoints:
    - Read codes were used to remove any study related calls or visits from the SLS-UC data. The physical contact only analysis was removed as calls cannot be consistently separated from physical contact in both CPRD and the SLS-UC data. In CPRD, a consultation file contains a lookup for the type of consultation that enabled this separation. In the SLS-EHR data however calls could only be identified if the GPs had entered a Read code which indicates that a phone call has taken place. The study team do not believe that GPs consistently used this Read code.
    - Adherence measures of Percent Days Covered (PDC) and Medication Possession Ratio (MPR) have been removed as there was not enough information contained in the CPRD to consistently and adequately derive these variables without making extremely strong assumptions. These were replaced by a simpler medication adherence outcome of counts of COPD medications only.

- The outcome variable for the sum of quantity of prescriptions was removed. This was for similar reasons to the removal of the medication adherence variables it was trying to replace. It was not possible to calculate the quantity items prescribed in each prescription consistently without making over ambitious assumptions. Also, given the variety of treatments, the same quantity may actually mean a different amount of medication, which could have led to a bias if there was differential prescribing of trial medication between the two groups.
- It was not possible to carry out analysis on COPD related or pneumonia related death as information on cause of death was not available in either the SLS-database or SLS-EHR datasets.

8.7. Quality control and quality assurance

The programming for derivation of datasets and comparison of CPRD with SLS-database was double coded, with the exception of the derivation of variables that used the raw EHR data. The primary analysis was performed at UoM and the quality control (QC) was carried out by GSK.

As GSK QC analysts did not have access to the raw SLS-EHR data, derivation of the dataset SLS-EHR was carried out at UoM, with an internal QC of all variables and double coding of the outcome variables. The derivation of the CPRD comparator used the same code that was double coded by GSK, as did all the code to run the analyses.

8.7.1. Limitations of the research methods

The Hawthorne effect can only be evaluated for the SLS-UC comparison. This does not give definite evidence about whether the predictive effect of FF/VI would differ in the general population; this information could only truly be obtained following use of FF/VI in the general population.

There is no direct metric by which ‘representativeness’ of the SLS-UC cohort can be measured.

While both the SLS-EHR and CPRD are sources of primary care data where data are collected in a broadly consistent manner, some data (hospital-validated COPD diagnoses, pneumonia data, and pharmacy data) for SLS-UC participants were collected using a different mechanism to CPRD. In this study protocol, only serious pneumonia defined by hospitalisation were assessed, which is a subset of total pneumonia cases recorded in the SLS-COPD study. Hence any differences (either in representativeness or treatment response) observed between the SLS and CPRD cohorts could be attributed to differences in data quality and the data collection mechanism. This was mitigated by an additional comparison of SLS data with CPRD data from within Greater Manchester.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

This study used anonymised data from the SLS-COPD study and CPRD.

For SLS-UC patients, individual subject consent had already been collected as part of the wider SLS-COPD study. General practices contributing to CPRD consent on behalf of their patients; patients and practices could opt out of CPRD at any time. Furthermore, internal ethical approval was sought and obtained from the UoM.

Linkage of the CPRD to other datasets such as HES was undertaken by a trusted third party (NHS Digital). The identifiers (date of birth, gender, NHS number, postcode of residence) required for linkage were sent directly from the originating general practice to NHS Digital. CPRD held a local subject identifier which was meaningful only at the subjects' registered general practice. This identifier was 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 removed 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 was conditional on approval of a study protocol by the CPRD Independent Scientific Advisory Committee (ISAC). In addition to ISAC approval, the protocol was also reviewed by GSK's Real World Evidence and Epidemiology Protocol Review Forum.

9.2. Subject confidentiality

The SLS data was anonymised at source by the SLS team before being passed to UoM. The CPRD only contained 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 study partners were done so 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. Participants

The SLS-UC care cohort comprised 1,403 participants. In total, within the CPRD, there were 164,400 COPD patients eligible for HES linkage. From this population, three versions of the CPRD-xGM-IC analytic populations were determined for different objectives;

- CPRD-xGM-IC (with COPD exacerbations defined from primary care data only); n=16,758. This cohort was compared to SLS-EHR data and used for PO1 and PO2. If a patient was having an exacerbation at a proposed index date, their index date was delayed until the exacerbation resolved.
- CPRD-xGM-IC (with COPD exacerbation defined from primary care+secondary care): n=16,745 patients. This cohort was compared to SLS-database data, due to the availability of secondary care data in both cohorts, and used for PO3.
- CPRD-xGM-IC (with COPD exacerbations defined from primary care data only); n=16,799. This cohort was compared to SLS-EHR data and used for SO3. In contrast to the above cohort, index dates were not delayed until after the end of an exacerbation. This was to avoid creating a false decrease in events when moving into the year of the trial.

10.2. Descriptive data including baseline characteristics

Per the study design, the results of the analyses of PO1 include discussion of the descriptive data. This information can be found in Section 10.3.1.

10.3. Results of essential analyses

10.3.1. PO1: Characterisation of study participants

Analyses for PO1 and PO2 were replicated using both SLS data sources, however we focus here on the comparison between the CPRD-GM-IC, CPRD-xGM-IC and the SLS-UC group using the SLS-EHR cohort, as this represents COPD exacerbations recorded in a consistent manner between datasets i.e. derived algorithmically. Further, as there was no secondary care linkage in the SLS-EHR, this comparison uses only primary care data from the CPRD.

Across most baseline variables the SLS-UC, CPRD-xGM-IC and CPRD-GM-IC cohorts were broadly comparable (Table 3). The distribution of index dates was generally consistent between the cohorts, and the most notable differences seen in the SLS-UC group compared with the CPRD cohorts were for age, where SLS-UC participants tended to be younger than subjects in the CPRD-GM-IC and CPRD-xGM-IC cohorts (mean ages 66.7, 69.8 and 71.1 years, respectively); socio-economic status, where the SLS-UC cohort was more deprived than the CPRD cohorts (51.5%, 47.1% and 21.4%, respectively, in the most deprived quintile), and the rate of COPD exacerbations in the 12-months prior to index date, where the SLS-UC cohort had a higher rate of

exacerbations than the CPRD cohorts (rate per person year of 1.94 [95% CI: 1.86, 2.02], 1.80 [95% CI: 1.74, 1.86] and 1.66 [95% CI: 1.64, 1.68] for SLS-UC, CPRD-GM-IC and CPRD-xGM-IC, respectively).

Table 3 Baseline variables for CPRD-GM-IC, CPRD-xGM-IC and SLS-UC (using SLS-EHR)

Variable	CPRD-GM-IC	CPRD-xGM-IC	SLS-UC (using SLS-EHR)
N	2049	16,758	1,403
Index date			
5th percentile	03 June 2012	31 May 2012	31 May 2012
25th percentile	09 October 2012	03 October 2012	03 October 2012
50th percentile	09 July 2013	17 July 2013	23 July 2013
75th percentile	24 April 2014	24 April 2014	12 May 2014
95th percentile	23 September 2014	22 September 2014	23 September 2014
Sex			
Male	869 (42.41%)	8,163 (48.71%)	732 (52.17%)
Female	1,180 (57.59%)	8,595 (51.29%)	671 (47.83%)
Age			
Mean (95% CI)	69.77 (69.30-70.23)	71.12 (70.96-71.29)	66.73 (66.21-67.25)
Median (2.5%-97.5% range)	69.96 (47.57-89.22)	71.41 (48.14-90.21)	67.00 (46.00-85.00)
Missing	0.00%	0.00%	0.00%
SES IMD 2010 quintiles			
Missing	0 (0.00%)	8 (0.05%)	8 (0.57%)
5 (least deprived)	127 (6.20%)	2,499 (14.91%)	72 (5.13%)
4	219 (10.69%)	3,428 (20.46%)	105 (7.48%)
3	283 (13.81%)	3,348 (19.98%)	202 (14.40%)
2	456 (22.25%)	3,897 (23.25%)	294 (20.96%)
1 (most deprived)	964 (47.05%)	3,578 (21.35%)	722 (51.46%)
Current medication (prescriptions in last 3 months)			
None of the below treatments in the last 3 months	165 (8.05%)	1,693 (10.10%)	145 (10.33%)
LABA only	32 (1.56%)	252 (1.50%)	19 (1.35%)
LAMA only	174 (8.49%)	1,480 (8.83%)	143 (10.19%)
ICS only	114 (5.56%)	758 (4.52%)	62 (4.42%)
LABA/LAMA	25 (1.22%)	177 (1.06%)	18 (1.28%)
LAMA/ICS	24 (1.17%)	235 (1.40%)	56 (3.99%)
LABA/ICS	594 (28.99%)	4,529 (27.03%)	337 (24.02%)
LABA/LAMA/ICS	921 (44.95%)	7,634 (45.55%)	623 (44.40%)
Comorbidities (history of)			
Anxiety	572 (27.92%)	3,661 (21.85%)	301 (21.45%)
Asthma	1,213 (59.20%)	10,083 (60.17%)	755 (53.81%)
Cardio-/cerebrovascular disease	387 (18.89%)	3,222 (19.23%)	238 (16.96%)
Depression	767 (37.43%)	5,466 (32.62%)	344 (24.52%)
Gastro-oesophageal reflux disease/peptic ulcer disease (GORD/PUD)	571 (27.87%)	4,120 (24.59%)	355 (25.30%)
Pneumonia	282 (13.76%)	2,635 (15.72%)	147 (10.48%)

Variable	CPRD-GM-IC	CPRD-xGM-IC	SLS-UC (using SLS-EHR)
Current comorbidity (reported in last 12 months)			
Asthma	485 (23.67%)	4,018 (23.98%)	298 (21.24%)
Charlson comorbidity index			
0	341 (16.64%)	2,569 (15.33%)	271 (19.32%)
1-2	1020 (49.78%)	8,226 (49.09%)	703 (50.11%)
3-4	462 (22.55%)	4,094 (24.43%)	297 (21.17%)
5+	226 (11.03%)	1,869 (11.15%)	132 (9.41%)
COPD exacerbation history in 12 months prior to index date			
Events	3,262	24,892	2,372
Rate per person year (95% CI)	1.80 (1.74-1.86)	1.66 (1.64-1.68)	1.94 (1.86-2.02)
FEV_1%			
Mean (95% CI)	56.72 (55.83-57.61)	55.84 (55.53-56.16)	60.30 (59.17-61.43)
Median (2.5%-97.5% range)	55.80 (22.68-95.23)	55.07 (22.34-95.97)	60.90 (24.30-98.90)
Missing	12.79% missing	14.25% missing	21.53% missing
FEV_1/FVC (%)			
Mean (95% CI)	61.06 (60.24-61.88)	60.51 (60.22-60.80)	54.39 (53.58-55.19)
Median (2.5-97.5% range)	60.60 (32.20-95.00)	60.00 (31.00-95.70)	54.80 (28.65-79.09)
Missing	23.13% missing	21.58% missing	21.53% missing
GOLD Stage			
Missing	479 (23.38%)	3,783 (22.57%)	217 (15.47%)
0 (FEV_1/FVC =>70)	451 (22.01%)	3,589 (21.42%)	147 (10.48%)
1 (FEV_1/FVC <70, FEV_1% =>80)	70 (3.42%)	522 (3.11%)	84 (5.99%)
2 (FEV_1/FVC <70, 50 <= FEV_1% <80)	527 (25.72%)	4,347 (25.94%)	522 (37.21%)
3 (FEV_1/FVC <70, 30 <= FEV_1% <50)	422 (20.60%)	3,528 (21.05%)	332 (23.66%)
4 (FEV_1/FVC <70, FEV_1% <30)	100 (4.88%)	989 (5.90%)	101 (7.20%)
MRC dyspnoea score			
Missing	199 (9.71%)	1,719 (10.26%)	12 (0.86%)
1 (least breathlessness)	179 (8.74%)	1,530 (9.13%)	154 (10.98%)
2	634 (30.94%)	4,912 (29.31%)	510 (36.35%)
3	532 (25.96%)	4,509 (26.91%)	470 (33.50%)
4	417 (20.35%)	3,299 (19.69%)	233 (16.61%)
5 (most breathlessness)	88 (4.29%)	789 (4.71%)	24 (1.71%)
Smoking			
Never	165 (8.05%)	1,349 (8.05%)	59 (4.21%)
Ex	1,177 (57.44%)	10,033 (59.87%)	678 (48.33%)
Current	707 (34.50%)	5,376 (32.08%)	666 (47.47%)
BMI (kg/m^2)			
Missing	68 (3.32%)	940 (5.61%)	281 (20.03%)
18.50-24.99	651 (31.77%)	5,005 (29.87%)	351 (25.02%)
<18.50	94 (4.59%)	793 (4.73%)	52 (3.71%)
25.00 - 29.99	608 (29.67%)	5,121 (30.56%)	349 (24.88%)
>=30.00	628 (30.65%)	4,899 (29.23%)	370 (26.37%)
Vaccinations			
Influenza	1,856 (90.58%)	15,105 (90.14%)	1,267 (90.31%)

Variable	CPRD-GM-IC	CPRD-xGM-IC	SLS-UC (using SLS-EHR)
Pneumococcal	320 (15.62%)	2,259 (13.48%)	241 (17.18%)

Source: Table 21

10.3.1.1. Missing data

In the CPRD-xGM-IC dataset, GOLD stage (22.6%), FEV_1/FVC ratio (21.6%), FEV_1% (14.3%) and MRC dyspnoea score (10.3%) had the most missing data (Table 4). In the SLS-EHR dataset, FEV_1/FVC ratio and FEV1% (21.5% each), BMI (20.0%) and GOLD stage (15.5%) had the most missing data (Table 4). The amount of missing data for the other covariates in both datasets was low (<10%).

Notably, the proportion of missing data for MRC dyspnoea score was higher in the CPRD-xGM-IC datasets than the SLS-EHR dataset (10.3% vs 0.86%, respectively), whereas the amount of missing data for BMI was higher in the SLS-HER dataset compared with the CPRD-xGM-IC datasets (20.0% vs 5.6%, respectively).

The amount of missing data for each variable was similar between the imputed and complete datasets for CPRD-xGM-IC (Source Data: Results Table 24.1) and SLS-EHR (Source Data: Results Table 25.1).

Table 4 Summary of percentage missing for each variable in CPRD-GM-IC, CPRD-xGM-IC and SLS-UC (using SLS-EHR)

Variable	Percentage missing CPRD-GM-IC	CPRD-xGM-IC	SLS-UC (using SLS-EHR)
SES IMD 2010 quintiles	0.00%	0.05%	0.57%
FEV_1%	12.79%	14.25%	21.53%
FEV_1/FVC ratio	23.13%	21.58%	21.53%
GOLD stage	23.38%	22.57%	15.47%
MRC dyspnoea score	9.71%	10.26%	0.86%
Smoking	0.00%	0.00%	0.00%
BMI	3.32%	5.61%	20.03%

Source: Table 23.2, Table 24.2 and Table 25.2

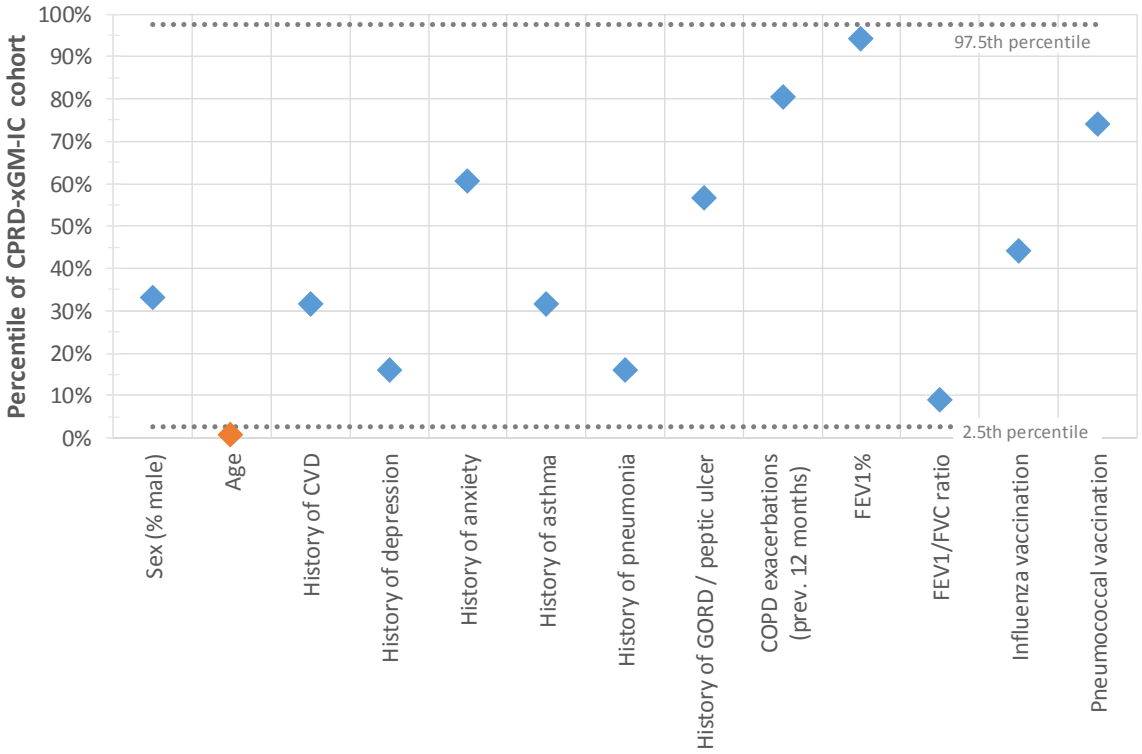
10.3.1.2. PO1 Descriptive modelling

Descriptive modelling was used to determine whether the characteristics observed within the SLS-UC cohort using the SLS-EHR are unusual by comparison with regional variation observed within CPRD-xGM-IC cohort (for continuous variables see Source Data: Results Table 26.1, for categorical variables see Source Data: Results Table 26.2). Graphical summaries of these data were created to illustrate where the SLS-UC percentile falls compared to the empirical distribution of the variable of interest by LA within the CPRD-xGM-IC and the CPRD-GM-IC (for continuous variables see Figure 1, for categorical variables see Figure 2).

Among the continuous variables, age was the only covariate that was found to be unusual for the SLS-UC cohort compared with the CPRD-xGM-IC cohort, with all other

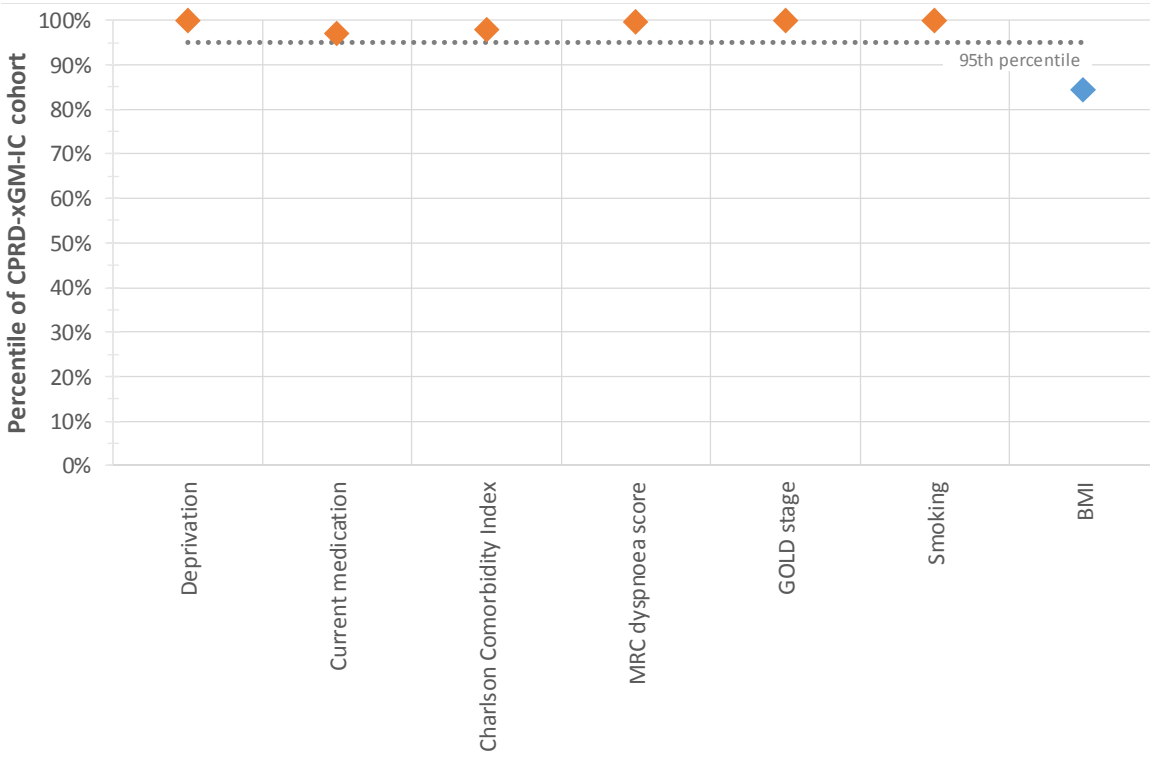
covariates deemed usual. The SLS-UC percentile for age was very low (0.67), indicating participants enrolled in the SLS COPD arm were younger than the average COPD patient in England. Among the categorical variables, SES (SLS-UC was more deprived), current medication group (SLS-UC had fewer patients receiving treatment with ICS/LABA and more receiving ICS/LAMA), Charlson comorbidity index (SLS-UC was less co-morbid), MRC dyspnoea score (SLS-UC had more severe scores), GOLD stage (SLS-UC had more severe scores) and smoking status (SLS-UC had more current smokers), were all unusual. Figure 3 presents this in more detail for the categorical variables.

Figure 1 Graphical representation of SLS-UC (using the SLS-EHR) percentiles in the context of regional variation within the CPRD-xGM-IC at LA level: Continuous variables



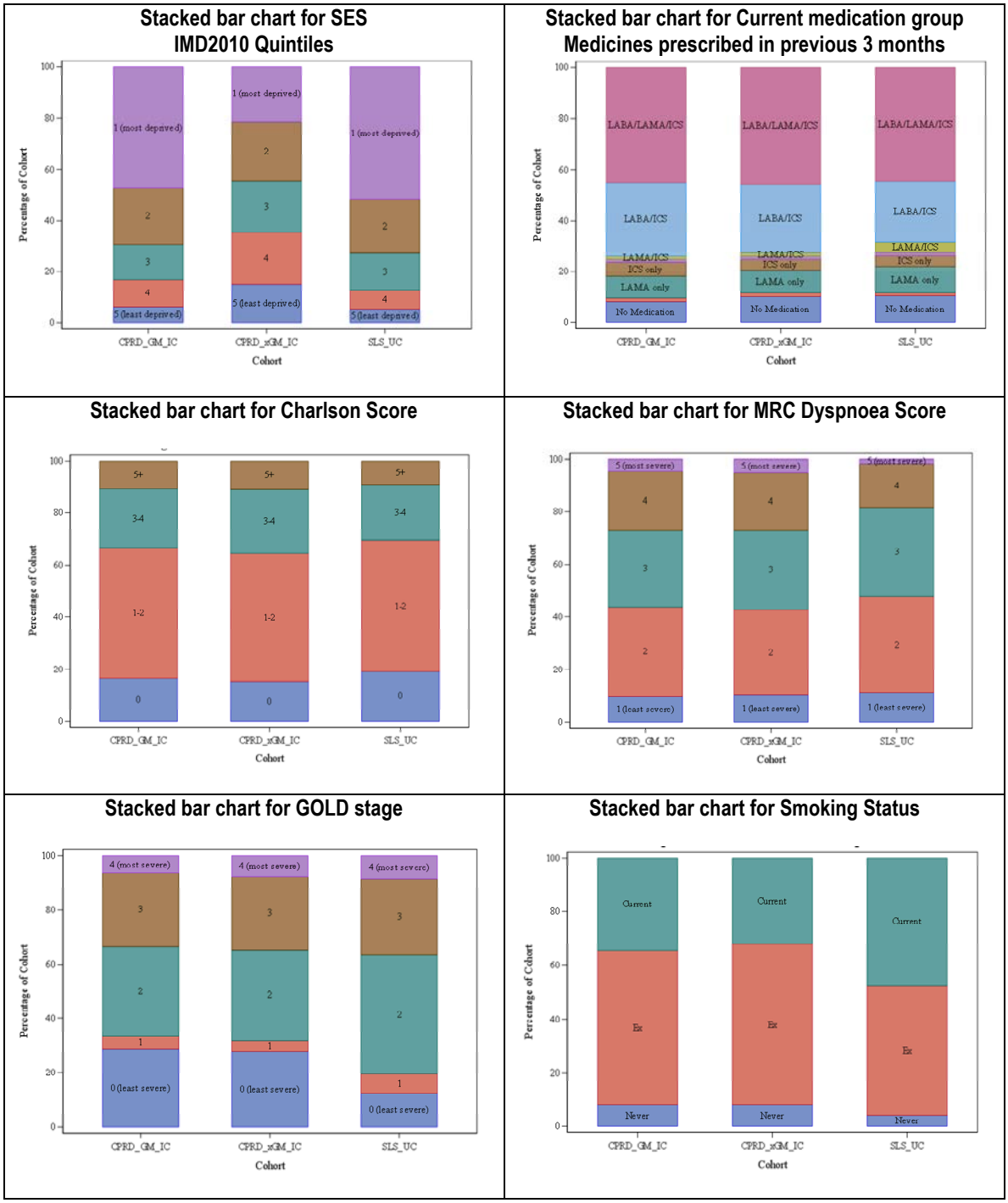
Covariates considered unusual for SLS are shown in orange.
Source: Table 26.1

Figure 2 **Graphical representation of SLS-UC (using the SLS-EHR) percentiles in the context of regional variation within the CPRD-xGM-IC at LA level: Categorical variables**



Covariates considered unusual for SLS are shown in orange.
Source: Table 26.2

Figure 3 Stacked bar charts for categorical variables comparing CPRD-GM-IC, CPRD-xGM-IC and SLS-UC cohorts (using SLS-EHR)



Source: Figure 19, Figure 20, Figure 21, Figure 22, Figure 24 and Figure 25.

Of interest among the categorical variables, for socioeconomic status, we see more social deprivation in both the SLS-UC and CPRD-GM-IC cohorts compared with the wider CPRD-xGM-IC cohort (51.5%, 47.1% and 21.4%, respectively, in the most deprived quintile; Table 3, Figure 3), deprivation levels were highest among the SLS-UC.

The proportion of current smokers was similar in the CPRD-GM-IC and CPRD-xGM-IC cohorts, with the highest proportion of current smokers in the SLS-UC (34.5%, 32.1% and 47.5%) respectably.

The GOLD stages of participants in the SLS-UC cohort were generally higher than those of subjects in the CPRD-GM-IC and CPRD-xGM-IC cohorts, indicating the SLS-UC cohort experienced more severe COPD (Table 3, Figure 3). The number of participants with GOLD stage of 0 ((FEV_1/FVC =>70) was much lower in the SLS-UC cohort than the CPRD-GM-IC and CPRD-xGM-IC cohorts (10.5%, 22.0 and 21.4%, respectively; Table 3).

The comparisons between the SLS-UC and the CPRD cohorts for PO1 were repeated using the SLS-database and CPRD with primary care+secondary care datasets; results of these analyses are presented in Source Data: Results Table 3, Table 5.2, Table 6.2, Table 7.2, Table 8.1, and Table 8.2 and Source Data: Figure 4, Figure 6 to Figure 9, Figure 11 and Figure 12.

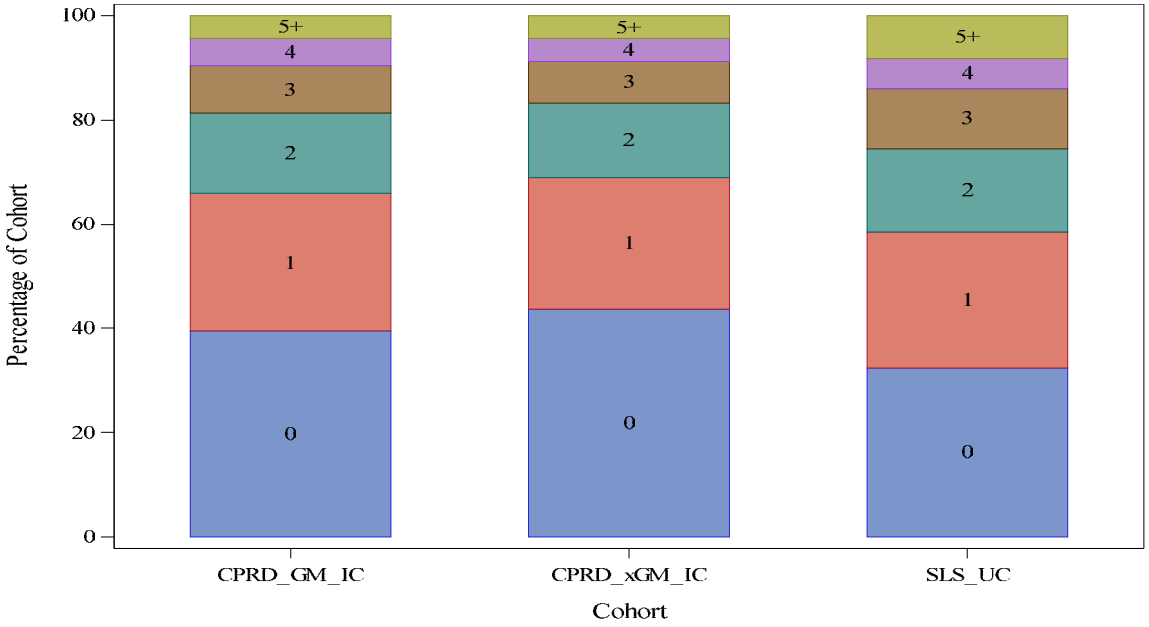
When these regional analyses of difference were repeated using the SLS-database, results remained consistent for vaccination history, however, COPD exacerbation in the past 12 months became unusual with the SLS-UC percentile reported at 98th percentile (SLS median 2.04 exacerbations vs. 1.53 in CPRD; Source Data: Results Table 8.1). This was not unexpected as it reflects self-reports of exacerbations in the SLS-database compared to algorithmically derived data in the CPRD.

10.3.2. PO2: Rate of COPD exacerbation episodes during the 12-month study period

As illustrated in Table 5, where the CPRD-xGM-IC and CPRD-GM-IC cohorts (using primary care only) are compared with SLS-UC cohort (using SLS-EHR), overall unadjusted rates of COPD exacerbations were higher in the SLS-UC cohort than those in both CPRD cohorts (Table 5) during the 12-month study period.

There are fewer patients in the SLS-UC cohort that had no COPD exacerbations than in either CPRD cohort (Figure 4), although almost double the number of patients had >5 exacerbations in SLS-UC compared with the CPRD cohorts. The number of episodes per patient was similar between the CPRD-GM-IC and CPRD-xGM-IC cohorts.

Figure 4 Stacked bar chart for number of COPD exacerbations during 12-month study period for CPRD-GM-IC, CPRD-xGM-IC and SLS-UC (using SLS-EHR)



Source: Figure 17

Table 5 Rate of COPD exacerbation episodes during the 12-month study period for CPRD-GM-IC, CPRD-xGM-IC, SLS-UC (using SLS-EHR)

Variable	CPRD-GM-IC	CPRD-xGM-IC	SLS-UC (using SLS-EHR)
N	2,049	16,758	1,403
Person time	1650.74 years	13,149.92 years	1199.70 years
Number of episodes	2693	20,184	2288
Rate per person year (95% CI)	1.63 (1.57-1.69)	1.53 (1.51-1.56)	1.91 (1.83-1.99)

Source: Table 22

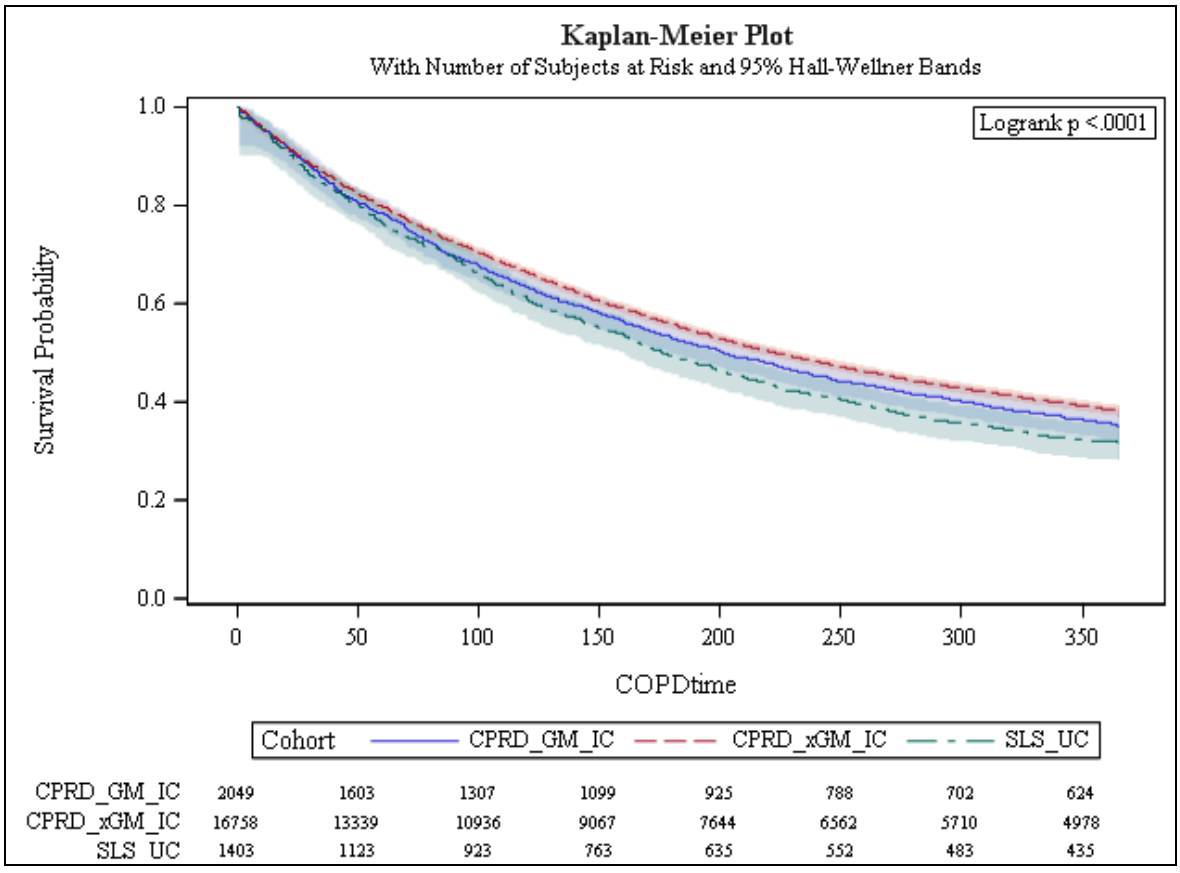
In comparing the crude rates (i.e. the event rate without considering any demographic differences or 'unadjusted') of COPD exacerbations between the three cohorts, the COPD exacerbation rates in the SLS-UC were not unusual in terms of the regional distribution within the CPRD and placed at the upper end of the distribution at 86.9th percentile Source Data: Results Table 27 and Table 28).

In contrast to the crude rates, adjusted Poisson models indicated that rates of COPD exacerbation were significantly higher in the SLS-UC cohort compared with the average in England (RR_{adj}=1.12 95%, CI 1.05, 1.19, p=0.0010; Source Data: Results Table 30) and correspondingly, in the context of local authority variation, SLS-UC rates were unusually high (98.4th percentile; Source Data: Results Table 33).

Similar results were observed when assessing time to first COPD exacerbation; the first COPD exacerbation for SLS-UC participants was recorded at 64 days compared to 84 days for CPRD (median of LAs). Fully adjusted Cox modelling illustrated participation in the SLS-UC was significant in terms of a shorter time to first COPD exacerbation (HR_{adj}=1.14, 95% CI 1.06, 1.22, p=0.004; Source Data: Results Table 32) and when assessing regional variation in fully adjusted models, SLS-UC was not considered unusually different but fell very close to the threshold (96.7th percentile; Source Data: Results Table 35).

In the Kaplan-Meier plot of time until first COPD exacerbation (Figure 5), survival curves for SLS-UC and CPRD-xGM-IC separated almost immediately and continued to diverge during the study period. Despite initial similarities in the survival curves between SLS-UC and CPRD-GM-IC, an increasingly greater proportion of the SLS-UC cohort experienced an exacerbation as time progressed (global log rank test p<0.0001), albeit with overlapping confidence intervals.

Figure 5 Kaplan-Meier plot comparing time until first COPD exacerbation forCPRD-GM-IC, CPRD-xGM-IC and SLS-UC (using SLS-EHR)



Source: Figure 16

10.3.3. PO3: Rate of pneumonia episodes during the 12-month study period

The analyses for PO3 were performed using the SLS-database and CPRD with primary care+secondary care data, as hospital data was required to determine pneumonia hospitalisations. To ensure comparability between datasources, the definition of pneumonia episodes in this study required a hospitalisation where an ICD-10 code of pneumonia was cited.

The crude rate of hospitalised pneumonia appears lower in the SLS-UC cohort in comparison to the CPRD-xGM-IC cohort (76.0 per 1,000 person-years [62.1 to 92.1] vs. 106.9 per 1,000 person-years [101.6 to 112.3]; Table 6).

Table 6 Rate of pneumonia episodes during the 12-month study period for CPRD-GM-IC, CPRD-xGM-IC, and SLS-UC (using SLS-Database)

Variable	CPRD-GM-IC	CPRD-xGM-IC	SLS-UC (using SLS-Database)
N	2,046	16,745	1,403
Person time	1,833.52 years	14,516.13 years	1,368.30 years
Number of episodes	187	1,551	104
Rate per 1,000 person years (95% CI)	101.99 (87.90-117.70)	106.85 (101.59-112.30)	76.01 (62.10-92.10)

Source: Table 37

Descriptive modelling illustrated that the rate of hospitalised pneumonia was not unusual in SLS-UC with respect to regional variation in CPRD and remained usual within subgroups of demographic characteristics or smoking status (Source Data: Results Table 38). Furthermore, there was no evidence of difference in the relative rates (RR_{adj} = 0.97, 95% CI 0.72-1.31, p=0.86; Source Data: Results Table 40) compared to the rest of England. In fully adjusted multi-level models, participation in the SLS was not associated with an unusual count of hospitalised pneumonia episodes (9.8^{th} percentile; Source Data: Results Table 43).

Similar results were seen for the time to first hospitalisation for pneumonia where time to event in the SLS-UC was not different to the rest of England (HR_{adj} = 0.87, 95% CI 0.69-1.12, p= 0.30; Source Data: Results Table 42) and participation in the SLS-UC was not unusual with respect to regional variation seen in the CPRD in time to first hospitalisation for pneumonia (SLS 9.1^{st} percentile; Source Data: Results Table 45).

10.4. Other analyses

10.4.1. SO1: Comparisons of healthcare utilisation, mortality and prescription counts for COPD therapies during the 12-month study period

The data sources used for analyses of coding practices, primary care contact, COPD medication and treatment switching were SLS-EHR compared with CPRD primary care

only. Analyses of mortality and secondary care utilised SLS-Database compared with CPRD primary care+secondary care.

Mortality and healthcare utilisation outcomes

Table 7 outlines mortality and all healthcare utilisation outcomes within the SLS-UC and the CPRD-xGM-IC cohort during the study period. Compared to the CPRD-xGM-IC cohort, the SLS-UC cohort was subject to a lower mortality rate (78.5 per 1000 person-years vs. 17.5 per 1000 person-years, respectively), fewer days spent as an inpatient (6.12 per person-year vs 3.51 per person-year, respectively) and a reduced proportion of patients undergoing a COPD treatment switch during observation (34.7% vs. 40.8%, respectively). There were more COPD medications prescribed in the SLS-UC cohort than the CPRD-xGM-IC cohort (23.4 per person-year vs. 12.9 per person-year, respectively) and a higher rate of primary care contact (49.1 per person-year vs. 27.4 per person-year, respectively) (Table 7, Source Data: Results Table 48).

Table 7 Mortality and healthcare utilisation outcomes during the 12-month study period for CPRD-GM-IC, CPRD-xGM-IC, and SLS-UC

Outcome	CPRD-GM-IC	CPRD-xGM-IC	SLS-UC
Mortality[a]			
N	2,049	16,758	1403
Person time	1,841.60 years	14,587.83 years	1,370.87 years
Count	144	1145	24
Rate per 1000 person years (95% CI)	78.19 (65.94-92.06)	78.49 (74.01-83.17)	17.51 (11.22-26.05)
Primary care contact[b]			
Person time	1,839.09 years	14,586.70 years	1,350.06 years
Count	48,167	399,291	66,308
Rate per person year (95% CI)	26.19 (25.96-26.43)	27.37 (27.29-27.46)	49.11 (48.74-49.49)
Secondary care contact (days as inpatient)[a]			
Count	10,483	89,207	4,555
Rate per person year (95% CI)	5.69 (5.58-5.80)	6.12 (6.08-6.16)	3.32 (3.23-3.42)
Count of trial related (COPD) prescription items[a]			
Count	25,433	187,396	32,133
Rate per person year (95% CI)	13.81 (13.64-13.98)	12.85 (12.79-12.90)	23.44 (23.18-23.70)
COPD treatment switching[b]			
At some point during 12-month study period	36.16%	40.77%	34.67%

Source: Table 48

a. CPRD primary+secondary care vs. SLS-database

b. CPRD primary care only vs. SLS-EHR

In analyses of these outcomes with respect to the regional variation seen in England, the mortality rate in the SLS-UC was low (percentile = 8.00) but not unusually so, which was mirrored by the sub-group analyses (Source Data: Results Table 54). Multi-level Cox modelling of time to death indicated a very low percentile, classed as unusual, for the SLS-UC; this can be interpreted as an unusually prolonged time to death in the SLS-UC;

taken in conjunction, fewer deaths occurred and, on average, took longer to do so in the SLS-UC cohort (Source Data: Results Table 64).

Primary care contacts were also unusually high for the SLS-UC compared to the rest of England. The unadjusted analyses indicated that the rate of contact with primary care was consistently high across nearly all subgroups (Source Data: Results Table 50); this was confirmed in adjusted Poisson models, where the SLS percentile was 100 (Source Data: Results Table 55). This was not seen for secondary, hospital care (measured as rate of days as an inpatient in secondary care; this was not unusual overall or for any subgroups in the unadjusted analyses (Source Data: Results Table 51) or in adjusted Poisson modelling, where the SLS percentile was fairly low at 12.2 (Source Data: Results Table 57).

In unadjusted analyses, COPD medication prescribing was unusually high in the SLS-UC compared to the rest of England, both overall and in almost all subgroups (Source Data: Results Table 52), however after full adjustment using a Poisson model, it was not classed as unusual but the percentile for the SLS was on the upper end of the distribution (percentile = 87.9; Source Data: Results Table 59). Treatment switching (recorded as a binary variable of whether patients made a switch during the 12-month study period or not) was classed as not unusual in the SLS-UC compared to the rest of England in both unadjusted and fully adjusted models (Source Data: Results Table 53 and Table 61, respectively); SLS percentile was low (percentile = 4.8).

EHR coding practices (Vision vs. EMIS)

An analysis was conducted to assess medical coding practices between primary care EHR systems (Vision or EMIS) for SLS-UC participants during the 12-month study period. There was some evidence of differential coding methodologies between practices using the different systems. Patients registered with an EMIS practice as opposed to a Vision practice tended to have more medical codes entered in their primary care notes, both when considering all medical codes and when restricted to COPD-related medical codes only (relative rate [RR] 1.64, 95% CI 1.50-1.79, p<0.0001 [Source Data: Results Table 47.1] and RR 1.20, 95% CI 1.09-1.32, p=0.0002 [Source Data: Results Table 47.2], respectively).

10.4.2. SO2: Alternate definitions of COPD exacerbation and pneumonia episodes

In order to derive outcomes consistently between data sources, analyses of different definitions of COPD exacerbations utilised SLS-EHR compared with CPRD primary care only.

COPD exacerbation definitions are presented in Section 8.3.5.2. In comparison to CPRD-xGM-IC, SLS-UC exhibited higher rates of COPD exacerbation episodes across all definitions of COPD exacerbation (Table 8). The difference was most marked for definition D, which is the most specific COPD exacerbation definition, as it uses the specific code for acute exacerbation.

Table 8 COPD exacerbation rates during the 12-month study period using alternative definitions for CRPD-GM-IC, CPRD-xGM-IC, and SLS-UC (SLS-EHR)

Outcome	CPRD-GM-IC	CPRD-xGM-IC	SLS-UC
COPD Definition B			
N	2049	16,758	1403
Person time	1,741.29 years	13,948.09 years	1,286.74 years
Count	1,433	9,152	1,176
Rate per person year (95% CI)	0.82 (0.78-0.87)	0.66 (0.64-0.67)	0.91 (0.86-0.97)
COPD Definition C			
Person time	1,748.81 years	14,017.80 years	1,300.85 years
Count	1,327	8,159	983
Rate per person year (95% CI)	0.76 (0.72-0.80)	0.58 (0.57-0.59)	0.76 (0.71-0.80)
COPD Definition D			
Person time	1,800.87 years	14,345.10 years	1,316.41 years
Count	583	3,497	766
Rate per person year (95% CI)	0.32 (0.30-0.35)	0.24 (0.24-0.25)	0.58 (0.54-0.62)

Source: Table 65

Using the alternative definitions, the SLS-EHR COPD exacerbation rate was consistently found to be not unusual in comparison to LAs in CPRD-xGM-IC across all COPD exacerbation episode definitions (Source Data: Results Table 66 to Table 68). These outcomes were then modelled both as a count (using Poisson models) and as time to event (using Cox models). Results for COPD definition B, the most similar definition to the main COPD definition used in PO1, found the SLS-UC was not unusual but percentiles were high (85.3 [number of exacerbations] and 92.6 [time to exacerbation]; Source Data: Results Table 70 to Table 72). Similar results were seen for COPD definition C, where the SLS-UC was classed as not unusual but had percentiles towards the upper end of the distribution (81.1 [number] and 85.1 [time]; Source Data: Results Table 74 to Table 76). Results for COPD definition D which was the most specific of the alternative definitions as only considered codes for acute exacerbations of COPD, illustrated very high rates for SLS-UC; the percentile for the number of exacerbations was 97.4, hence bordering the usual/unusual cut-off, and the percentile for time to event was 98.4, indicating an unusually short time to exacerbation (Source Data: Results Table 78 to Table 80).

The analyses for SO2 were repeated an alternate definition of pneumonia as below using the SLS-database and CPRD primary care+secondary care, due to the requirement for hospitalisation data, where pneumonia was classed as the primary/main diagnosis of the hospitalisation (see Section 8.6.1.6).

Table 9 Rate of pneumonia (as a primary/main diagnosis only) during the 12-month study period for CPRD-GM-IC, CPRD-xGM-IC, SLS-UC (using SLS-Database)

Variable	CPRD-GM-IC	CPRD-xGM-IC	SLS-UC (using SLS-Database)
N	2,044	16,721	1,403
Person time (years)	1,817.39	14,389.30	1,362.14
Count	120	951	77
Rate per 1,000 person years (95% CI)	66.03 (54.74-78.95)	66.09 (61.96-70.43)	56.53 (44.61-70.65)

Source Table 65

Similar to results in PO3, rates of pneumonia, defined here as primary/main diagnosis only, appeared slightly lower, though not significantly so, in the SLS-UC compared to the CPRD cohorts (Table 9; Source Data: Results Table 65). The SLS-UC was not unusual compared to the rest of England, when modelled as rate or time to event, where the percentiles are towards the higher end of the distribution but still well within normal range (percentile 79.8 [Poisson model using number] and 67.0 [Cox model using time]; Source Data: Results Table 82 to Table 84).

10.4.3. SO3: COPD exacerbation rates and health care utilisation compared in the 12 months prior to the SLS trial to the SLS study period

This analysis compares COPD exacerbation episodes and health care utilisation in the 12-months prior to the SLS trial to those seen during the 12-month study period itself, using SLS-EHR database and the CPRD primary care data. It provides further contextual information for the results above as to whether key outcomes which were unusual during the SLS study period were different before the trial commenced, indicating that the trial itself was not the determining factor.

Table 10 Crude rate of outcomes in the 12-months prior to the SLS trial and during the SLS study period for the CPRD-xGM-IC and SLS-UC (using SLS-EHR)

Outcome	Outcomes in the year prior to the trial		Outcomes in the year of the trial	
	CPRD-xGM-IC	SLS-UC (SLS-EHR)	CPRD-xGM-IC	SLS-UC (SLS-EHR)
COPD exacerbations[a]				
N	16,799	1,403	16,799	1,403
Person time	15,062.97 years	1,223.16 years	13,137.07 years	1,199.74 years
Count	23,598	2,395	20,177	2,282
Rate per person year (95% CI)	1.57 (1.55-1.59)	1.96 (1.88-2.04)	1.54 (1.51-1.56)	1.90 (1.82-1.98)
Primary care contacts				
Person time	16,786.20 years	1,389.03 years	14,642.32 years	1,350.10 years
Count	434,636	63,485	401,260	66,311
Rate per person year (95% CI)	25.89 (25.82-25.97)	45.70 (45.35-46.06)	27.40 (27.32-27.49)	49.12 (48.74-49.49)
COPD-related prescription items count				
Person time	16,787.50 years	1,402.04 years	14,643.45 years	1,370.90 years
Count	208,374	52,549	188,018	32,133
Rate per person year (95% CI)	12.41 (12.36-12.47)	37.48 (37.16-37.80)	12.84 (12.78-12.90)	23.44 (23.18-23.70)
Treatment switching				
At some point during the 12-month study period	51.06%	48.40%	40.76%	34.67%

Source: Table 86.1 and Table 86.2

a. COPD exacerbations defined using the full algorithm as per PO2

As illustrated in Table 10, overall unadjusted rates of COPD exacerbations (defined using the full algorithm in PO2) both in the 12 months before and during the 12-month study period were higher in the SLS-UC arm compared to the wider CPRD population. In both CPRD-xGM-IC and SLS-UC, rates of COPD exacerbation appear to drop slightly (but not significantly) during the 12-month study period compared to the 12-months before. Similar patterns were seen when the alternative definitions of COPD exacerbations (B, C and D) were assessed (Source Data: Results Table 86.1 and Table 86.2), with the exception being that was a large increase in COPD exacerbations (as a proportion of the total) defined by algorithm D [specific acute exacerbation code only] from 0.43 to 0.58 exacerbations per year in the pre-trial compared with the trial period.

In comparing the crude changes in rates of COPD exacerbations between the cohorts from before to during the trial, the change in COPD exacerbation rate (main PO2 definition) in the SLS-UC was not unusual in terms of the regional distribution within the CPRD and placed at the 49.4th percentile (Source Data: Results Table 87). This finding was replicated for the other definitions, where the unadjusted percentiles were 60.4, 79.8 and 91.2 for definitions B, C and D, respectively (Source Data: Results Table 88 to Table 90).

These findings are reflected in the multilevel adjusted Poisson models (summarised in Table 11), the relative rate of COPD exacerbation (main PO2 definition) in SLS-UC comparing the 12-month period before the trial to during the 12-month study period was 1.02, which placed the SLS within the usual range of regional variation at the 64th percentile (Source Data: Results Table 94.1). COPD exacerbation definition B was also usual with an SLS-UC percentile of 93.2 (Source Data: Results Table 96.1). However, for COPD exacerbation definitions C and D, the change in the SLS-UC was deemed unusual, with percentiles of 97.6 and 100, respectively (Source Data: Results Table 98.1 and Table 100.1). For the most specific definition, definition D, this represented a substantial rise in recorded exacerbations with a before to during trial rate ratio of 1.34 in SLS-UC (Source Data: Results Table 100.1)

Table 11 Summary of relative rate ratios of outcomes comparing before to during the trial in in fully adjusted multilevel models

Variable	CPRD-xGM-IC-2.5-percentile	CPRD-xGM-IC-median	CPRD-xGM-IC-97.5-percentile	SLS-UC-value	SLS-UC-percentile	Unusual-Flag	Source table number
COPD exacerbation (PO2 definition; Definition A)	0.88	0.10	1.15	1.02	64.17	0	94.1
COPD exacerbation (Definition B)	0.72	0.91	1.04	1.02	93.19	0	96.1
COPD exacerbation (Definition C)	0.78	0.93	1.05	1.05	97.63	1	98.1
COPD exacerbation (Definition D)	0.81	0.96	1.21	1.34	100.00	1	100.1
Primary care contacts	0.97	1.07	1.19	1.08	57.06	0	102.1
COPD prescription count	0.95	1.03	1.08	0.63	0	1	104.1
Treatment switching	0.60	0.63	0.65	0.59	0.27	1	106.1

Rate ratio denotes the combined effect of the random coefficient and fixed effect.

Contact with primary care

The crude rate of primary care contacts was significantly higher in the SLS-UC cohort compared to the wider population, both before and during the trial. There was a slight increase in primary care contacts within the SLS-UC cohort between the periods (45.7 days [prior period] to 49.1 days [during trial); this was also seen within in the CPRD (25.9 days to 27.4 days, respectively) but was not as marked (Table 10). In assessing these changes with respect to regional variation, this change in primary care contact was high but not unusually (Source Data: Results Table 91) and when fully adjusted, the relative rate of contacts in the SLS-UC comparing the before and during the trial periods was 1.08, placing the SLS-UC at the 57.1th percentile (Table 11). Although the change in the SLS-UC was not unusual over time, the rate of contact with primary care overall in the SLS-UC was very high and still deemed as unusual, after full adjustment for all covariates (SLS-UC = 100th percentile; Source Data: Results Table 102.2).

Prescription counts and treatment switching

In the 12-month period before and during the 12-month study period, the crude rate of COPD prescriptions was almost 3 times higher in the SLS-UC cohort compared with the CPRD cohort (Table 10). Comparing the two periods, prescription counts remained largely unchanged for the CPRD cohort, but sharply decreased for the SLS-UC cohort (12.4 to 12.8 per person-year vs. 37.5 to 23.4 per person-year, respectively; Table 11). This substantial decline in the SLS-UC is unusual compared to all other LAs in CPRD, both overall and for each subgroup (Source Data: Results Table 92); this observation holds true when fully adjusted for all covariates, with the SLS-UC placed on the 0th percentile, indicating a large drop in prescriptions from before to during the trial (Table 11). Despite this, the rate of COPD prescriptions in the SLS-UC is still very high overall (100th percentile) (Source Data: Results Table 104.2).

The proportion of individuals undergoing a switch of COPD treatment decreased for both CPRD and SLS-UC between the 12-months prior to and 12-month study period, but the absolute difference was more marked during the year of the trial (48.4% vs. 51.1% [CPRD-xGM-IC] and 34.7% vs 40.8% [SLS-UC]; Table 11). The probability of treatment switching also decreased significantly in the SLS-UC cohort; there was an unusually low proportion of participants undergoing a treatment switch in SLS versus other LAs in terms of before/during trial rate (Table 11).

All additional results are described in Appendix 1 and source data is available in ANNEX 1.

10.5. Adverse events/adverse reactions

This was a retrospective study.

Based on the study objectives, and retrospective design of the study, it was unlikely that adverse events would have been identified during this study. Adverse events arising from the SLS trial will have previously been reported during the trial period. The CPRD is a anonymised source of patient data, as such, does not contain the minimum criteria for

adverse events reporting: an identifiable patient. Free text data were not available from CPRD, precluding causality determination of any potential adverse events.

11. DISCUSSION

This aim of this study was to contextualise the SLS by evaluating the representativeness of Salford and the potential Hawthorne effect. In particular, we assessed differences in demographics (PO1), COPD exacerbation (PO2) and hospitalised pneumonia (PO3) between the UC arm of the SLS and the wider England COPD population using cohorts derived from the CPRD. We also compared healthcare utilisation endpoints (SO1), conducted a thorough sensitivity analysis to a variety of definitions of COPD exacerbations and of pneumonia (SO2), and conducted a 'difference of difference' approach to compare outcomes in the year before the SLS was initiated compared to the year of the trial itself (SO3).

11.1. Interpretation of results

11.1.1. PO1: Representativeness of SLS-UC cohort

Compared with the wider population of COPD patients in England, COPD patients in SLS-UC were deemed not unusual in the context of regional variation for gender, past history of other medical conditions (CVD, depression, anxiety, asthma, pneumonia or gastro-oesophageal reflux/peptic ulcer disease), COPD exacerbation history in the year before the trial, immunisation for respiratory disease or spirometry (measured by FEV_1% and FEV_1/FVC ratios).

In contrast, there were several factors which were classified as unusual when comparing the distributions among patients in SLS-UC versus regional variation seen in COPD patients in England. The SLS-UC participants tended to be younger, had a lower Charlson index, a higher GOLD stage but lower MRC dyspnoea scores (a patient-reported measure) and a different distribution of usual care medications. The Charlson index is a predictive measure of mortality based on the presence of specific comorbidities; it is not unexpected that Charlson scores were lower among SLS-UC participants given their younger age and that they were medically deemed to be fit enough to participate in a trial (i.e. those with life threatening conditions were excluded from the SLS-COPD), a criterion which could not be implemented for the CPRD populations. SLS-UC participants also had unusually high smoking rates and levels of deprivation. Obesity rates (BMI >30 kg/m^2) were high, but not unusually so. Such observations were to be as expected as Salford is known to have amongst the highest levels of smoking, deprivation and obesity across the population (Public Health England, 2015).

As a general note, the bounds for deeming a value of a variable, coefficient or intercept associated with being a member of the SLS-UC cohort in comparison to membership of a non-Greater Manchester LA (i.e. outside the bounds of 2.5 to 97.5 percentile and 0 to 95 percentile for continuous and categorical analyses, respectively) were set by the CHESS study team. It could be argued that these cut-offs are arbitrary, but they were designed to identify those observations that lie in the most 'unusual' 5% of the distribution, in a

manner that is analogous to conventional hypothesis testing (i.e. assumption of significance at α=0.05). Therefore, whether a result was declared 'usual' or 'unusual', especially for results on the border of our cut-off points, should be interpreted in the context of the percentile in which the observation for membership of the SLS-UC cohort lies.

Differences between the SLS-UC and CPRD cohorts could be the result of number of underlying factors in how these separate cohorts were selected. Identification of patients for potential inclusion in SLS is unlikely to have been random; GPs would have knowledge of their patients which could mean that patients with more severe disease, a notable risk factor history, and who were considered able to complete the trial, may have been more likely to be selected. In terms of selection for the CPRD cohort, patients only needed to fulfil the criteria of the SLS-COPD trial. Other patient characteristics (e.g. attitude towards clinical research, social support, life-limiting disease) that could potentially modulate the probability of being considered for the trial by GPs were not considered; this may have also contributed to the differences between the CPRD and SLS-UC cohorts.

11.1.2. PO2: Hawthorne effect as assessed by COPD exacerbations

When using the EHR data to define exacerbations in the SLS-UC cohort, rates of COPD exacerbation were higher than the England average and were unusually high in Salford in fully adjusted models. Despite having adjusted for population characteristics such as deprivation and smoking which may influence COPD exacerbations, reported exacerbation rates in SLS-UC compared to wider CPRD population overall are high. In line with this, high recorded exacerbation rates were already present in Salford before the trial commenced. In addition, we noted that when using the most specific definition of COPD exacerbations (use of acute exacerbation codes only), the difference in difference analyses revealed a significant increase in COPD exacerbations was also observed in the SLS-UC arm compared with the wider population.

These findings could suggest a change in the behaviour of physicians in terms of diagnostic coding. Local GPs had received training on the SLS, whereas CPRD practices had not; therefore, there is the potential that non-specific respiratory symptoms (e.g. 'increased shortness of breath') reported by SLS patients may have been more likely to be assigned a specific COPD code than the same symptoms reported by a patient included in the CPRD cohorts. It is possible that such symptoms were more likely to be explicitly classified as an exacerbation of COPD during SLS-COPD as GPs knew that a key outcome measure of the SLS-COPD trial was COPD exacerbations and, under the guise of wanting to ensure high-quality data, may have been more likely to use COPD-related medical codes. No such change in coding practices would be expected in the general CPRD cohort.

Although the time to first COPD exacerbation episode for the SLS-UC cohort was not considered unusual according to the criteria set out in this study's methodology, it was at the upper end of the distribution (96.7th percentile). This may indicate that the threshold for seeking a primary care consultation for a given set of symptoms could have changed for SLS-UC participants. Participants were aware that COPD exacerbation episodes were

a key outcome, which may have manifested as a desire to make their doctors aware of any complaints that may be an exacerbation of COPD. In conjunction with the differences in COPD exacerbation episode count discussed above, earlier care seeking by patients with symptoms may have led to the observed shortened time to first COPD exacerbation episode.

We would therefore conclude that reported exacerbations, after adjustment for confounding factors, appear to be higher in the trial usual care population than in the non-trial population as recorded by CPRD. This is likely to be a Hawthorne effect, in which exacerbations are either more likely to be detected in the trial population, or more likely to be recorded, or both.

11.1.3. PO3: Hospitalised pneumonia

In this study, rates of hospitalised pneumonia (as defined by ICD-10 codes) in the SLS usual care arm did not differ significantly from the rest of England after adjustment for population characteristics. Similar results were seen for the time to first pneumonia episode and in sensitivity analyses, where the same finding was made for pneumonia as primary admission diagnosis of hospitalisation (SO2).

The approach to identification of pneumonia in the main SLS-COPD, where it was considered a serious adverse event of special interest (SAESI), was different to that employed in this study due to key differences in data type, availability and rationale for collection. The specific definition and validation of SAESIs in the main SLS were not reproducible in the context of the comparator data (CPRD) for this study.

To maximise the comparability and reproducibility of the outcome measures, a ‘common ground’ was required for the identification of pneumonia across both the SLS and CPRD datasets, necessitating definition of pneumonia according to the presence of an ICD-10 code(s) denoting pneumonia in any diagnosis position for a given hospital episode. The use of ICD-10 codes has been established as a valid method for the retrospective collection of hospitalised pneumonia cases [Skull, 2008].

HES is essentially an administrative dataset, the main use of which is reimbursement of care delivered by secondary care providers; nevertheless, it has been widely used for epidemiologic studies including those of pneumonia [Trotter, 2008]. Up to 20 diagnoses can be assigned to a hospital episode, using ICD-10 codes, by coding clerks who manually review patient case notes. Codes are not directly assigned by the attending physician, and some variability in the quality and consistency of coding is likely. No full-text records describing the hospital care received by patients are available in HES, necessitating reliance on ICD-10 coding to identify diagnoses of interest for a study such as CHESS. Identification of pneumonia in this manner may identify episodes where pneumonia was an incidental diagnosis or a non-pneumonia event such as disease exacerbation; however, no alternative means that could be utilised in both SLS and CPRD primary+secondary care datasets were available.

11.1.4. SO1: Comparisons of healthcare utilisation, mortality and prescription counts for COPD therapies

Some evidence of differential coding behaviour was observed within the SLS-UC cohort between practices using EMIS and Vision, two commonly-used EHR systems in UK primary care. From the data available for this project, it was not possible to ascertain the mechanism behind these differences; however, it is likely there are software-specific differences in how users are prompted to add or codify information in patient records. The CPRD data utilised in this project only contained practices that utilised the Vision EHR system; for the time period of CPRD data used in this study, selected so as to match the SLS study period, only Vision practices were able to contribute to CPRD data.

Our analyses examining differences between the year prior to and during the SLS study period utilise multilevel models, which were designed to take account of the independent effects of cohort membership and time period, and are discussed in greater depth below for SO3. However, these models provide a robust assessment of the change in outcomes and allow for a fair comparison between the magnitude of these changes between the CPRD and SLS-UC cohorts. That being said, these differences between GP practices are an important potential source of bias when considering trial outcomes and is one that is not unique to our study; elucidation of and potential adjustments for practice EHR system should be considered in analytical plans and incorporated into the design of any future real-world randomised controlled trials.

There was no evidence to suggest unusual differences in terms of the rate of inpatient days, proportion of patients undergoing a switch of COPD treatment or mortality rate between the CPRD and SLS-UC cohorts. The rate of non-trial-related primary care contacts (100^{th} percentile, an unusually high count) and the time until death (0^{th} percentile, unusually long) were noted. Furthermore, the rate of trial-related prescription items was deemed unusually high for the SLS-UC cohort compared to the CPRD cohort.

The unusually high rate of primary care contact for the SLS-UC cohort may represent a change in subject behaviour as a result of trial membership; participants were likely aware that their health outcomes were being monitored, which may have encouraged them to visit their GP during the trial, even if for minor complaints. The unusually prolonged time to death observed for the SLS-UC cohort is likely to reflect the fact that subjects who were not expected to survive for the 12-month duration of the study were not recruited to SLS. As such, this would likely manifest as an increased time to death in comparison to their unselected peers in the CPRD cohort.

11.1.5. SO2: Effect of alternate definitions of COPD exacerbation rate in CPRD on estimations of exacerbation rate

When assessing the alternative algorithms used to define COPD exacerbations, algorithms, there were no unusual differences in terms of COPD exacerbation count (or time) associated with SLS-UC membership. The exception to this was time to first COPD exacerbation when the most specific definition (acute exacerbation code only, definition D) was used. In addition, the number of episodes for definition D was borderline unusual (97.4^{th} percentile).

The fact that definition A (i.e. that used in PO2) showed an unusual difference between SLS-UC and CPRD cohorts, whereas definition B did not, may indicate a change in behaviour in terms of the threshold of prescribing OCS and antibiotics in combination under the conditions of a pragmatic trial. Definitions B and C did not require both antibiotics and OCS to be prescribed on the same day, and definition D does not stipulate that OCS or antibiotics are prescribed. Case definitions for COPD exacerbation episodes were as described in Table 2.

11.1.6. SO3: Comparisons of outcomes in SLS-UC before and during the SLS-COPD study period

In unadjusted analyses, the change in rate of COPD exacerbation for SLS-UC cohort, comparing the year before the trial with the SLS study period, was not unusual in the context of changes in the rest of England. After adjustment, COPD exacerbation rates still did not appear to be unusually increased in SLS-UC patients. As the definition of COPD exacerbation becomes more specific, SLS becomes more unusual in both the unadjusted and adjusted analysis. The SLS-UC percentiles for the adjusted multilevel analysis increased from 93.2th (definition B), 97.6th (definition C) and 100th (definition D). These findings could suggest a change in the behaviour of physicians in terms of diagnostic coding. Local GPs had received training on the SLS study, whereas CPRD practices had not – there is the potential that vague respiratory symptoms (e.g. 'increased shortness of breath') reported by SLS patients may have been more likely to be assigned a specific COPD code. This may indicate a change in recording of events as opposed to a change in underlying event rates.

A considerable and unusual decrease in COPD prescription item rates (i.e. medications used for the management of COPD) was observed during the SLS study period for the SLS-UC cohort. This reduction in prescription items likely results from multifactorial aspects of trial participation acting on either or both of GPs' and participants' behaviours. Firstly, for example, in the SLS-COPD trial, participants may have had a formal review of their medication and the quality of their symptom control in a face-to-face consultation with their GP immediately prior to commencing the trial at their randomisation visit (index date) that may have resulted in changes in their regimen. Patients in the CPRD cohort did not have a comparable 'index date visit' that may have precipitated an acute change in treatment regimen, be it treatment change or rationalisation of multiple products into a single, combined form. Secondly, a change in GP behaviour in terms of prescription length is another potential factor that may contribute to the decrease in volume of prescription items in the SLS-UC cohort. GPs were likely to be aware that their patients were enrolled in the SLS-COPD trial, where safety monitoring was ongoing, albeit, in an unobtrusive manner, and as such may have felt more comfortable prescribing longer courses of treatment. As the metric of prescription items is not dependent on days supplied, patients who, after review, moved to 3-monthly prescriptions rather than monthly prescriptions for their COPD treatment would be expected to reduce their prescription volume by two-thirds. Additional data would be needed to explore which of these (or other) phenomena may underlie this marked reduction in prescription item rate in the SLS-UC arm, but given the magnitude of the difference observed this is an aspect of the design of such trials that warrants further investigation in future studies. It is also possible that the reduction in items prescribed

observed in the SLS-UC cohort may be artefactual in nature. For this analysis, the date of randomisation (index date) was set in the 'before' period, thus any rationalisation of treatment and issuing of new prescriptions that occurred during the build up to the trial, or at the trial's first visit, were recorded in the 'before' period.

There is some evidence that non-trial related primary care visits were unusually high for the SLS-UC cohort compared to the CPRD cohort during the SLS study period, but that there was no unusual change in this rate in comparison to the pre-trial year. This may simply reflect that the SLS-UC participants tended to utilise health care more intensively than their peers in CPRD (e.g. trial participants had higher baseline healthcare system engagement levels).

The change in proportion of patients undergoing a treatment switch was also observed to be unusually high for SLS-UC, which may imply a change in behaviour (either on the part of the physician or subject) in willingness to change medication under conditions of the trial. However, it should be noted that members of the SLS-UC cohort were not permitted to swap to FF/VI, the investigational product utilised in the treatment arm of SLS-COPD, as it had not received approval at the time the study commenced. Accordingly, the study design of SLS-COPD may have further contributed to the low proportion of switchers in the SLS-UC cohort. These observations may also reflect the training of GP practices on the protocol design, whereby patients randomised to the UC treatment group were not allowed to switch to FF/VI as it was not an approved medicine available to GPs for prescription when the study was initiated; this may have continued, even though the medicine became licensed and available during the study period.

11.2. Limitations and strengths

The key limitations common to this type of study are differences in data quality and compatibility between the various data sources. Within the SLS-database, data quality is high in accordance with the research standards afforded in a clinical trial. Routinely collected EHR data tends to be of lower quality and completeness, likely reflecting the fact that these data are primarily collected for patient care and management rather than being explicitly designed for research purposes. These differences in the nature of the data collection methods make the comparison with non-trial patients more challenging. To mitigate these inherent differences and to maximise comparability between the populations of interest, we presented analyses for the primary outcome of COPD exacerbation that utilised EHR data-derived information for SLS-UC participants rather than using the data collected in the SLS- database for the primary comparisons for PO2.

Study strengths:
The quality of EHRs in England has improved since the implementation of the Quality and Outcomes Framework (QOF) where clinical management is now linked to payments. The inclusion of chronic diseases such as COPD and asthma in key performance measures incentivises practices to systematically capture spirometry and dyspnoea (MRC) to confirm diagnoses, manage disease and measure outcomes (Smith, 2008; Rothnie, 2017). This study was able to utilise validated EHR-based algorithms (Rothnie, 2016) to ascertain COPD exacerbations hence increased the accuracy of the outcome definition and improved the internal validity of EHR-based research. While EHR data are

not collected initially for research purposes, the ability to link additional information at the patient level to create a more comprehensive, in-depth and longitudinal data source, creates high value for these types of data re-use analyses because they fundamentally capture the experience of patients and providers in the settings in which medical decisions and outcomes occur. Indeed, CPRD has been utilised in over 1,700 peer-reviewed publications and has been instrumental in realising improvements in drug safety, best practice and clinical guidelines.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

In terms of most demographic and clinical characteristics, the SLS-UC cohort was broadly similar to the COPD patient population of England. There was some evidence supporting a Hawthorne effect on the primary outcome of COPD exacerbations; exacerbations were unusually high in the SLS-UC population, however they were also unusually high for this population before the trial commenced. Further evidence of a Hawthorne effect was seen in the secondary outcomes, through behavioural changes such as coding practices of GP and the number of COPD medications prescribed. There was no evidence of increased rates of hospitalised pneumonia (as defined by ICD-10 codes) in the SLS-UC cohort compared with the rest of England.

This study provided a provided a novel set of methods for assessing the generalisability of a trial set in routine care and to our knowledge, is the first of its kind. Given trials set in routine care are becoming more feasible, studies such as this will become more important.
GSK is committed to improving the quality of 'real world' trials such as SLS and will incorporate the means to explore findings such as this into future study designs to generate meaningful and scientifically robust evidence informing decision making for patients, physicians, regulators and payors.

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APPENDICES

Appendix 1: Additional results

PO1

The comparisons between the SLS-UC and the CPRD cohorts for PO1 were repeated using the SLS-Database and CPRD primary+secondary datasets. For PO1, results of these analyses are presented in Source Data: Results Table 3, Table 6.1, Table 6.2, Table 7.1, Table 7.2, Table 8.1, and Table 8.2 and Source Data: Results Figure 6, Figure 7, Figure 11 and Figure 12. Additional figures comparing the key covariates and outcome variables between the SLS-Database and CPRD primary+secondary cohorts are presented in Source Data: Results Figure 18, Figure 23, and Figure 26 for comparisons using the SLS-EHR and CPRD primary care datasets, and Source Data: Results Figure 2, Figure 5 to Figure 13 for comparisons using the SLS-Database and CPRD primary+secondary care datasets.

Comparison of CPRD-GM and CPRD-xGM cohorts

The CPRD-GM and CPRD-xGM cohorts were compared using the same analyses as PO1. The results of these analyses are presented in Source Data: Results Table 19, Table 20, Table 23.1, and Table 23.2 and Source Data: Results Figure 14 for the comparisons using the SLS-EHR and CPRD primary care datasets, and Source Data: Results Table 1, Table 2, Table 5.1, Table 5.2, Table 6.1, and Table 6.2 and Source Data: Results Figure 1 for the comparisons using the SLS-Database and CPRD primary+secondary care datasets.

PO2

The comparisons between the SLS-UC and the CPRD cohorts for PO2 were repeated using the SLS-Database and CPRD primary+secondary datasets; results of these analyses are presented in Source Data: Results Table 4, Table 9 to Table 18, and Source Data: Results Figure 3 and Figure 4.

Data from the exploratory modelling of the outcome variables for PO2 are presented in Source Data: Results Table 29 and Table 31 for the comparisons using the SLS-EHR and CPRD primary datasets, and Source Table 11 to Table 15, and Table 17 for the comparisons using the SLS-Database and CPRD primary+secondary datasets (for exploratory and final models). Data for the fixed effects of the fully adjusted multilevel Poisson models are presented in Source Data: Results Table 34 (SLS-EHR and CPRD primary care dataset comparison) and Table 16 (SLS-Database and CPRD primary+secondary care comparison) for the number of COPD exacerbations and in Source Data: Results Table 36 (SLS-EHR and CPRD primary care dataset comparison) and Table 18 (SLS-Database and CPRD primary+secondary dataset comparison) for the time until first COPD exacerbation.

PO3

Additional data from the modelling of pneumonia episodes is presented in Source Data: Results Table 39, Table 40, Table 41, Table 44, and Table 46.

SO1

Data for the fixed effects of the fully adjusted multilevel Poisson models are presented in Source Data: Results Table 56 (number of contacts with primary care), Table 58, (number of days as an inpatient in secondary care), Table 60 (count of trial-related COPD prescription items), Table 62 (any treatment switch during 12-month study period), and Table 64 (time until death).

Sensitivity analyses

Sensitivity analyses using complete cases only were carried out for PO1 and PO2. Results are presented in Source Data: Table 112 to Table 115 for the sensitivity analyses using the SLS-EHR and CPRD primary care datasets and Source Data: Table 108 to Table 111 for the sensitivity analyses using the SLS-Database and CPRD primary+secondary care datasets.

A comparison between the SLS-Database and SLS-EHR datasets was performed to determine the amount of missing data in the SLS; results are presented in Source Data: Results Table 116.

ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	*2017N341352_00*	*25-SEP-2017*	Results: Tables and Figures

ANNEX 2: ADDITIONAL INFORMATION

Protocol

Code lists for main definitions.

PRJ2282/201491: CHESS: CPRD-COPD Hawthorne Effect Study in Salford: A UK cohort study to characterise patients enrolled in the Salford Lung Study and to evaluate a potential Hawthorne effect

Results: Tables and Figures

Table A: Data sources utilised by objective

Section	Objective	Tables/figures	SLS data source	CPRD data source
1.1	Primary objective 1/primary objective 2	Tables 1 – 18 Figures 1 – 13	SLS-Database	CPRD primary care +secondary care
1.2	Primary objective 1/primary objective 2	Tables 19 – 36 Figures 14 – 26	SLS-EHR	CPRD primary care
2	Primary objective 3	Tables 37 – 46	SLS-Database	CPRD primary care +secondary care
3	Secondary objective 1 (EMIS-Vision comparison, primary care use, COPD prescriptions and treatment switching)	Tables 47.1-50, 52-53, 55-56, 59 62	SLS-EHR	CPRD primary care
	Secondary objective 1 (mortality and secondary care use)	Tables 48, 51, 54, 57-58, 63-64	SLS-Database	CPRD primary care
4.1	Secondary objective 2 (alternate COPD definitions)	Tables 65 – 81	SLS-EHR	CPRD primary care
4.2	Secondary objective 2 (alternate pneumonia definition)	Tables 82 – 85	SLS-Database	CPRD primary care +secondary care
5	Secondary objective 3	Tables 86.1 – 107	SLS-EHR	CPRD primary care

6.1	Sensitivity analyses, using complete cases only (primary objective 1/primary objective 2)	Tables 108 – 111	SLS-Database	CPRD primary care +secondary care
6.2	Sensitivity analyses, using complete cases only (primary objective 1/primary objective 2)	Tables 112 – 115	SLS-EHR	CPRD primary care
7	Summary of missing data	Table 116	SLS-EHR , SLS-Database	N/A

1 Primary Objective 1: Representativeness of the SLS and Primary Objective 2: Comparison of COPD Exacerbations

1.1 PO1/PO2: CPRD Primary+Secondary Care Data vs. SLS-Database

Table 1: Comparison of CPRD-GM and CPRD-xGM cohorts - Baseline variables

Variable	Category	CPRD_GM	CPRD_xGM
N		5,669	49,499
Sex	Male	2,699 (47.61%)	25,423 (51.36%)
	Female	2,970 (52.39%)	24,076 (48.64%)
Age	mean (95% CI) median (2.5 - 97.5% range) missing	69.12 (68.83 - 69.41) 69.06 (46.06 - 89.06) 0.00% missing	70.66 (70.56 - 70.76) 71.06 (47.06 - 91.06) 0.00% missing
SES IMD 2010 Quintiles	Missing	1 (0.02%)	26 (0.05%)
	5 (least deprived)	424 (7.48%)	7,739 (15.63%)
	4	633 (11.17%)	10,525 (21.26%)
	3	748 (13.19%)	10,090 (20.38%)
	2	1,184 (20.89%)	11,399 (23.03%)
	1 (most deprived)	2,679 (47.26%)	9,720 (19.64%)
Current Medication (prescriptions in last 3 months)	None of the below treatments in the last 3 months	1,759 (31.03%)	15,987 (32.30%)
	LABA only	89 (1.57%)	794 (1.60%)
	LAMA only	525 (9.26%)	4,330 (8.75%)
	ICS only	330 (5.82%)	2,440 (4.93%)
	LABA/LAMA	75 (1.32%)	520 (1.05%)
	LAMA/ICS	85 (1.50%)	664 (1.34%)

Variable	Category	CPRD_GM	CPRD_xGM
	LABA/ICS	1,279 (22.56%)	10,557 (21.33%)
	LABA/LAMA/ICS	1,527 (26.94%)	14,207 (28.70%)
Any history of comorbidity (ever)	Anxiety	1,503 (26.51%)	9,750 (19.70%)
	Asthma	2,766 (48.79%)	24,723 (49.95%)
	Cardio- / Cerebrovascular disease	1,004 (17.71%)	8,580 (17.33%)
	Depression	1,983 (34.98%)	14,558 (29.41%)
	Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	1,520 (26.81%)	11,343 (22.92%)
	Pneumonia	554 (9.77%)	5,801 (11.72%)
Current comorbidity (reported in last 12 months)	Asthma	1130 (19.93%)	10441 (21.09%)
Charlson Comorbidity Index	0	1,149 (20.27%)	10,066 (20.34%)
	1-2	2,717 (47.93%)	23,360 (47.19%)
	3-4	1,230 (21.70%)	11,213 (22.65%)
	5+	573 (10.11%)	4,860 (9.82%)
COPD Exacerbation History in previous 12 months in previous 12 months	mean (95% CI) median (2.5 - 97.5% range) missing	0.97 (0.93 - 1.00) 0.00 (0.00 - 5.00) 0.00% missing	0.87 (0.86 - 0.88) 0.00 (0.00 - 5.00) 0.00% missing
FEV1%	mean (95% CI) median (2.5 - 97.5% range) missing	62.13 (61.57 - 62.69) 61.80 (26.10 - 100.49) 18.50% missing	60.38 (60.19 - 60.58) 59.92 (24.90 - 100.41) 20.50% missing

Variable	Category	CPRD_GM	CPRD_xGM
FEV1/FVC (%)	mean (95% CI) median (2.5 - 97.5% range) missing	63.09 (62.63 - 63.55) 63.00 (34.00 - 94.00) 28.59% missing	62.39 (62.23 - 62.56) 62.90 (33.00 - 94.20) 27.37% missing
GOLD Stage	Missing	1,641 (28.95%)	13,935 (28.15%)
	0 (fev1_fvc => 70)	1,309 (23.09%)	10,942 (22.11%)
	1 (fev1_fvc < 70, fev1% => 80)	287 (5.06%)	2,171 (4.39%)
	2 (fev1_fvc < 70, 50 <= fev1% < 80)	1,462 (25.79%)	13,024 (26.31%)
	3 (fev1_fvc < 70, 30 <= fev1% < 50)	820 (14.46%)	7,713 (15.58%)
	4 (fev1_fvc < 70, fev1% < 30)	150 (2.65%)	1,714 (3.46%)
MRC Dyspnoea score	Missing	960 (16.93%)	8,596 (17.37%)
	1 (least breathlessness)	796 (14.04%)	7,047 (14.24%)
	2	1,844 (32.53%)	15,209 (30.73%)
	3	1,239 (21.86%)	10,459 (21.13%)
	4	710 (12.52%)	6,680 (13.50%)
	5 (most breathlessness)	120 (2.12%)	1,508 (3.05%)
Smoking	Missing	9 (0.16%)	86 (0.17%)
	Never	509 (8.98%)	4,676 (9.45%)
	Ex	2,972 (52.43%)	28,113 (56.80%)
	Current	2,179 (38.44%)	16,624 (33.58%)
BMI	Missing	258 (4.55%)	3,486 (7.04%)
	18.50 - 24.99	1,712 (30.20%)	14,752 (29.80%)

Variable	Category	CPRD_GM	CPRD_xGM
	<18.50	243 (4.29%)	2,056 (4.15%)
	25.00 - 29.99	1,749 (30.85%)	15,322 (30.95%)
	>=30.00	1,707 (30.11%)	13,883 (28.05%)
Vaccinations	Influenza	4,841 (85.39%)	41,920 (84.69%)
	Pneumococcal	867 (15.29%)	6,655 (13.44%)

Table 2: Comparison of CPRD-GM and CPRD-xGM cohorts - Rate of COPD exacerbation episodes in year of follow up

DataSource	Variable	CPRD_GM	CPRD_xGM
Primary care and secondary care	N	5,669	49,499
	Person time	5,002.64 years	39,936.66 years
	# Episodes Rate per person year (95% CI)	5,225 1.04 (1.02 - 1.07)	39,747 1.00 (0.99 - 1.01)

Table 3: Comparison of CPRD-xGM-IC, CPRD-GM-IC and SLS-UC - Baseline variables

Variable	Category	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
N		2,046	16,745	1,403
Index Date		5th pctl = 05/06/12 25th pctl = 09/10/12 50th pctl = 10/07/13 75th pctl = 24/04/14 95th pctl = 23/09/14	5th pctl = 31/05/12 25th pctl = 03/10/12 50th pctl = 17/07/13 75th pctl = 24/04/14 95th pctl = 22/09/14	5th pctl = 31/05/12 25th pctl = 03/10/12 50th pctl = 23/07/13 75th pctl = 12/05/14 95th pctl = 23/09/14
Sex	Male	868 (42.42%)	8,153 (48.69%)	732 (52.17%)
	Female	1,178 (57.58%)	8,592 (51.31%)	671 (47.83%)
Age	mean (95% CI) median (2.5-97.5% range) missing	69.74 (69.27 - 70.20) 69.95 (47.57 - 89.20) 0.00% missing	71.12 (70.96 - 71.29) 71.41 (48.14 - 90.23) 0.00% missing	66.73 (66.21 - 67.25) 67.00 (46.00 - 85.00) 0.00% missing
SES IMD 2010 Quintiles	Missing	0 (0.00%)	8 (0.05%)	8 (0.57%)
	5 (least deprived)	127 (6.21%)	2,499 (14.92%)	72 (5.13%)
	4	219 (10.70%)	3,425 (20.45%)	105 (7.48%)
	3	283 (13.83%)	3,343 (19.96%)	202 (14.40%)
	2	455 (22.24%)	3,892 (23.24%)	294 (20.96%)
	1 (most deprived)	962 (47.02%)	3,578 (21.37%)	722 (51.46%)
Current Medication (prescriptions in last 3 months)	None of the below treatments in the last 3 months	166 (8.11%)	1,695 (10.12%)	145 (10.33%)

Variable	Category	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
	LABA only	32 (1.56%)	251 (1.50%)	19 (1.35%)
	LAMA only	175 (8.55%)	1,481 (8.84%)	143 (10.19%)
	ICS only	114 (5.57%)	758 (4.53%)	62 (4.42%)
	LABA/LAMA	25 (1.22%)	177 (1.06%)	18 (1.28%)
	LAMA/ICS	24 (1.17%)	235 (1.40%)	56 (3.99%)
	LABA/ICS	592 (28.93%)	4,523 (27.01%)	337 (24.02%)
	LABA/LAMA/ICS	918 (44.87%)	7,625 (45.54%)	623 (44.40%)
Any history of comorbidity (ever)	Anxiety	571 (27.91%)	3,661 (21.86%)	301 (21.45%)
	Asthma	1,211 (59.19%)	10,075 (60.17%)	755 (53.81%)
	Cardio- / Cerebrovascular disease	386 (18.87%)	3,216 (19.21%)	238 (16.96%)
	Depression	766 (37.44%)	5,461 (32.61%)	344 (24.52%)
	Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	572 (27.96%)	4,115 (24.57%)	355 (25.30%)
	Pneumonia	279 (13.64%)	2,633 (15.72%)	147 (10.48%)
Current comorbidity (reported in last 12 months)	Asthma	485 (23.70%)	4016 (23.98%)	298 (21.24%)
Charlson Comorbidity Index	0	341 (16.67%)	2,571 (15.35%)	271 (19.32%)
	1-2	1,019 (49.80%)	8,220 (49.09%)	703 (50.11%)
	3-4	460 (22.48%)	4,087 (24.41%)	297 (21.17%)
	5+	226 (11.05%)	1,867 (11.15%)	132 (9.41%)

Variable	Category	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
COPD Exacerbation History in previous 12 months	mean (95% CI) median (2.5-97.5% range) missing	1.69 (1.62 - 1.75) 1.00 (0.00 - 6.00) 0.00% missing	1.57 (1.55 - 1.59) 1.00 (0.00 - 5.00) 0.00% missing	2.04 (1.93 - 2.15) 1.00 (0.00 - 8.00) 0.00% missing
FEV1%	mean (95% CI) median (2.5-97.5% range) missing	56.74 (55.85 - 57.63) 55.82 (22.68 - 95.23) 12.81% missing	55.86 (55.55 - 56.18) 55.08 (22.31 - 96.00) 14.27% missing	60.30 (59.17 - 61.43) 60.90 (24.30 - 98.90) 21.53% missing
FEV1/FVC (%)	mean (95% CI) median (2.5-97.5% range) missing	61.08 (60.26 - 61.90) 60.60 (32.20 - 95.00) 23.12% missing	60.52 (60.23 - 60.82) 60.00 (31.00 - 95.70) 21.60% missing	54.39 (53.58 - 55.19) 54.80 (28.65 - 79.09) 21.53% missing
GOLD Stage	Missing	478 (23.36%)	3,784 (22.60%)	217 (15.47%)
	0 (fev1_fvc => 70)	451 (22.04%)	3,590 (21.44%)	147 (10.48%)
	1 (fev1_fvc < 70, fev1% => 80)	70 (3.42%)	524 (3.13%)	84 (5.99%)
	2 (fev1_fvc < 70, 50 <= fev1% < 80)	526 (25.71%)	4,340 (25.92%)	522 (37.21%)
	3 (fev1_fvc < 70, 30 <= fev1% < 50)	421 (20.58%)	3,522 (21.03%)	332 (23.66%)
	4 (fev1_fvc < 70, fev1% < 30)	100 (4.89%)	985 (5.88%)	101 (7.20%)
MRC Dyspnoea score	Missing	200 (9.78%)	1,721 (10.28%)	12 (0.86%)
	1 (least breathlessness)	179 (8.75%)	1,528 (9.13%)	154 (10.98%)
	2	633 (30.94%)	4,910 (29.32%)	510 (36.35%)
	3	532 (26.00%)	4,504 (26.90%)	470 (33.50%)

Variable	Category	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
	4	415 (20.28%)	3,293 (19.67%)	233 (16.61%)
	5 (most breathlessness)	87 (4.25%)	789 (4.71%)	24 (1.71%)
Smoking	Never	165 (8.06%)	1,348 (8.05%)	59 (4.21%)
	Ex	1,176 (57.48%)	10,018 (59.83%)	678 (48.33%)
	Current	705 (34.46%)	5,379 (32.12%)	666 (47.47%)
BMI	Missing	68 (3.32%)	941 (5.62%)	281 (20.03%)
	18.50 - 24.99	650 (31.77%)	4,998 (29.85%)	351 (25.02%)
	<18.50	94 (4.59%)	793 (4.74%)	52 (3.71%)
	25.00 - 29.99	608 (29.72%)	5,116 (30.55%)	349 (24.88%)
	>=30.00	626 (30.60%)	4,897 (29.24%)	370 (26.37%)
Vaccinations	Influenza	1,853 (90.57%)	15,091 (90.12%)	1,285 (91.59%)
	Pneumococcal	321 (15.69%)	2,256 (13.47%)	243 (17.32%)

COPD Exacerbation History in previous 12 months is treated as a continuous variable

Table 4: Comparison of CPRD-xGM-IC, CPRD-GM-IC and SLS-UC - Rate of COPD exacerbation episodes in year of follow up

DataSource	Variable	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
Primary care and secondary care	N	2,046	16,745	1,403
	Person time	1,636.80 years	13,068.93 years	1,288.20 years
	# Episodes Rate per person year (95% CI)	2,873 1.76 (1.69 - 1.82)	21,401 1.64 (1.62 - 1.66)	2,465 1.91 (1.84 - 1.99)

Table 5.1: Comparison of imputed and complete case datasets for variables with missingness - CPRD-GM-IC

Variable	Category	CPRD_GM_IC_Complete_Case	CPRD_GM_IC_Imputed
N		1,491	2,046
SES IMD 2010 Quintiles	5 (least deprived)	107 (7.18%)	127 (6.21%)
	4	180 (12.07%)	219 (10.70%)
	3	214 (14.35%)	283 (13.83%)
	2	331 (22.20%)	455 (22.24%)
	1 (most deprived)	659 (44.20%)	962 (47.02%)
FEV1%	mean (95% CI) median (5-95% range)	56.80 (55.83 - 57.78) 55.80 (27.28 - 89.98)	57.24 (56.40 - 58.07) 56.36 (27.54 - 90.00)
FEV1/FVC (%)	mean (95% CI) median (5-95% range)	60.75 (59.91 - 61.58) 60.00 (36.00 - 88.00)	61.12 (60.43 - 61.81) 61.00 (35.72 - 88.60)
GOLD Stage	0 (fev1_fvc => 70)	416 (27.90%)	611 (29.86%)
	1 (fev1_fvc < 70, fev1% => 80)	65 (4.36%)	99 (4.84%)
	2 (fev1_fvc < 70, 50 <= fev1% < 80)	505 (33.87%)	673 (32.89%)
	3 (fev1_fvc < 70, 30 <= fev1% < 50)	409 (27.43%)	534 (26.10%)
	4 (fev1_fvc < 70, fev1% < 30)	96 (6.44%)	129 (6.30%)
MRC Dyspnoea score	1 (least breathlessness)	147 (9.86%)	203 (9.92%)
	2	524 (35.14%)	715 (34.95%)
	3	446 (29.91%)	585 (28.59%)
	4	313 (20.99%)	441 (21.55%)

Variable	Category	CPRD_GM_IC_Complete_Case	CPRD_GM_IC_Imputed
	5 (most breathlessness)	61 (4.09%)	102 (4.99%)
Smoking	Never	97 (6.51%)	165 (8.06%)
	Ex	880 (59.02%)	1,176 (57.48%)
	Current	514 (34.47%)	705 (34.46%)
BMI	18.50 - 24.99	494 (33.13%)	675 (32.99%)
	<18.50	70 (4.69%)	94 (4.59%)
	25.00 - 29.99	466 (31.25%)	631 (30.84%)
	>=30.00	461 (30.92%)	646 (31.57%)

Table 5.2: Summary of percentage missing for each variable - CPRD-GM-IC

Variable	Percentage_Miss
SES IMD 2010 Quintiles	0.00%
FEV1%	12.81%
FEV1/FVC ratio	23.12%
GOLD Stage	23.36%
MRC Dyspnoea Score	9.78%
Smoking	0.00%
BMI	3.32%

Table 6.1: Comparison of imputed and complete case datasets for variables with missingness - CPRD-xGM-IC

Variable	Category	CPRD_xGM_IC_Complete_Case	CPRD_xGM_IC_Imputed
N		12,063	16,745
SES IMD 2010 Quintiles	5 (least deprived)	1,765 (14.63%)	2,502 (14.94%)
	4	2,487 (20.62%)	3,425 (20.45%)
	3	2,357 (19.54%)	3,345 (19.98%)
	2	2,851 (23.63%)	3,893 (23.25%)
	1 (most deprived)	2,603 (21.58%)	3,580 (21.38%)
FEV1%	mean (95% CI) median (5-95% range)	55.86 (55.52 - 56.20) 55.11 (26.83 - 87.66)	55.92 (55.63 - 56.21) 55.23 (26.00 - 88.09)
FEV1/FVC (%)	mean (95% CI) median (5-95% range)	60.25 (59.95 - 60.55) 60.00 (34.00 - 87.00)	60.46 (60.21 - 60.70) 60.47 (34.00 - 88.00)
GOLD Stage	0 (fev1_fvc => 70)	3,206 (26.58%)	4,695 (28.04%)
	1 (fev1_fvc < 70, fev1% => 80)	481 (3.99%)	648 (3.87%)
	2 (fev1_fvc < 70, 50 <= fev1% < 80)	4,089 (33.90%)	5,550 (33.14%)
	3 (fev1_fvc < 70, 30 <= fev1% < 50)	3,371 (27.94%)	4,485 (26.78%)
	4 (fev1_fvc < 70, fev1% < 30)	916 (7.59%)	1,367 (8.16%)
MRC Dyspnoea score	1 (least breathlessness)	1,192 (9.88%)	1,759 (10.50%)
	2	4,095 (33.95%)	5,523 (32.98%)
	3	3,702 (30.69%)	4,968 (29.67%)
	4	2,558 (21.21%)	3,631 (21.68%)

Variable	Category	CPRD_xGM_IC_Complete_Case	CPRD_xGM_IC_Imputed
	5 (most breathlessness)	516 (4.28%)	864 (5.16%)
Smoking	Never	772 (6.40%)	1,348 (8.05%)
	Ex	7,332 (60.78%)	10,018 (59.83%)
	Current	3,959 (32.82%)	5,379 (32.12%)
BMI	18.50 - 24.99	3,829 (31.74%)	5,334 (31.85%)
	<18.50	564 (4.68%)	846 (5.05%)
	25.00 - 29.99	3,945 (32.70%)	5,397 (32.23%)
	>=30.00	3,725 (30.88%)	5,168 (30.86%)

Table 6.2: Summary of percentage missing for each variable - CPRD-xGM-IC

Variable	Percentage_Miss
SES IMD 2010 Quintiles	0.05%
FEV1%	14.27%
FEV1/FVC ratio	21.60%
GOLD Stage	22.60%
MRC Dyspnoea Score	10.28%
Smoking	0.00%
BMI	5.62%

Table 7.1: Comparison of imputed and complete case datasets for variables with missingness - SLS-UC-study-database

Variable	Category	SLS_UC_study_database_Complete_Case	SLS_UC_study_database_Imputed
N		863	1,403
SES IMD 2010 Quintiles	5 (least deprived)	54 (6.26%)	72 (5.13%)
	4	61 (7.07%)	105 (7.48%)
	3	128 (14.83%)	205 (14.61%)
	2	191 (22.13%)	295 (21.03%)
	1 (most deprived)	429 (49.71%)	726 (51.75%)
FEV1%	mean (95% CI) median (5-95% range)	60.68 (59.40 - 61.96) 61.00 (29.70 - 93.00)	60.45 (59.44 - 61.45) 60.90 (28.40 - 92.20)
FEV1/FVC (%)	mean (95% CI) median (5-95% range)	54.37 (53.45 - 55.30) 54.55 (31.73 - 76.15)	54.44 (53.73 - 55.16) 54.65 (31.44 - 76.15)
GOLD Stage	0 (fev1_fvc => 70)	107 (12.40%)	172 (12.26%)
	1 (fev1_fvc < 70, fev1% => 80)	66 (7.65%)	133 (9.48%)
	2 (fev1_fvc < 70, 50 <= fev1% < 80)	371 (42.99%)	694 (49.47%)
	3 (fev1_fvc < 70, 30 <= fev1% < 50)	242 (28.04%)	320 (22.81%)
	4 (fev1_fvc < 70, fev1% < 30)	77 (8.92%)	84 (5.99%)
MRC Dyspnoea score	1 (least breathlessness)	112 (12.98%)	155 (11.05%)
	2	328 (38.01%)	516 (36.78%)
	3	288 (33.37%)	473 (33.71%)
	4	120 (13.90%)	235 (16.75%)

Variable	Category	SLS_UC_study_database_Complete_Case	SLS_UC_study_database_Imputed
	5 (most breathlessness)	15 (1.74%)	24 (1.71%)
Smoking	Never	35 (4.06%)	59 (4.21%)
	Ex	417 (48.32%)	678 (48.33%)
	Current	411 (47.62%)	666 (47.47%)
BMI	18.50 - 24.99	279 (32.33%)	442 (31.50%)
	<18.50	37 (4.29%)	65 (4.63%)
	25.00 - 29.99	273 (31.63%)	430 (30.65%)
	>=30.00	274 (31.75%)	466 (33.21%)

Table 7.2: Summary of percentage missing for each variable - SLS-UC-study-database

Variable	Percentage_Miss
SES IMD 2010 Quintiles	0.57%
FEV1%	21.53%
FEV1/FVC ratio	21.53%
GOLD Stage	15.47%
MRC Dyspnoea Score	0.86%
Smoking	0.00%
BMI	20.03%

Table 8.1: Variables in SLS-UC in the context of regional variation in the CPRD at local authority level (continuous/boolean)

The average response is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5 percentile range. The value for SLS-UC is deemed unusual if it lies outside of this range.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Sex (% male)	31.52%	51.10%	69.07%	47.83%	32.23	0
Age	67.29	71.37	76.32	66.73	0.67	1
Any history (ever) of: Cardio- / Cerebrovascular disease	7.54%	19.41%	33.75%	16.96%	31.88	0
Any history (ever) of: Depression	12.44%	31.98%	50.34%	24.52%	15.96	0
Any history (ever) of: Anxiety	6.85%	19.96%	44.24%	21.45%	60.70	0
Any history (ever) of: Asthma	30.34%	58.97%	84.60%	53.81%	32.23	0
Any history (ever) of: Pneumonia	0.00%	16.26%	36.12%	10.48%	16.49	0
Any history (ever) of: Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	10.00%	23.39%	43.69%	25.30%	56.74	0
COPD Exacerbation History in previous 12 months	0.78	1.53	2.01	2.04	98.12	1
FEV1%	48.81	55.69	62.12	60.45	91.15	0
FEV1/FVC (%)	52.16	59.84	68.67	54.44	7.67	0

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Influenza Vaccination	78.57%	91.05%	98.34%	91.59%	56.75	0
Pneumococcal Vaccination	1.41%	12.50%	29.44%	17.32%	76.38	0

Table 8.2: Variables in SLS-UC in the context of regional variation in the CPRD at local authority level (categorical)

For each local authority in CPRD_xGM_IC a Chi Squared test is performed comparing the distribution of the variable of interest in the local authority to its distribution in the rest of CPRD_xGM_IC. The test statistics from each local authority are used to construct an empirical 0 - 95 percentile range of test statistics. A chi squared test comparing the distribution of the variable of interest in SLS-UC to CPRD_xGM_IC is then performed. SLS-UC is deemed unusual with respect to this variable if the Chi Squared test statistic lies outside the 0 - 95% range.

Variable	CPRD_xGM_IC_0_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_95_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
SES IMD 2010 Quintiles	0.68	43.38	236.28	724.72	100.00	1
Current Medication (prescriptions in last 3 months)	1.78	10.08	41.96	62.28	96.93	1
Charlson Comorbidity Index	0.08	3.73	15.37	22.43	97.73	1
MRC Dyspnoea Score	0.20	6.36	32.01	59.30	99.57	1
Gold Stage	0.36	6.34	29.63	330.47	100.00	1
Smoking	0.00	2.95	21.24	145.27	100.00	1
BMI	0.13	3.03	10.03	3.82	62.58	0

Table 9: The rate* of COPD exacerbations episodes in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups -

For each subgroup the rate of COPD episodes is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The number of exacerbations in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	0.42299	1.58304	2.39296	1.91352	81.2424	0
Male	0.24841	1.54307	2.75858	1.66522	59.8172	0
Female	0.36869	1.58070	2.64859	2.18991	86.2208	0
Never Smoked	0.00000	1.24676	3.58474	1.55190	65.7497	0
Ex Smoker	0.48619	1.48676	2.82797	1.90987	84.1214	0
Current Smoker	0.10194	1.74212	3.31375	1.95022	65.8397	0
Over 75	0.17193	1.48673	2.54209	1.89749	76.9492	0
Below 75	0.43998	1.62034	3.07724	1.91813	74.0372	0
SES IMD 2010 = 5 (least deprived)	0.00000	1.32908	2.91700	1.33490	50.6131	0
SES IMD 2010 = 4	0.00000	1.44885	2.94027	1.81603	75.4732	0
SES IMD 2010 = 3	0.00000	1.56938	4.13957	1.81198	65.5865	0
SES IMD 2010 = 2	0.03407	1.59491	5.48557	2.07491	74.3610	0
SES IMD 2010 = 1 (most deprived)	0.00000	1.71112	4.02433	1.94985	66.6246	0

Rate is calculated per person year

Table 10: Survival times until first COPD exacerbation in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups -

For each subgroup the 25th percentile survival time is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The 25th percentile survival time for SLS-UC is deemed unusual if it lies outside of this range.*

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	41.675 days	76 days	338.43 days	64 days	28.91	0
Male	30.35 days	75 days	=> 365 days	82 days	59.18	0
Female	38.85 days	76.5 days	360.28 days	54 days	16.33	0
Never Smoked	20.838 days	99.5 days	=> 365 days	56 days	19.46	0
Ex Smoker	28.675 days	80 days	=> 365 days	67 days	34.47	0
Current Smoker	24.65 days	66 days	=> 365 days	64 days	46.58	0
Over 75	28.05 days	80 days	=> 365 days	75 days	44.22	0
Below 75	34.675 days	74 days	308.1 days	63 days	34.69	0
SES IMD 2010 = 5 (least deprived)	11 days	83 days	=> 365 days	119 days	63.61	0
SES IMD 2010 = 4	20.85 days	86 days	=> 365 days	56 days	20.90	0
SES IMD 2010 = 3	18 days	77.5 days	=> 365 days	75 days	47.15	0
SES IMD 2010 = 2	12.925 days	70.5 days	=> 365 days	60 days	36.22	0
SES IMD 2010 = 1 (most deprived)	17.375 days	70 days	=> 365 days	63 days	33.64	0

25th percentile survival time is chosen because some local authorities within subgroups are small and hence there is large variation. If the median survival time was chosen many local authorities would have a time > 365 days, which could not be determined as it exceeds follow up. Choosing a relatively low percentile leads to a higher proportion of local authorities having a 25th percentile survival time <= 365. If the upper or lower bound of the empirical range is > 365, this is specified as > 365.

Table 11: Exploratory Poisson models - Outcome = number of COPD exacerbation episodes

Cohorts CPRD_xGM_IC and SLS-UCare combined into a single dataset retaining a flag for membership of SLS
Model one covariates: SLS indicator
Model two covariates: SLS indicator, age and sex

parameter	Level1	RelativeRate	RR_LowerCL	RR_UpperCL	P
SLS	1	1.1685	1.0866	1.2566	<.0001
parameter	**Level1**	**RelativeRate**	**RR_LowerCL**	**RR_UpperCL**	**P**
SLS	1	1.1601	1.0782	1.2482	<.0001
SLS	0	1.0000	1.0000	1.0000	.
age		0.9733	0.9518	0.9953	0.0175
sex	1	1.0806	1.0337	1.1296	0.0006
sex	0	1.0000	1.0000	1.0000	.

Table 12: Fully adjusted Poisson model - Outcome = number of COPD exacerbation episodes

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
SLS member	Yes	0.95307	0.8918	1.01856	0.1563
	No	1	1	1	.
Sex	Female	1.07005	1.02937	1.11235	0.0006
	Male	1	1	1	.
Age		1.00201	0.98036	1.02414	0.8572
Age Squared		0.9913	0.97604	1.00679	0.2695
SES IMD 2010 Quintiles	4	1.05635	0.98624	1.13144	0.1177
	3	1.04996	0.98007	1.12483	0.1654
	2	1.07669	1.00736	1.1508	0.0296
	1 (most deprived)	1.08228	1.01213	1.1573	0.0207
	5 (least deprived)	1	1	1	.
Current Medication (prescriptions in last 3 months)	LABA only	1.15673	0.96508	1.38644	0.1152
	LAMA only	1.13962	1.03723	1.25212	0.0065
	ICS only	0.9028	0.79451	1.02586	0.1168
	LABA/LAMA	1.0681	0.86549	1.31814	0.5393
	LAMA/ICS	1.03432	0.87079	1.22856	0.7007
	LABA/ICS	1.12067	1.03782	1.21013	0.0036
	LABA/LAMA/ICS	1.23596	1.1495	1.32892	<.0001

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
	None of these treatments in the last 3 months	1	1	1	.
Any history (ever) of Depression	Present	1.04363	0.99789	1.09147	0.0618
	Absent	1	1	1	.
Any history (ever) of Anxiety	Present	1.05059	1.00089	1.10275	0.0459
	Absent	1	1	1	.
Any history (ever) of Asthma	Present	1.03826	0.99813	1.08001	0.0619
	Absent	1	1	1	.
Any history (ever) of Pneumonia	Present	1.02032	0.96997	1.07329	0.4359
	Absent	1	1	1	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.03757	0.99379	1.08327	0.0936
	Absent	1	1	1	.
COPD Exacerbation History in previous 12 months		1.75616	1.7149	1.79841	<.0001

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
COPD Exacerbation History in previous 12 months Squared		0.95192	0.94533	0.95854	<.0001
FEV1%		0.93145	0.90888	0.95458	<.0001
FEV1% Squared		1.01666	1.00298	1.03054	0.0168
FEV1/FVC (%)		0.96632	0.94436	0.98879	0.0035
FEV1/FVC (%) squared		1.00017	0.98559	1.01497	0.9819
MRC Dyspnoea score	2	1.06577	0.98788	1.14981	0.0999
	3	1.16071	1.07478	1.25352	0.0001
	4	1.23492	1.13899	1.33892	<.0001
	5 (most breathlessness)	1.31111	1.17946	1.45747	<.0001
	1 (least breathlessness)	1	1	1	.
Smoking	Ex	1.06962	0.98741	1.15868	0.0991
	Current	1.19168	1.09559	1.29619	<.0001
	Never	1	1	1	.
Influenza Vaccine	Present	1.0344	0.96876	1.10449	0.3120
	Absent	1	1	1	.

Table 13: Exploratory Cox Proportional Hazards models - Outcome = time until first COPD exacerbation episode

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS
Model one covariates: SLS indicator
Model two covariates: SLS indicator, age and sex

Parameter	HazardRatio	HR_LowerCL	HR_UpperCL	P
SLS	1.180	1.105	1.260	<.0001
Parameter	**HazardRatio**	**HR_LowerCL**	**HR_UpperCL**	**P**
SLS	1.183	1.107	1.264	<.0001
age	0.992	0.974	1.011	0.4009
sex	1.085	1.045	1.127	<.0001

Table 14: Fully adjusted Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
SLS member		1.06355	0.99163	1.14068	0.0846
Sex	Female	1.07949	1.03814	1.12248	0.0001
	Male	.	.	.	.
Age		1.01292	0.9912	1.03512	0.2457
Age Squared		0.99188	0.97664	1.00735	0.3016
SES IMD 2010 Quintiles	4	1.05068	0.98222	1.1239	0.1504
	3	1.02993	0.96246	1.10213	0.3936
	2	1.08471	1.01581	1.15829	0.0152
	1 (most deprived)	1.08657	1.0168	1.16112	0.0142
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.21135	1.02291	1.43449	0.0262
	LAMA only	1.06972	0.97615	1.17227	0.1490
	ICS only	0.89235	0.79335	1.0037	0.0576
	LABA/LAMA	1.07661	0.87974	1.31754	0.4737
	LAMA/ICS	1.04277	0.88526	1.2283	0.6162
	LABA/ICS	1.05527	0.98034	1.13593	0.1523
	LABA/LAMA/ICS	1.17095	1.09191	1.25573	<.0001
	No medication (in last 3 months)	.	.	.	.

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Depression	Present	1.03168	0.98586	1.07962	0.1784
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.0128	0.9636	1.06451	0.6166
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.07366	1.03179	1.11722	0.0005
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.02673	0.97513	1.08105	0.3160
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.05658	1.01142	1.10376	0.0135
	Absent	.	.	.	.
COPD Exacerbation History in previous 12 months		1.71895	1.67628	1.76271	<.0001
COPD Exacerbation History in previous 12 months Squared		0.95553	0.94657	0.96457	<.0001
FEV1%		0.91959	0.89689	0.94287	<.0001

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
FEV1% Squared		1.0126	0.99901	1.02636	0.0693
FEV1/FVC (%)		0.98451	0.96183	1.00773	0.1893
FEV1/FVC (%) squared		0.99839	0.9836	1.01341	0.8324
MRC Dyspnoea score	2	1.07033	0.99568	1.15057	0.0654
	3	1.12814	1.04749	1.21501	0.0014
	4	1.21083	1.1192	1.30995	<.0001
	5 (most breathlessness)	1.24651	1.12006	1.38724	<.0001
	1 (least breathlessness)	.	.	.	.
Smoking	Ex	1.06551	0.98619	1.1512	0.1079
	Current	1.17886	1.08596	1.27972	<.0001
	Never Smoked	.	.	.	.
Influenza Vaccine	Present	1.07211	1.00307	1.1459	0.0403
	Absent	.	.	.	.

Tables 15: Distribution of random effects in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.91945	0.99752	1.10548	0.98402	35.8361	0

Table 16: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	1.08302	1.04792	1.11929	<.0001
	Male	1	.	.	.
Age	.	1.00829	0.98984	1.02708	0.3811
Age Squared	.	0.99329	0.98033	1.00641	0.3144
SES IMD 2010 Quintiles	4	1.05329	0.99306	1.11718	0.0840
	3	1.04335	0.98274	1.10768	0.1646
	2	1.08148	1.02016	1.1465	0.0085
	1 (most deprived)	1.08615	1.02327	1.15289	0.0066
	5 (least deprived)	1	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.15638	0.99454	1.34456	0.0589
	LAMA only	1.11979	1.03426	1.21239	0.0053
	ICS only	0.91135	0.82	1.01287	0.0850
	LABA/LAMA	1.05602	0.88529	1.25967	0.5447
	LAMA/ICS	1.04896	0.90967	1.20958	0.5108
	LABA/ICS	1.09889	1.03035	1.17198	0.0041
	LABA/LAMA/ICS	1.2237	1.1514	1.30055	<.0001
	No treatment	1	.	.	.
Any history (ever) of Depression	Present	1.03833	0.99941	1.07876	0.0537
	Absent	1	.	.	.

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Anxiety	Present	1.03405	0.99196	1.07793	0.1142
	Absent	1	.	.	.
Any history (ever) of Asthma	Present	1.04945	1.01462	1.08546	0.0051
	Absent	1	.	.	.
Any history (ever) of Pneumonia	Present	1.03238	0.98884	1.07783	0.1472
	Absent	1	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.03902	1.00157	1.07787	0.0410
	Absent	1	.	.	.
COPD Exacerbation History in previous 12 months	.	1.73213	1.69671	1.7683	<.0001
COPD Exacerbation History in previous 12 months Squared	.	0.95226	0.94623	0.95833	<.0001
FEV1%	.	0.92352	0.90443	0.94302	<.0001
FEV1% Squared	.	1.01523	1.00353	1.02706	0.0106
FEV1/FVC (%)	.	0.97105	0.95215	0.99032	0.0034

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
FEV1/FVC (%) squared	.	1.00068	0.98829	1.01323	0.9149
MRC Dyspnoea score	2	1.05777	0.99247	1.12736	0.0841
	3	1.14671	1.07463	1.22362	<.0001
	4	1.22417	1.14317	1.31092	<.0001
	5 (most breathlessness)	1.31033	1.19782	1.43341	<.0001
	1 (least breathlessness)	1	.	.	.
Smoking	Ex	1.07047	1.00088	1.14489	0.0471
	Current	1.17964	1.09887	1.26636	<.0001
	Never	1	.	.	.
Influenza Vaccine	Present	1.04627	0.98897	1.10688	0.1155
	Absent	1	.	.	.

Table 17: Distribution of random effects in fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.91009	0.99711	1.10487	1.06616	88.3112	0

Table 18: Fixed effects for fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Sex	Female	1.08334	1.0417	1.12665	<.0001
	Male	.	.	.	.
Age		1.01374	0.99191	1.03605	0.2192
Age Squared		0.99142	0.97614	1.00693	0.2765
SES IMD 2010 Quintiles	4	1.04609	0.97683	1.12025	0.1973
	3	1.02867	0.95945	1.10288	0.4265
	2	1.08407	1.01262	1.16057	0.0203
	1 (most deprived)	1.07759	1.00489	1.15555	0.0360
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.19518	1.00855	1.41634	0.0396
	LAMA only	1.06484	0.97146	1.1672	0.1797
	ICS only	0.89286	0.79358	1.00456	0.0595
	LABA/LAMA	1.0652	0.86979	1.30451	0.5413
	LAMA/ICS	1.04747	0.88892	1.23429	0.5797
	LABA/ICS	1.04876	0.97411	1.12913	0.2063
	LABA/LAMA/ICS	1.17049	1.09118	1.25557	<.0001
	No trial medication (in last 3 months)	.	.	.	.

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Depression	Present	1.03076	0.98479	1.07887	0.1930
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.00875	0.95947	1.06057	0.7332
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.07205	1.02991	1.11592	0.0007
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.03382	0.9816	1.08881	0.2086
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.0566	1.01123	1.10401	0.0140
	Absent	.	.	.	.
COPD Exacerbation History in previous 12 months		1.713	1.67034	1.75674	<.0001
COPD Exacerbation History in previous 12 months Squared		0.95614	0.94716	0.9652	<.0001
FEV1%		0.91897	0.89617	0.94236	<.0001

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
FEV1% Squared		1.01229	0.99865	1.02612	0.0775
FEV1/FVC (%)		0.98113	0.95829	1.00451	0.1129
FEV1/FVC (%) squared		0.99789	0.98305	1.01295	0.7822
MRC Dyspnoea score	2	1.06944	0.99462	1.14989	0.0696
	3	1.12731	1.04628	1.21461	0.0016
	4	1.21285	1.12057	1.31273	<.0001
	5 (most breathlessness)	1.24821	1.12072	1.39019	<.0001
	1 (least breathlessness)	.	.	.	.
Smoking	Ex	1.06791	0.9881	1.15415	0.0973
	Current	1.18064	1.08709	1.28224	<.0001
	Never Smoked	.	.	.	.
Influenza Vaccine	Present	1.06454	0.99572	1.13812	0.0666
	Absent	.	.	.	.

Figure 1: Kaplan-Meier Plots Comparing CPRD_GM and CPRD_xGM

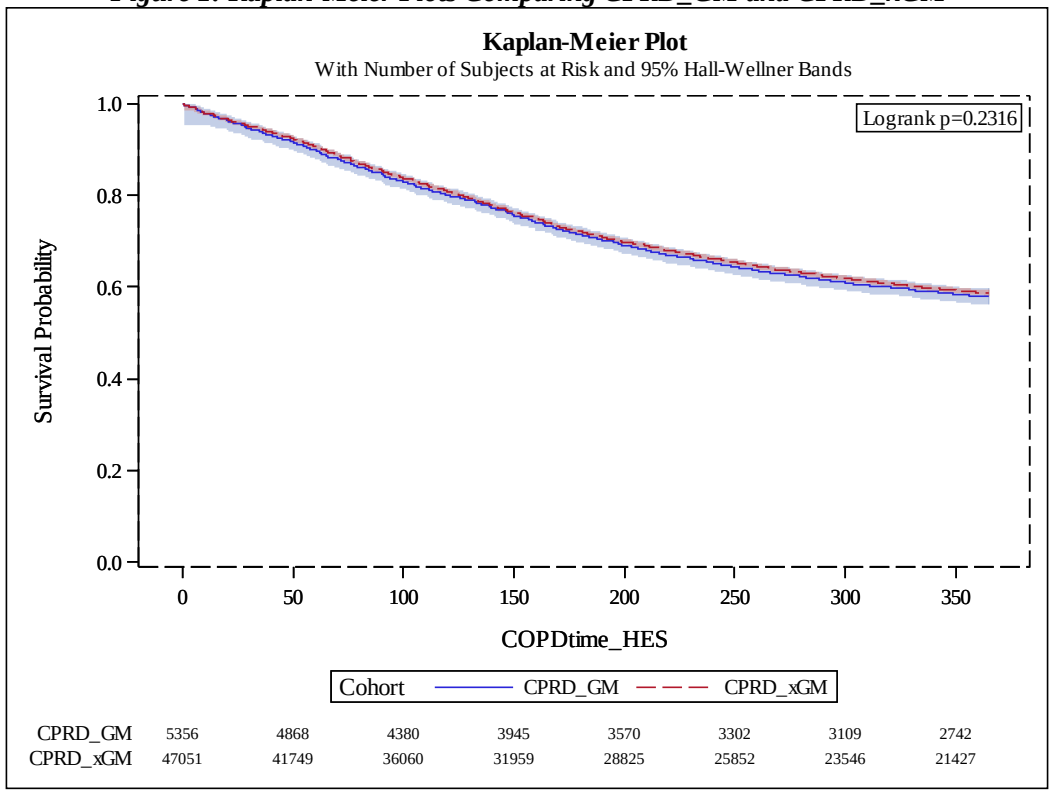


Figure 2: Q-Q Plot for Index Dates of Matched Cohorts CPRD_IC and SLS_UC

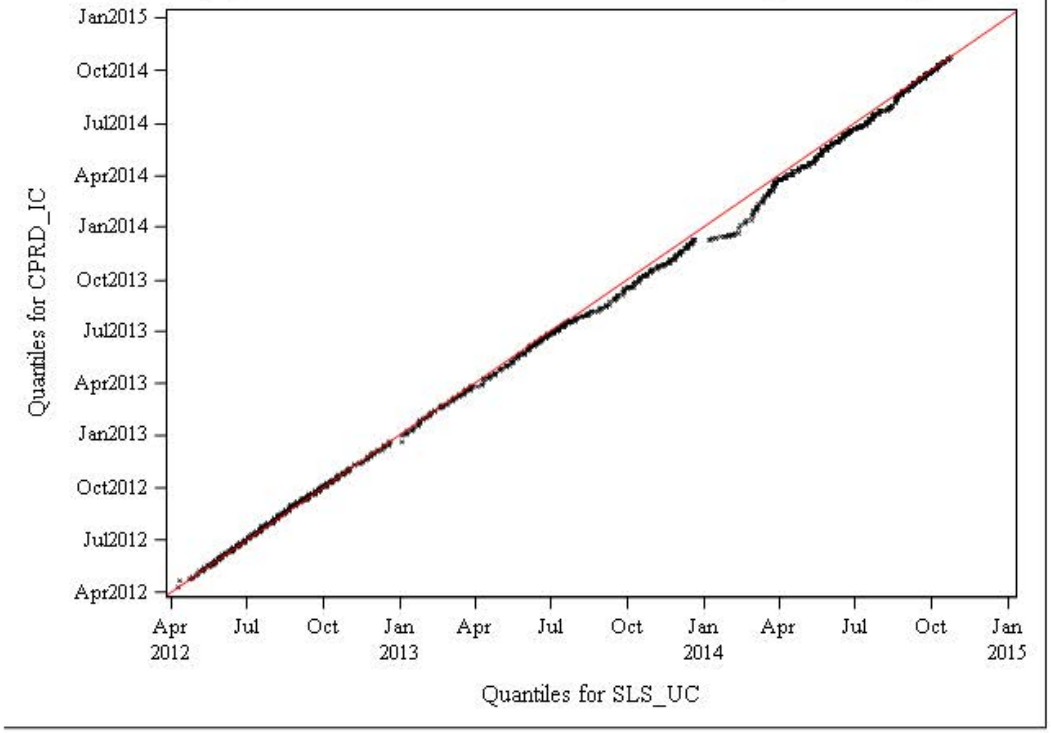


Figure 3: Kaplan-Meier Plots Comparing CPRD_GM_IC, CPRD_xGM_IC and SLS_UC

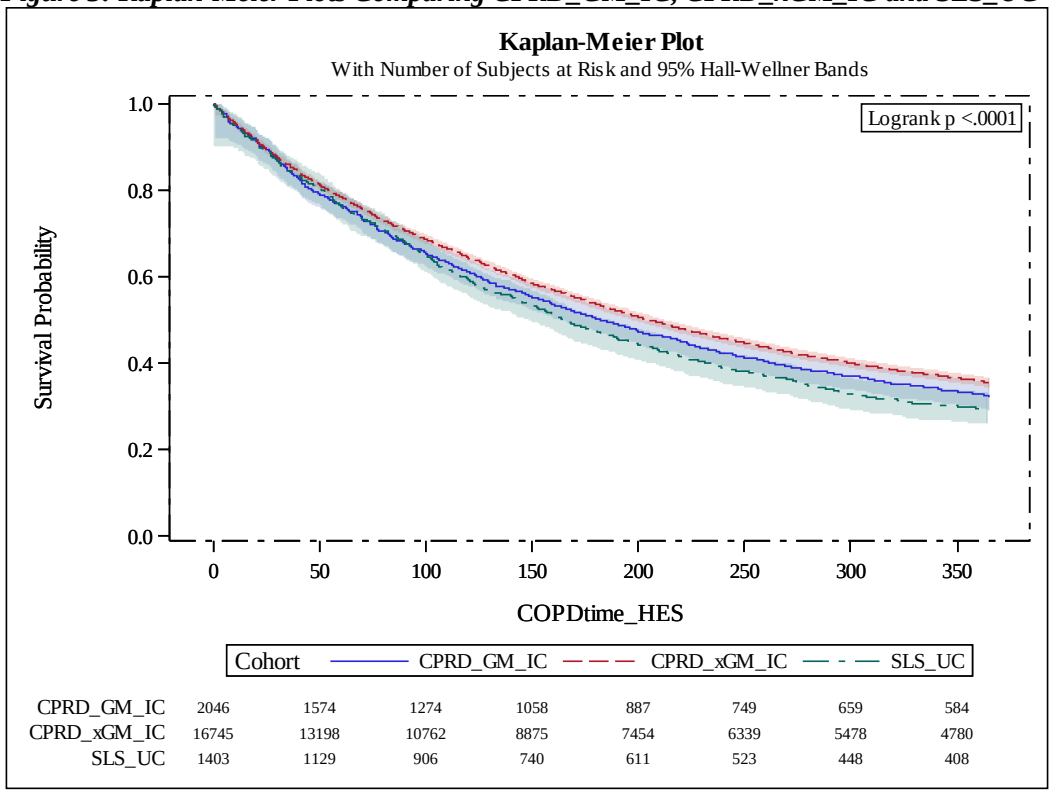


Figure 4: Stacked Bar Chart for Number of COPD Exacerbations

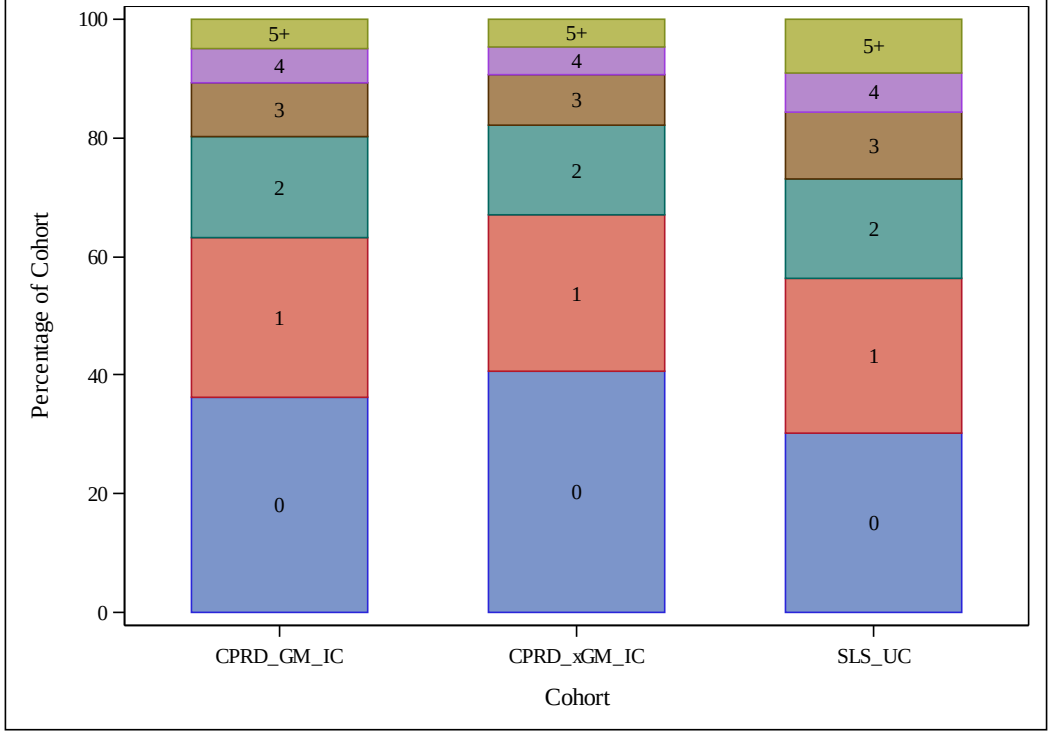
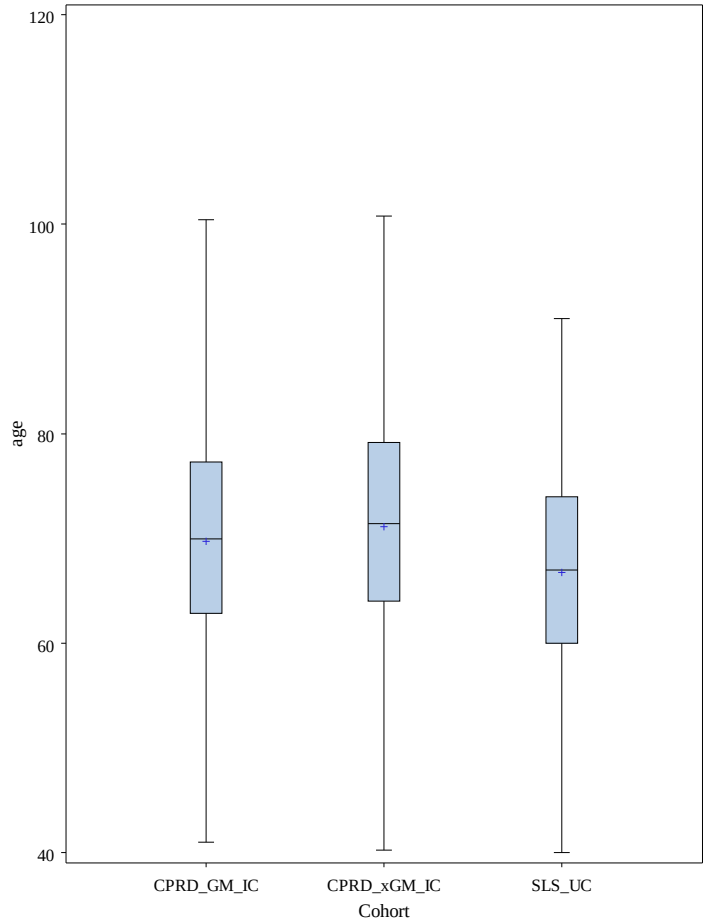


Figure 5: Box Plots Comparing Age



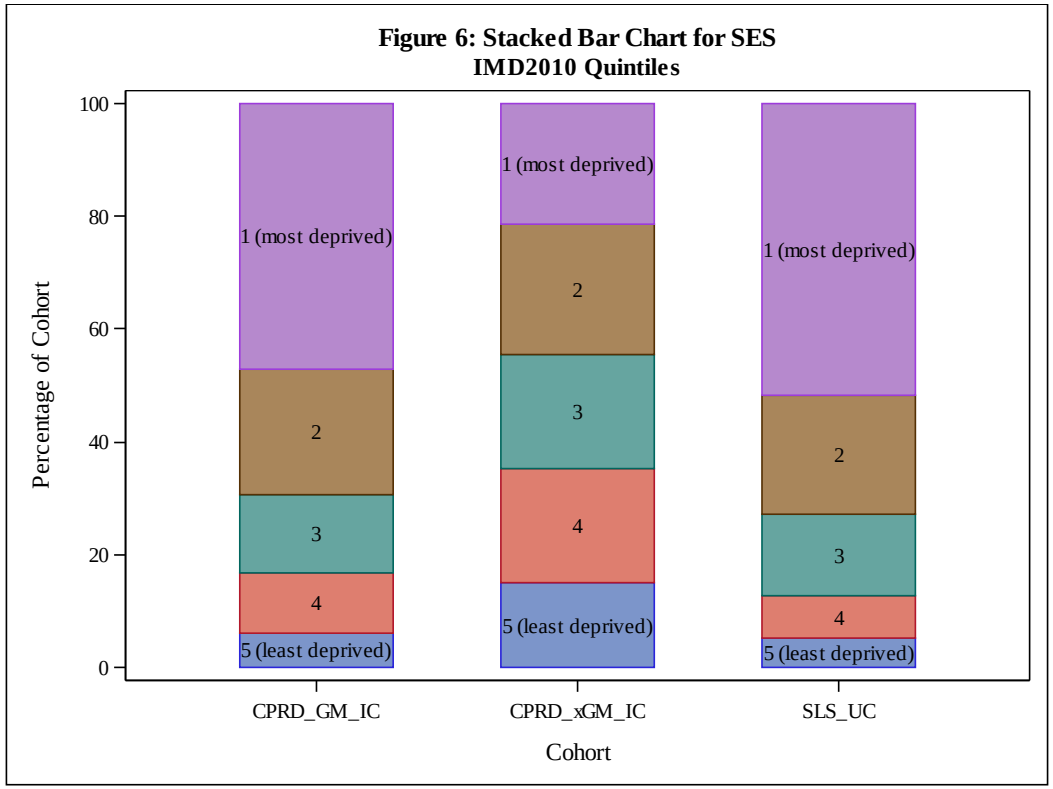


Figure 6: Stacked Bar Chart for SES
IMD2010 Quintiles
Percentage of Cohort
100
80
60
40
20
0
1 (most deprived)
2
3
4
5 (least deprived)
CPRD_GM_IC
CPRD_xGM_IC
SLS_UC
Cohort

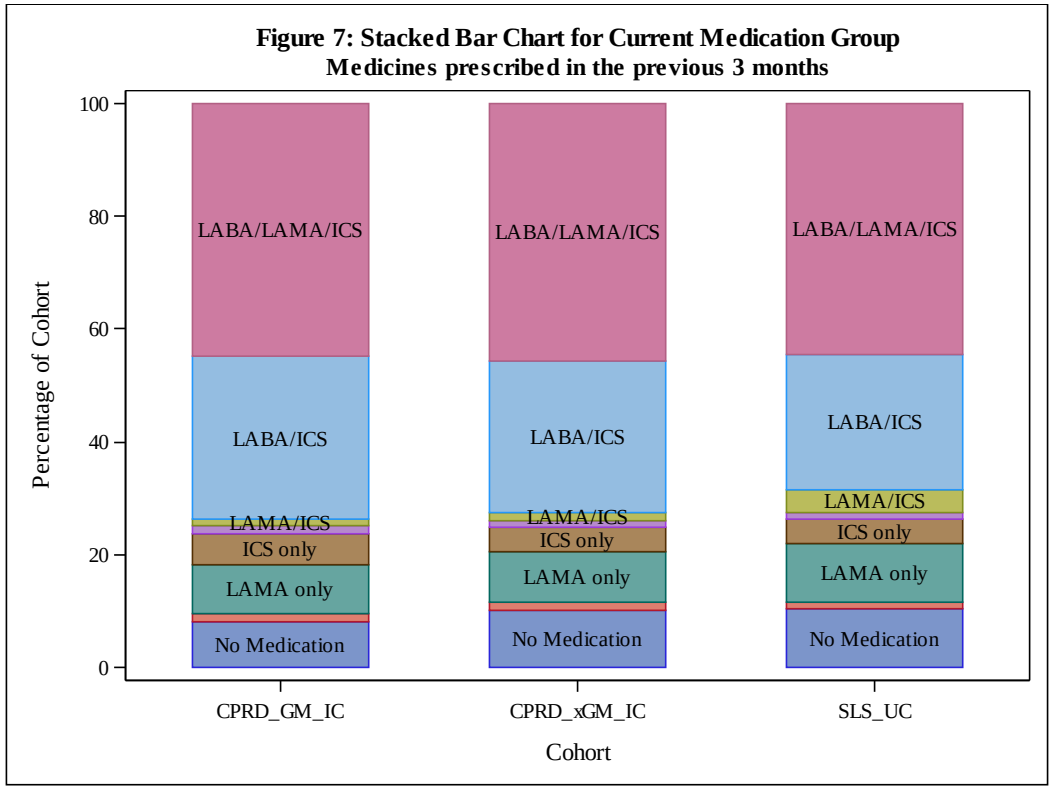


Figure 7: Stacked Bar Chart for Current Medication Group
Medicines prescribed in the previous 3 months
Percentage of Cohort
100
80
60
40
20
0
LABA/LAMA/ICS
LABA/ICS
LAMA/ICS
ICS only
LAMA only
No Medication
CPRD_GM_IC
CPRD_xGM_IC
SLS_UC
Cohort

Figure 8: Stacked Bar Chart for Charlson Score

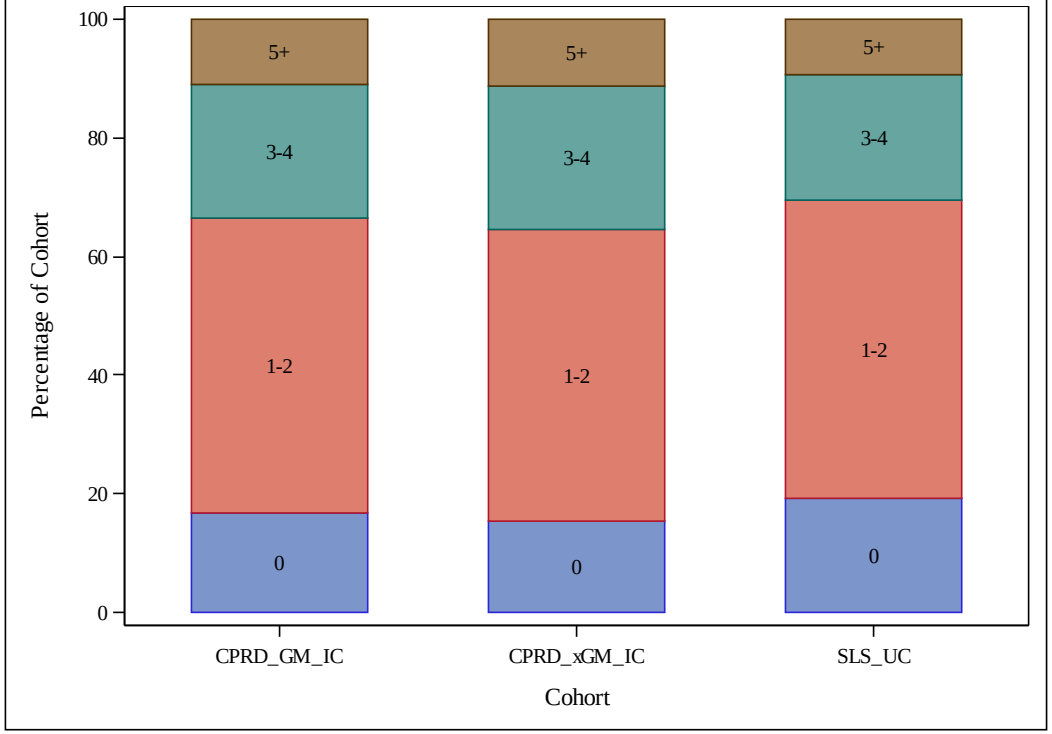


Figure 9: Stacked Bar Chart for Smoking Status

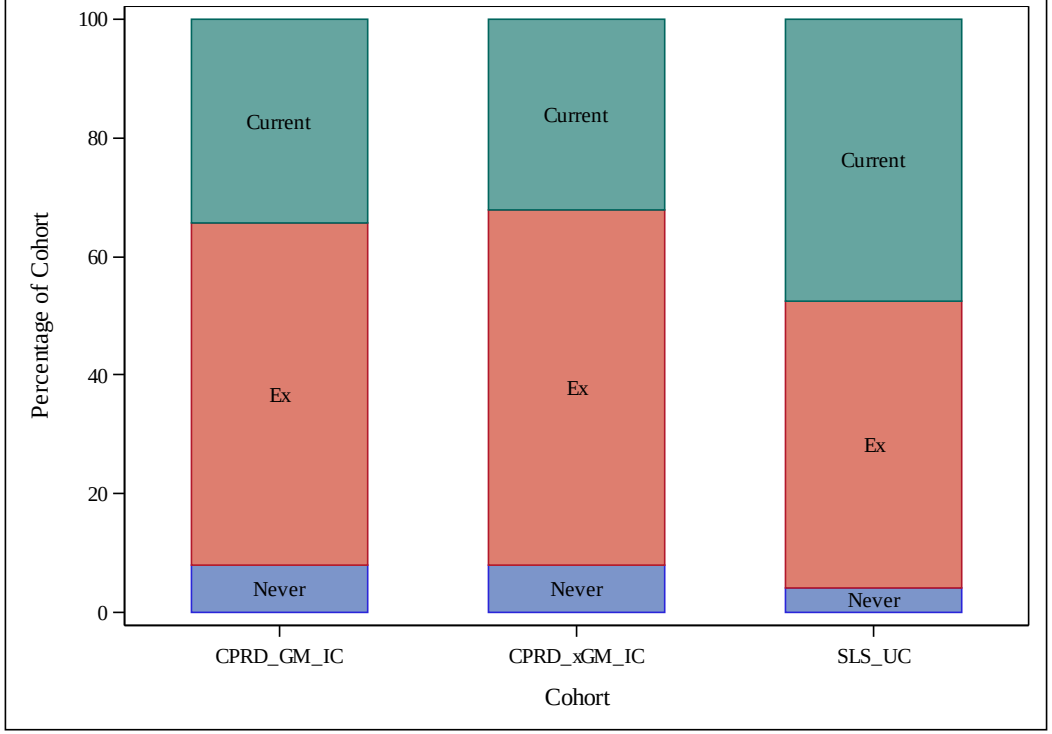


Figure 10: Stacked Bar Chart for BMI WHO categories

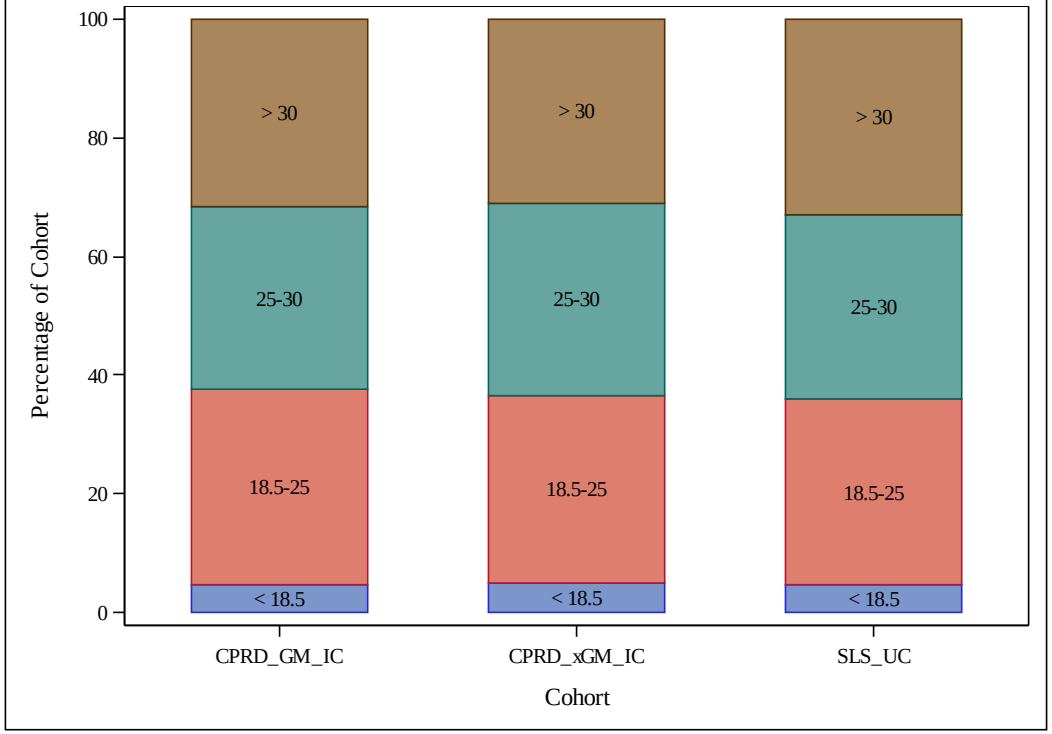


Figure 11: Stacked Bar Chart for MRC Dyspnoea score

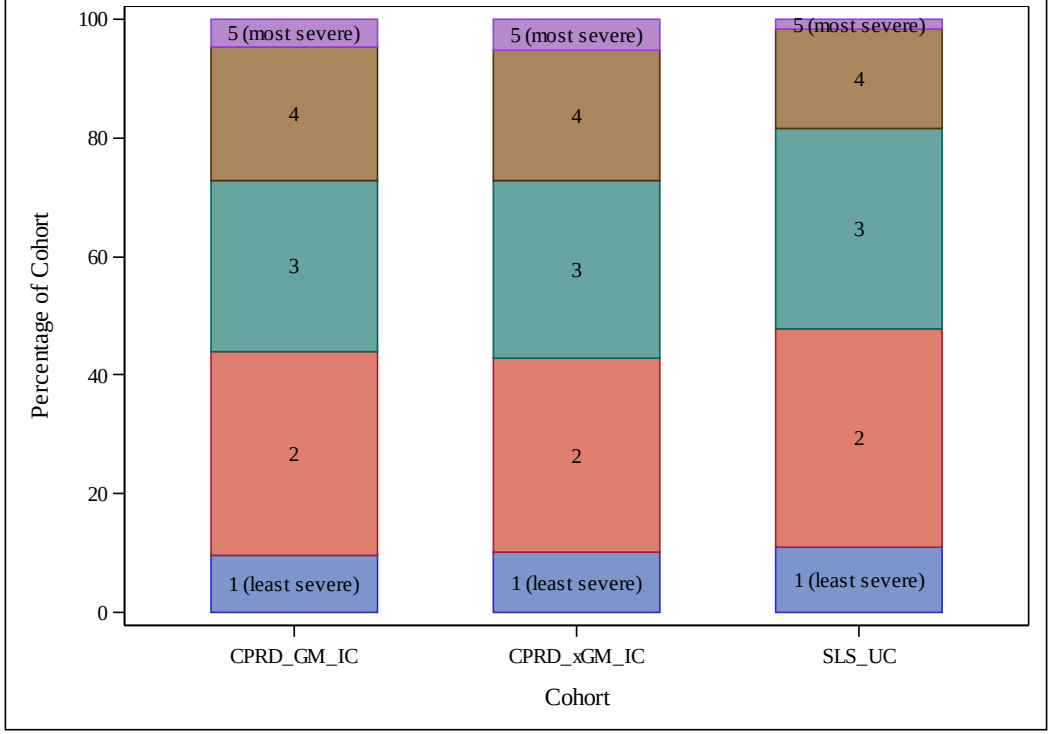


Figure 12: Stacked Bar Chart for GOLD Stage

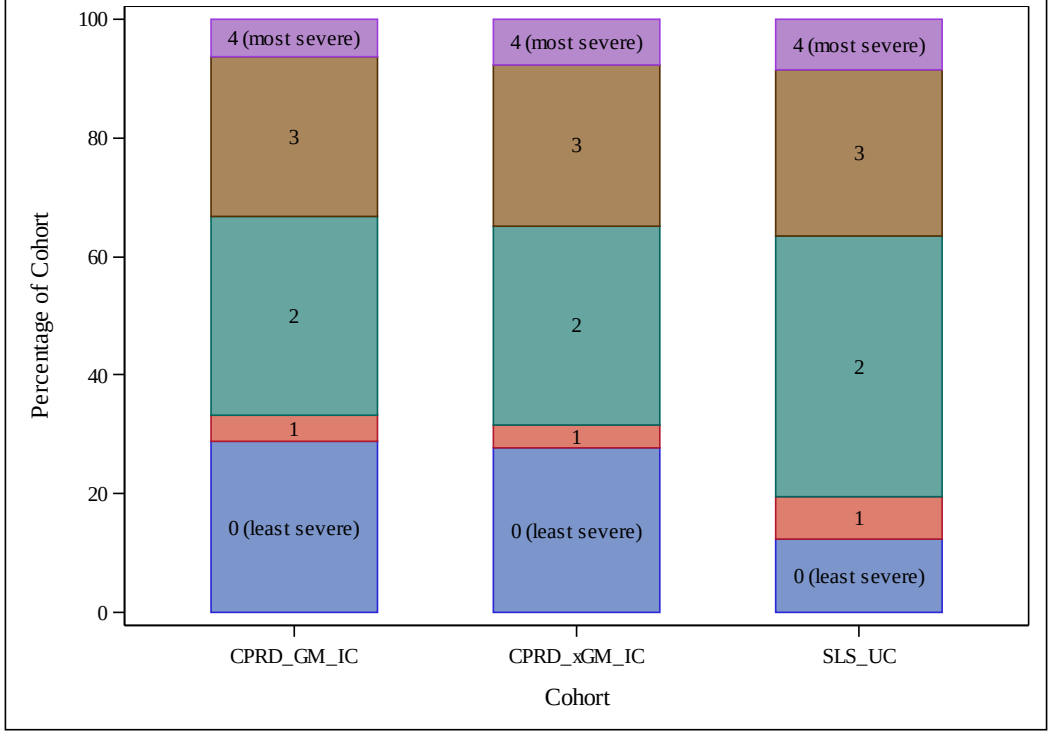
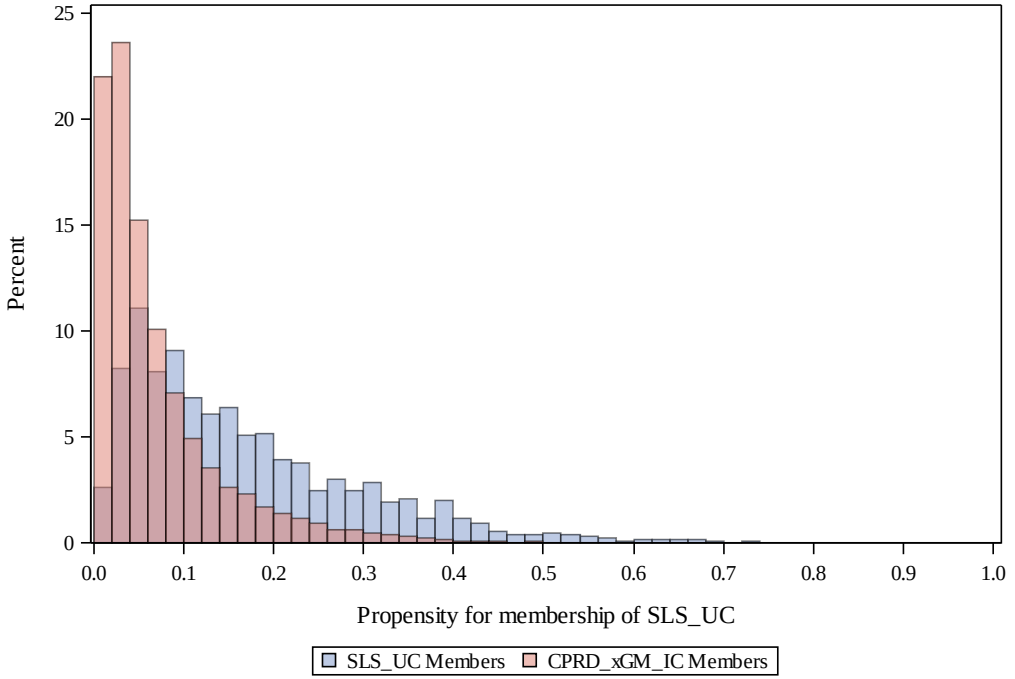


Figure 13: Propensity for membership of SLS_UC for SLS_UC and CPRD_xGM_IC members



1.2 PO1/PO2: CPRD Primary Care Data vs. SLS-EHR

Table 19: Comparison of CPRD-GM and CPRD-xGM cohorts - Baseline variables

Variable	Category	CPRD_GM	CPRD_xGM
N		5,669	49,499
Sex	Male	2,699 (47.61%)	25,423 (51.36%)
	Female	2,970 (52.39%)	24,076 (48.64%)
Age	mean (95% CI) median (2.5 - 97.5% range) missing	69.12 (68.83 - 69.41) 69.06 (46.06 - 89.06) 0.00% missing	70.66 (70.56 - 70.76) 71.06 (47.06 - 91.06) 0.00% missing
SES IMD 2010 Quintiles	Missing	1 (0.02%)	26 (0.05%)
	5 (least deprived)	424 (7.48%)	7,739 (15.63%)
	4	633 (11.17%)	10,525 (21.26%)
	3	748 (13.19%)	10,090 (20.38%)
	2	1,184 (20.89%)	11,399 (23.03%)
	1 (most deprived)	2,679 (47.26%)	9,720 (19.64%)
Current Medication (prescriptions in last 3 months)	No treatment	1,759 (31.03%)	15,987 (32.30%)
	LABA only	89 (1.57%)	794 (1.60%)
	LAMA only	525 (9.26%)	4,330 (8.75%)
	ICS only	330 (5.82%)	2,440 (4.93%)
	LABA/LAMA	75 (1.32%)	520 (1.05%)
	LAMA/ICS	85 (1.50%)	664 (1.34%)
	LABA/ICS	1,279 (22.56%)	10,557 (21.33%)

Variable	Category	CPRD_GM	CPRD_xGM
	LABA/LAMA/ICS	1,527 (26.94%)	14,207 (28.70%)
Comorbidities (history of)	Anxiety	1,503 (26.51%)	9,750 (19.70%)
	Asthma	2,766 (48.79%)	24,723 (49.95%)
	Cardio- / Cerebrovascular disease	1,004 (17.71%)	8,580 (17.33%)
	Depression	1,983 (34.98%)	14,558 (29.41%)
	Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	1,520 (26.81%)	11,343 (22.92%)
	Pneumonia	554 (9.77%)	5,801 (11.72%)
Current comorbidity (reported in last 12 months)	Asthma	1130 (19.93%)	10441 (21.09%)
Charlson Comorbidity Index	0	1,149 (20.27%)	10,066 (20.34%)
	1-2	2,717 (47.93%)	23,360 (47.19%)
	3-4	1,230 (21.70%)	11,213 (22.65%)
	5+	573 (10.11%)	4,860 (9.82%)
COPD Exacerbation History in previous 12 months	# Episodes Rate (95% CI)	5,288 1.01 (0.99 - 1.04)	41,808 0.92 (0.91 - 0.93)

Variable	Category	CPRD_GM	CPRD_xGM
FEV1%	mean (95% CI) median (2.5 - 97.5% range) missing	62.13 (61.57 - 62.69) 61.80 (26.10 - 100.49) 18.50% missing	60.38 (60.19 - 60.58) 59.92 (24.90 - 100.41) 20.50% missing
FEV1/FVC (%)	mean (95% CI) median (2.5 - 97.5% range) missing	63.09 (62.63 - 63.55) 63.00 (34.00 - 94.00) 28.59% missing	62.39 (62.23 - 62.56) 62.90 (33.00 - 94.20) 27.37% missing
GOLD Stage	Missing	1,641 (28.95%)	13,935 (28.15%)
	0 (fev1_fvc => 70)	1,309 (23.09%)	10,942 (22.11%)
	1 (fev1_fvc < 70, fev1% => 80)	287 (5.06%)	2,171 (4.39%)
	2 (fev1_fvc < 70, 50 <= fev1% < 80)	1,462 (25.79%)	13,024 (26.31%)
	3 (fev1_fvc < 70, 30 <= fev1% < 50)	820 (14.46%)	7,713 (15.58%)
	4 (fev1_fvc < 70, fev1% < 30)	150 (2.65%)	1,714 (3.46%)
MRC Dyspnoea score	Missing	960 (16.93%)	8,596 (17.37%)
	1 (least breathlessness)	796 (14.04%)	7,047 (14.24%)
	2	1,844 (32.53%)	15,209 (30.73%)
	3	1,239 (21.86%)	10,459 (21.13%)
	4	710 (12.52%)	6,680 (13.50%)
	5 (most breathlessness)	120 (2.12%)	1,508 (3.05%)
Smoking	Missing	9 (0.16%)	86 (0.17%)
	Never	509 (8.98%)	4,676 (9.45%)
	Ex	2,972 (52.43%)	28,113 (56.80%)

Variable	Category	CPRD_GM	CPRD_xGM
	Current	2,179 (38.44%)	16,624 (33.58%)
BMI	Missing	258 (4.55%)	3,486 (7.04%)
	18.50 - 24.99	1,712 (30.20%)	14,752 (29.80%)
	<18.50	243 (4.29%)	2,056 (4.15%)
	25.00 - 29.99	1,749 (30.85%)	15,322 (30.95%)
	>=30.00	1,707 (30.11%)	13,883 (28.05%)
Vaccinations	Influenza	4,841 (85.39%)	41,920 (84.69%)
	Pneumococcal	867 (15.29%)	6,655 (13.44%)

COPD Exacerbation History in previous 12 months is treated as a rate and calculated per person year
All other variables are the same as in Table 1, as the cohort is the same and no other variables have different definitions

Table 20: Comparison of CPRD-GM and CPRD-xGM cohorts - Rate of COPD exacerbation episodes in year of follow up

DataSource	Variable	CPRD_GM	CPRD_xGM
Primary care only	N	5,669	49,499
	Person time	5,024.96 years	40,076.88 years
	# Episodes Rate per person year (95% CI)	4,887 0.97 (0.95 - 1.00)	37,512 0.94 (0.93 - 0.95)

Table 21: Comparison of CPRD-xGM-IC, CPRD-GM-IC and SLS-UC - Baseline variables

Variable	Category	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
N		2,049	16,758	1,403
Index Date		5th pctl = 03/06/12 25th pctl = 09/10/12 50th pctl = 09/07/13 75th pctl = 24/04/14 95th pctl = 23/09/14	5th pctl = 31/05/12 25th pctl = 03/10/12 50th pctl = 17/07/13 75th pctl = 24/04/14 95th pctl = 22/09/14	5th pctl = 31/05/12 25th pctl = 03/10/12 50th pctl = 23/07/13 75th pctl = 12/05/14 95th pctl = 23/09/14
Sex	Male	869 (42.41%)	8,163 (48.71%)	732 (52.17%)
	Female	1,180 (57.59%)	8,595 (51.29%)	671 (47.83%)
Age	mean (95% CI) median (2.5-97.5% range) missing	69.77 (69.30 - 70.23) 69.96 (47.57 - 89.22) 0.00% missing	71.12 (70.96 - 71.29) 71.41 (48.14 - 90.21) 0.00% missing	66.73 (66.21 - 67.25) 67.00 (46.00 - 85.00) 0.00% missing
SES IMD 2010 Quintiles	Missing	0 (0.00%)	8 (0.05%)	8 (0.57%)
	5 (least deprived)	127 (6.20%)	2,499 (14.91%)	72 (5.13%)
	4	219 (10.69%)	3,428 (20.46%)	105 (7.48%)
	3	283 (13.81%)	3,348 (19.98%)	202 (14.40%)
	2	456 (22.25%)	3,897 (23.25%)	294 (20.96%)
	1 (most deprived)	964 (47.05%)	3,578 (21.35%)	722 (51.46%)
Current Medication (prescriptions in last 3 months)	None of the below treatments in the last 3 months	165 (8.05%)	1,693 (10.10%)	145 (10.33%)
	LABA only	32 (1.56%)	252 (1.50%)	19 (1.35%)
	LAMA only	174 (8.49%)	1,480 (8.83%)	143 (10.19%)
	ICS only	114 (5.56%)	758 (4.52%)	62 (4.42%)
	LABA/LAMA	25 (1.22%)	177 (1.06%)	18 (1.28%)

Variable	Category	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
	LAMA/ICS	24 (1.17%)	235 (1.40%)	56 (3.99%)
	LABA/ICS	594 (28.99%)	4,529 (27.03%)	337 (24.02%)
	LABA/LAMA/ICS	921 (44.95%)	7,634 (45.55%)	623 (44.40%)
Comorbidities (history of)	Anxiety	572 (27.92%)	3,661 (21.85%)	301 (21.45%)
	Asthma	1,213 (59.20%)	10,083 (60.17%)	755 (53.81%)
	Cardio- / Cerebrovascular disease	387 (18.89%)	3,222 (19.23%)	238 (16.96%)
	Depression	767 (37.43%)	5,466 (32.62%)	344 (24.52%)
	Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	571 (27.87%)	4,120 (24.59%)	355 (25.30%)
	Pneumonia	282 (13.76%)	2,635 (15.72%)	147 (10.48%)
Current comorbidity (reported in last 12 months)	Asthma	485 (23.67%)	4018 (23.98%)	298 (21.24%)
Charlson Comorbidity Index	0	341 (16.64%)	2,569 (15.33%)	271 (19.32%)
	1-2	1,020 (49.78%)	8,226 (49.09%)	703 (50.11%)
	3-4	462 (22.55%)	4,094 (24.43%)	297 (21.17%)
	5+	226 (11.03%)	1,869 (11.15%)	132 (9.41%)
COPD Exacerbation History in previous 12 months	Events Rate (95% CI)	3,262 1.80 (1.74 - 1.86)	24,892 1.66 (1.64 - 1.68)	2,372 1.94 (1.86 - 2.02)

Variable	Category	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
FEV1%	mean (95% CI) median (2.5-97.5% range) missing	56.72 (55.83 - 57.61) 55.80 (22.68 - 95.23) 12.79% missing	55.84 (55.53 - 56.16) 55.07 (22.34 - 95.97) 14.25% missing	60.30 (59.17 - 61.43) 60.90 (24.30 - 98.90) 21.53% missing
FEV1/FVC (%)	mean (95% CI) median (2.5-97.5% range) missing	61.06 (60.24 - 61.88) 60.60 (32.20 - 95.00) 23.13% missing	60.51 (60.22 - 60.80) 60.00 (31.00 - 95.70) 21.58% missing	54.39 (53.58 - 55.19) 54.80 (28.65 - 79.09) 21.53% missing
GOLD Stage	Missing	479 (23.38%)	3,783 (22.57%)	217 (15.47%)
	0 (fev1_fvc => 70)	451 (22.01%)	3,589 (21.42%)	147 (10.48%)
	1 (fev1_fvc < 70, fev1% => 80)	70 (3.42%)	522 (3.11%)	84 (5.99%)
	2 (fev1_fvc < 70, 50 <= fev1% < 80)	527 (25.72%)	4,347 (25.94%)	522 (37.21%)
	3 (fev1_fvc < 70, 30 <= fev1% < 50)	422 (20.60%)	3,528 (21.05%)	332 (23.66%)
	4 (fev1_fvc < 70, fev1% < 30)	100 (4.88%)	989 (5.90%)	101 (7.20%)
MRC Dyspnoea score	Missing	199 (9.71%)	1,719 (10.26%)	12 (0.86%)
	1 (least breathlessness)	179 (8.74%)	1,530 (9.13%)	154 (10.98%)
	2	634 (30.94%)	4,912 (29.31%)	510 (36.35%)
	3	532 (25.96%)	4,509 (26.91%)	470 (33.50%)
	4	417 (20.35%)	3,299 (19.69%)	233 (16.61%)
	5 (most breathlessness)	88 (4.29%)	789 (4.71%)	24 (1.71%)
Smoking	Never	165 (8.05%)	1,349 (8.05%)	59 (4.21%)
	Ex	1,177 (57.44%)	10,033 (59.87%)	678 (48.33%)
	Current	707 (34.50%)	5,376 (32.08%)	666 (47.47%)

Variable	Category	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
BMI	Missing	68 (3.32%)	940 (5.61%)	281 (20.03%)
	18.50 - 24.99	651 (31.77%)	5,005 (29.87%)	351 (25.02%)
	<18.50	94 (4.59%)	793 (4.73%)	52 (3.71%)
	25.00 - 29.99	608 (29.67%)	5,121 (30.56%)	349 (24.88%)
	>=30.00	628 (30.65%)	4,899 (29.23%)	370 (26.37%)
Vaccinations	Influenza	1,856 (90.58%)	15,105 (90.14%)	1,267 (90.31%)
	Pneumococcal	320 (15.62%)	2,259 (13.48%)	241 (17.18%)

COPD Exacerbation History in previous 12 months is treated as a rate and calculated per person year

Table 22: Comparison of CPRD-xGM-IC, CPRD-GM-IC and SLS-UC - Rate of COPD exacerbation episodes in year of follow up

DataSource	Variable	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
Primary care only	N	2,049	16,758	1,403
	Person time	1,650.74 years	13,149.92 years	1,199.70 years
	# Episodes Rate per person year (95% CI)	2,693 1.63 (1.57 - 1.69)	20,184 1.53 (1.51 - 1.56)	2,288 1.91 (1.83 - 1.99)

Table 23.1: Comparison of imputed and complete case datasets for variables with missingness - CPRD-GM-IC

Variable	Category	CPRD_GM_IC_Complete_Case	CPRD_GM_IC_Imputed
N		1,493	2,049
SES IMD 2010 Quintiles	5 (least deprived)	107 (7.17%)	127 (6.20%)
	4	180 (12.06%)	219 (10.69%)
	3	214 (14.33%)	283 (13.81%)
	2	332 (22.24%)	456 (22.25%)
	1 (most deprived)	660 (44.21%)	964 (47.05%)
FEV1%	mean (95% CI) median (5-95% range)	56.80 (55.82 - 57.77) 55.80 (27.28 - 89.98)	57.01 (56.17 - 57.85) 55.87 (27.25 - 89.98)
FEV1/FVC (%)	mean (95% CI) median (5-95% range)	60.73 (59.89 - 61.56) 60.00 (36.00 - 88.00)	61.14 (60.44 - 61.84) 60.91 (35.38 - 89.00)
GOLD Stage	0 (fev1_fvc => 70)	416 (27.86%)	601 (29.33%)
	1 (fev1_fvc < 70, fev1% => 80)	65 (4.35%)	86 (4.20%)
	2 (fev1_fvc < 70, 50 <= fev1% < 80)	506 (33.89%)	676 (32.99%)
	3 (fev1_fvc < 70, 30 <= fev1% < 50)	410 (27.46%)	547 (26.70%)
	4 (fev1_fvc < 70, fev1% < 30)	96 (6.43%)	139 (6.78%)
MRC Dyspnoea score	1 (least breathlessness)	147 (9.85%)	203 (9.91%)
	2	525 (35.16%)	707 (34.50%)
	3	446 (29.87%)	592 (28.89%)
	4	314 (21.03%)	453 (22.11%)

Variable	Category	CPRD_GM_IC_Complete_Case	CPRD_GM_IC_Imputed
	5 (most breathlessness)	61 (4.09%)	94 (4.59%)
Smoking	Never	97 (6.50%)	165 (8.05%)
	Ex	880 (58.94%)	1,177 (57.44%)
	Current	516 (34.56%)	707 (34.50%)
BMI	18.50 - 24.99	496 (33.22%)	669 (32.65%)
	<18.50	70 (4.69%)	96 (4.69%)
	25.00 - 29.99	466 (31.21%)	629 (30.70%)
	>=30.00	461 (30.88%)	655 (31.97%)

Table 23.2: Summary of percentage missing for each variable - CPRD-GM-IC

Variable	Percentage_Miss
SES IMD 2010 Quintiles	0.00%
FEV1%	12.79%
FEV1/FVC ratio	23.13%
GOLD Stage	23.38%
MRC Dyspnoea Score	9.71%
Smoking	0.00%
BMI	3.32%

Table 24.1: Comparison of imputed and complete case datasets for variables with missingness - CPRD-xGM-IC

Variable	Category	CPRD_xGM_IC_Complete_Case	CPRD_xGM_IC_Imputed
N		12,077	16,758
SES IMD 2010 Quintiles	5 (least deprived)	1,765 (14.61%)	2,500 (14.92%)
	4	2,490 (20.62%)	3,431 (20.47%)
	3	2,361 (19.55%)	3,348 (19.98%)
	2	2,858 (23.66%)	3,899 (23.27%)
	1 (most deprived)	2,603 (21.55%)	3,580 (21.36%)
FEV1%	mean (95% CI) median (5-95% range)	55.84 (55.50 - 56.17) 55.11 (26.80 - 87.62)	56.01 (55.72 - 56.30) 55.28 (26.11 - 88.46)
FEV1/FVC (%)	mean (95% CI) median (5-95% range)	60.23 (59.93 - 60.53) 60.00 (34.00 - 87.00)	60.57 (60.32 - 60.81) 60.57 (34.00 - 88.32)
GOLD Stage	0 (fev1_fvc => 70)	3,205 (26.54%)	4,743 (28.30%)
	1 (fev1_fvc < 70, fev1% => 80)	479 (3.97%)	646 (3.85%)
	2 (fev1_fvc < 70, 50 <= fev1% < 80)	4,096 (33.92%)	5,512 (32.89%)
	3 (fev1_fvc < 70, 30 <= fev1% < 50)	3,377 (27.96%)	4,503 (26.87%)
	4 (fev1_fvc < 70, fev1% < 30)	920 (7.62%)	1,354 (8.08%)
MRC Dyspnoea score	1 (least breathlessness)	1,193 (9.88%)	1,778 (10.61%)
	2	4,096 (33.92%)	5,545 (33.09%)
	3	3,708 (30.70%)	4,957 (29.58%)
	4	2,564 (21.23%)	3,612 (21.55%)

Variable	Category	CPRD_xGM_IC_Complete_Case	CPRD_xGM_IC_Imputed
	5 (most breathlessness)	516 (4.27%)	866 (5.17%)
Smoking	Never	773 (6.40%)	1,349 (8.05%)
	Ex	7,344 (60.81%)	10,033 (59.87%)
	Current	3,960 (32.79%)	5,376 (32.08%)
BMI	18.50 - 24.99	3,835 (31.75%)	5,334 (31.83%)
	<18.50	564 (4.67%)	838 (5.00%)
	25.00 - 29.99	3,950 (32.71%)	5,423 (32.36%)
	>=30.00	3,728 (30.87%)	5,163 (30.81%)

Table 24.2: Summary of percentage missing for each variable - CPRD-xGM-IC

Variable	Percentage_Miss
SES IMD 2010 Quintiles	0.05%
FEV1%	14.25%
FEV1/FVC ratio	21.58%
GOLD Stage	22.57%
MRC Dyspnoea Score	10.26%
Smoking	0.00%
BMI	5.61%

Table 25.1: Comparison of imputed and complete case datasets for variables with missingness - SLS-UC-EHR

Variable	Category	SLS_UC_NwEH_Complete_Case	SLS_UC_NwEH_Imputed
N		863	1,403
SES IMD 2010 Quintiles	5 (least deprived)	54 (6.26%)	72 (5.13%)
	4	61 (7.07%)	106 (7.56%)
	3	128 (14.83%)	203 (14.47%)
	2	191 (22.13%)	295 (21.03%)
	1 (most deprived)	429 (49.71%)	727 (51.82%)
FEV1%	mean (95% CI) median (5-95% range)	60.68 (59.40 - 61.96) 61.00 (29.70 - 93.00)	60.29 (59.30 - 61.29) 60.90 (28.40 - 91.94)
FEV1/FVC (%)	mean (95% CI) median (5-95% range)	54.37 (53.45 - 55.30) 54.55 (31.73 - 76.15)	54.90 (54.18 - 55.62) 55.70 (31.73 - 76.53)
GOLD Stage	0 (fev1_fvc => 70)	107 (12.40%)	175 (12.47%)
	1 (fev1_fvc < 70, fev1% => 80)	66 (7.65%)	132 (9.41%)
	2 (fev1_fvc < 70, 50 <= fev1% < 80)	371 (42.99%)	692 (49.32%)
	3 (fev1_fvc < 70, 30 <= fev1% < 50)	242 (28.04%)	320 (22.81%)
	4 (fev1_fvc < 70, fev1% < 30)	77 (8.92%)	84 (5.99%)
MRC Dyspnoea score	1 (least breathlessness)	112 (12.98%)	157 (11.19%)
	2	328 (38.01%)	515 (36.71%)
	3	288 (33.37%)	473 (33.71%)
	4	120 (13.90%)	234 (16.68%)

Variable	Category	SLS_UC_NwEH_Complete_Case	SLS_UC_NwEH_Imputed
	5 (most breathlessness)	15 (1.74%)	24 (1.71%)
Smoking	Never	35 (4.06%)	59 (4.21%)
	Ex	417 (48.32%)	678 (48.33%)
	Current	411 (47.62%)	666 (47.47%)
BMI	18.50 - 24.99	279 (32.33%)	442 (31.50%)
	<18.50	37 (4.29%)	76 (5.42%)
	25.00 - 29.99	273 (31.63%)	417 (29.72%)
	>=30.00	274 (31.75%)	468 (33.36%)

Table 25.2: Summary of percentage missing for each variable - SLS-UC-EHR

Variable	Percentage_Miss
SES IMD 2010 Quintiles	0.57%
FEV1%	21.53%
FEV1/FVC ratio	21.53%
GOLD Stage	15.47%
MRC Dyspnoea Score	0.86%
Smoking	0.00%
BMI	20.03%

Table 26.1: Variables in SLS-UC in the context of regional variation in the CPRD at local authority level (continuous/boolean)

The average response is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5 percentile range. The value for SLS-UC is deemed unusual if it lies outside of this range.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Sex (% male)	31.52%	51.07%	69.07%	47.83%	33.20	0
Age	67.29	71.37	76.32	66.73	0.67	1
Any history (ever) of: Cardio- / Cerebrovascular disease	7.54%	19.33%	33.75%	16.96%	31.73	0
Any history (ever) of: Depression	12.44%	32.17%	50.19%	24.52%	15.96	0
Any history (ever) of: Anxiety	6.85%	19.98%	44.24%	21.45%	60.70	0
Any history (ever) of: Asthma	30.70%	59.06%	84.60%	53.81%	31.55	0
Any history (ever) of: Pneumonia	0.00%	16.26%	36.12%	10.48%	15.96	0
Any history (ever) of: Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	10.00%	23.50%	43.69%	25.30%	56.74	0
COPD Exacerbation History in previous 12 months	0.73	1.59	2.30	1.94	80.42	0
FEV1%	48.76	55.68	64.50	60.29	94.08	0
FEV1/FVC (%)	51.75	59.88	68.61	54.90	9.02	0

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Influenza Vaccination	78.57%	91.07%	98.32%	90.31%	44.00	0
Pneumococcal Vaccination	1.41%	12.50%	29.44%	17.18%	74.21	0

Table 26.2: Variables in SLS-UC in the context of regional variation in the CPRD at local authority level (categorical)

For each local authority in CPRD_xGM_IC a Chi Squared test is performed comparing the distribution of the variable of interest in the local authority to its distribution in the rest of CPRD_xGM_IC. The test statistics from each local authority are used to construct an empirical 0 - 95 percentile range of test statistics. A chi squared test comparing the distribution of the variable of interest in UC to CPRD_xGM_IC is then performed. UC is deemed unusual with respect to this variable if the Chi Squared test statistic lies outside the 0 - 95% range.

Variable	CPRD_xGM_IC_0_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_95_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
SES IMD 2010 Quintiles	0.68	43.17	236.56	727.70	100.00	1
Current Medication (prescriptions in last 3 months)	1.44	10.04	41.99	62.50	96.93	1
Charlson Comorbidity Index	0.08	3.75	15.35	22.70	97.80	1
MRC Dyspnoea Score	0.20	6.86	29.57	58.99	99.59	1
Gold Stage	0.59	5.82	32.37	330.52	100.00	1
Smoking	0.00	2.95	21.36	146.10	100.00	1
BMI	0.25	2.74	9.61	6.00	84.17	0

Table 27: The rate* of COPD exacerbations episodes in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups -

For each subgroup the rate of COPD episodes is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The number of exacerbations in UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	0.32639	1.42616	2.16377	1.90715	86.9414	0
Male	0.00000	1.39530	2.72095	1.74961	77.9863	0
Female	0.32693	1.48688	2.54968	2.08295	85.5382	0
Never Smoked	0.00000	1.13784	3.16446	1.30197	60.8187	0
Ex Smoker	0.39498	1.35711	2.37092	2.00065	92.1258	0
Current Smoker	0.10194	1.67966	2.93576	1.86937	66.0892	0
Over 75	0.00000	1.25305	2.33918	1.86470	88.6344	0
Below 75	0.29272	1.55616	2.56671	1.91937	79.0466	0
SES IMD 2010 = 5 (least deprived)	0.00000	1.21372	2.91700	1.29401	55.9918	0
SES IMD 2010 = 4	0.00000	1.37739	2.76709	1.92364	87.4083	0
SES IMD 2010 = 3	0.00000	1.43960	3.73570	1.84567	74.4249	0
SES IMD 2010 = 2	0.00000	1.46213	3.76428	2.08149	83.9114	0
SES IMD 2010 = 1 (most deprived)	0.00000	1.56514	3.63765	1.91516	74.2195	0

**Rate is calculated per person year*

Table 28: Survival times until first COPD exacerbation in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups -

For each subgroup the 25th percentile survival time is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The 25th percentile survival time for SLS-UC is deemed unusual if it lies outside of this range.*

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	41.35 days	84 days	360.28 days	64 days	24.83	0
Male	34.675 days	91.5 days	=> 365 days	79 days	42.86	0
Female	38.038 days	83 days	=> 365 days	57 days	16.33	0
Never Smoked	21.263 days	108.25 days	=> 365 days	90 days	37.23	0
Ex Smoker	36.338 days	93.75 days	=> 365 days	65 days	25.17	0
Current Smoker	24.65 days	70 days	=> 365 days	64 days	43.15	0
Over 75	37.35 days	102 days	=> 365 days	76 days	35.08	0
Below 75	35.675 days	77.5 days	339.35 days	61 days	26.87	0
SES IMD 2010 = 5 (least deprived)	7 days	99 days	=> 365 days	87 days	41.33	0
SES IMD 2010 = 4	20.85 days	92 days	=> 365 days	61 days	22.39	0
SES IMD 2010 = 3	18 days	82.5 days	=> 365 days	75 days	39.96	0
SES IMD 2010 = 2	23.588 days	80 days	=> 365 days	57 days	23.94	0
SES IMD 2010 = 1 (most deprived)	23.05 days	77 days	=> 365 days	67 days	37.38	0

**25th percentile survival time is chosen because some local authorities within subgroups are small and hence there is large variation. If the median survival time was chosen many local authorities would have a time > 365 days, which could not be determined as it exceeds follow up. Choosing a relatively low percentile leads to a higher proportion of local authorities having a 25th percentile survival time <= 365. If the upper or lower bound of the empirical range is > 365, this is specified as > 365.*

Table 29: Exploratory Poisson models - Outcome = number of COPD exacerbation episodes

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS
Model one covariates: SLS indicator
Model two covariates: SLS indicator, age and sex

parameter	Level1	RelativeRate	RR_LowerCL	RR_UpperCL	P
SLS	1	1.2425	1.1525	1.3396	<.0001
parameter	**Level1**	**RelativeRate**	**RR_LowerCL**	**RR_UpperCL**	**P**
SLS	1	1.2164	1.1278	1.3120	<.0001
age		0.9379	0.9167	0.9595	<.0001
sex	1	1.0877	1.0393	1.1384	0.0003

Table 30: Fully adjusted Poisson model - Outcome = number of COPD exacerbation episodes

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
SLS member		1.11638	1.04525	1.19234	0.0010
Sex	Female	1.07768	1.03621	1.1208	0.0002
Age		0.96629	0.94486	0.98821	0.0027
Age Squared		0.97747	0.96198	0.99321	0.0052
SES IMD 2010 Quintiles	4	1.0735	1.00148	1.15069	0.0453
	3	1.06972	0.99774	1.14689	0.0579
	2	1.07772	1.00735	1.153	0.0298
	1 (most deprived)	1.08578	1.01455	1.16202	0.0175
Current Medication (prescriptions in last 3 months)	LABA only	1.16808	0.97489	1.39956	0.0921
	LAMA only	1.14244	1.03831	1.25701	0.0063
	ICS only	0.90286	0.79305	1.02787	0.1225
	LABA/LAMA	1.0578	0.85147	1.31414	0.6118
	LAMA/ICS	0.98976	0.83052	1.17955	0.9085
	LABA/ICS	1.12998	1.04539	1.22141	0.0021
	LABA/LAMA/ICS	1.23268	1.14509	1.32696	<.0001
Any history (ever) of Depression	Present	1.03444	0.98868	1.08231	0.1424
Any history (ever) of Anxiety	Present	1.06869	1.01786	1.12206	0.0075

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Asthma	Present	1.05649	1.01509	1.09959	0.0071
Any history (ever) of Pneumonia	Present	1.04177	0.98962	1.09667	0.1183
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.05944	1.01446	1.10642	0.0091
COPD Exacerbation History in previous 12 months		52877.1	33023.8	84665.9	<.0001
COPD Exacerbation History in previous 12 months Squared		1.81E-6	5.64E-7	5.82E-6	<.0001
FEV1%		0.9384	0.91526	0.96212	<.0001
FEV1% Squared		1.00779	0.99353	1.02225	0.2861
FEV1/FVC (%)		0.9591	0.93707	0.98164	0.0004
FEV1/FVC (%) squared		1.01738	1.00268	1.03229	0.0203
MRC Dyspnoea score	2	1.06842	0.99129	1.15154	0.0834
	3	1.13694	1.0535	1.22698	0.0010
	4	1.20555	1.11254	1.30632	<.0001

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
	5 (most breathlessness)	1.19679	1.07408	1.33352	0.0011
Smoking	Ex	1.05212	0.97072	1.14035	0.2162
	Current	1.15098	1.05765	1.25254	0.0011
Influenza Vaccine	Present	1.05676	0.98896	1.12921	0.1027

Table 31: Exploratory Cox Proportional Hazards models - Outcome = time until first COPD exacerbation episode

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS
Model one covariates: SLS indicator
Model two covariates: SLS indicator, age and sex

Parameter	HazardRatio	HR_LowerCL	HR_UpperCL	P
SLS	1.197	1.119	1.279	<.0001

Parameter	HazardRatio	HR_LowerCL	HR_UpperCL	P
SLS	1.178	1.101	1.260	<.0001
age	0.951	0.933	0.970	<.0001
sex	1.096	1.054	1.139	<.0001

Table 32: Fully adjusted Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
SLS member		1.13663	1.05906	1.21989	0.0004
Sex	Female	1.08173	1.03913	1.12608	0.0001
	Male	.	.	.	.
Age		0.97492	0.95313	0.99721	0.0277
Age Squared		0.97712	0.96147	0.99302	0.0049
SES IMD 2010 Quintiles	4	1.0712	0.99959	1.14794	0.0514
	3	1.03084	0.96137	1.10534	0.3935
	2	1.07044	1.00043	1.14535	0.0486
	1 (most deprived)	1.07132	1.00051	1.14713	0.0483
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.1746	0.98662	1.3984	0.0705
	LAMA only	1.08497	0.9869	1.19278	0.0916
	ICS only	0.88409	0.78255	0.99881	0.0478
	LABA/LAMA	1.04819	0.84793	1.29575	0.6635
	LAMA/ICS	1.08946	0.92237	1.28681	0.3131
	LABA/ICS	1.07605	0.9971	1.16126	0.0594
	LABA/LAMA/ICS	1.1905	1.10716	1.28011	<.0001
	No trial medication (in last 3 months)	.	.	.	.

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Depression	Present	1.03361	0.98657	1.08289	0.1642
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.02807	0.97694	1.08187	0.2876
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.10173	1.05748	1.14782	<.0001
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.03141	0.97775	1.08802	0.2566
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.06215	1.01564	1.11079	0.0083
	Absent	.	.	.	.
COPD Exacerbation History in previous 12 months		82401.5	47478.3	143013	<.0001
COPD Exacerbation History in previous 12 months Squared		3.21E-7	6.58E-8	1.57E-6	<.0001
FEV1%		0.93612	0.91236	0.9605	<.0001

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
FEV1% Squared		1.00503	0.99072	1.01954	0.4930
FEV1/FVC (%)		0.98216	0.95885	1.00603	0.1417
FEV1/FVC (%) squared		1.01623	1.00093	1.03176	0.0375
MRC Dyspnoea score	2	1.05927	0.98487	1.13929	0.1212
	3	1.10684	1.02682	1.1931	0.0080
	4	1.17219	1.08224	1.26961	<.0001
	5 (most breathlessness)	1.12423	1.00525	1.25729	0.0402
	1 (least breathlessness)	.	.	.	.
Smoking	Ex	1.0651	0.98381	1.15311	0.1195
	Current	1.178	1.08295	1.2814	0.0001
	Never Smoked	.	.	.	.
Influenza Vaccine	Present	1.09596	1.02339	1.17368	0.0088
	Absent	.	.	.	.

Table 33: Distribution of random effects in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.89942	0.99455	1.13250	1.13828	98.3718	1

Table 34: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	1.08994	1.05325	1.12792	<.0001
	Male	1	.	.	.
Age	.	0.96885	0.95016	0.98792	0.0015
Age Squared	.	0.97703	0.96354	0.99071	0.0011
SES IMD 2010 Quintiles	4	1.06991	1.00651	1.1373	0.0302
	3	1.05665	0.99282	1.12459	0.0830
	2	1.07648	1.01266	1.14434	0.0181
	1 (most deprived)	1.08225	1.01665	1.15208	0.0132
	5 (least deprived)	1	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.16166	0.99418	1.35735	0.0592
	LAMA only	1.13204	1.04193	1.22993	0.0034
	ICS only	0.91132	0.81595	1.01784	0.0997
	LABA/LAMA	1.04529	0.86657	1.26086	0.6434
	LAMA/ICS	1.02233	0.88157	1.18557	0.7701
	LABA/ICS	1.11464	1.04222	1.19209	0.0015
	LABA/LAMA/ICS	1.23063	1.15456	1.31172	<.0001
	No treatment	1	.	.	.
Any history (ever) of Depression	Present	1.03141	0.99141	1.07301	0.1254
	Absent	1	.	.	.

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Anxiety	Present	1.04679	1.00279	1.09271	0.0369
	Absent	1	.	.	.
Any history (ever) of Asthma	Present	1.06904	1.03207	1.10734	0.0002
	Absent	1	.	.	.
Any history (ever) of Pneumonia	Present	1.05209	1.00577	1.10054	0.0271
	Absent	1	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.05905	1.01961	1.10003	0.0031
	Absent	1	.	.	.
COPD Exacerbation History in previous 12 months	.	61095.6	38407.8	97185.5	<.0001
COPD Exacerbation History in previous 12 months Squared	.	6.49E-7	1.81E-7	2.33E-6	<.0001
FEV1%	.	0.93419	0.91403	0.95479	<.0001
FEV1% Squared	.	1.00706	0.99458	1.0197	0.2690
FEV1/FVC (%)	.	0.96622	0.94674	0.9861	0.0009

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
FEV1/FVC (%) squared	.	1.0196	1.00677	1.0326	0.0027
MRC Dyspnoea score	2	1.05591	0.99007	1.12614	0.0977
	3	1.12344	1.05186	1.19989	0.0005
	4	1.18724	1.10737	1.27287	<.0001
	5 (most breathlessness)	1.17723	1.07105	1.29394	0.0007
	1 (least breathlessness)	1	.	.	.
Smoking	Ex	1.06065	0.98923	1.13723	0.0978
	Current	1.14782	1.06654	1.23529	0.0002
	Never	1	.	.	.
Influenza Vaccine	Present	1.06939	1.00868	1.13376	0.0245
	Absent	1	.	.	.

Table 35: Distribution of random effects in fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.89234	0.99676	1.17048	1.14003	96.7078	0

Table 36: Fixed effects for fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	1.08994	1.05325	1.12792	<.0001
	Male	1	.	.	.
Age	.	0.96885	0.95016	0.98792	0.0015
Age Squared	.	0.97703	0.96354	0.99071	0.0011
SES IMD 2010 Quintiles	4	1.06991	1.00651	1.1373	0.0302
	3	1.05665	0.99282	1.12459	0.0830
	2	1.07648	1.01266	1.14434	0.0181
	1 (most deprived)	1.08225	1.01665	1.15208	0.0132
	5 (least deprived)	1	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.16166	0.99418	1.35735	0.0592
	LAMA only	1.13204	1.04193	1.22993	0.0034
	ICS only	0.91132	0.81595	1.01784	0.0997
	LABA/LAMA	1.04529	0.86657	1.26086	0.6434
	LAMA/ICS	1.02233	0.88157	1.18557	0.7701
	LABA/ICS	1.11464	1.04222	1.19209	0.0015
	LABA/LAMA/ICS	1.23063	1.15456	1.31172	<.0001
	No treatment	1	.	.	.
Any history (ever) of Depression	Present	1.03141	0.99141	1.07301	0.1254

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
	Absent	1	.	.	.
Any history (ever) of Anxiety	Present	1.04679	1.00279	1.09271	0.0369
	Absent	1	.	.	.
Any history (ever) of Asthma	Present	1.06904	1.03207	1.10734	0.0002
	Absent	1	.	.	.
Any history (ever) of Pneumonia	Present	1.05209	1.00577	1.10054	0.0271
	Absent	1	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.05905	1.01961	1.10003	0.0031
	Absent	1	.	.	.
COPD Exacerbation History in previous 12 months	.	61095.6	38407.8	97185.5	<.0001
COPD Exacerbation History in previous 12 months Squared	.	6.49E-7	1.81E-7	2.33E-6	<.0001
FEV1%	.	0.93419	0.91403	0.95479	<.0001
FEV1% Squared	.	1.00706	0.99458	1.0197	0.2690

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
FEV1/FVC (%)	.	0.96622	0.94674	0.9861	0.0009
FEV1/FVC (%) squared	.	1.0196	1.00677	1.0326	0.0027
MRC Dyspnoea score	2	1.05591	0.99007	1.12614	0.0977
	3	1.12344	1.05186	1.19989	0.0005
	4	1.18724	1.10737	1.27287	<.0001
	5 (most breathlessness)	1.17723	1.07105	1.29394	0.0007
	1 (least breathlessness)	1	.	.	.
Smoking	Ex	1.06065	0.98923	1.13723	0.0978
	Current	1.14782	1.06654	1.23529	0.0002
	Never	1	.	.	.
Influenza Vaccine	Present	1.06939	1.00868	1.13376	0.0245
	Absent	1	.	.	.

Figure 14: Kaplan-Meier Plots Comparing CPRD_GM and CPRD_xGM

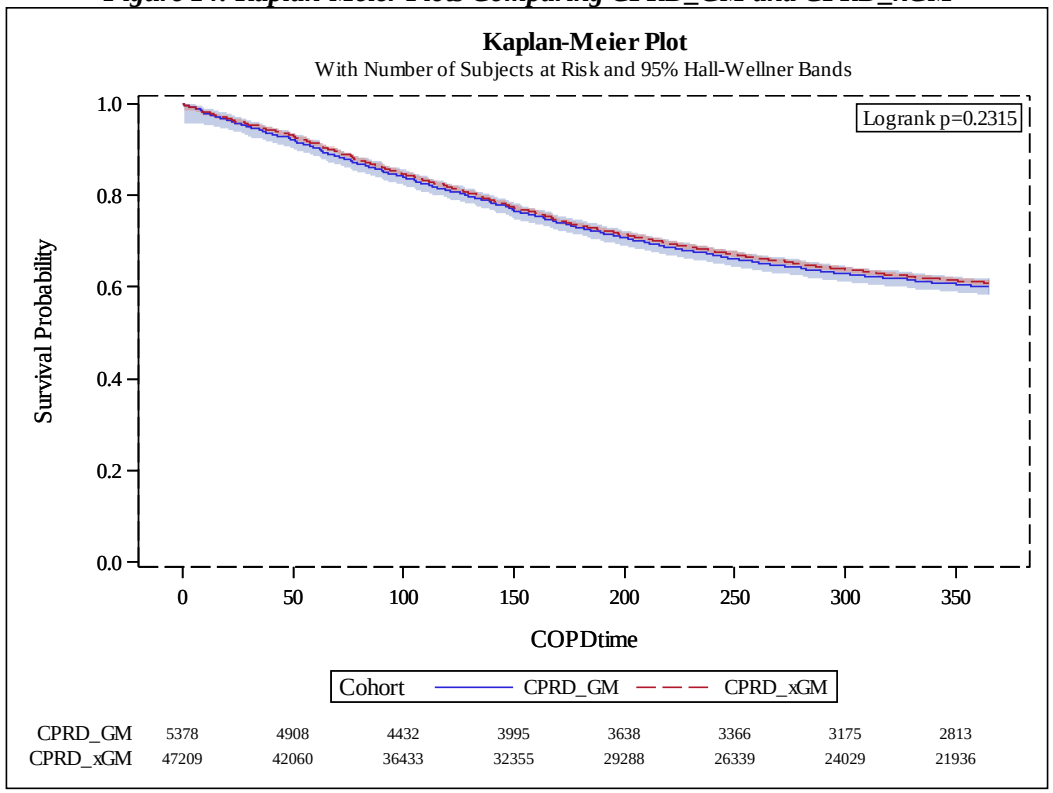


Figure 15: Q-Q Plot for Index Dates of Matched Cohorts CPRD_IC and SLS_UC

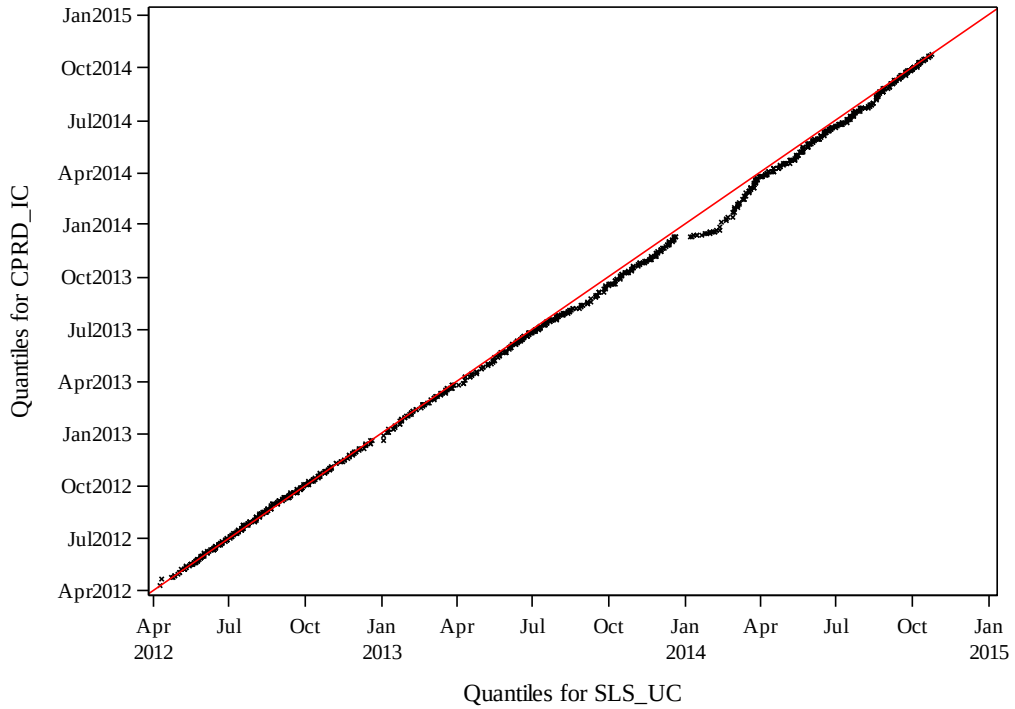


Figure 16: Kaplan-Meier Plots Comparing CPRD_GM_IC, CPRD_xGM_IC and SLS_UC

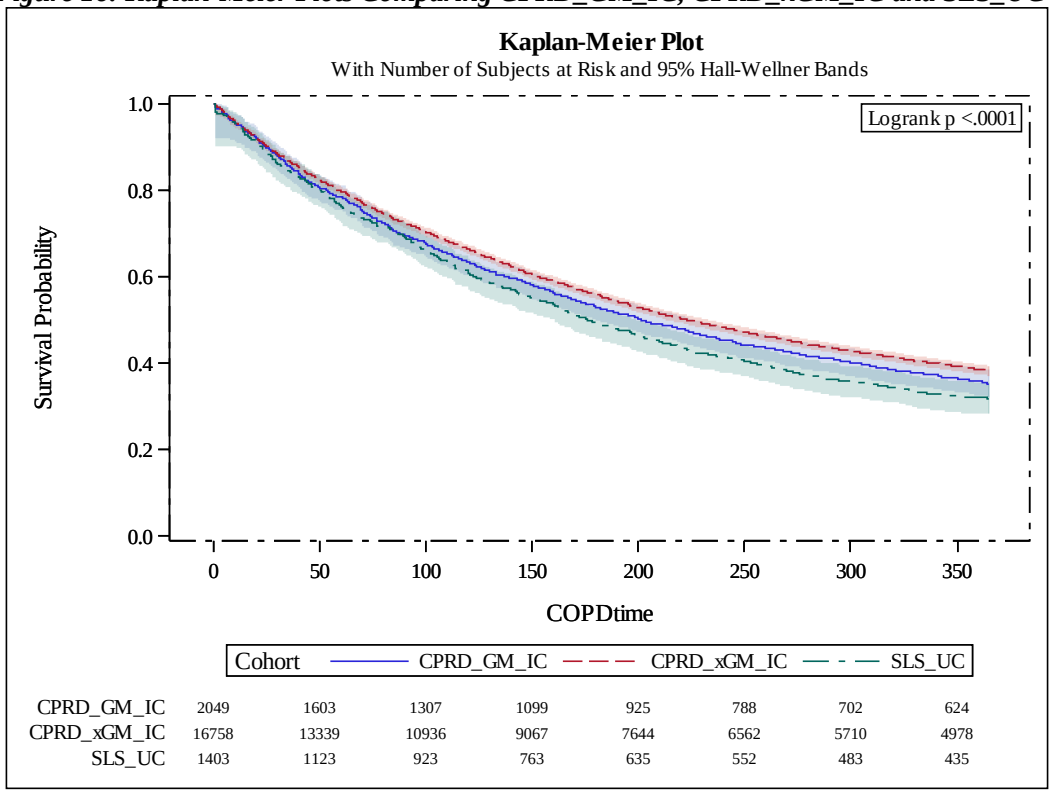


Figure 17: Stacked Bar Chart for Number of COPD Exacerbations

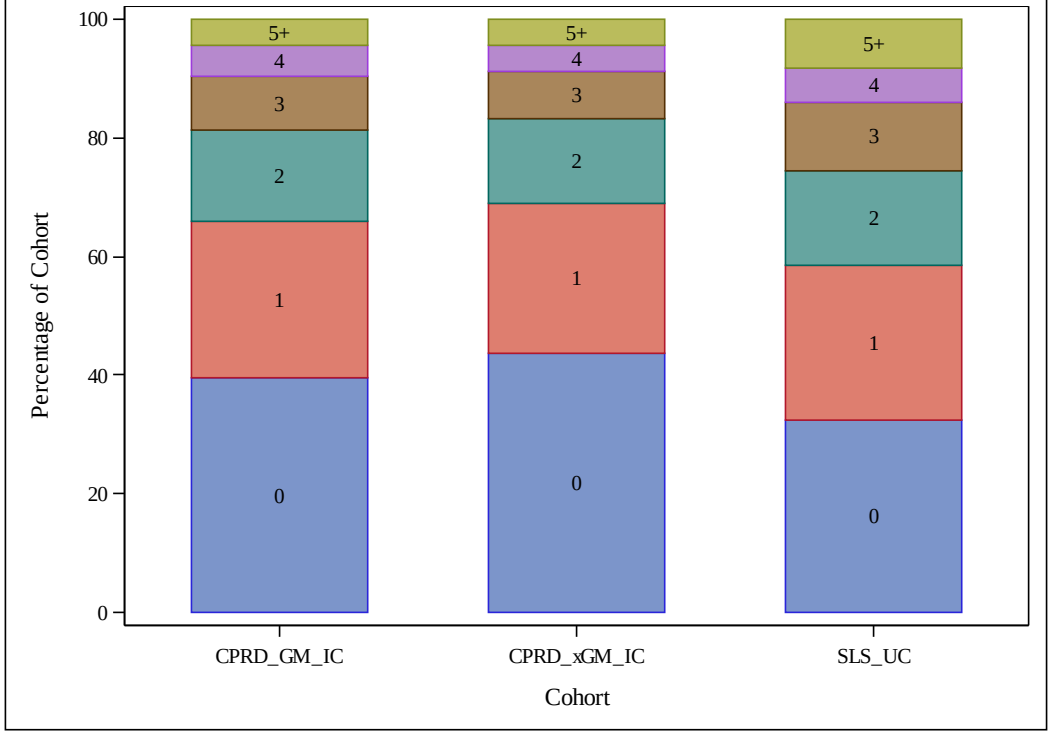
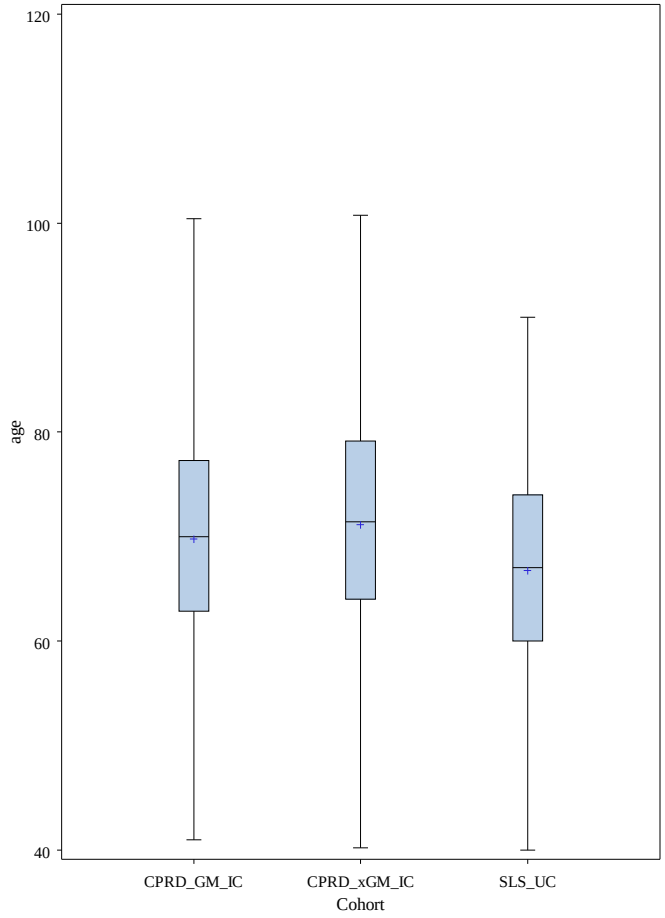


Figure 18: Box Plots Comparing Age



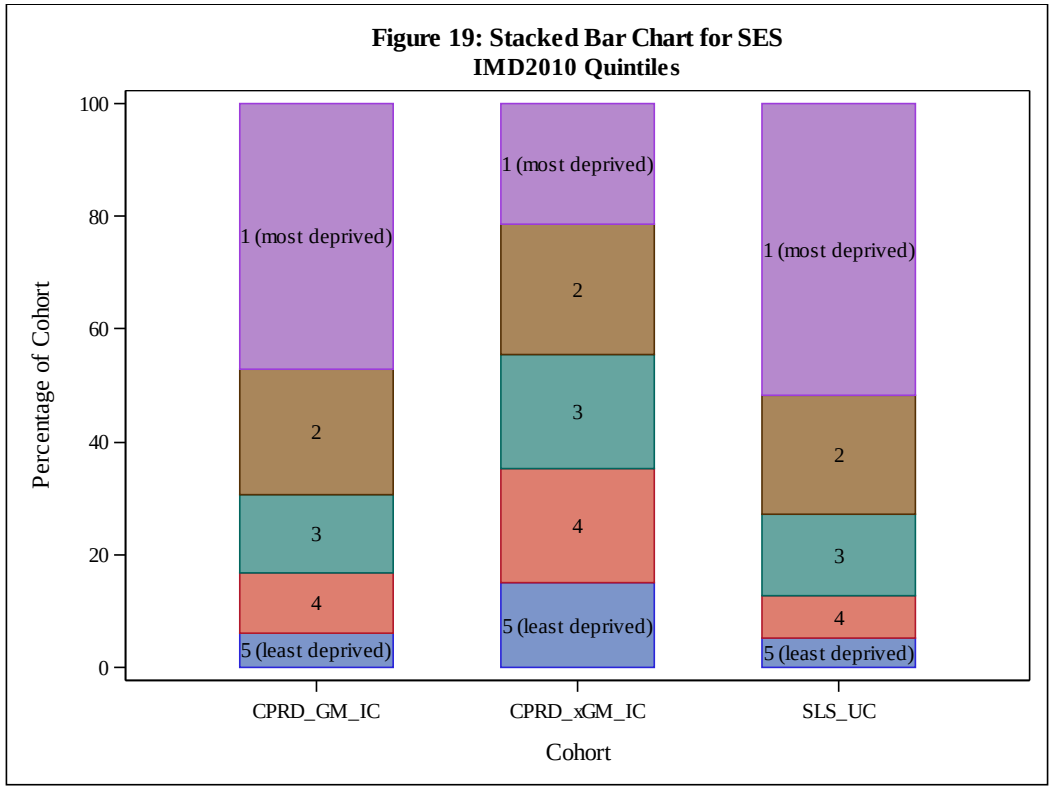


Figure 19: Stacked Bar Chart for SES
IMD2010 Quintiles
Percentage of Cohort
100
80
60
40
20
0
1 (most deprived)
2
3
4
5 (least deprived)
CPRD_GM_IC
CPRD_xGM_IC
SLS_UC
Cohort

Figure 20: Stacked Bar Chart for Current Medication Group
Medicines prescribed in the previous 3 months

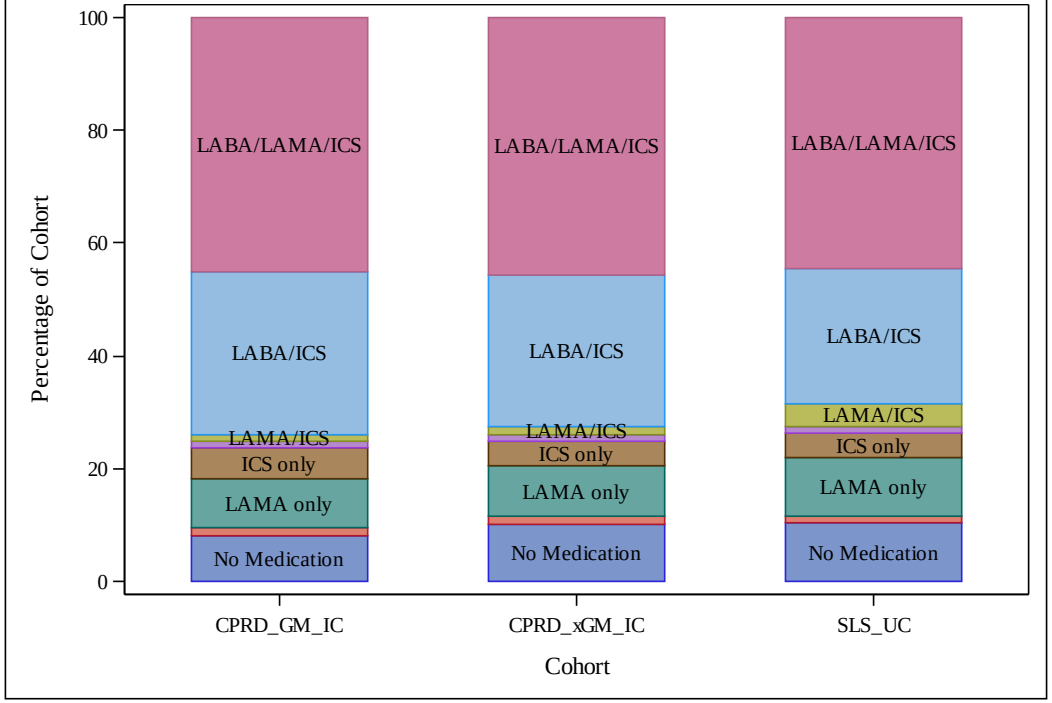


Figure 21: Stacked Bar Chart for Charlson Score

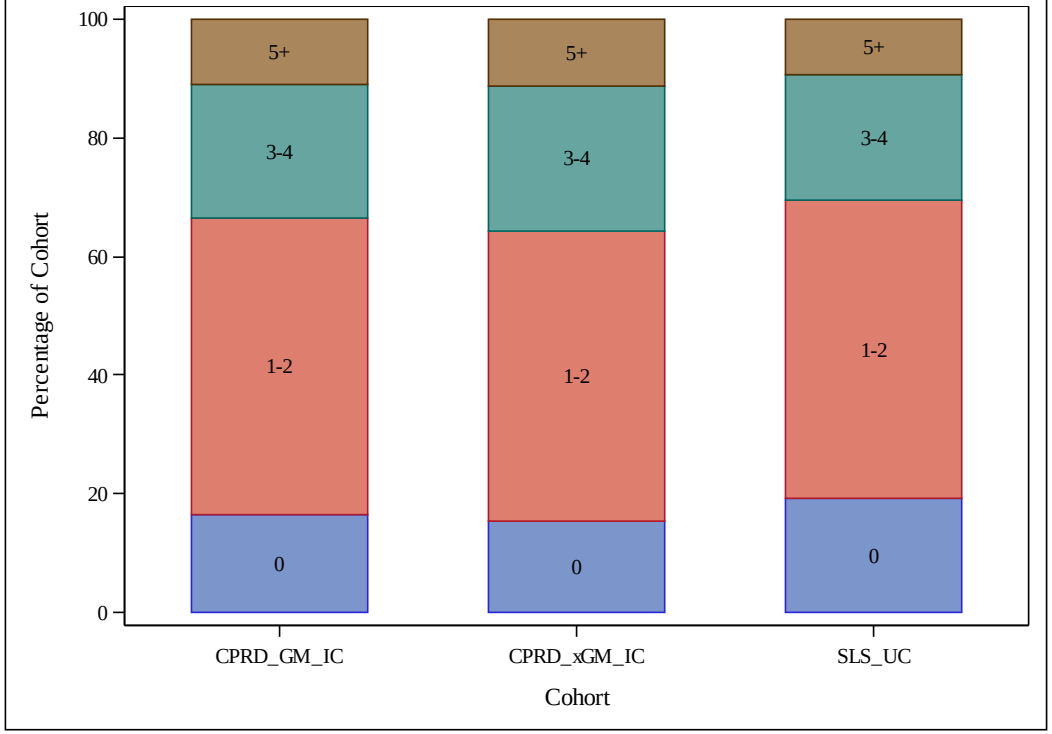


Figure 22: Stacked Bar Chart for Smoking Status

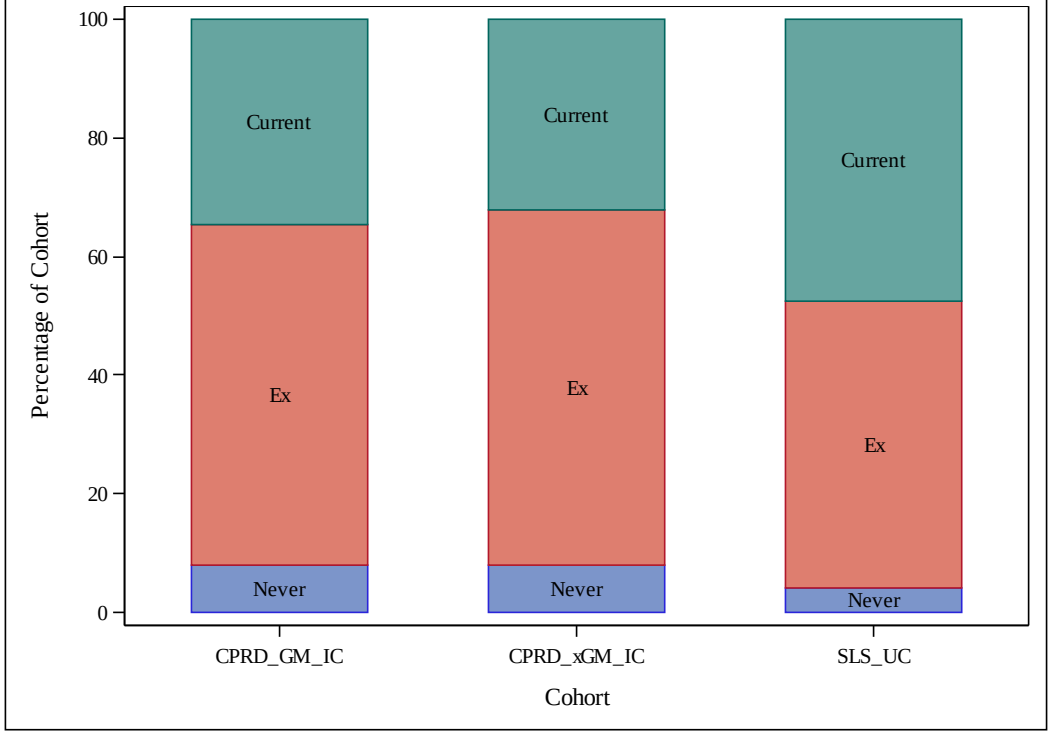


Figure 23: Stacked Bar Chart for BMI WHO categories

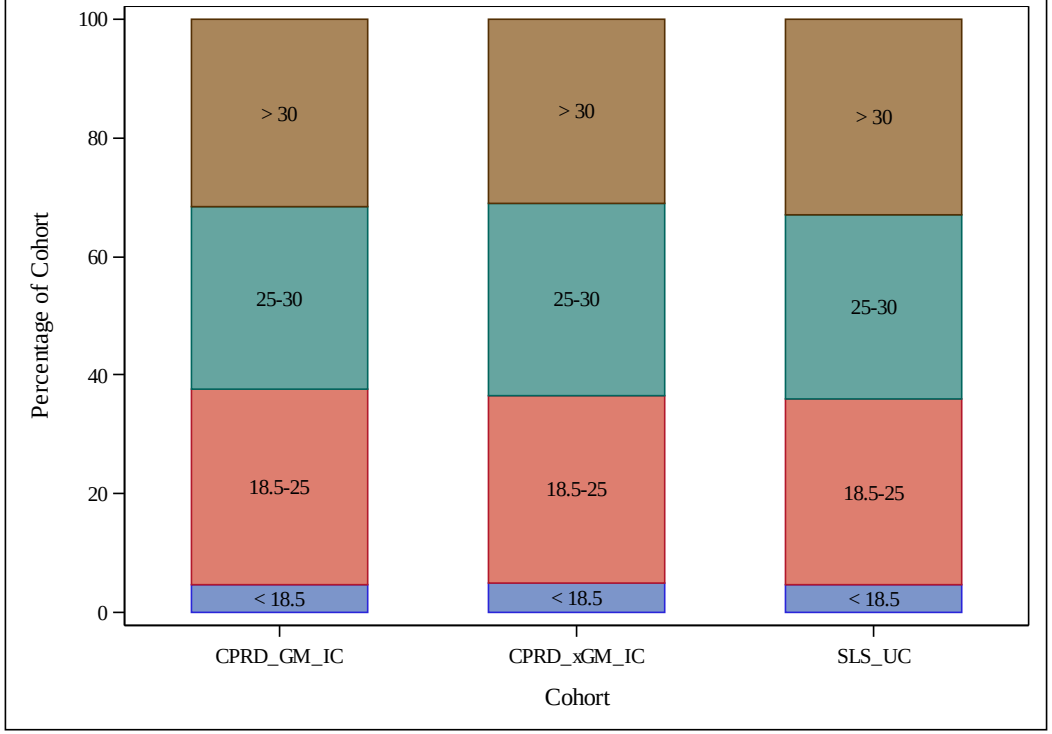


Figure 24: Stacked Bar Chart for MRC Dyspnoea score

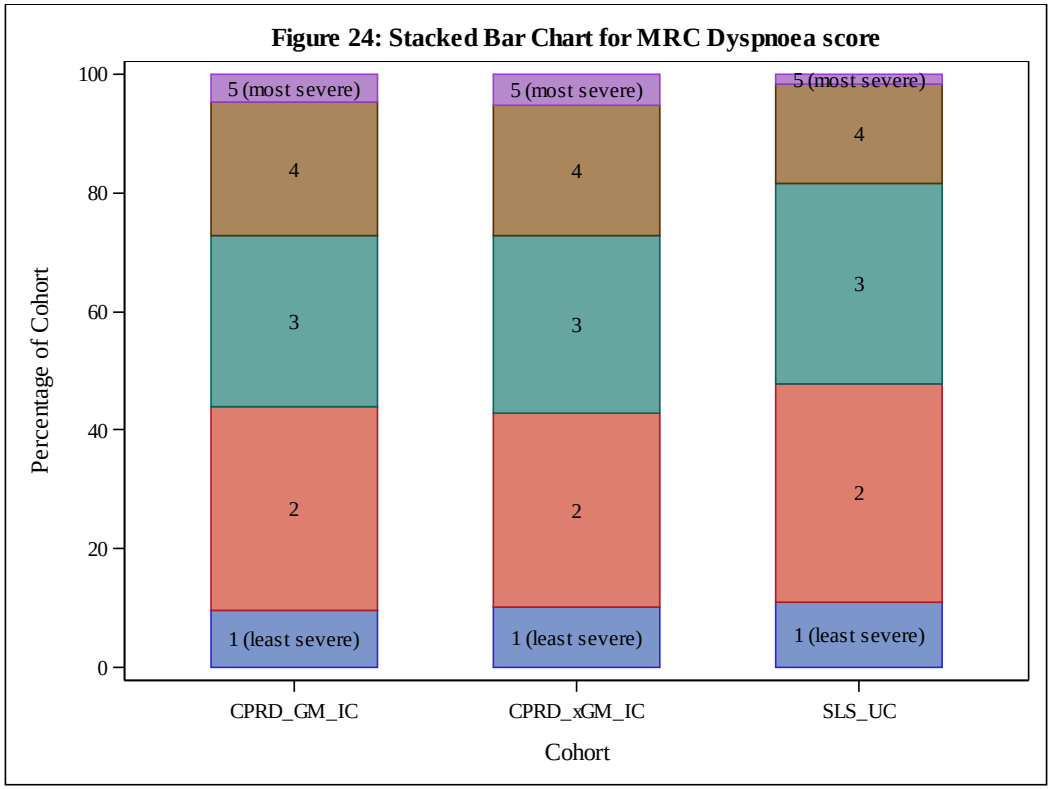


Figure 25: Stacked Bar Chart for GOLD Stage

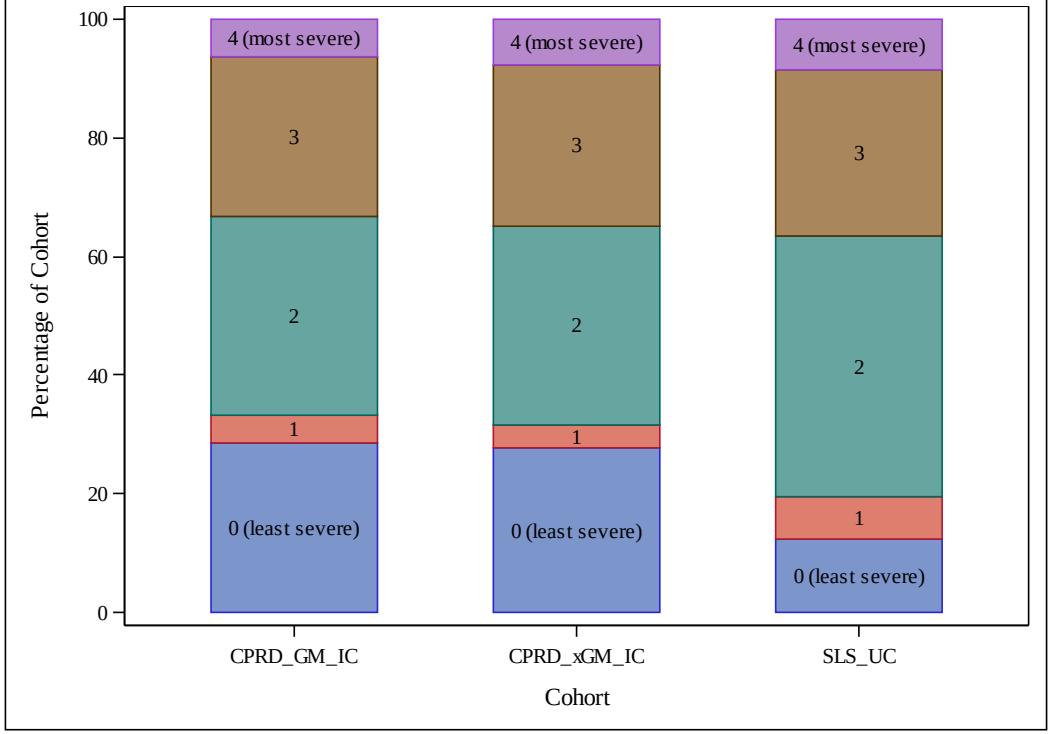
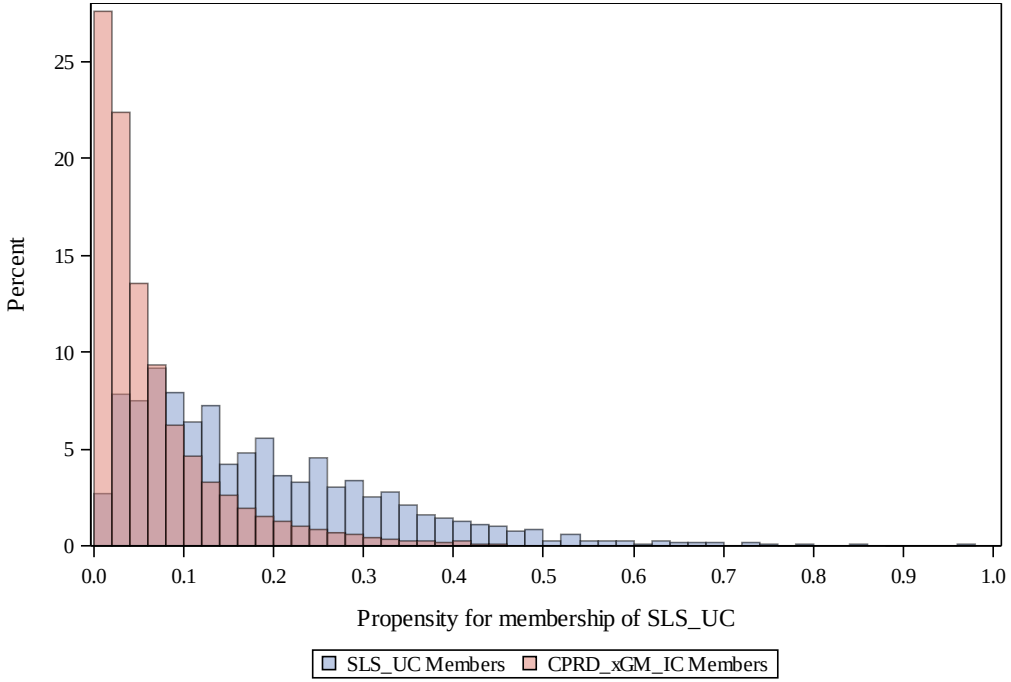


Figure 26: Propensity for membership of SLS_UC for SLS_UC and CPRD_xGM_IC members



2 Primary Objective 3: Comparison of Rates of Pneumonia Episodes

Tables in this section cover PO3, using CPRD primary+secondary care data compared to the SLS-Database.

Table 37: Comparison of CPRD-xGM-IC, CPRD-GM-IC and SLS-UC cohorts - Rate of Pneumonia episodes

Variable	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
N	2,046	16,745	1,403
Person time	1,833.52 years	14,516.13 years	1,368.30 years
# Episodes Rate per 1000 person years (95% CI)	187 101.99 (87.90 - 117.70)	1,551 106.85 (101.59 - 112.30)	104 76.01 (62.10 - 92.10)

Table 38: The rate* of Pneumonia episodes in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of Pneumonia episodes is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The number of exacerbations in SLS_UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	0	101.533	313.11	76.007	26.8471	0
Male	0	115.333	490.65	85.473	33.5781	0
Female	0	80.875	355.63	65.687	42.2215	0
Never Smoked	0	0.000	755.33	51.297	60.0274	0
Ex Smoker	0	107.157	452.70	100.300	43.7516	0
Current Smoker	0	70.799	406.34	53.699	42.6218	0
Over 75	0	158.117	696.99	138.317	41.4023	0
Below 75	0	56.598	266.33	58.235	53.3749	0
SES IMD 2010 = 5 (least deprived)	0	36.108	1,023.11	28.236	48.5286	0
SES IMD 2010 = 4	0	70.771	458.71	19.443	37.0665	0
SES IMD 2010 = 3	0	72.643	537.28	81.142	52.9081	0
SES IMD 2010 = 2	0	73.874	494.80	76.124	51.0637	0
SES IMD 2010 = 1 (most deprived)	0	88.982	454.66	87.520	49.4048	0

Rate is calculated per 1000 person years

Table 39: Exploratory Poisson models - Outcome = number of Pneumonia episodes

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS
Model one covariates: SLS indicator
Model two covariates: SLS indicator, age and sex

parameter	Level1	RelativeRate	RR_LowerCL	RR_UpperCL	P
SLS	1	0.71137	0.5093	0.9936	0.0458
parameter	**Level1**	**RelativeRate**	**RR_LowerCL**	**RR_UpperCL**	**P**
SLS	1	0.9003	0.6512	1.2447	0.5251
age		1.7965	1.6464	1.9603	<.0001
sex	1	0.7674	0.6558	0.8980	0.0010

Table 40: Fully adjusted Poisson model - Outcome = number of Pneumonia episodes

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
SLS member		0.97275	0.72075	1.31285	0.8567
Sex	Female	0.82084	0.70924	0.95	0.0081
Age		1.67019	1.52482	1.82943	<.0001
Age Squared		1.04142	0.97781	1.10916	0.2069
SES IMD 2010 Quintiles	4	1.19582	0.92275	1.5497	0.1763
	3	1.22404	0.94409	1.58702	0.1271
	2	1.27197	0.98765	1.63814	0.0624
	1 (most deprived)	1.52525	1.18518	1.9629	0.0010
Current Medication (prescriptions in last 3 months)	LABA only	0.7483	0.33002	1.69673	0.4876
	LAMA only	0.84698	0.59382	1.20807	0.3593
	ICS only	0.90605	0.57364	1.4311	0.6723
	LABA/LAMA	0.74898	0.30923	1.81409	0.5219
	LAMA/ICS	0.89776	0.45028	1.78996	0.7594
	LABA/ICS	1.09249	0.83216	1.43427	0.5241
	LABA/LAMA/ICS	1.21379	0.94306	1.56223	0.1324
Any history (ever) of Depression	Present	1.06431	0.89774	1.2618	0.4729
Any history (ever) of Anxiety	Present	1.04838	0.86758	1.26686	0.6247

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Asthma	Present	0.84048	0.72811	0.97018	0.0176
Any history (ever) of Pneumonia	Present	1.5445	1.31274	1.81717	<.0001
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.05296	0.898	1.23466	0.5252
Pneumonia exacerbation history		47.1825	25.1965	88.3532	<.0001
Pneumonia exacerbation history squared		0.2161	0.12339	0.37846	<.0001
FEV1%		0.84529	0.77377	0.92342	0.0002
FEV1% Squared		1.03437	0.98539	1.08579	0.1721
FEV1/FVC (%)		1.00339	0.92415	1.08942	0.9358
FEV1/FVC (%) squared		1.00424	0.95311	1.0581	0.8740
MRC Dyspnoea score	2	1.05182	0.74248	1.49005	0.7762
	3	1.44681	1.02859	2.03509	0.0338
	4	1.76715	1.24929	2.49968	0.0013
	5 (most breathlessness)	1.98373	1.33066	2.9573	0.0008

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Smoking	Ex	1.23708	0.91144	1.67908	0.1723
	Current	1.31557	0.94472	1.83199	0.1045
Influenza Vaccine	Present	1.06711	0.81448	1.39812	0.6375

Table 41: Exploratory Cox Proportional Hazards models - Outcome = time until first Pneumonia episode

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS
Model one covariates: SLS indicator
Model two covariates: SLS indicator, age and sex

Parameter	HazardRatio	HR_LowerCL	HR_UpperCL	P
SLS	0.635	0.503	0.802	0.0001
Parameter	**HazardRatio**	**HR_LowerCL**	**HR_UpperCL**	**P**
SLS	0.813	0.643	1.028	0.0832
age	1.829	1.722	1.942	<.0001
sex	0.792	0.710	0.882	<.0001

Table 42: Fully adjusted Cox Proportional Hazards model - Outcome = time until first Pneumonia episode

Cohorts CPRD_xGM_IC and SLS-UC are combined into a single dataset retaining a flag for membership of SLS

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
SLS member		0.8783	0.68884	1.11985	0.2952
Sex	Female	0.83664	0.74728	0.93669	0.0020
Age		1.70863	1.59291	1.83276	<.0001
Age Squared		1.05286	1.00331	1.10485	0.0362
SES IMD 2010 Quintiles	4	1.19026	0.97614	1.45136	0.0852
	3	1.22664	1.00499	1.49717	0.0445
	2	1.29582	1.06751	1.57295	0.0088
	1 (most deprived)	1.54721	1.27502	1.8775	<.0001
Current Medication (prescriptions in last 3 months)	LABA only	0.74123	0.39958	1.37499	0.3422
	LAMA only	0.82535	0.6287	1.08352	0.1669
	ICS only	0.89727	0.63471	1.26846	0.5394
	LABA/LAMA	0.82505	0.43251	1.57385	0.5595
	LAMA/ICS	0.82069	0.47957	1.40446	0.4710
	LABA/ICS	1.04866	0.85063	1.2928	0.6563
	LABA/LAMA/ICS	1.16529	0.95937	1.4154	0.1231
Any history (ever) of Depression	Present	1.11301	0.97604	1.2692	0.1100
Any history (ever) of Anxiety	Present	1.01741	0.87799	1.17898	0.8184

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Asthma	Present	0.8287	0.74147	0.9262	0.0009
Any history (ever) of Pneumonia	Present	1.57891	1.39173	1.79127	<.0001
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	0.99524	0.87827	1.12778	0.9403
Pneumonia exacerbation history		33.7619	20.3251	56.0818	<.0001
Pneumonia exacerbation history squared		0.25841	0.16389	0.40745	<.0001
FEV1%		0.827	0.77203	0.88589	<.0001
FEV1% Squared		1.03431	0.9953	1.07485	0.0855
FEV1/FVC (%)		1.00667	0.94472	1.07267	0.8376
FEV1/FVC (%) squared		1.00436	0.96469	1.04566	0.8323
MRC Dyspnoea score	2	1.11784	0.85225	1.46619	0.4209
	3	1.45685	1.11516	1.90324	0.0058
	4	1.85247	1.41265	2.42923	<.0001
	5 (most breathlessness)	2.03175	1.48736	2.77539	<.0001

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Smoking	Ex	1.22832	0.9724	1.5516	0.0845
	Current	1.2855	0.99722	1.65713	0.0526
Influenza Vaccine	Present	1.07449	0.87283	1.32274	0.4981

Table 43: Distribution of random effects in fully adjusted multilevel Poisson model - Outcome = number of Pneumonia episodes

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.91340	0.99459	1.12735	0.93773	9.76185	0

Table 44: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of Pneumonia episodes

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	0.83316	0.74518	0.93153	0.0013
Age	.	1.70426	1.58959	1.82719	<.0001
Age Squared	.	1.04827	0.99929	1.09964	0.0535
SES IMD 2010 Quintiles	4	1.19861	0.98334	1.46102	0.0729
	3	1.23576	1.01159	1.50961	0.0382
	2	1.29337	1.06415	1.57195	0.0097
	1 (most deprived)	1.53227	1.25895	1.86494	<.0001
Current Medication (prescriptions in last 3 months)	LABA only	0.75709	0.40874	1.40231	0.3762
	LAMA only	0.85453	0.65352	1.11738	0.2506
	ICS only	0.9104	0.64528	1.28443	0.5929
	LABA/LAMA	0.80915	0.42392	1.54446	0.5208
	LAMA/ICS	0.8326	0.48725	1.42272	0.5027
	LABA/ICS	1.07848	0.8773	1.32579	0.4732
	LABA/LAMA/ICS	1.19197	0.98435	1.44338	0.0721
Any history (ever) of Depression	Present	1.09466	0.96107	1.24682	0.1732
Any history (ever) of Anxiety	Present	1.0219	0.88312	1.18249	0.7711
Any history (ever) of Asthma	Present	0.83497	0.74777	0.93235	0.0014

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Pneumonia	Present	1.54621	1.36461	1.75198	<.0001
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.01171	0.8943	1.14452	0.8533
Pneumonia exacerbation history	.	39.7157	24.4867	64.4162	<.0001
Pneumonia exacerbation history squared	.	0.24325	0.16075	0.36808	<.0001
FEV1%	.	0.82968	0.77527	0.88791	<.0001
FEV1% Squared	.	1.03006	0.99153	1.07009	0.1278
FEV1/FVC (%)	.	1.00631	0.94511	1.07148	0.8441
FEV1/FVC (%) squared	.	1.00588	0.96663	1.04672	0.7729
MRC Dyspnoea score	2	1.10103	0.84212	1.43955	0.4816
	3	1.4453	1.10963	1.88251	0.0063
	4	1.82122	1.39283	2.38138	<.0001
	5 (most breathlessness)	2.0575	1.51304	2.79789	<.0001
Smoking	Ex	1.21615	0.96525	1.53228	0.0969

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
	Current	1.28561	1.00012	1.65259	0.0499
Influenza Vaccine	Present	1.06587	0.86707	1.31025	0.5447

Table 45: Distribution of random effects in fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first Pneumonia episode

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.89989	0.99509	1.15653	0.92345	9.11214	0

Table 46: Fixed effects for fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first Pneumonia episode

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	0.83316	0.74518	0.93153	0.0013
Age	.	1.70426	1.58959	1.82719	<.0001
Age Squared	.	1.04827	0.99929	1.09964	0.0535
SES IMD 2010 Quintiles	4	1.19861	0.98334	1.46102	0.0729
	3	1.23576	1.01159	1.50961	0.0382
	2	1.29337	1.06415	1.57195	0.0097
	1 (most deprived)	1.53227	1.25895	1.86494	<.0001
Current Medication (prescriptions in last 3 months)	LABA only	0.75709	0.40874	1.40231	0.3762
	LAMA only	0.85453	0.65352	1.11738	0.2506
	ICS only	0.9104	0.64528	1.28443	0.5929
	LABA/LAMA	0.80915	0.42392	1.54446	0.5208
	LAMA/ICS	0.8326	0.48725	1.42272	0.5027
	LABA/ICS	1.07848	0.8773	1.32579	0.4732
	LABA/LAMA/ICS	1.19197	0.98435	1.44338	0.0721
Any history (ever) of Depression	Present	1.09466	0.96107	1.24682	0.1732
Any history (ever) of Anxiety	Present	1.0219	0.88312	1.18249	0.7711
Any history (ever) of Asthma	Present	0.83497	0.74777	0.93235	0.0014

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Pneumonia	Present	1.54621	1.36461	1.75198	<.0001
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.01171	0.8943	1.14452	0.8533
Pneumonia exacerbation history	.	39.7157	24.4867	64.4162	<.0001
Pneumonia exacerbation history squared	.	0.24325	0.16075	0.36808	<.0001
FEV1%	.	0.82968	0.77527	0.88791	<.0001
FEV1% Squared	.	1.03006	0.99153	1.07009	0.1278
FEV1/FVC (%)	.	1.00631	0.94511	1.07148	0.8441
FEV1/FVC (%) squared	.	1.00588	0.96663	1.04672	0.7729
MRC Dyspnoea score	2	1.10103	0.84212	1.43955	0.4816
	3	1.4453	1.10963	1.88251	0.0063
	4	1.82122	1.39283	2.38138	<.0001
	5 (most breathlessness)	2.0575	1.51304	2.79789	<.0001
Smoking	Ex	1.21615	0.96525	1.53228	0.0969

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
	Current	1.28561	1.00012	1.65259	0.0499
Influenza Vaccine	Present	1.06587	0.86707	1.31025	0.5447

3 Secondary Objective 1: Comparison of EMIS vs VISION, Healthcare Utilisation, and Mortality for COPD Therapies

Comparisons of EMIS vs VISION and healthcare utilisation (defined as primary care use, COPD medication prescriptions and treatment switching) use the CPRD primary care dataset compared to the SLS-EHR dataset.

Tables assessing mortality and secondary care use utilise CPRD primary+secondary care data compared to the SLS Database dataset.

Table 47.1: Comparison of coding rates for patients in EMIS and Vision practices in the SLS-UC. Outcome = any medical code

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Data source = EMIS		1.6371	1.5000	1.7867	<.0001
Sex	Female	0.9805	0.9068	1.0601	0.6206
Age		1.1049	1.0573	1.1546	<.0001
Age Squared		0.9886	0.9594	1.0187	0.4534
SES IMD 2010 Quintiles	4	1.2486	0.9965	1.5644	0.0536
	3	1.2109	0.9825	1.4925	0.0728
	2	1.1459	0.9383	1.3995	0.1818
	1 (most deprived)	1.4409	1.1904	1.7442	0.0002
Current Medication (prescriptions in last 3 months)	LABA only	0.8584	0.6289	1.1716	0.3359
	LAMA only	0.6895	0.5844	0.8135	<.0001
	ICS only	0.6303	0.5015	0.7920	<.0001
	LABA/LAMA	0.8919	0.6434	1.2363	0.4922
	LAMA/ICS	0.5678	0.4507	0.7152	<.0001
	LABA/ICS	0.6440	0.5626	0.7371	<.0001

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
	LABA/LAMA/ICS	0.6883	0.6110	0.7754	<.0001
Depression		1.1634	1.0642	1.2718	0.0009
Anxiety		1.1148	1.0159	1.2233	0.0219
Asthma		1.0797	0.9987	1.1674	0.0541
Pneumonia		1.1049	0.9796	1.2462	0.1043
Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)		1.1297	1.0381	1.2294	0.0047
COPD Exacerbation History in previous 12 months		2.0549	0.9487	4.4509	0.0678
COPD Exacerbation History in previous 12 months Squared		0.6163	0.1670	2.2749	0.4676
FEV1%		0.9770	0.9215	1.0359	0.4358
FEV1% Squared		1.0091	0.9774	1.0418	0.5772
FEV1/FVC ratio		1.0657	1.0075	1.1271	0.0262
FEV1/FVC ratio squared		0.9979	0.9652	1.0318	0.9039
MRC Dyspnoea score	2	1.2051	1.0426	1.3929	0.0116
	3	1.2863	1.1102	1.4902	0.0008
	4	1.3788	1.1724	1.6215	0.0001

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
	5 (most breathlessness)	1.3868	1.0118	1.9007	0.0421
Smoking	Ex	1.0509	0.8637	1.2787	0.6201
	Current	1.0964	0.8960	1.3416	0.3715
Influenza Vaccine		1.3242	1.1325	1.5483	0.0004

Table 47.2: Comparison of COPD coding rates for patients in EMIS and Vision practices in the SLS-UC. Outcome = any COPD related medical code

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Data source = EMIS		1.1990	1.0894	1.3196	0.0002
Sex	Female	1.1399	1.0485	1.2392	0.0021
Age		0.9972	0.9495	1.0473	0.9109
Age Squared		0.9281	0.8958	0.9616	<.0001
SES IMD 2010 Quintiles	4	0.9534	0.7585	1.1985	0.6828
	3	0.9966	0.8109	1.2249	0.9745
	2	1.0061	0.8263	1.2251	0.9518
	1 (most deprived)	0.9173	0.7584	1.1095	0.3739
Current Medication (prescriptions in last 3 months)	LABA only	0.7109	0.4713	1.0723	0.1037
	LAMA only	0.7933	0.6559	0.9595	0.0170
	ICS only	0.9115	0.7177	1.1577	0.4476
	LABA/LAMA	0.6387	0.3981	1.0250	0.0632
	LAMA/ICS	0.7178	0.5531	0.9317	0.0127
	LABA/ICS	0.8918	0.7650	1.0397	0.1436
	LABA/LAMA/ICS	0.9283	0.8066	1.0684	0.2995
Depression		1.0172	0.9217	1.1226	0.7343
Anxiety		1.0914	0.9866	1.2073	0.0895
Asthma		1.0031	0.9233	1.0899	0.9410
Pneumonia		1.1540	1.0185	1.3076	0.0246

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)		0.9593	0.8732	1.0539	0.3861
COPD Exacerbation History in previous 12 months		17.0134	7.6218	37.9771	<.0001
COPD Exacerbation History in previous 12 months Squared		0.0363	0.0086	0.1524	<.0001
FEV1%		1.0022	0.9416	1.0667	0.9443
FEV1% Squared		0.9987	0.9647	1.0338	0.9408
FEV1/FVC ratio		0.9373	0.8834	0.9944	0.0317
FEV1/FVC ratio squared		1.0323	0.9967	1.0693	0.0762
MRC Dyspnoea score	2	0.9934	0.8571	1.1512	0.9295
	3	1.0458	0.8995	1.2159	0.5606
	4	1.0836	0.9156	1.2825	0.3503
	5 (most breathlessness)	1.1348	0.8286	1.5541	0.4306
Smoking	Ex	0.9812	0.7966	1.2086	0.8585
	Current	0.9216	0.7442	1.1413	0.4544
Influenza Vaccine		1.0950	0.9382	1.2780	0.2496

Table 48: Comparison of CPRD-xGM-IC, CPRD-GM-IC and SLS-UC - Healthcare Utilisation outcomes and death

Outcome	Variable	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
Death	N	2,049	16,758	1,403
	Person time	1,841.60 years	14,587.83 years	1,370.87 years
	Count Rate per 1000 person years (95% CI)	144 78.19 (65.94 - 92.06)	1,145 78.49 (74.01 - 83.17)	24 17.51 (11.22 - 26.05)
HCU secondary care contact (days as inpatient)	Count Rate per person year (95% CI)	10,483 5.69 (5.58 - 5.80)	89,207 6.12 (6.08 - 6.16)	4,555 3.32 (3.23 - 3.42)
HCU count of COPD trial related prescription items	Count Rate per person year (95% CI)	25,433 13.81 (13.64 - 13.98)	187,396 12.85 (12.79 - 12.90)	32,133 23.44 (23.18 - 23.70)
HCU primary care contact	Person time	1,839.09 years	14,586.70 years	1,350.06 years
	Count Rate per person year (95% CI)	48,167 26.19 (25.96 - 26.43)	399,291 27.37 (27.29 - 27.46)	66,308 49.11 (48.74 - 49.49)
Treatment Switching	At some point in follow up	36.16 %	40.77 %	34.67 %

The person time for HCU primary care contact is reduced from the other variables as days where a trial related code is recorded in the EMR are counted as days not at risk.

Table 49: Comparison of CPRD-xGM-IC, CPRD-GM-IC and SLS-UC - Breakdown of treatment switching outcome

Time_Period	Switch_Type	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
Period 0 - 1	None	1569 (81.04%)	12299 (78.61%)	1191 (85.32%)
	Step Down	177 (9.14%)	1601 (10.23%)	165 (11.82%)
	Step Up	179 (9.25%)	1675 (10.71%)	38 (2.72%)
	Switch	11 (0.57%)	70 (0.45%)	2 (0.14%)
Period 1 - 2	None	1524 (82.65%)	11699 (79.91%)	1159 (84.17%)
	Step Down	153 (8.30%)	1356 (9.26%)	87 (6.32%)
	Step Up	163 (8.84%)	1516 (10.36%)	130 (9.44%)
	Switch	4 (0.22%)	69 (0.47%)	1 (0.07%)
Period 2 - 3	None	1459 (83.71%)	10843 (79.91%)	1141 (84.08%)
	Step Down	143 (8.20%)	1336 (9.85%)	105 (7.74%)
	Step Up	137 (7.86%)	1328 (9.79%)	110 (8.11%)
	Switch	4 (0.23%)	62 (0.46%)	1 (0.07%)
Period 3 - 4	None	1384 (83.83%)	9937 (80.26%)	987 (82.53%)
	Step Down	120 (7.27%)	1112 (8.98%)	103 (8.61%)
	Step Up	145 (8.78%)	1278 (10.32%)	102 (8.53%)
	Switch	2 (0.12%)	54 (0.44%)	4 (0.33%)
Any point	.	113 (5.51%)	1113 (6.64%)	7 (0.50%)
	=> 1	700 (34.16%)	6379 (38.07%)	484 (34.50%)
	none	1236 (60.32%)	9266 (55.29%)	912 (65.00%)

Table 50: The rate* of primary care contact in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate days with primary care contact is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rates in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	19.5250	26.6463	37.1015	49.1147	100.000	1
Male	13.9598	26.1010	39.5762	49.4100	99.342	1
Female	17.0111	27.2151	39.8802	48.7922	99.644	1
Never Smoked	10.9503	26.6018	43.4486	44.8288	97.743	1
Ex Smoker	17.8725	27.0801	38.6326	50.1249	100.000	1
Current Smoker	15.2091	25.3334	37.9129	48.4780	100.000	1
Over 75	19.2817	30.2865	43.8050	51.8042	100.000	1
Below 75	16.0134	24.1793	34.9508	48.3440	100.000	1
SES IMD 2010 = 5 (least deprived)	11.7318	25.6868	38.4104	36.5709	95.227	0
SES IMD 2010 = 4	11.1134	26.4106	42.6566	41.8458	96.267	0
SES IMD 2010 = 3	14.0926	26.4263	40.2552	48.0240	98.451	1
SES IMD 2010 = 2	15.2973	27.1144	63.6215	47.0623	95.667	0
SES IMD 2010 = 1 (most deprived)	11.3968	27.2349	46.3870	52.5655	98.474	1

Rate is calculated per person year

Table 51: The rate* of days as an inpatient in secondary care in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of days in secondary care is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rate in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	2.14638	6.23859	14.8369	3.32272	7.6331	0
Male	0.46054	6.44772	16.5569	3.62874	16.0742	0
Female	0.88632	5.89742	16.7783	2.98871	13.3000	0
Never Smoked	0.00000	4.16341	30.7090	2.66469	38.8609	0
Ex Smoker	0.08799	6.32073	19.5662	3.89117	14.0545	0
Current Smoker	0.17559	4.65287	21.9037	2.80713	29.0116	0
Over 75	0.78517	8.75353	18.5454	5.49714	16.1824	0
Below 75	0.81508	4.04170	15.1736	2.70032	19.1893	0
SES IMD 2010 = 5 (least deprived)	0.00000	4.58692	30.9778	2.32733	31.6249	0
SES IMD 2010 = 4	0.00000	5.04897	22.0939	2.02035	19.1686	0
SES IMD 2010 = 3	0.00000	5.21429	28.0809	2.95550	28.3545	0
SES IMD 2010 = 2	0.00000	6.28319	79.6545	3.94582	31.0393	0
SES IMD 2010 = 1 (most deprived)	0.00000	5.55739	30.6253	3.45903	28.2552	0

Rate is calculated per person year

Table 52: The rate* of trial related COPD prescriptions items in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups -

For each subgroup the rate of the count of prescriptions is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rates in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5 _percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	8.22732	12.7003	18.2928	23.4399	100.000	1
Male	7.68392	12.9588	18.1501	22.9508	100.000	1
Female	7.98032	12.2587	18.6043	23.9738	100.000	1
Never Smoked	3.96866	9.8919	20.1483	26.5785	100.000	1
Ex Smoker	7.84922	12.6099	18.5796	24.2277	100.000	1
Current Smoker	7.62990	12.9007	19.4491	22.3620	99.510	1
Over 75	7.06729	12.4977	18.7836	23.8373	99.268	1
Below 75	8.35813	12.4532	18.8613	23.3262	100.000	1
SES IMD 2010 = 5 (least deprived)	6.00411	11.8417	21.1587	30.6785	100.000	1
SES IMD 2010 = 4	5.17045	12.6236	20.1391	28.9679	100.000	1
SES IMD 2010 = 3	6.90110	12.6082	22.9994	23.8537	98.319	1
SES IMD 2010 = 2	4.73125	12.6753	20.7362	26.0403	100.000	1
SES IMD 2010 = 1 (most deprived)	3.78100	12.0237	21.1447	20.7302	96.908	0

Rate is calculated per person year

Table 53: The proportion of treatment switchers in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the proportion of treatment switchers is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The proportion in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	0.14569	0.39604	0.57219	0.34670	29.8427	0
Male	0.09375	0.40000	0.59197	0.34568	32.2997	0
Female	0.04219	0.39594	0.62313	0.34783	33.0967	0
Never Smoked	0.00000	0.46154	1.00000	0.27119	22.3375	0
Ex Smoker	0.00000	0.38832	0.60195	0.33828	31.2380	0
Current Smoker	0.00000	0.40000	0.67167	0.36199	34.5857	0
Over 75	0.00000	0.40000	0.63764	0.36741	35.9075	0
Below 75	0.09211	0.40000	0.58555	0.34072	25.7623	0
SES IMD 2010 = 5 (least deprived)	0.00000	0.39286	1.00000	0.45833	69.1075	0
SES IMD 2010 = 4	0.00000	0.40000	0.75000	0.43396	60.0772	0
SES IMD 2010 = 3	0.00000	0.37500	1.00000	0.32836	36.7275	0
SES IMD 2010 = 2	0.00000	0.40202	0.70000	0.32653	27.0781	0
SES IMD 2010 = 1 (most deprived)	0.00000	0.40909	1.00000	0.33610	36.9135	0

Table 54: The rate* of mortality in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of deaths during follow up is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rate in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	0	74.768	174.56	17.5072	7.9966	0
Male	0	76.054	260.95	19.5695	20.8115	0
Female	0	66.135	206.92	15.2563	20.0270	0
Never Smoked	0	0.000	353.75	17.0813	68.2645	0
Ex Smoker	0	88.013	255.59	21.2218	11.6211	0
Current Smoker	0	45.605	273.50	13.7905	31.9987	0
Over 75	0	128.184	419.00	36.0576	12.1719	0
Below 75	0	37.027	140.27	12.1974	31.2849	0
SES IMD 2010 = 5 (least deprived)	0	33.126	345.23	14.1050	46.3418	0
SES IMD 2010 = 4	0	48.390	264.08	9.6207	40.6113	0
SES IMD 2010 = 3	0	62.467	380.31	25.5666	39.8546	0
SES IMD 2010 = 2	0	66.675	1038.94	10.3294	29.6759	0
SES IMD 2010 = 1 (most deprived)	0	48.842	241.70	19.7176	42.9072	0

Rate is calculated as the number of deaths per 1000 person years

Table 55: Distribution of random effects in fully adjusted multilevel Poisson model - Outcome = number of contacts with primary care

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.84703	0.99675	1.29573	1.74984	100	1

Table 56: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of contacts with primary care

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	0.98859	0.9728	1.00464	0.1626
Age	.	1.10445	1.09478	1.1142	<.0001
Age Squared	.	1.02027	1.01393	1.02665	<.0001
SES IMD 2010 Quintiles	4	1.01897	0.99016	1.04862	0.1990
	3	1.03568	1.00568	1.06658	0.0194
	2	1.05242	1.02196	1.08379	0.0007
	1 (most deprived)	1.088	1.05536	1.12165	<.0001
Current Medication (prescriptions in last 3 months)	LABA only	1.01616	0.94842	1.08875	0.6487
	LAMA only	1.0353	0.99869	1.07325	0.0589
	ICS only	0.95847	0.91602	1.00288	0.0664
	LABA/LAMA	0.94584	0.87322	1.02451	0.1720
	LAMA/ICS	0.9354	0.87572	0.99915	0.0471
	LABA/ICS	0.9964	0.96786	1.02579	0.8081
	LABA/LAMA/ICS	1.00189	0.97438	1.03017	0.8942
Any history (ever) of Depression	Present	1.12824	1.10731	1.14957	<.0001
Any history (ever) of Anxiety	Present	1.06869	1.04707	1.09075	<.0001
Any history (ever) of Asthma	Present	1.03053	1.01359	1.04776	0.0004

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Pneumonia	Present	1.13689	1.11323	1.16105	<.0001
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.10455	1.08505	1.12439	<.0001
COPD Exacerbation History in previous 12 months	.	5.56301	4.48412	6.90147	<.0001
COPD Exacerbation History in previous 12 months Squared	.	0.10105	0.05649	0.18076	<.0001
FEV1%	.	0.98959	0.97911	1.00018	0.0540
FEV1% Squared	.	0.99906	0.99341	1.00474	0.7443
FEV1/FVC (%)	.	1.04253	1.03207	1.05309	<.0001
FEV1/FVC (%) squared	.	0.99911	0.99288	1.00539	0.7811
MRC Dyspnoea score	2	1.07389	1.04289	1.10581	<.0001
	3	1.17972	1.14458	1.21594	<.0001
	4	1.23301	1.19378	1.27353	<.0001
	5 (most breathlessness)	1.32969	1.27167	1.39036	<.0001

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Smoking	Ex	1.01103	0.98048	1.04254	0.4833
	Current	0.99521	0.96285	1.02865	0.7758
Influenza Vaccine	Present	1.09087	1.0609	1.1217	<.0001

Table 57: Distribution of random effects in fully adjusted multilevel Poisson model - Outcome = number of days as an inpatient in secondary care

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.84605	1.00861	1.15377	0.93002	12.1572	0

Table 58: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of days as an inpatient in secondary care

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	0.92044	0.87852	0.96435	0.0005
Age	.	1.31846	1.28537	1.3524	<.0001
Age Squared	.	1.05318	1.03417	1.07255	<.0001
SES IMD 2010 Quintiles	4	1.01171	0.93382	1.09609	0.7758
	3	1.08192	0.99747	1.17352	0.0576
	2	1.10664	1.0217	1.19864	0.0129
	1 (most deprived)	1.10346	1.01561	1.19892	0.0200
Current Medication (prescriptions in last 3 months)	LABA only	0.86034	0.70031	1.05694	0.1520
	LAMA only	0.9299	0.83822	1.03159	0.1699
	ICS only	0.81636	0.714	0.93339	0.0030
	LABA/LAMA	0.70422	0.54677	0.90701	0.0066
	LAMA/ICS	0.75389	0.61605	0.92257	0.0061
	LABA/ICS	0.90552	0.83318	0.98414	0.0195
	LABA/LAMA/ICS	0.95464	0.88202	1.03324	0.2502
Any history (ever) of Depression	Present	1.16899	1.10768	1.23369	<.0001
Any history (ever) of Anxiety	Present	1.05043	0.98999	1.11455	0.1037
Any history (ever) of Asthma	Present	0.97781	0.93251	1.02531	0.3538

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Pneumonia	Present	1.37399	1.29747	1.45503	<.0001
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.17239	1.11457	1.23321	<.0001
COPD Exacerbation History in previous 12 months	.	5.1307	2.74705	9.58268	<.0001
COPD Exacerbation History in previous 12 months Squared	.	0.08558	0.0156	0.46961	0.0047
FEV1%	.	0.93942	0.91204	0.96762	<.0001
FEV1% Squared	.	1.02728	1.01243	1.04234	0.0003
FEV1/FVC (%)	.	1.0476	1.01879	1.07723	0.0011
FEV1/FVC (%) squared	.	1.00982	0.99256	1.02737	0.2665
MRC Dyspnoea score	2	1.10226	1.00705	1.20647	0.0346
	3	1.35894	1.24013	1.48913	<.0001
	4	1.50349	1.36573	1.65515	<.0001
	5 (most breathlessness)	1.84439	1.629	2.08827	<.0001

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Smoking	Ex	1.15565	1.05372	1.26744	0.0021
	Current	1.1796	1.06793	1.30295	0.0011
Influenza Vaccine	Present	1.12434	1.03433	1.22218	0.0059

Table 59: Distribution of random effects in fully adjusted multilevel Poisson model - Outcome = count of trial related COPD prescriptions items

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.80367	1.01120	1.26134	1.17162	87.8839	0

Table 60: Fixed effects for fully adjusted multilevel Poisson model - Outcome = count of trial related COPD prescriptions items

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	1.01491	0.99786	1.03225	0.0868
Age	.	1.01583	1.00613	1.02562	0.0013
Age Squared	.	0.98126	0.97443	0.98813	<.0001
SES IMD 2010 Quintiles	4	1.02937	0.99894	1.06074	0.0587
	3	1.03713	1.00548	1.06978	0.0211
	2	1.02975	0.99836	1.06213	0.0635
	1 (most deprived)	1.02074	0.98797	1.05459	0.2176
Current Medication (prescriptions in last 3 months)	LABA only	1.87859	1.71974	2.05211	<.0001
	LAMA only	2.18217	2.07246	2.29768	<.0001
	ICS only	1.60153	1.50261	1.70697	<.0001
	LABA/LAMA	3.33221	3.06939	3.61753	<.0001
	LAMA/ICS	3.23097	3.00661	3.47206	<.0001
	LABA/ICS	2.01862	1.92891	2.11251	<.0001
	LABA/LAMA/ICS	3.42173	3.27453	3.57555	<.0001
Any history (ever) of Depression	Present	1.01674	0.99677	1.03712	0.1010
Any history (ever) of Anxiety	Present	0.98515	0.96362	1.00716	0.1844
Any history (ever) of Asthma	Present	1.04114	1.02315	1.05945	<.0001

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Pneumonia	Present	0.99283	0.97033	1.01586	0.5387
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.00085	0.98178	1.02028	0.9314
COPD Exacerbation History in previous 12 months	.	1.29593	1.02375	1.64047	0.0312
COPD Exacerbation History in previous 12 months Squared	.	2.03109	1.06751	3.86441	0.0308
FEV1%	.	0.96795	0.95734	0.97868	<.0001
FEV1% Squared	.	1.01247	1.00651	1.01848	<.0001
FEV1/FVC (%)	.	0.97716	0.96707	0.98736	<.0001
FEV1/FVC (%) squared	.	1.00078	0.99428	1.00732	0.8155
MRC Dyspnoea score	2	1.06954	1.03656	1.10357	<.0001
	3	1.10405	1.06897	1.14029	<.0001
	4	1.08952	1.05253	1.1278	<.0001
	5 (most breathlessness)	1.11283	1.0606	1.16762	<.0001

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Smoking	Ex	1.0474	1.01188	1.08416	0.0085
	Current	1.07859	1.03981	1.11882	<.0001
Influenza Vaccine	Present	1.07322	1.04193	1.10545	<.0001

Table 61: Distribution of random effects in fully adjusted multilevel Logistic model - Outcome = any treatment switch throughout the follow up

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.
The follow up time is used as an offset in the model

Variable	CPRD_xGM_IC_2.5 _percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.66267	0.99321	1.54621	0.69212	4.83276	0

Table 62: Fixed effects for fully adjusted multilevel Logistic model - Outcome = any treatment switch throughout the follow up

Parameter	Category	Odds Ratio	OR_LowerCL	OR_UpperCL	P
Sex	Female	0.9173	0.85624	0.98275	0.0141
Age	.	0.9976	0.96063	1.03591	0.8990
Age Squared	.	1.0570	1.02941	1.08543	<.0001
SES IMD 2010 Quintiles	4	0.9269	0.82365	1.04318	0.2081
	3	0.8919	0.78979	1.00721	0.0652
	2	0.9010	0.79892	1.01605	0.0891
	1 (most deprived)	0.8855	0.78075	1.00432	0.0584
Current Medication (prescriptions in last 3 months)	LABA only	0.3914	0.29675	0.51628	<.0001
	LAMA only	0.4858	0.41677	0.56629	<.0001
	ICS only	0.4842	0.40252	0.58252	<.0001
	LABA/LAMA	0.4153	0.30155	0.57191	<.0001
	LAMA/ICS	0.4244	0.32474	0.55471	<.0001
	LABA/ICS	0.2359	0.20784	0.26771	<.0001
	LABA/LAMA/ICS	0.1221	0.10785	0.13835	<.0001
Any history (ever) of Depression	Present	1.0608	0.97833	1.15013	0.1529
Any history (ever) of Anxiety	Present	1.1188	1.02364	1.22289	0.0133
Any history (ever) of Asthma	Present	1.0367	0.9659	1.11263	0.3182

Parameter	Category	Odds Ratio	OR_LowerCL	OR_UpperCL	P
Any history (ever) of Pneumonia	Present	1.1050	1.00621	1.21353	0.0367
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.0391	0.96103	1.12346	0.3359
COPD Exacerbation History in previous 12 months	.	4.6345	1.77988	12.0674	0.0017
COPD Exacerbation History in previous 12 months Squared	.	0.01495	0.00102	0.21991	0.0022
FEV1%	.	1.0365	0.99043	1.08476	0.1222
FEV1% Squared	.	0.9848	0.96106	1.00907	0.2173
FEV1/FVC (%)	.	1.0063	0.9639	1.05061	0.7743
FEV1/FVC (%) squared	.	0.9775	0.95142	1.00434	0.0997
MRC Dyspnoea score	2	1.0901	0.97025	1.22472	0.1466
	3	1.1178	0.9895	1.2628	0.0734
	4	1.2934	1.13296	1.47646	0.0001

Parameter	Category	Odds Ratio	OR_LowerCL	OR_UpperCL	P
	5 (most breathlessness)	1.2380	1.01967	1.50309	0.0310
Smoking	Ex	0.9962	0.87534	1.13376	0.9540
	Current	0.9319	0.81095	1.07091	0.3201
Influenza Vaccine	Present	0.8720	0.77896	0.97607	0.0173

Table 63: Distribution of random effects in fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until death

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.90631	0.99542	1.15430	0.60872	0	1

Table 64: Fixed effects for fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until death

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Sex	Female	0.89795	0.79604	1.01291	0.0799
	Male	.	.	.	.
Age		2.23914	2.0427	2.45446	<.0001
Age Squared		1.01432	0.95701	1.07506	0.6319
SES IMD 2010 Quintiles	4	0.97982	0.8021	1.1969	0.8417
	3	1.12654	0.92227	1.37605	0.2431
	2	1.18134	0.97101	1.43722	0.0957
	1 (most deprived)	1.10403	0.89758	1.35795	0.3488
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	0.93613	0.53657	1.6332	0.8162
	LAMA only	0.98759	0.75737	1.28778	0.9265
	ICS only	1.01701	0.72507	1.42649	0.9222
	LABA/LAMA	0.54472	0.23931	1.23988	0.1477
	LAMA/ICS	0.64864	0.35758	1.17664	0.1543
	LABA/ICS	0.92953	0.7496	1.15265	0.5056
	LABA/LAMA/ICS	0.90846	0.74296	1.11083	0.3495
	No trial medication (in last 3 months)	.	.	.	.

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Depression	Present	1.12337	0.97527	1.29396	0.1068
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.10097	0.94129	1.28774	0.2289
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	0.83938	0.74509	0.94561	0.0040
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.5663	1.37138	1.78893	<.0001
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	0.94961	0.8278	1.08935	0.4604
	Absent	.	.	.	.
COPD Exacerbation History in previous 12 months		0.78903	0.1775	3.50752	0.7556
COPD Exacerbation History in previous 12 months Squared		7.59801	0.22931	251.75	0.2562
FEV1%		0.75996	0.70685	0.81705	<.0001

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
FEV1% Squared		1.07078	1.03106	1.11203	0.0004
FEV1/FVC (%)		0.97971	0.91617	1.04766	0.5490
FEV1/FVC (%) squared		1.01461	0.97291	1.0581	0.4981
MRC Dyspnoea score	2	0.98574	0.7277	1.33528	0.9261
	3	1.50882	1.1236	2.0261	0.0062
	4	1.89753	1.40769	2.55783	<.0001
	5 (most breathlessness)	3.057	2.21115	4.22642	<.0001
	1 (least breathlessness)	.	.	.	.
Smoking	Ex	1.4708	1.12827	1.91731	0.0043
	Current	1.6634	1.25072	2.21225	0.0005
	Never Smoked	.	.	.	.
Influenza Vaccine	Present	0.94395	0.76239	1.16875	0.5966
	Absent	.	.	.	.

4 Secondary Objective 2: Alternate Definitions of COPD Exacerbation and Pneumonia Episodes

4.1 For COPD exacerbations; CPRD primary care data is compared with SLS-EHR

Table 65: Comparison of CPRD-xGM-IC, CPRD-GM-IC and SLS-UC - Outcomes

Outcome	Variable	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
COPD Definition B	N	2,049	16,758	1,403
	Person time	1,741.29 years	13,948.09 years	1,286.74 years
	Count Rate per person year (95% CI)	1,433 0.82 (0.78 - 0.87)	9,152 0.66 (0.64 - 0.67)	1,176 0.91 (0.86 - 0.97)
COPD Definition C	Person time	1,748.81 years	14,017.80 years	1,300.85 years
	Count Rate per person year (95% CI)	1,327 0.76 (0.72 - 0.80)	8,159 0.58 (0.57 - 0.59)	983 0.76 (0.71 - 0.80)
COPD Definition D	Person time	1,800.87 years	14,345.10 years	1,316.41 years
	Count Rate per person year (95% CI)	583 0.32 (0.30 - 0.35)	3,497 0.24 (0.24 - 0.25)	766 0.58 (0.54 - 0.62)
Pneumonia as primary admission diagnosis_	N	2,044	16,721	1,403
	Person time	1,817.39 years	14,389.30 years	1,362.14 years
	Count Rate per 1000 person years (95% CI)	120 66.03 (54.74 - 78.95)	951 66.09 (61.96 - 70.43)	77 56.53 (44.61 - 70.65)

Table 66: The rate* of COPD exacerbation episodes (sub definition B) in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of COPD episodes is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rates in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	0.081922	0.59718	1.29098	0.91394	81.6362	0
Male	0.000000	0.55443	1.44182	0.77887	77.7199	0
Female	0.046913	0.66986	1.66644	1.06432	81.4969	0
Never Smoked	0.000000	0.48468	1.88067	0.55155	55.7292	0
Ex Smoker	0.046465	0.57229	1.45270	0.99180	89.7986	0
Current Smoker	0.000000	0.71199	2.22854	0.86902	66.9061	0
Over 75	0.000000	0.60033	1.30420	0.86391	78.9239	0
Below 75	0.070744	0.62844	1.69184	0.92830	81.3847	0
SES IMD 2010 = 5 (least deprived)	0.000000	0.50452	1.85138	0.75858	74.3933	0
SES IMD 2010 = 4	0.000000	0.55601	1.56813	1.03038	87.4719	0
SES IMD 2010 = 3	0.000000	0.57242	2.21726	0.89267	78.4901	0
SES IMD 2010 = 2	0.000000	0.63608	1.88845	0.91324	74.9715	0
SES IMD 2010 = 1 (most deprived)	0.000000	0.60052	1.86009	0.91880	75.3392	0

Rate is calculated per person year

Table 67: The rate* of COPD exacerbation episodes (sub definition C) in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of COPD episodes is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rate in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	0.081922	0.55222	1.24596	0.75566	74.7979	0
Male	0.000000	0.48445	1.44182	0.63975	69.0537	0
Female	0.000000	0.59499	1.54060	0.88444	76.7296	0
Never Smoked	0.000000	0.43270	1.69822	0.44110	51.6633	0
Ex Smoker	0.000000	0.54389	1.45270	0.80953	83.2376	0
Current Smoker	0.000000	0.64499	1.88391	0.73023	60.3505	0
Over 75	0.000000	0.51044	1.22704	0.69546	74.6344	0
Below 75	0.030803	0.56772	1.61936	0.77297	72.1868	0
SES IMD 2010 = 5 (least deprived)	0.000000	0.42553	1.59289	0.61864	70.0410	0
SES IMD 2010 = 4	0.000000	0.51589	1.46588	0.83416	82.3686	0
SES IMD 2010 = 3	0.000000	0.51175	2.15491	0.76620	76.9152	0
SES IMD 2010 = 2	0.000000	0.51998	1.66440	0.75125	67.8413	0
SES IMD 2010 = 1 (most deprived)	0.000000	0.52963	1.80738	0.75692	71.1524	0

***Rate is calculated per person years**

Table 68: The rate* of COPD exacerbation episodes (sub definition D) in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of COPD episodes is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rates in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	0	0.19927	0.66933	0.58189	91.5192	0
Male	0	0.18268	0.81942	0.48730	91.1718	0
Female	0	0.20585	0.87046	0.68658	91.6601	0
Never Smoked	0	0.00000	0.69580	0.36882	86.3703	0
Ex Smoker	0	0.17916	0.64907	0.62198	95.8128	0
Current Smoker	0	0.23264	1.19514	0.56085	85.5842	0
Over 75	0	0.16310	0.75944	0.49934	91.9264	0
Below 75	0	0.20980	0.80836	0.60566	92.9037	0
SES IMD 2010 = 5 (least deprived)	0	0.10781	0.74238	0.39171	85.2948	0
SES IMD 2010 = 4	0	0.15770	0.74578	0.63176	94.6664	0
SES IMD 2010 = 3	0	0.17225	1.11116	0.61405	89.8832	0
SES IMD 2010 = 2	0	0.19862	0.96998	0.59634	88.5011	0
SES IMD 2010 = 1 (most deprived)	0	0.16500	1.34657	0.57908	89.2241	0

Rate is calculated per person year

Table 69: The rate* of Pneumonia as primary admission diagnosis of hospitalisation in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of Pneumonia episodes is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rate in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	0	64.5338	199.400	56.529	41.6407	0
Male	0	65.9313	351.880	59.128	45.8325	0
Female	0	51.6466	195.861	53.697	51.1307	0
Never Smoked	0	0.0000	468.293	34.331	70.2148	0
Ex Smoker	0	66.5834	257.036	74.854	57.1863	0
Current Smoker	0	34.4364	295.229	40.045	53.6647	0
Over 75	0	85.7615	313.055	106.120	59.9505	0
Below 75	0	37.3056	220.279	42.429	55.7103	0
SES IMD 2010 = 5 (least deprived)	0	0.0000	337.725	14.159	62.4907	0
SES IMD 2010 = 4	0	28.9330	380.865	9.746	44.4323	0
SES IMD 2010 = 3	0	23.8179	452.661	76.306	66.3622	0
SES IMD 2010 = 2	0	48.1379	348.839	55.682	55.0038	0
SES IMD 2010 = 1 (most deprived)	0	43.0244	259.824	62.414	56.3281	0

Rate is calculated per 1000 person years

Table 70: Distribution of random effects in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition B)

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.54205	1.00835	1.71135	1.39916	85.2636	0

Table 71: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition B)

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	1.13869	1.08618	1.19373	<.0001
Age	.	1.01908	0.99287	1.04598	0.1551
Age Squared	.	1.01496	0.99657	1.0337	0.1114
SES IMD 2010 Quintiles	4	1.05955	0.97236	1.15456	0.1867
	3	1.0887	0.9972	1.1886	0.0578
	2	1.0785	0.98791	1.17739	0.0914
	1 (most deprived)	1.09685	1.00188	1.20081	0.0454
Current Medication (prescriptions in last 3 months)	LABA only	1.13972	0.92771	1.40019	0.2130
	LAMA only	1.08918	0.97539	1.21624	0.1292
	ICS only	0.99229	0.86148	1.14296	0.9145
	LABA/LAMA	0.92902	0.71559	1.20611	0.5804
	LAMA/ICS	1.00575	0.82383	1.22785	0.9551
	LABA/ICS	1.09869	1.00529	1.20077	0.0379
	LABA/LAMA/ICS	1.0998	1.01003	1.19754	0.0286
Any history (ever) of Depression	Present	1.08268	1.02574	1.14279	0.0040
Any history (ever) of Anxiety	Present	1.08062	1.01972	1.14514	0.0088
Any history (ever) of Asthma	Present	1.06277	1.01235	1.1157	0.0141

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Pneumonia	Present	1.18372	1.11494	1.25673	<.0001
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.15495	1.09775	1.21513	<.0001
COPD Exacerbation History in previous 12 months	.	5775.56	2946.44	11321.2	<.0001
COPD Exacerbation History in previous 12 months Squared	.	1.54E-6	2.13E-7	0.00001	<.0001
FEV1%	.	0.95103	0.9225	0.98044	0.0012
FEV1% Squared	.	0.99587	0.97857	1.01347	0.6433
FEV1/FVC (%)	.	1.0108	0.98212	1.04031	0.4644
FEV1/FVC (%) squared	.	1.01115	0.99331	1.02931	0.2221
MRC Dyspnoea score	2	1.01784	0.93494	1.10809	0.6833
	3	1.0619	0.97306	1.15886	0.1778
	4	1.06607	0.97098	1.17048	0.1795
	5 (most breathlessness)	1.07421	0.94254	1.22427	0.2833

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Smoking	Ex	1.03883	0.94669	1.13994	0.4214
	Current	1.18137	1.07093	1.30319	0.0009
Influenza Vaccine	Present	1.06914	0.98737	1.15769	0.0996

Table 72: Distribution of random effects in fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode (sub definition B)

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.52255	1.00345	1.73004	1.40258	92.5937	0

Table 73: Fixed effects for fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode (sub definition B)

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Sex	Female	1.12795	1.0718	1.18704	<.0001
	Male	.	.	.	.
Age		1.02236	0.99398	1.05155	0.1236
Age Squared		1.01627	0.99635	1.03658	0.1100
SES IMD 2010 Quintiles	4	1.06024	0.9673	1.16211	0.2114
	3	1.07126	0.97517	1.17682	0.1511
	2	1.08793	0.99059	1.19484	0.0780
	1 (most deprived)	1.07745	0.97762	1.18746	0.1326
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.15428	0.92778	1.43608	0.1980
	LAMA only	1.07433	0.95441	1.20931	0.2351
	ICS only	0.94942	0.81598	1.10469	0.5018
	LABA/LAMA	0.95316	0.72446	1.25405	0.7318
	LAMA/ICS	1.02776	0.82965	1.27318	0.8021
	LABA/ICS	1.06413	0.96773	1.17014	0.1995
	LABA/LAMA/ICS	1.08158	0.98749	1.18464	0.0912
	No trial medication (in last 3 months)	.	.	.	.

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Depression	Present	1.08954	1.02733	1.15551	0.0043
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.05471	0.98968	1.12402	0.1009
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.09769	1.04141	1.157	0.0005
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.18012	1.10492	1.26045	<.0001
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.16029	1.09762	1.22655	<.0001
	Absent	.	.	.	.
COPD Exacerbation History in previous 12 months		3712.25	1822.07	7563.27	<.0001
COPD Exacerbation History in previous 12 months Squared		2.5E-6	3.14E-7	0.00002	<.0001
FEV1%		0.94779	0.91686	0.97975	0.0015

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
FEV1% Squared		0.99594	0.97757	1.01465	0.6681
FEV1/FVC (%)		1.01024	0.97917	1.04229	0.5226
FEV1/FVC (%) squared		1.01462	0.99516	1.03447	0.1419
MRC Dyspnoea score	2	1.00306	0.91609	1.0983	0.9473
	3	1.03098	0.93873	1.13231	0.5235
	4	1.04049	0.94096	1.15054	0.4391
	5 (most breathlessness)	1.0619	0.92188	1.22319	0.4051
	1 (least breathlessness)	.	.	.	.
Smoking	Ex	1.03409	0.93608	1.14237	0.5093
	Current	1.18059	1.06213	1.31225	0.0021
	Never Smoked	.	.	.	.
Influenza Vaccine	Present	1.06111	0.97363	1.15646	0.1766
	Absent	.	.	.	.

Table 74: Distribution of random effects in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition C)

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.54037	1.01800	1.73506	1.31048	81.0872	0

Table 75: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition C)

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	1.12469	1.0699	1.1823	<.0001
Age	.	1.01953	0.99186	1.04797	0.1682
Age Squared	.	1.01816	0.99871	1.03798	0.0674
SES IMD 2010 Quintiles	4	1.05733	0.9657	1.15766	0.2281
	3	1.09997	1.0028	1.20655	0.0435
	2	1.06755	0.97289	1.17143	0.1677
	1 (most deprived)	1.09865	0.99839	1.20898	0.0540
Current Medication (prescriptions in last 3 months)	LABA only	1.13301	0.91077	1.40948	0.2623
	LAMA only	1.06567	0.94774	1.19828	0.2878
	ICS only	0.98043	0.84355	1.13953	0.7967
	LABA/LAMA	0.96317	0.73277	1.26602	0.7879
	LAMA/ICS	0.99951	0.80649	1.23872	0.9964
	LABA/ICS	1.08319	0.98589	1.19009	0.0961
	LABA/LAMA/ICS	1.09168	0.99766	1.19456	0.0563
Any history (ever) of Depression	Present	1.10599	1.0447	1.17089	0.0005
Any history (ever) of Anxiety	Present	1.08805	1.02343	1.15674	0.0069
Any history (ever) of Asthma	Present	1.07467	1.02064	1.13156	0.0062

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Pneumonia	Present	1.20048	1.12748	1.27821	<.0001
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.15703	1.09648	1.22092	<.0001
COPD Exacerbation History in previous 12 months	.	6952.49	3441.83	14044	<.0001
COPD Exacerbation History in previous 12 months Squared	.	1.28E-6	1.66E-7	9.93E-6	<.0001
FEV1%	.	0.939	0.90948	0.96947	0.0001
FEV1% Squared	.	1.00796	0.98993	1.02631	0.3895
FEV1/FVC (%)	.	1.00715	0.97713	1.03809	0.6446
FEV1/FVC (%) squared	.	1.01324	0.99451	1.03232	0.1671
MRC Dyspnoea score	2	1.01113	0.92408	1.10637	0.8096
	3	1.04393	0.9516	1.1452	0.3628
	4	1.07022	0.96976	1.18108	0.1772
	5 (most breathlessness)	1.08138	0.94295	1.24013	0.2629

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Smoking	Ex	1.00541	0.91218	1.10816	0.9135
	Current	1.14629	1.03423	1.27049	0.0093
Influenza Vaccine	Present	1.05279	0.96818	1.14479	0.2288

Table 76: Distribution of random effects in fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode (sub definition C)

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.52842	1.01283	1.75524	1.31131	85.1342	0

Table 77: Fixed effects for fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode (sub definition C)

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Sex	Female	1.11587	1.05771	1.17721	<.0001
	Male	.	.	.	.
Age		1.02219	0.99246	1.05281	0.1449
Age Squared		1.0145	0.99367	1.03578	0.1739
SES IMD 2010 Quintiles	4	1.04708	0.95122	1.15259	0.3477
	3	1.0813	0.98021	1.1928	0.1186
	2	1.06563	0.9658	1.17577	0.2053
	1 (most deprived)	1.08188	0.97725	1.19771	0.1294
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.15175	0.91556	1.44887	0.2276
	LAMA only	1.07009	0.94477	1.21203	0.2864
	ICS only	0.968	0.82531	1.13536	0.6894
	LABA/LAMA	0.96633	0.72489	1.28819	0.8154
	LAMA/ICS	0.99668	0.79278	1.25302	0.9773
	LABA/ICS	1.0552	0.9549	1.16604	0.2917
	LABA/LAMA/ICS	1.07988	0.98148	1.18815	0.1149
	No trial medication (in last 3 months)	.	.	.	.

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Depression	Present	1.11749	1.05086	1.18835	0.0004
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.06271	0.99431	1.13581	0.0732
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.11123	1.05141	1.17446	0.0002
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.20625	1.1266	1.29154	<.0001
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.15093	1.08584	1.21992	<.0001
	Absent	.	.	.	.
COPD Exacerbation History in previous 12 months		4759.1	2267.41	9988.95	<.0001
COPD Exacerbation History in previous 12 months Squared		1.81E-6	2.1E-7	0.00002	<.0001
FEV1%		0.93587	0.90412	0.96875	0.0002

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
FEV1% Squared		1.00787	0.98885	1.02726	0.4199
FEV1/FVC (%)		1.0079	0.97556	1.04132	0.6362
FEV1/FVC (%) squared		1.01474	0.99445	1.03543	0.1556
MRC Dyspnoea score	2	0.99978	0.90886	1.09978	0.9963
	3	1.01563	0.92033	1.12079	0.7578
	4	1.04162	0.93753	1.15726	0.4478
	5 (most breathlessness)	1.08052	0.93305	1.25131	0.3010
	1 (least breathlessness)	.	.	.	.
Smoking	Ex	1.00003	0.90153	1.10929	0.9995
	Current	1.15073	1.03082	1.28459	0.0124
	Never Smoked	.	.	.	.
Influenza Vaccine	Present	1.04452	0.95478	1.1427	0.3419
	Absent	.	.	.	.

Table 78: Distribution of random effects in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition D)

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.35514	1.01350	2.62067	2.59068	97.3561	0

Table 79: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition D)

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	1.18521	1.1028	1.27377	<.0001
Age	.	0.99727	0.95641	1.03987	0.8981
Age Squared	.	0.97013	0.94148	0.99965	0.0474
SES IMD 2010 Quintiles	4	1.15318	1.00071	1.32888	0.0489
	3	1.18846	1.0296	1.37183	0.0184
	2	1.20143	1.04091	1.38671	0.0121
	1 (most deprived)	1.19182	1.02985	1.37927	0.0185
Current Medication (prescriptions in last 3 months)	LABA only	1.70288	1.26708	2.28858	0.0004
	LAMA only	1.23189	1.02757	1.47685	0.0242
	ICS only	0.97109	0.75555	1.24811	0.8188
	LABA/LAMA	1.06203	0.69835	1.61511	0.7784
	LAMA/ICS	0.92159	0.65655	1.29362	0.6369
	LABA/ICS	1.23569	1.06303	1.43639	0.0059
	LABA/LAMA/ICS	1.46876	1.27421	1.69301	<.0001
Any history (ever) of Depression	Present	1.09143	1.00539	1.18484	0.0368
Any history (ever) of Anxiety	Present	1.11012	1.01698	1.21178	0.0195
Any history (ever) of Asthma	Present	1.03498	0.96166	1.11389	0.3591

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Pneumonia	Present	1.10999	1.01184	1.21765	0.0272
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.0972	1.01402	1.1872	0.0211
COPD Exacerbation History in previous 12 months	.	5703.62	2226.96	14607.9	<.0001
COPD Exacerbation History in previous 12 months Squared	.	2.24E-6	1.78E-7	0.00003	<.0001
FEV1%	.	0.88582	0.84536	0.92822	<.0001
FEV1% Squared	.	1.00238	0.97491	1.03062	0.8670
FEV1/FVC (%)	.	0.94155	0.90115	0.98376	0.0071
FEV1/FVC (%) squared	.	1.02276	0.99565	1.0506	0.1006
MRC Dyspnoea score	2	1.07166	0.93265	1.2314	0.3289
	3	1.15094	0.99967	1.3251	0.0505
	4	1.20779	1.04122	1.401	0.0127
	5 (most breathlessness)	1.24764	1.02318	1.52134	0.0288

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Smoking	Ex	1.38976	1.17194	1.64806	0.0002
	Current	1.61095	1.35001	1.92233	<.0001
Influenza Vaccine	Present	1.09826	0.97055	1.24276	0.1373

Table 80: Distribution of random effects in fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode (sub definition D)

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.36216	0.99523	2.41839	2.51434	98.3620	1

Table 81: Fixed effects for fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first COPD exacerbation episode (sub definition D)

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Sex	Female	1.17677	1.09189	1.26826	<.0001
	Male	.	.	.	.
Age		1.00807	0.96558	1.05243	0.7145
Age Squared		0.977	0.94743	1.00748	0.1377
SES IMD 2010 Quintiles	4	1.15677	1.00013	1.33794	0.0498
	3	1.20064	1.03607	1.39134	0.0151
	2	1.22196	1.05481	1.41559	0.0076
	1 (most deprived)	1.21682	1.04742	1.41362	0.0103
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.73163	1.27652	2.34898	0.0004
	LAMA only	1.23003	1.02015	1.48309	0.0301
	ICS only	0.95178	0.73588	1.23101	0.7065
	LABA/LAMA	1.09864	0.71788	1.68134	0.6648
	LAMA/ICS	0.89699	0.63327	1.27055	0.5406
	LABA/ICS	1.21099	1.03715	1.41396	0.0155
	LABA/LAMA/ICS	1.46312	1.26387	1.69377	<.0001
	No trial medication (in last 3 months)	.	.	.	.

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Depression	Present	1.10643	1.0157	1.20526	0.0205
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.09565	0.99975	1.20074	0.0506
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.06618	0.98768	1.15092	0.1005
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.11338	1.0109	1.22624	0.0293
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.07874	0.99361	1.17118	0.0708
	Absent	.	.	.	.
COPD Exacerbation History in previous 12 months		4780.37	1815.43	12587.6	<.0001
COPD Exacerbation History in previous 12 months Squared		2.43E-6	1.79E-7	0.00003	<.0001
FEV1%		0.88426	0.8424	0.9282	<.0001

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
FEV1% Squared		1.00305	0.97491	1.03202	0.8337
FEV1/FVC (%)		0.94933	0.90712	0.99351	0.0251
FEV1/FVC (%) squared		1.0234	0.99516	1.05244	0.1052
MRC Dyspnoea score	2	1.04372	0.90513	1.20353	0.5561
	3	1.11301	0.96289	1.28654	0.1475
	4	1.16877	1.00296	1.362	0.0457
	5 (most breathlessness)	1.25161	1.02009	1.53568	0.0315
	1 (least breathlessness)	.	.	.	.
Smoking	Ex	1.41011	1.18403	1.67936	0.0001
	Current	1.63671	1.3651	1.96236	<.0001
	Never Smoked	.	.	.	.
Influenza Vaccine	Present	1.0951	0.96381	1.24427	0.1633
	Absent	.	.	.	.

4.2 Alternative pneumonia definition (comparison between CPRD Primary+Secondary Care Data vs. SLS-Database)

Table 82: Distribution of random effects in fully adjusted multilevel Poisson model - Outcome = number of Pneumonia as primary admission diagnosis of hospitalisation episodes

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.95820	0.99750	1.04139	1.01948	79.8115	0

Table 83: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of Pneumonia as primary admission diagnosis of hospitalisation episodes

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	0.88487	0.77114	1.01536	0.0814
Age	.	1.6438	1.51108	1.78819	<.0001
Age Squared	.	1.06154	1.00135	1.12535	0.0449
SES IMD 2010 Quintiles	4	1.40196	1.08996	1.80326	0.0085
	3	1.45272	1.12813	1.87071	0.0038
	2	1.37703	1.07258	1.76791	0.0121
	1 (most deprived)	1.67644	1.30773	2.1491	<.0001
Current Medication (prescriptions in last 3 months)	LABA only	0.81742	0.37676	1.77347	0.6099
	LAMA only	0.7647	0.53468	1.09367	0.1417
	ICS only	0.91059	0.58174	1.42535	0.6820
	LABA/LAMA	0.92473	0.42481	2.01297	0.8437
	LAMA/ICS	1.11699	0.60688	2.05588	0.7222
	LABA/ICS	1.21055	0.93031	1.57522	0.1549
	LABA/LAMA/ICS	1.306	1.02126	1.67011	0.0334
Any history (ever) of Depression	Present	1.02637	0.87253	1.20733	0.7534
Any history (ever) of Anxiety	Present	1.01866	0.85023	1.22047	0.8411
Any history (ever) of Asthma	Present	0.86629	0.75572	0.99305	0.0394

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Pneumonia	Present	1.58986	1.36407	1.85302	<.0001
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.09462	0.94219	1.27171	0.2373
Pneumonia exacerbation history	.	49.6227	27.6994	88.8976	<.0001
Pneumonia exacerbation history squared	.	0.22523	0.13658	0.37144	<.0001
FEV1%	.	0.8395	0.77156	0.91341	<.0001
FEV1% Squared	.	1.0272	0.97906	1.0777	0.2732
FEV1/FVC (%)	.	0.95165	0.88083	1.02817	0.2091
FEV1/FVC (%) squared	.	1.00987	0.96144	1.06075	0.6952
MRC Dyspnoea score	2	1.2161	0.85745	1.72477	0.2725
	3	1.75289	1.24486	2.46824	0.0013
	4	1.9973	1.40943	2.83036	0.0001
	5 (most breathlessness)	2.29822	1.5478	3.41246	<.0001
Smoking	Ex	1.26989	0.95199	1.69396	0.1041

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
	Current	1.2701	0.9281	1.73812	0.1352
Influenza Vaccine	Present	0.97453	0.76161	1.24698	0.8375

Table 84: Distribution of random effects in fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first Pneumonia as primary admission diagnosis of hospitalisation

Random intercepts are defined at the local authority level, with SLS-UC defined as its own local authority. Point estimates for the random intercepts for each local authority in CPRD_xGM_IC are combined to construct a 2.5-97.5 percentile range. SLS-UC is deemed unusual if the point estimate of its random intercept lies outside of this interval. Random coefficients are not considered in the model.

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.92396	0.99593	1.07489	1.01036	66.9619	0

Table 85: Fixed effects for fully adjusted multilevel Cox Proportional Hazards model - Outcome = time until first Pneumonia as primary admission diagnosis of hospitalisation

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Sex	Female	0.87938	0.76506	1.01077	0.0704
	Male	.	.	.	.
Age		1.63837	1.50561	1.78284	<.0001
Age Squared		1.06896	1.00819	1.1334	0.0256
SES IMD 2010 Quintiles	4	1.4086	1.09345	1.81458	0.0080
	3	1.46291	1.13386	1.88743	0.0034
	2	1.376	1.06922	1.77081	0.0131
	1 (most deprived)	1.69585	1.31967	2.17926	<.0001
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	0.80999	0.37235	1.76204	0.5951
	LAMA only	0.74213	0.51639	1.06654	0.1070
	ICS only	0.90234	0.57563	1.41448	0.6541
	LABA/LAMA	0.98719	0.45366	2.14821	0.9741
	LAMA/ICS	1.11036	0.60201	2.04797	0.7375
	LABA/ICS	1.19852	0.91865	1.56367	0.1820
	LABA/LAMA/ICS	1.29067	1.00647	1.65512	0.0443
	No trial medication (in last 3 months)	.	.	.	.

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Depression	Present	1.03153	0.87552	1.21533	0.7106
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.02343	0.8527	1.22835	0.8036
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	0.84961	0.74018	0.97521	0.0205
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.57616	1.34895	1.84164	<.0001
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.0951	0.94081	1.27469	0.2410
	Absent	.	.	.	.
Pneumonia exacerbation history		46.9027	25.3471	86.7898	<.0001
Pneumonia exacerbation history squared		0.21429	0.12235	0.37531	<.0001
FEV1%		0.833	0.76496	0.90709	<.0001
FEV1% Squared		1.03053	0.98216	1.08128	0.2201

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
FEV1/FVC (%)		0.96066	0.88831	1.03889	0.3150
FEV1/FVC (%) squared		1.01087	0.96193	1.06229	0.6694
MRC Dyspnoea score	2	1.19745	0.8416	1.70377	0.3166
	3	1.75232	1.2408	2.47472	0.0014
	4	1.99819	1.40588	2.84004	0.0001
	5 (most breathlessness)	2.25821	1.51406	3.36811	<.0001
	1 (least breathlessness)	.	.	.	.
Smoking	Ex	1.24433	0.93137	1.66246	0.1392
	Current	1.22746	0.89507	1.68328	0.2034
	Never Smoked	.	.	.	.
Influenza Vaccine	Present	0.96616	0.75371	1.2385	0.7858
	Absent	.	.	.	.

5 Secondary Objective 3: COPD Exacerbation Rates and Health Care Utilisation Compared in the Year Prior to the SLS Trial to the SLS Trial Period

Tables in this section cover SO3, using the CRPD primary care dataset compared to the SLS-EHR dataset.

Table 86.1: Comparison of CPRD-xGM-IC, CPRD-GM-IC and SLS-UC - Outcomes in year prior to the trial

Outcome	Variable	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
COPD Definition A	N	2,060	16,799	1,403
	Person time	1,829.80 years	15,062.97 years	1,223.16 years
	Count Rate per person year (95% CI)	3,115 1.70 (1.64 - 1.76)	23,598 1.57 (1.55 - 1.59)	2,395 1.96 (1.88 - 2.04)
COPD Definition B	Person time	1,931.16 years	15,942.93 years	1,310.47 years
	Count Rate per person year (95% CI)	1,751 0.91 (0.86 - 0.95)	11,664 0.73 (0.72 - 0.75)	1,245 0.95 (0.90 - 1.00)
COPD Definition C	Person time	1,948.61 years	16,065.07 years	1,334.09 years
	Count Rate per person year (95% CI)	1,513 0.78 (0.74 - 0.82)	10,005 0.62 (0.61 - 0.64)	932 0.70 (0.65 - 0.74)

Outcome	Variable	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
COPD Definition D	Person time	2,007.93 years	16,488.31 years	1,359.79 years
	Count Rate per person year (95% CI)	713 0.36 (0.33 - 0.38)	4,152 0.25 (0.24 - 0.26)	585 0.43 (0.40 - 0.47)
HCU trial related COPD prescription items count	Person time	2,058.59 years	16,787.50 years	1,402.04 years
	Count Rate per person year (95% CI)	27,681 13.45 (13.29 - 13.61)	208,374 12.41 (12.36 - 12.47)	52,549 37.48 (37.16 - 37.80)
HCU primary care contact	Person time	2,056.29 years	16,786.20 years	1,389.03 years
	Count Rate per person year (95% CI)	51,049 24.83 (24.61 - 25.04)	434,636 25.89 (25.82 - 25.97)	63,485 45.70 (45.35 - 46.06)
Treatment Switching	At some point in follow up	46.31 %	51.06 %	48.40 %

Table 86.2: Comparison of CPRD-xGM-IC, CPRD-GM-IC and SLS-UC - Outcomes during the year of the trial

Outcome	Variable	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
COPD Definition A	N	2,060	16,799	1,403
	Person time	1,650.05 years	13,137.07 years	1,199.74 years
	Count Rate per person year (95% CI)	2,717 1.65 (1.59 - 1.71)	20,177 1.54 (1.51 - 1.56)	2,282 1.90 (1.82 - 1.98)
COPD Definition B	Person time	1,746.32 years	13,970.93 years	1,286.06 years
	Count Rate per person year (95% CI)	1,440 0.82 (0.78 - 0.87)	9,157 0.66 (0.64 - 0.67)	1,176 0.91 (0.86 - 0.97)
COPD Definition C	Person time	1,754.53 years	14,044.80 years	1,300.31 years
	Count Rate per person year (95% CI)	1,332 0.76 (0.72 - 0.80)	8,168 0.58 (0.57 - 0.59)	983 0.76 (0.71 - 0.80)
COPD Definition D	Person time	1,808.59 years	14,388.49 years	1,316.00 years

Outcome	Variable	CPRD_GM_IC	CPRD_xGM_IC	SLS_UC
	Count Rate per person year (95% CI)	586 0.32 (0.30 - 0.35)	3,505 0.24 (0.24 - 0.25)	766 0.58 (0.54 - 0.62)
HCU trial related COPD prescription items count	Person time	1,852.08 years	14,643.45 years	1,370.90 years
	Count Rate per person year (95% CI)	25,596 13.82 (13.65 - 13.99)	188,018 12.84 (12.78 - 12.90)	32,133 23.44 (23.18 - 23.70)
HCU primary care contact	Person time	1,849.57 years	14,642.32 years	1,350.10 years
	Count Rate per person year (95% CI)	48,567 26.26 (26.03 - 26.49)	401,260 27.40 (27.32 - 27.49)	66,311 49.12 (48.74 - 49.49)
Treatment Switching	At some point in follow up	36.28 %	40.76 %	34.67 %

Table 87: The change in rate* of COPD exacerbation episodes prior and during trial in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of COPD exacerbations is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rates in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	-0.65436	-0.04908	0.73417	-0.05597	49.3971	0
Male	-0.78584	-0.07522	0.99718	0.05047	69.2837	0
Female	-1.08666	-0.03623	0.75182	-0.15055	32.9484	0
Never Smoked	-2.23256	-0.10421	1.71654	-0.59849	26.5170	0
Ex Smoker	-0.86627	-0.13707	1.15049	-0.07249	57.5082	0
Current Smoker	-0.98849	0.06723	1.17503	0.01124	44.6480	0
Over 75	-0.93979	-0.15872	0.71791	-0.27693	33.9117	0
Below 75	-0.80635	-0.05053	1.26538	0.00702	58.1423	0
SES IMD 2010 = 5 (least deprived)	-1.47576	-0.25532	1.61397	-0.03995	64.0889	0
SES IMD 2010 = 4	-1.94933	-0.10255	1.07320	0.10908	70.2840	0
SES IMD 2010 = 3	-1.44329	-0.01178	1.65665	-0.24656	34.6382	0
SES IMD 2010 = 2	-1.62937	-0.07567	1.06154	-0.12265	41.5513	0
SES IMD 2010 = 1 (most deprived)	-1.37183	-0.08138	2.23421	-0.24368	38.2459	0

Rate is calculated per person year

Table 88: The change in rate* of COPD exacerbation episodes (sub definition B) prior and during trial in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of COPD exacerbations is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rate in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5 _percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	-0.42006	-0.09304	0.41049	-0.03562	60.3934	0
Male	-0.76602	-0.11333	0.38243	0.02294	78.8614	0
Female	-0.71093	-0.04789	0.53679	-0.08749	44.2011	0
Never Smoked	-1.37922	-0.06100	0.93248	-0.31458	29.5891	0
Ex Smoker	-0.56636	-0.13016	0.63180	0.03802	83.6665	0
Current Smoker	-0.77551	-0.01710	1.02095	-0.08370	38.6635	0
Over 75	-0.67100	-0.11882	0.50112	-0.16711	39.5431	0
Below 75	-0.47003	-0.09495	0.55293	0.00209	68.8529	0
SES IMD 2010 = 5 (least deprived)	-1.40023	-0.10279	0.86126	-0.03244	60.0805	0
SES IMD 2010 = 4	-1.71156	-0.08075	0.72177	0.02000	68.7525	0
SES IMD 2010 = 3	-0.72433	-0.07738	1.13181	-0.13882	36.4321	0
SES IMD 2010 = 2	-1.07893	-0.07400	0.77699	-0.03053	54.9510	0
SES IMD 2010 = 1 (most deprived)	-1.20405	-0.08984	0.91723	-0.01681	58.8395	0

Rate is calculated per person year

Table 89: The change in rate* of COPD exacerbation episodes (sub definition C) prior and during trial in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of COPD exacerbations is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rates in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5 _percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	-0.39087	-0.04113	0.42725	0.05737	79.7853	0
Male	-0.62722	-0.07415	0.38688	0.10477	83.3946	0
Female	-0.60554	-0.04100	0.68433	0.01529	61.2230	0
Never Smoked	-1.24062	0.00000	0.95346	-0.12224	38.3652	0
Ex Smoker	-0.49287	-0.10582	0.71379	0.07412	85.4798	0
Current Smoker	-0.65378	0.01866	0.99548	0.05746	58.7229	0
Over 75	-0.54069	-0.07631	0.53987	-0.10991	39.3640	0
Below 75	-0.43289	-0.03815	0.68602	0.10530	80.8795	0
SES IMD 2010 = 5 (least deprived)	-1.07743	-0.05559	0.80684	0.08135	77.2565	0
SES IMD 2010 = 4	-1.50462	-0.01321	0.72177	0.09279	73.4624	0
SES IMD 2010 = 3	-0.72994	-0.01182	1.11421	-0.02461	46.2420	0
SES IMD 2010 = 2	-0.86680	-0.02489	1.12005	0.03351	66.3524	0
SES IMD 2010 = 1 (most deprived)	-1.10446	-0.03622	0.91723	-0.06439	48.1005	0

Rate is calculated per person year

Table 90: The change in rate* of COPD exacerbation episodes (sub definition D) prior and during trial in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of COPD exacerbations is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rate in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5 _percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	-0.20721	-0.007978	0.36259	0.15185	91.2132	0
Male	-0.30931	-0.006092	0.26858	0.18946	93.4182	0
Female	-0.30426	0.000000	0.51373	0.11824	83.4019	0
Never Smoked	-0.41715	0.000000	0.42713	0.02202	73.0210	0
Ex Smoker	-0.28145	-0.017427	0.40899	0.16311	93.2949	0
Current Smoker	-0.42273	0.000000	0.71202	0.15264	85.0849	0
Over 75	-0.34167	-0.014762	0.44827	0.00470	62.3632	0
Below 75	-0.30865	0.000000	0.47963	0.19417	89.7611	0
SES IMD 2010 = 5 (least deprived)	-0.80609	0.000000	0.51882	0.15823	87.2163	0
SES IMD 2010 = 4	-0.51882	0.000000	0.39803	0.16523	84.4360	0
SES IMD 2010 = 3	-0.51513	0.000000	0.89614	0.11963	75.5342	0
SES IMD 2010 = 2	-0.70366	0.000000	0.57951	0.12241	81.0348	0
SES IMD 2010 = 1 (most deprived)	-0.55910	0.000000	1.10643	0.16653	87.7686	0

Rate is calculated per person year

Table 91: The change in rate* of contact with primary care prior and during trial in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the number of COPD exacerbations is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rates in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	-64.214	-2.18974	3.33215	2.09318	94.6400	0
Male	-67.975	-2.94516	3.45161	1.57616	85.6384	0
Female	-68.357	-2.58115	3.99393	2.56647	92.8205	0
Never Smoked	-54.038	-2.49030	6.87925	-1.24741	56.5158	0
Ex Smoker	-60.240	-2.66371	4.27206	1.50345	92.3409	0
Current Smoker	-53.253	-1.95067	6.66786	2.98969	89.6181	0
Over 75	-80.679	-2.68979	5.63956	2.02846	85.9040	0
Below 75	-60.182	-1.67096	3.43405	2.11173	93.0067	0
SES IMD 2010 = 5 (least deprived)	-53.423	-2.63783	9.88176	3.33889	87.5225	0
SES IMD 2010 = 4	-104.312	-2.38098	7.48113	1.82298	78.3453	0
SES IMD 2010 = 3	-61.146	-2.18677	8.16227	0.38013	74.7008	0
SES IMD 2010 = 2	-80.184	-3.79563	6.86789	-2.07640	59.5006	0
SES IMD 2010 = 1 (most deprived)	-109.999	-2.51346	9.03334	1.54767	82.0858	0

Rate is calculated per person year

Table 92: The change in rate* of count of COPD (trial related) prescriptions prior and during trial in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the rate of count of prescriptions is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The rate in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	-1.8479	0.32442	2.56363	-14.0410	0	1
Male	-2.3745	0.43334	3.29136	-13.7410	0	1
Female	-2.4646	0.32205	2.34892	-14.3159	0	1
Never Smoked	-3.6592	0.03848	3.51095	-28.0062	0	1
Ex Smoker	-2.5165	0.16724	2.92148	-19.0084	0	1
Current Smoker	-2.2957	0.79476	3.54649	-7.7449	0	1
Over 75	-3.0314	0.23623	2.68245	-21.2836	0	1
Below 75	-2.6704	0.45301	3.29713	-11.9519	0	1
SES IMD 2010 = 5 (least deprived)	-4.4044	0.02318	4.64689	-11.2977	0	1
SES IMD 2010 = 4	-3.9763	0.32225	3.91202	-18.5312	0	1
SES IMD 2010 = 3	-3.6318	0.37210	5.66576	-14.1602	0	1
SES IMD 2010 = 2	-4.4198	0.16863	4.15296	-14.8718	0	1
SES IMD 2010 = 1 (most deprived)	-12.8101	0.32847	5.84531	-21.8575	0	1

Rate is calculated per person year

Table 93: The change in proportion of treatment switchers prior and during trial in SLS-UC in the context of regional variation in the CPRD at local authority level, stratified by subgroups

For each subgroup the proportion of treatment switchers is calculated for each local authority in CPRD_xGM_IC to create an empirical 2.5-97.5% range. The proportion in SLS-UC for a given subgroup is deemed unusual if it lies outside of this range.

Subgroup	CPRD_xGM_IC_2.5 _percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
All	-0.37125	-0.11161	0.08349	-0.13726	33.9732	0
Male	-0.45636	-0.12500	0.14773	-0.13205	45.1174	0
Female	-0.45799	-0.09503	0.10443	-0.14203	30.0460	0
Never Smoked	-0.50000	-0.05263	0.50000	-0.25424	17.6364	0
Ex Smoker	-0.51548	-0.11006	0.14426	-0.08650	61.2272	0
Current Smoker	-0.52757	-0.13034	0.15865	-0.17855	35.6975	0
Over 75	-0.55833	-0.09496	0.14950	-0.05934	65.3476	0
Below 75	-0.53250	-0.11576	0.15474	-0.15974	29.6664	0
SES IMD 2010 = 5 (least deprived)	-0.60016	-0.09302	0.14624	-0.14828	34.1029	0
SES IMD 2010 = 4	-1.00000	-0.10780	0.22667	-0.15432	36.1347	0
SES IMD 2010 = 3	-1.00000	-0.12261	0.31904	-0.13957	45.1086	0
SES IMD 2010 = 2	-0.53083	-0.08959	0.20771	-0.09434	47.0569	0
SES IMD 2010 = 1 (most deprived)	-1.00000	-0.11429	0.38095	-0.01389	73.3996	0

Rate is calculated per person year

Table 94.1: Distribution of random coefficients for the period variable in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Coefficient	0.90135	1.02336	1.17611	1.04394	64.1689	0
Before/during trial rate ratio*	0.87801	0.99686	1.14566	1.01691	64.1689	0

* Denotes the combined effect of the random coefficient and fixed effect

Table 94.2: Distribution of random intercepts at the LAR level in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.90046	1.03424	1.20877	1.36108	100	1

Table 95: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
(Intercept)		0.00145	0.00129	0.00162	<.0001
Period fixed effect	Year of trial	0.97411	0.94834	1.00058	0.0552
Sex	Female	1.07169	1.03806	1.10641	<.0001
	Male	.	.	.	.
Age		0.92703	0.91069	0.94366	<.0001
Age Squared	Female	0.96994	0.95782	0.98222	<.0001
SES	4	1.07368	1.01931	1.13096	0.0073
	3	1.04847	0.99369	1.10627	0.0839
	2	1.05485	0.99964	1.11312	0.0516
	1 (most deprived)	1.12407	1.0624	1.18933	<.0001
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.0145	0.88098	1.16827	0.8415
	LAMA only	1.08107	1.00411	1.16393	0.0385
	ICS only	0.8791	0.80007	0.96595	0.0073
	LABA/LAMA	0.90736	0.76912	1.07045	0.2490
	LAMA/ICS	1.08095	0.94551	1.23578	0.2544
	LABA/ICS	1.16127	1.09434	1.2323	<.0001
	LABA/LAMA/ICS	1.37607	1.30048	1.45605	<.0001
	No trial medication (in last 3 months	.	.	.	.
Any history (ever) of Depression	Present	1.01877	0.98126	1.05772	0.3312
	Absent	.	.	.	.

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Anxiety	Present	1.08793	1.04414	1.13356	<.0001
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.10267	1.06705	1.13948	<.0001
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.08686	1.0412	1.13451	0.0001
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.10324	1.06407	1.14386	<.0001
	Absent	.	.	.	.
MRC Dyspnoea Score	2	1.13525	1.0715	1.20279	<.0001
	3	1.28165	1.20766	1.36018	<.0001
	4	1.41099	1.32411	1.50356	<.0001
	5 (most breathlessness)	1.48274	1.35683	1.62033	<.0001
	1 (least breathlessness)	.	.	.	.
Influenza Vaccine	Present	1.13314	1.07381	1.19574	<.0001
	Absent	.	.	.	.
FEV1 %		0.8998	0.88136	0.91863	<.0001
FEV1 % Squared		1.01665	1.00518	1.02824	0.0043
FEV1/FVC (%)		0.97665	0.95787	0.99579	0.0171
FEV1/FVC (%) squared		1.00934	0.99715	1.02169	0.1338
Smoking	Ex	1.06169	0.99754	1.12996	0.0598
	Current	1.12697	1.05454	1.20438	0.0004
	Never Smoked	.	.	.	.

Table 96.1: Distribution of random coefficients for the period variable in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition B)

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Coefficient	0.83281	1.05187	1.19764	1.17112	93.1911	0
Before/during trial rate ratio*	0.72374	0.91411	1.04079	1.01774	93.1911	0

* Denotes the combined effect of the random coefficient and fixed effect

Table 96.2: Distribution of random intercepts at the LAR level in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition B)

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.56931	1.16865	1.74347	1.62710	93.1911	0

Table 97: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition B)

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
(Intercept)		0.00068	0.00059	0.00079	<.0001
Period fixed effect	Year of trial	0.86903	0.83938	0.89974	<.0001
Sex	Female	1.08398	1.04272	1.12687	<.0001
	Male	.	.	.	.
Age		0.98095	0.96011	1.00224	0.0792
Age Squared	Female	1.00562	0.99058	1.02089	0.4659
SES	4	1.03769	0.97299	1.1067	0.2600
	3	1.04981	0.98201	1.1223	0.1536
	2	1.07681	1.00634	1.15222	0.0321
	1 (most deprived)	1.14008	1.06072	1.22539	0.0004
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.0357	0.87243	1.22954	0.6886
	LAMA only	1.07447	0.98249	1.17506	0.1157
	ICS only	0.95693	0.85459	1.07154	0.4456
	LABA/LAMA	0.84812	0.69021	1.04216	0.1171
	LAMA/ICS	1.13698	0.96871	1.33448	0.1162
	LABA/ICS	1.12335	1.04526	1.20729	0.0016
	LABA/LAMA/ICS	1.21495	1.13422	1.30142	<.0001
	No trial medication (in last 3 months	.	.	.	.
Any history (ever) of Depression	Present	1.08339	1.03543	1.13358	0.0005
	Absent	.	.	.	.

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Anxiety	Present	1.11379	1.06029	1.17	<.0001
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.05302	1.0116	1.09612	0.0116
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.22321	1.16243	1.28717	<.0001
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.22108	1.16954	1.2749	<.0001
	Absent	.	.	.	.
MRC Dyspnoea Score	2	1.12867	1.05177	1.21119	0.0008
	3	1.22699	1.14107	1.31938	<.0001
	4	1.307	1.20937	1.41252	<.0001
	5 (most breathlessness)	1.36129	1.22123	1.51741	<.0001
	1 (least breathlessness)	.	.	.	.
Influenza Vaccine	Present	1.10099	1.03118	1.17553	0.0040
	Absent	.	.	.	.
FEV1 %		0.93732	0.91393	0.96132	<.0001
FEV1 % Squared		1.00483	0.99105	1.0188	0.4940
FEV1/FVC (%)		1.01903	0.99501	1.04362	0.1213
FEV1/FVC (%) squared		1.00322	0.9884	1.01825	0.6720
Smoking	Ex	1.03202	0.95696	1.11296	0.4134
	Current	1.11575	1.02931	1.20946	0.0078
	Never Smoked	.	.	.	.

Table 98.1: Distribution of random coefficients for the period variable in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition C)

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Coefficient	0.85388	1.01594	1.14864	1.15105	97.6348	1
Before/during trial rate ratio*	0.77997	0.92800	1.04922	1.05141	97.6348	1

* Denotes the combined effect of the random coefficient and fixed effect

Table 98.2: Distribution of random intercepts at the LAR level in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition C)

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.48362	1.13022	1.74132	1.34864	79.4688	0

Table 99: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition C)

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
(Intercept)		0.00071	0.00071	0.00071	<.0001
Period fixed effect	Year of trial	0.91344	0.91319	0.91369	<.0001
Sex	Female	1.06477	1.06449	1.06506	<.0001
	Male	.	.	.	.
Age		0.98243	0.98217	0.98269	<.0001
Age Squared	Female	0.99763	0.99736	0.9979	<.0001
SES	4	1.02959	1.02932	1.02987	<.0001
	3	1.04981	1.04951	1.05011	<.0001
	2	1.05924	1.05895	1.05952	<.0001
	1 (most deprived)	1.14128	1.14095	1.14162	<.0001
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.00985	1.00956	1.01014	<.0001
	LAMA only	1.02797	1.02769	1.02825	<.0001
	ICS only	0.93314	0.93288	0.93341	<.0001
	LABA/LAMA	0.88903	0.88878	0.88929	<.0001
	LAMA/ICS	1.08746	1.08715	1.08777	<.0001
	LABA/ICS	1.08551	1.08521	1.08581	<.0001
	LABA/LAMA/ICS	1.17758	1.17725	1.17791	<.0001
	No trial medication (in last 3 months	.	.	.	.
Any history (ever) of Depression	Present	1.10058	1.10029	1.10088	<.0001
	Absent	.	.	.	.

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Anxiety	Present	1.11362	1.1133	1.11393	<.0001
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.05752	1.05724	1.0578	<.0001
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.25749	1.25713	1.25785	<.0001
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.20335	1.20299	1.20371	<.0001
	Absent	.	.	.	.
MRC Dyspnoea Score	2	1.11998	1.11968	1.12028	<.0001
	3	1.22757	1.22724	1.2279	<.0001
	4	1.33806	1.33769	1.33843	<.0001
	5 (most breathlessness)	1.40758	1.40719	1.40798	<.0001
	1 (least breathlessness)	.	.	.	.
Influenza Vaccine	Present	1.04771	1.04743	1.04799	<.0001
	Absent	.	.	.	.
FEV1 %		0.92725	0.927	0.9275	<.0001
FEV1 % Squared		1.00275	1.00248	1.00302	<.0001
FEV1/FVC (%)		1.0054	1.00513	1.00567	<.0001
FEV1/FVC (%) squared		0.99336	0.99309	0.99363	<.0001
Smoking	Ex	1.01471	1.01444	1.01498	<.0001
	Current	1.08159	1.08128	1.0819	<.0001
	Never Smoked	.	.	.	.

Table 100.1: Distribution of random coefficients for the period variable in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition D)

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Coefficient	0.86609	1.02589	1.29475	1.43289	100	1
Before/during trial rate ratio*	0.80831	0.95745	1.20838	1.33730	100	1

* Denotes the combined effect of the random coefficient and fixed effect

Table 100.2: Distribution of random intercepts at the LAR level in fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition D)

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.48501	1.38581	3.46472	2.88969	95.3661	0

Table 101: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of COPD exacerbation episodes (sub definition D)

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
(Intercept)		0.00009	0.00007	0.00011	<.0001
Period fixed effect	Year of trial	0.93329	0.87053	1.00056	0.0519
Sex	Female	1.1002	1.03694	1.16733	0.0016
	Male	.	.	.	.
Age		0.97799	0.94536	1.01176	0.1988
Age Squared	Female	0.96299	0.9399	0.98664	0.0023
SES	4	1.06995	0.96834	1.18221	0.1841
	3	1.07669	0.9708	1.19412	0.1618
	2	1.14433	1.02982	1.27156	0.0122
	1 (most deprived)	1.19967	1.07209	1.34244	0.0015
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.44157	1.11646	1.86135	0.0050
	LAMA only	1.16649	1.01017	1.34701	0.0359
	ICS only	0.88025	0.72463	1.06928	0.1987
	LABA/LAMA	1.09999	0.80671	1.49988	0.5469
	LAMA/ICS	1.18907	0.92341	1.53117	0.1795
	LABA/ICS	1.2138	1.07885	1.36562	0.0013
	LABA/LAMA/ICS	1.56019	1.39617	1.74349	<.0001
	No trial medication (in last 3 months	.	.	.	.
Any history (ever) of Depression	Present	1.07741	1.00548	1.15449	0.0344
	Absent	.	.	.	.

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Anxiety	Present	1.20552	1.11921	1.29849	<.0001
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.05647	0.99383	1.12307	0.0782
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.18102	1.09275	1.27643	<.0001
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.1647	1.08982	1.24471	<.0001
	Absent	.	.	.	.
MRC Dyspnoea Score	2	1.25549	1.11639	1.41192	0.0001
	3	1.43764	1.27606	1.61968	<.0001
	4	1.59595	1.4075	1.80963	<.0001
	5 (most breathlessness)	1.83125	1.55078	2.16244	<.0001
	1 (least breathlessness)	.	.	.	.
Influenza Vaccine	Present	1.03338	0.93494	1.14219	0.5203
	Absent	.	.	.	.
FEV1 %		0.82627	0.79521	0.85854	<.0001
FEV1 % Squared		1.025	1.00291	1.04757	0.0263
FEV1/FVC (%)		0.94147	0.90818	0.97598	0.0010
FEV1/FVC (%) squared		1.00911	0.98669	1.03203	0.4289
Smoking	Ex	1.48187	1.29716	1.69289	<.0001
	Current	1.65074	1.43552	1.89823	<.0001
	Never Smoked	.	.	.	.

Table 102.1: Distribution of random coefficients for the period variable in fully adjusted multilevel Poisson model - Outcome = number of contacts with primary care

Variable	CPRD_xGM_IC_2.5_percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Coefficient	0.90367	1.00002	1.10990	1.00686	57.0556	0
Before/during trial rate ratio*	0.96824	1.07148	1.18921	1.07880	57.0556	0

* Denotes the combined effect of the random coefficient and fixed effect

Table 102.2: Distribution of random intercepts at the LAR level in fully adjusted multilevel Poisson model - Outcome = number of contacts with primary care

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.82308	0.99526	1.34805	1.95712	100	1

Table 103: Fixed effects for fully adjusted multilevel Poisson model - Outcome = number of contacts with primary care

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
(Intercept)		0.03987	0.03753	0.04235	<.0001
Period fixed effect	Year of trial	1.07145	1.05863	1.08442	<.0001
Sex	Female	0.99024	0.97452	1.00621	0.2295
	Male	.	.	.	.
Age		1.09417	1.08459	1.10384	<.0001
Age Squared	Female	1.02152	1.0152	1.02789	<.0001
SES	4	0.99646	0.97059	1.02302	0.7917
	3	0.99871	0.97165	1.02653	0.9268
	2	1.02565	0.99745	1.05465	0.0750
	1 (most deprived)	1.02054	0.99028	1.05172	0.1855
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	0.98918	0.92394	1.05903	0.7546
	LAMA only	1.0276	0.99154	1.06498	0.1352
	ICS only	0.93878	0.89817	0.98123	0.0051
	LABA/LAMA	0.93121	0.86036	1.0079	0.0776
	LAMA/ICS	0.9551	0.89424	1.02009	0.1714
	LABA/ICS	0.98188	0.95406	1.01052	0.2125
	LABA/LAMA/ICS	1.00441	0.97714	1.03245	0.7539
	No trial medication (in last 3 months	.	.	.	.
Any history (ever) of Depression	Present	1.15202	1.13046	1.174	<.0001
	Absent	.	.	.	.

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Anxiety	Present	1.10204	1.07933	1.12523	<.0001
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.01964	1.00295	1.03661	0.0209
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.16728	1.14224	1.19288	<.0001
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.13819	1.1176	1.15915	<.0001
	Absent	.	.	.	.
MRC Dyspnoea Score	2	1.09192	1.06173	1.12296	<.0001
	3	1.23917	1.20362	1.27577	<.0001
	4	1.32143	1.28061	1.36355	<.0001
	5 (most breathlessness)	1.49242	1.42718	1.56063	<.0001
	1 (least breathlessness)	.	.	.	.
Influenza Vaccine	Present	1.10793	1.07872	1.13794	<.0001
	Absent	.	.	.	.
FEV1 %		0.99201	0.98163	1.00251	0.1354
FEV1 % Squared		0.99835	0.99278	1.00396	0.5636
FEV1/FVC (%)		1.04667	1.03635	1.0571	<.0001
FEV1/FVC (%) squared		0.99885	0.99269	1.00504	0.7141
Smoking	Ex	1.01417	0.98374	1.04555	0.3654
	Current	0.98012	0.94852	1.01278	0.2299
	Never Smoked	.	.	.	.

Table 104.1: Distribution of random coefficients for the period variable in fully adjusted multilevel Poisson model - Outcome = count of COPD trial related prescription items

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Coefficient	0.93740	1.00732	1.05946	0.61687	0	1
Before/during trial rate ratio*	0.95441	1.02560	1.07868	0.62806	0	1

* Denotes the combined effect of the random coefficient and fixed effect

Table 104.2: Distribution of random intercepts at the LAR level in fully adjusted multilevel Poisson model - Outcome = count of COPD trial related prescription items

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.79491	1.01692	1.28704	2.26545	100	1

Table 105: Fixed effects for fully adjusted multilevel Poisson model - Outcome = count of COPD trial related prescription items

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
(Intercept)		0.00804	0.00753	0.00859	<.0001
Period fixed effect	Year of trial	1.01814	1.00477	1.03169	0.0077
Sex	Female	1.022	1.00543	1.03884	0.0091
	Male	.	.	.	.
Age		1.03072	1.02143	1.0401	<.0001
Age Squared	Female	0.98559	0.97928	0.99195	<.0001
SES	4	1.08374	1.05497	1.1133	<.0001
	3	1.09698	1.06654	1.12828	<.0001
	2	1.10823	1.07703	1.14033	<.0001
	1 (most deprived)	1.15331	1.11829	1.18944	<.0001
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.73325	1.61196	1.86366	<.0001
	LAMA only	1.99454	1.91831	2.07379	<.0001
	ICS only	1.46612	1.39689	1.53878	<.0001
	LABA/LAMA	3.30639	3.05337	3.58037	<.0001
	LAMA/ICS	3.15241	2.94866	3.37025	<.0001
	LABA/ICS	1.9158	1.85514	1.97843	<.0001
	LABA/LAMA/ICS	3.51081	3.40443	3.62051	<.0001
	No trial medication (in last 3 months	.	.	.	.
Any history (ever) of Depression	Present	1.0148	0.99535	1.03463	0.1368
	Absent	.	.	.	.

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Anxiety	Present	1.01241	0.99101	1.03427	0.2579
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.06918	1.05128	1.08739	<.0001
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	0.99671	0.97477	1.01915	0.7718
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	0.9922	0.9738	1.01095	0.4123
	Absent	.	.	.	.
MRC Dyspnoea Score	2	1.07378	1.04309	1.10539	<.0001
	3	1.13569	1.10208	1.17033	<.0001
	4	1.12795	1.09208	1.165	<.0001
	5 (most breathlessness)	1.15583	1.10399	1.21009	<.0001
	1 (least breathlessness)	.	.	.	.
Influenza Vaccine	Present	1.12832	1.0976	1.1599	<.0001
	Absent	.	.	.	.
FEV1 %		0.97254	0.96215	0.98303	<.0001
FEV1 % Squared		1.01185	1.00609	1.01764	<.0001
FEV1/FVC (%)		0.96584	0.95613	0.97565	<.0001
FEV1/FVC (%) squared		1.00978	1.00344	1.01616	0.0025
Smoking	Ex	1.04014	1.00775	1.07358	0.0148
	Current	1.05136	1.01628	1.08766	0.0038
	Never Smoked	.	.	.	.

Table 106.1: Distribution of random coefficients for the period variable in fully adjusted multilevel logistic model - Outcome = any treatment switch throughout follow up

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Coefficient	0.96559	1.00303	1.04723	0.94570	0.27309	1
Before/during trial rate ratio*	0.60240	0.62576	0.65334	0.58999	0.27309	1

* Denotes the combined effect of the random coefficient and fixed effect

Table 106.2: Distribution of random intercepts at the LAR level in fully adjusted multilevel logistic model - Outcome = any treatment switch throughout follow up

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.67960	1.02940	1.54229	0.75315	5.88388	0

Table 107: Fixed effects for fully adjusted multilevel logistic model - Outcome = any treatment switch throughout follow up

Parameter	Category	Odds Ratio	OR_LowerCL	OR_UpperCL	P
(Intercept)		4.21909	3.30961	5.37849	<.0001
Period fixedeffect	Year of trial	0.62387	0.58973	0.65998	<.0001
Sex	Female	0.88426	0.82928	0.94288	0.0002
	Male	.	.	.	.
Age		0.95007	0.91706	0.98426	0.0045
Age Squared	Female	1.07528	1.04872	1.10251	<.0001
SES	4	0.92294	0.8315	1.02443	0.1319
	3	0.91788	0.82333	1.02329	0.1224
	2	0.94787	0.8497	1.05739	0.3372
	1 (most deprived)	0.89035	0.79183	1.00113	0.0523
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	0.17681	0.13443	0.23255	<.0001
	LAMA only	0.227	0.19392	0.26573	<.0001
	ICS only	0.18074	0.14996	0.21783	<.0001
	LABA/LAMA	0.17561	0.1281	0.24074	<.0001
	LAMA/ICS	0.16286	0.12492	0.21232	<.0001
	LABA/ICS	0.08161	0.07105	0.09374	<.0001
	LABA/LAMA/ICS	0.04478	0.03892	0.05152	<.0001
	No trial medication (in last 3 months	.	.	.	.
Any history (ever) of Depression	Present	1.08626	1.00677	1.17203	0.0328

Parameter	Category	Odds Ratio	OR_LowerCL	OR_UpperCL	P
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.12833	1.03775	1.22682	0.0047
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	0.84552	0.79136	0.90338	<.0001
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.0943	1.00223	1.19483	0.0445
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.04399	0.97026	1.12333	0.2493
	Absent	.	.	.	.
MRC Dyspnoea Score	2	1.08978	0.9752	1.21783	0.1293
	3	1.14316	1.0183	1.28334	0.0234
	4	1.27888	1.12833	1.44953	0.0001
	5 (most breathlessness)	1.25627	1.04816	1.5057	0.0135
	1 (least breathlessness)	.	.	.	.
Influenza Vaccine	Present	0.74288	0.66751	0.82676	<.0001
	Absent	.	.	.	.
FEV1 %		1.0277	0.98508	1.07218	0.2061
FEV1 % Squared		0.96469	0.94307	0.9868	0.0019
FEV1/FVC (%)		1.06895	1.02722	1.11237	0.0010
FEV1/FVC (%) squared		0.95851	0.93481	0.98281	0.0009
Smoking	Ex	0.98488	0.87147	1.11304	0.8071

Parameter	Category	Odds Ratio	OR_LowerCL	OR_UpperCL	P
	Current	0.95406	0.83661	1.088	0.4829
	Never Smoked	.	.	.	.

6 Sensitivity Analyses for Primary Objective 1/Primary Objective 2 Using Complete Cases Only

6.1 PO1/PO2: CPRD Primary+Secondary Care Data vs. SLS-Database

Table 108: Repeat of Table 15 using complete case dataset

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.92048	1.00096	1.12738	0.98495	35.2937	0

Table 109: Repeat of Table 16 using complete case data

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	1.11922	1.07675	1.16337	<.0001
	Male	1	.	.	.
Age	.	0.99824	0.9769	1.02005	0.8730
Age Squared	.	0.99391	0.97896	1.00908	0.4293
SES IMD 2010 Quintiles	4	1.06979	0.99861	1.14605	0.0548
	3	1.06069	0.9888	1.13781	0.0999
	2	1.08753	1.01566	1.1645	0.0162
	1 (most deprived)	1.12618	1.05043	1.20739	0.0008
	5 (least deprived)	1	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.23361	1.04112	1.46169	0.0153
	LAMA only	1.05091	0.95488	1.15659	0.3098
	ICS only	0.95308	0.83406	1.08908	0.4801
	LABA/LAMA	0.96358	0.78403	1.18425	0.7243
	LAMA/ICS	1.01339	0.85409	1.2024	0.8789
	LABA/ICS	1.09169	1.00912	1.18101	0.0288
	LABA/LAMA/ICS	1.21552	1.12946	1.30814	<.0001
	No treatment	1	.	.	.
Any history (ever) of Depression	Present	1.03215	0.98658	1.07982	0.1696
	Absent	1	.	.	.

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Anxiety	Present	1.03643	0.9869	1.08844	0.1521
	Absent	1	.	.	.
Any history (ever) of Asthma	Present	1.06048	1.01947	1.10314	0.0035
	Absent	1	.	.	.
Any history (ever) of Pneumonia	Present	1.01696	0.96587	1.07076	0.5224
	Absent	1	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.05386	1.00943	1.10023	0.0170
	Absent	1	.	.	.
COPD Exacerbation History in previous 12 months	.	1.71676	1.67582	1.7587	<.0001
COPD Exacerbation History in previous 12 months Squared	.	0.95244	0.94522	0.95972	<.0001
FEV1%	.	0.92433	0.90153	0.9477	<.0001
FEV1% Squared	.	1.01545	1.0021	1.02897	0.0231
FEV1/FVC (%)	.	0.95117	0.92794	0.97499	<.0001

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
FEV1/FVC (%) squared	.	1.01305	1.0053	1.02085	0.0009
MRC Dyspnoea score	2	1.08613	1.00615	1.17247	0.0343
	3	1.18419	1.09551	1.28005	<.0001
	4	1.24956	1.1508	1.35679	<.0001
	5 (most breathlessness)	1.38417	1.23878	1.54661	<.0001
	1 (least breathlessness)	1	.	.	.
Smoking	Ex	1.06346	0.97546	1.1594	0.1626
	Current	1.17336	1.07208	1.2842	0.0005
	Never	1	.	.	.
Influenza Vaccine	Present	1.04028	0.97009	1.11555	0.2678
	Absent	1	.	.	.

Table 110: Repeat of Table 17 using complete case data

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.91584	0.99728	1.10566	1.06178	88.0252	0

Table 111: Repeat of Table 18 using complete case data

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Sex	Female	1.10961	1.05954	1.16205	<.0001
	Male	.	.	.	.
Age		1.00237	0.97704	1.02836	0.8562
Age Squared		0.9897	0.97202	1.00771	0.2606
SES IMD 2010 Quintiles	4	1.04802	0.96678	1.1361	0.2546
	3	1.04116	0.95897	1.13039	0.3364
	2	1.09731	1.01275	1.18893	0.0232
	1 (most deprived)	1.11264	1.02495	1.20782	0.0108
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.2796	1.05609	1.55041	0.0118
	LAMA only	0.99897	0.89474	1.11534	0.9854
	ICS only	0.9239	0.79604	1.07231	0.2977
	LABA/LAMA	0.94976	0.74967	1.20326	0.6694
	LAMA/ICS	0.9878	0.81175	1.20202	0.9024
	LABA/ICS	1.0242	0.93527	1.12157	0.6059
	LABA/LAMA/ICS	1.1575	1.06312	1.26025	0.0008
	No trial medication (in last 3 months)	.	.	.	.

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Depression	Present	1.01791	0.96416	1.07465	0.5213
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.02659	0.96745	1.08934	0.3860
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.08248	1.03268	1.13468	0.0010
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.02805	0.9659	1.09419	0.3846
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.06502	1.01128	1.12161	0.0171
	Absent	.	.	.	.
COPD Exacerbation History in previous 12 months		1.69711	1.64736	1.74836	<.0001
COPD Exacerbation History in previous 12 months Squared		0.95699	0.94594	0.96817	<.0001
FEV1%		0.93021	0.90243	0.95885	<.0001

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
FEV1% Squared		1.01097	0.99531	1.02688	0.1707
FEV1/FVC (%)		0.9589	0.93048	0.9882	0.0063
FEV1/FVC (%) squared		1.01255	1.00323	1.02196	0.0082
MRC Dyspnoea score	2	1.07293	0.98355	1.17043	0.1127
	3	1.14616	1.04814	1.25334	0.0028
	4	1.22314	1.11202	1.34537	<.0001
	5 (most breathlessness)	1.28711	1.12551	1.47191	0.0002
	1 (least breathlessness)	.	.	.	.
Smoking	Ex	1.05547	0.95532	1.16612	0.2885
	Current	1.16137	1.04568	1.28987	0.0052
	Never Smoked	.	.	.	.
Influenza Vaccine	Present	1.08275	0.9956	1.17751	0.0633
	Absent	.	.	.	.

6.2 PO1/PO2: CPRD Primary Care Data vs. SLS-EHR (Complete case data only)

Table 112: Repeat of Table 33 using complete case data

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.91402	0.99680	1.13393	1.10685	94.0563	0

Table 113: Repeat of Table 34 using complete case data

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Sex	Female	1.11606	1.07226	1.16165	<.0001
	Male	1	.	.	.
Age	.	0.96493	0.94333	0.98703	0.0020
Age Squared	.	0.98237	0.96682	0.99816	0.0288
SES IMD 2010 Quintiles	4	1.0766	1.00275	1.1559	0.0418
	3	1.07755	1.0022	1.15857	0.0435
	2	1.08338	1.00918	1.16303	0.0269
	1 (most deprived)	1.11816	1.04017	1.202	0.0025
	5 (least deprived)	1	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.20988	1.01605	1.44069	0.0325
	LAMA only	1.0422	0.94366	1.15102	0.4147
	ICS only	0.92586	0.8055	1.0642	0.2783
	LABA/LAMA	0.92565	0.74387	1.15186	0.4886
	LAMA/ICS	1.02546	0.86183	1.22015	0.7768
	LABA/ICS	1.08018	0.99574	1.17179	0.0633
	LABA/LAMA/ICS	1.21652	1.12721	1.31291	<.0001
	No treatment	1	.	.	.
Any history (ever) of Depression	Present	1.02734	0.98048	1.07644	0.2575
	Absent	1	.	.	.

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
Any history (ever) of Anxiety	Present	1.05444	1.00247	1.1091	0.0398
	Absent	1	.	.	.
Any history (ever) of Asthma	Present	1.08104	1.0377	1.12619	0.0002
	Absent	1	.	.	.
Any history (ever) of Pneumonia	Present	1.03258	0.97857	1.08958	0.2421
	Absent	1	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.06782	1.02148	1.11626	0.0038
	Absent	1	.	.	.
COPD Exacerbation History in previous 12 months	.	59755.4	34001.3	105017	<.0001
COPD Exacerbation History in previous 12 months Squared	.	4.38E-7	8.72E-8	2.2E-6	<.0001
FEV1%	.	0.93094	0.90718	0.95533	<.0001
FEV1% Squared	.	1.01385	0.99997	1.02791	0.0505
FEV1/FVC (%)	.	0.9519	0.92787	0.97656	0.0002

Parameter	Category	RelativeRate	RR_LowerCL	RR_UpperCL	P
FEV1/FVC (%) squared	.	1.01343	1.00539	1.02153	0.0010
MRC Dyspnoea score	2	1.07249	0.99275	1.15864	0.0758
	3	1.14272	1.05604	1.23651	0.0009
	4	1.2014	1.10482	1.30642	<.0001
	5 (most breathlessness)	1.25286	1.11543	1.40724	0.0001
	1 (least breathlessness)	1	.	.	.
Smoking	Ex	1.06332	0.9722	1.16297	0.1792
	Current	1.15469	1.05151	1.26799	0.0026
	Never	1	.	.	.
Influenza Vaccine	Present	1.05036	0.97703	1.12921	0.1833
	Absent	1	.	.	.

Table 114: Repeat of Table 35 using complete case data

Variable	CPRD_xGM_IC_2.5_ percentile	CPRD_xGM_IC_median	CPRD_xGM_IC_97.5_ percentile	SLS_UC_value	SLS_UC_percentile	Unusual_Flag
Random Intercept	0.91720	0.99559	1.12616	1.10416	94.0061	0

Table 115: Repeat of Table 36 using complete case data

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Sex	Female	1.11236	1.06103	1.16616	<.0001
	Male	.	.	.	.
Age		0.97505	0.94953	1.00127	0.0620
Age Squared		0.98063	0.96246	0.99915	0.0405
SES IMD 2010 Quintiles	4	1.06314	0.97885	1.15469	0.1463
	3	1.05604	0.97067	1.14893	0.2049
	2	1.09064	1.0043	1.18441	0.0392
	1 (most deprived)	1.0946	1.00589	1.19114	0.0361
	5 (least deprived)	.	.	.	.
Current Medication (prescriptions in last 3 months)	LABA only	1.20835	0.99189	1.47205	0.0602
	LAMA only	0.9936	0.88713	1.11284	0.9116
	ICS only	0.88635	0.75976	1.03405	0.1250
	LABA/LAMA	0.89623	0.69877	1.1495	0.3883
	LAMA/ICS	1.07572	0.88379	1.30933	0.4667
	LABA/ICS	1.02266	0.93173	1.12246	0.6372
	LABA/LAMA/ICS	1.17038	1.07236	1.27735	0.0004
	No trial medication (in last 3 months)	.	.	.	.

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
Any history (ever) of Depression	Present	1.02029	0.96525	1.07846	0.4778
	Absent	.	.	.	.
Any history (ever) of Anxiety	Present	1.04086	0.97958	1.10598	0.1958
	Absent	.	.	.	.
Any history (ever) of Asthma	Present	1.10865	1.05633	1.16356	<.0001
	Absent	.	.	.	.
Any history (ever) of Pneumonia	Present	1.02279	0.95887	1.09098	0.4937
	Absent	.	.	.	.
Any history (ever) of Gastro-oesophageal reflux disease / peptic ulcer disease (GORD / PUD)	Present	1.07062	1.01551	1.12873	0.0114
	Absent	.	.	.	.
COPD Exacerbation History in previous 12 months		76422.6	39121.8	149288	<.0001
COPD Exacerbation History in previous 12 months Squared		2.27E-7	3.15E-8	1.64E-6	<.0001
FEV1%		0.93838	0.90981	0.96786	<.0001

Parameter	Category	HazardRatio	HR_LowerCL	HR_UpperCL	P
FEV1% Squared		1.01157	0.99557	1.02783	0.1574
FEV1/FVC (%)		0.96057	0.93156	0.99048	0.0101
FEV1/FVC (%) squared		1.01354	1.004	1.02317	0.0053
MRC Dyspnoea score	2	1.05486	0.96633	1.1515	0.2324
	3	1.10294	1.00757	1.20732	0.0337
	4	1.1672	1.05964	1.28569	0.0017
	5 (most breathlessness)	1.16062	1.00915	1.33484	0.0368
	1 (least breathlessness)	.	.	.	.
Smoking	Ex	1.05911	0.95639	1.17285	0.2699
	Current	1.17374	1.05432	1.30669	0.0034
	Never Smoked	.	.	.	.
Influenza Vaccine	Present	1.0922	1.00208	1.19043	0.0447
	Absent	.	.	.	.

7 Summary of Missing Data

The table in this section cover proportion of missing data in variables from SLS-Database compared to the SLS-EHR.

Table 116: Missingness Figures for SLS EHR data

Variable	SLS-database Missingness	SLS EHR Missingness
Sex	0 (0%)	1391 (99.14%)
Age	0 (0%)	1,347 (96.01%)
BMI	281 (20.03%)	967 (68.92%)
FEV	302 (21.53%)	29 (2.07%)

TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	PRJ2282 / 201491: CHESS: CPRD-COPD Hawthorne Effect Study in Salford: A UK cohort study to characterise patients enrolled in the Salford Lung Study and to evaluate a potential Hawthorne effect

Compound Number:	GW685698 / GW642444
Development Phase	IV
Effective Date:	23 October 2015
Subject:	COPD in the UK general population and comparison with the Salford Lung Study
Author(s):	**University of Manchester:** PPD **GlaxoSmithKline:** PPD **Clinical Practice Research Datalink:** PPD

TABLE OF CONTENTS

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1. LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
CHESS	CPRD-COPD Hawthorne Effect Study in Salford
CPRD	Clinical Practice Research Datalink
COPD	Chronic Obstructive Pulmonary Disease
EHR	Electronic Health Record
EMR	Electronic Medical Record
FEV1	Forced expiratory volume in 1 second
FF	Fluticasone furoate
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPRD	General Practice Research Database
GP	General Practitioner
GSK	GlaxoSmithKline
HCU	Health Care Utilisation
HES	Hospital Episode Statistics
ICS	Inhaled Corticosteroid
ISAC	CPRD Independent Scientific Advisory Committee
LABA	Long Acting Bronchodilator
LAMA	Long Acting Muscarinic Antagonist
MHRA	Medicines and Healthcare Products Regulatory Agency
MPR	Medication Possession Ratio
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NWeH	North West eHealth
ONS	Office for National Statistics
PDC	Percent Days Covered
SAS	Statistical Analysis System
SES	Socio-Economic Status
SIR	Salford Integrated Record
SLS	Salford Lung Study
SOC	Standard of Care

SOP	Standard Operating Procedure
UoM	University of Manchester
VI	Vilanterol

Trademark Information

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2. RESPONSIBLE PARTIES

The study will be led by University of Manchester (UoM) who will collaborate with North West eHealth (NWeH), Clinical Practice Research Datalink (CPRD) and GSK.

Study Task	Responsible group(s)
Protocol finalization	UoM
Develop specifications for data sets	UoM, GSK, CPRD, NWeH
Data extraction for SLS Standard of Care arm	NWeH
Creation of CPRD cohort dataset	UoM, CPRD
Analyses (using SAS) comparing SLS and CPRD	UoM
QC/QA of analysis	GSK (Observational Data Analytics)
Final study report	Drafting: UoM Review, comment, and edits: Scientific Committee Reporting to regulatory agency and web-based register: GSK
Manuscripts	Drafting: medical writer Review and edits: study team, scientific committee members

A Scientific Committee (see section below) will be assembled and will be required to review and input into study design and major study documents (final study protocol, final research analysis plan, final study report, peer-review publications).

WWEpi Project number: PRJ2282

SPONSOR SIGNATORY:

PPD

23rd Oct 2015

Jeanne M. Pimenta
Primary Author / Project officer

Date

PPD

7th December, 2015

Kourtney J. Davis
Therapy Area Leader (Respiratory), Worldwide Epidemiology)

Date

PPD

2nd Nov 2015

Andrew W. Roddam
Vice President, Worldwide Epidemiology

Date

CONFIDENTIAL

WWEpi Project number: PRJ2282

SPONSOR INFORMATION PAGE

WWEpi Project Identifier:

PRJ2282

eTrack Project Identifier:

201491

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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.

Investigator Name: **Matthew Sperrin**

PPD

23/10/15

Investigator Signature

Date

STUDY SCIENTIFIC COMMITTEE

External Members:

PPD

Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

PPD

Clinical Professor in Public Health Informatics, Health eResearch Centre, Farr Institute for Health Informatics Research, University of Manchester

PPD

Professor of Health eResearch, Health eResearch Centre, Farr Institute for Health Informatics Research, University of Manchester

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Chief Clinical Officer, North West eHealth, Salford Royal Hospital

PPD

Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine

PPD

Professor, Consultant in Respiratory Medicine, Department of Public Health, Section of Social Medicine, University of Copenhagen

PPD

Research Statistician, Clinical Practice Research Datalink

PPD

Head of Research, Clinical Practice Research Datalink

GSK Members:

PPD

Senior Director, Worldwide Epidemiology, Respiratory Therapeutic Area Lead, Worldwide Epidemiology GlaxoSmithKline

PPD

Global Medical Advisory Lead, Respiratory Franchise, GlaxoSmithKline

PPD

Director, Clinical Statistics, GlaxoSmithKline

3. ABSTRACT

Background: The Salford Lung Study (SLS) is a unique Phase IIIB pragmatic trial evaluating the effectiveness of a novel medicine – RELVAR (fluticasone furoate [FF], GW685698) and vilanterol [VI] GW642444) – compared with standard of care (SOC) among patients with Chronic Obstructive Pulmonary Disease (COPD). The trial is taking place in Salford, England. While the pragmatic nature of the trial is designed to test effectiveness in routine care, there are at least two possible concerns: 1) Salford may not be representative of the wider population in which the medicine may be used, and 2) there may be differences in local practice or changes to local practice caused by the study (the Hawthorne effect), which may artificially inflate the benefits of both RELVAR and SOC.

Objectives: The aim of the study is to evaluate the representativeness of Salford, and the potential Hawthorne effect, to place the SLS in wider context. The objectives are:

Co-primary objectives:

- **PO1**: To characterize the patients enrolled in the Standard of Care (SOC) arm of SLS COPD compared with the UK population of COPD patients (using the Clinical Practice Research Datalink (CPRD)), including distribution of SES/deprivation level, to evaluate the extent to which the SLS participants are representative of the UK patient population targeted for RELVAR. The comparator set will be specified on two bases: firstly, overall, and secondly, the subset fulfilling the protocol inclusion/exclusion criteria.

- **PO2**: To compare the rate of COPD exacerbation over the 12 months in Standard of Care arm of the SLS compared with the Standard of Care (SOC) recorded in the CPRD, in order to detect a potential Hawthorne effect.

- **PO3**: To compare the rate of serious pneumonia (defined by hospitalisation) over the 12 months in Standard of Care arm of the SLS compared with the Standard of Care recorded in the CPRD.

Secondary objectives:

- **SO1**: To make comparisons between the SLS SOC and the CPRD cohort on the following health care utilisation (HCU) endpoints: GP visits, hospital admissions, mortality and adherence.

- **SO2**: To evaluate other definitions of COPD exacerbations in SOC from CPRD.
.

- **SO3**: Self-controlled comparison of COPD and HCU endpoints in Salford before and after SLS commenced, using data from the SLS.

Study Design: Observational COPD cohort study, comparing Salford, UK (data source: SLS) with rest of UK (data source: CPRD) over a 12 month period.

Population: The setting is Salford, UK compared with rest of UK. The study population is, in Salford, participants recruited to the SLS and randomised to the SOC arm. In the rest of the UK, the comparison group is persons with COPD recorded in the CPRD who meet the eligibility criteria of the SLS.

Study Size: The target sample size for the SLS is 2,800. Study size in the CPRD will be based on the prevalence of COPD diagnosis codes; this will be a minimum 2,800 to match but is expected to be considerably larger (x5-10).

Analysis: Data analysis will use descriptive statistics for PO1. PO2 and PO3 will be addressed using multilevel modelling.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Deliverable	Timelines
Contract signed	November, 2014
Agreed Protocol for GSK protocol-review forum	November, 2014†
Completion of Statistical analyses plan. Development of programs for analyses.	November 2014 – 1st October 2015
"Data look" SLS data and CPRD data to UoM (Interim 1).	Jan 2016
Analyses of primary objectives (PO1 only) on subset of data using "data look" data (start working on PO2/3)	Feb-March 2016
Final SLS data (one year FU for all subjects) to UoM	1st-8th April 2016
Analyses of PO2 (COPD exacerbation data) using final SLS data: First report with P01/P02 to GSK	By 29th April 2016
Share output from Primary Objectives with SLS Scientific Committee; and CHESS Steering Committee	9-10th May 2016†
First manuscript developed and ready for submission with SLS paper to Thorax based PO1 and PO2 data	June-July 2016†
Programming for secondary objectives and PO3	May-October 2016
100% CPRD-HES data available to UoM (required for PO3 analyses).	Estimated at October 2016
Analysis for PO3 and draft tables circulated	November 2016
Draft complete study report with PO1/PO2/PO3 to GSK	December 2016†
Regulatory reporting of PO3	Q1 2017
Final follow-up manuscript	Q1-2 2017†

† Milestone payment

6. RATIONALE AND BACKGROUND

6.1. Background

Chronic Obstructive Pulmonary Disease (COPD) is a chronic obstructive disease of the airways associated with a significant social and healthcare burden [1, 2, 3]. Most patients with COPD are managed in primary care, as reflected in recent UK guidelines, which are specifically targeted at primary care physicians [4]. The major goals of treatment are to relieve symptoms, improve activity/exercise tolerance, prevent and treat exacerbations, reduce mortality risk and improve health status. However, despite such guidelines, COPD remains under-diagnosed and under-treated; variations in treatments, standards of care and adherence to guidelines have been reported across different geographical regions [2, 5, 6, 7, 8].

Large computerised patient databases provide a useful source of real life observational data, and the General Practice Research Database (GPRD) has been successfully used to generate descriptive epidemiology data in COPD [9, 10, 11, 12] from a large group of UK primary care practices. Historically, the limitations of the GPRD were a time gap between data capture and availability for the researcher and limited links to other healthcare databases, although these are currently being addressed with the development of the Clinical Practice Research Datalink (CPRD) and in recent Phase 4 pragmatic clinical trials [12]. The use of electronic medical record (EMR) data in health research is a key objective in the Department of Health's national research strategy [13].

The Salford Lung Study (SLS) is an ongoing Ph IIIB pragmatic trial comparing a new once daily ICS/LABA fixed dose combination (RELVAR: fluticasone furorate + vilanterol) in which patients are identified by EMR, enrolled in their GP office, randomized to RELVAR or Standard of Care (SOC) maintenance therapy and followed for safety and effectiveness via linked primary care/secondary routine care with primary endpoint of COPD moderate/severe exacerbations over 12 months [14]. MHRA and NICE provided joint advice for the SLS protocol and were supportive of the design to generate "real world" evidence which will demonstrate the value and safety of the medicine against the most relevant standard of care.

6.2. Rationale

Although the SLS will give evidence on the relative effectiveness of RELVAR compared with SOC, the SOC may be prone to the Hawthorne effect, which may distort the effect size.

The Hawthorne effect (also referred to as the observer effect) is a type of reactivity in which individuals improve or modify an aspect of their behaviour in response to their awareness of being observed. The original "Hawthorne effect" studies at the Hawthorne Works in Chicago, USA between 1924 and 1933 suggested that the novelty of being research subjects and the increased attention from such could lead to temporary increases in workers' productivity [15].

In the situation of this study, a potential Hawthorne effect may be a result of potentially different behaviours and decision making of GPs and nurses in their practices of caring for patients with COPD during the SLS study period.

Salford may not be representative of general UK population; hence the prognostic profiles, and potential effect of RELVAR in terms of the outcomes may differ in the general target COPD population compared with Salford.

Both of these issues mean that extrapolation of the results of the SLS to the wider UK population would be subject to major caveats. This proposal aims to explore, and assess how severe the caveats need to be.

7. RESEARCH QUESTION AND OBJECTIVE(S)

Co-primary objectives:

PO1: To characterize the patients enrolled in the Standard of Care (SOC) arm of the SLS compared with the UK population of COPD patients (using the Clinical Practice Research Datalink (CPRD)), including distribution of SES/deprivation level, to evaluate the extent to which the SLS participants are representative of the UK patient population targeted for RELVAR. The comparator set will be specified on two bases: firstly, overall, and secondly, the subset fulfilling the protocol inclusion/exclusion criteria.

PO2: To compare the rate of COPD exacerbation over the 12 months in Standard of Care arm of the SLS compared with the Standard of Care (SOC) recorded in the CPRD, in order to detect a potential Hawthorne effect or other differences.

PO3: To compare the rate of serious pneumonia (defined by hospitalisation) over the 12 months in Standard of Care arm of the SLS compared with the Standard of Care recorded in the CPRD.

Secondary objectives:

SO1: To make comparisons between the SLS Standard of Care and the CPRD cohort on the following health care utilisation (HCU) endpoints: GP visits, hospital admissions mortality and adherence.

SO2: To evaluate other definitions of COPD exacerbation in SOC from CPRD.

SO3: Self-controlled comparison of COPD and other HCU endpoints in Salford before and after SLS commenced.

8. RESEARCH METHODS

8.1. Study Design

This will be an observational COPD cohort study that will utilize the CPRD and the Salford EHR system – to compare selected cohorts with SLS.

For SLS, reference/index date is study entry. This will be matched in CPRD by the following algorithm:

1. Draw up a long-list of potentially eligible individuals in CPRD (patients who would be eligible at some point during the SLS recruitment phase).
2. For each individual:
    a. Randomly sample an entry date from full list of SLS entry dates.
    b. If patient is eligible at that entry date, then they will be included, accounting for relevant immortal time biases up to that entry date, otherwise, they will be excluded. Further details on methods of reducing immortal time bias (i.e left truncated at the entry date and survival modelling) will be outlined in the SAP.

First, the COPD populations in both Salford and in the wider CPRD (excluding Greater Manchester area) will be compared. Second, we will focus on comparisons between all patients enrolled in the SLS SOC arm versus a CPRD cohort that would have been eligible for SLS as per the inclusion and exclusion criteria.

8.2. Setting

In terms of geography, Salford, UK, and surrounding areas within Greater Manchester, for the SLS group; UK-wide, excluding Greater Manchester, for the CPRD group. In terms of health settings, general practice – restricted to practices in Salford and to practices that contribute to CPRD (~10%).

8.2.1. Inclusion Criteria

Two cohorts will be produced. First, a CPRD cohort, using linked primary care, medication, Hospital Episode Statistics, and socio-economic data, according to the following inclusion criteria:

1. Diagnosis of COPD before index date (time period will be defined in the SAP)
2. Aged ≥40 at index date.
3. Alive, and registered with a GP, at index date.
4. Not registered with a GP in the Greater Manchester area.

Second, a Salford cohort will be constructed using the Salford Integrated Record (SIR), according to the inclusion criteria:

1. Diagnosis of COPD before index date.
2. Aged ≥40 at index date.

3. Alive, and registered with a GP, at index date.

Restricted cohorts will then be constructed in both the Salford and CPRD populations, based on the inclusion/exclusion criteria and study period for the SLS:

1. Patients with documented GP diagnosis of COPD, and currently receiving maintenance therapy
2. Male or female subjects aged ≥40 years of age at index date
3. Patients who have a history of treatment with systemic/oral corticosteroids, antibiotics (in association with GP contact) and/or hospitalisation for at least one COPD exacerbation in the 3 years prior to index date.
4. Current COPD Therapy

   All patients currently receiving either:

   - inhaled corticosteroid (ICS) alone or in combination with a long acting bronchodilator (this could be a fixed dose combination or an ICS/LABA provided in two separate inhalers, or ICS and LAMA),
   - or long-acting bronchodilator therapy alone (e.g. tiotropium or salmeterol, or the use of two bronchodilators i.e. LABA/LAMA),
   - or "triple therapy" i.e. ICS/LABA plus a Long Acting Muscarinic Antagonist (LAMA)

Finally, the third data source, the SLS, will be used as-is.

8.2.2. Exclusion Criteria

Subjects meeting any of the following criteria must not be included in the restricted cohorts:

1. Patients with any life threatening condition or uncontrolled/clinically significant disease (code list to be specified in the Study Analysis Plan)
2. Patients with unstable COPD: Patients with an exacerbation (defined by treatment with oral corticosteroids and/or antibiotic or hospital discharge listing COPD) with an onset within 2 weeks of index date. Delay index date until at least 2 weeks after the onset of an exacerbation and until the exacerbation has resolved.
3. Chronic user of oral corticosteroids: Subjects who are considered to be a chronic user of oral corticosteroids for respiratory or other indications (Algorithm to be specified in the Study Analysis Plan).
4. In the Salford population only, those patients who are entered in the SLS and randomised to the RELVAR arm.

8.3. Variables

8.3.1. Outcome definitions

Primary outcomes/endpoint:

- **Rate of COPD exacerbation:** The definition of a COPD exacerbation to be informed by the ongoing study being conducted by PPD et al. (collaborative project between London School of Hygiene and Tropical Medicine and GSK; GSK study number WEUSKOP5893).

  Moderate/severe COPD exacerbations will be identified using an algorithm combining GP visits, prescriptions for oral corticosteroids and/or antibiotics, or hospital admission, as defined using information from study WEUSKOP5893. Rate of exacerbation during the 12 month follow-up will be calculated and compared with the SLS rate in the standard of care arm; if technically possible, exacerbation rates for the 12 months prior to index date (matched enrolment date) would also be compared.

- **Pneumonia:** To be defined as per the codelist in Table 1 (see 13.1).

Secondary outcomes/endpoints:

- **Healthcare utilisation:** All GP visits/encounters and all hospital admissions during the 12 month study period.
- **Adherence to index prescription:** Defined as percent days covered (PDC) and medication possession ratio (MPR) will also be calculated for the matched cohort, as well as discontinuation, switching medicine or adding on other medicines, to be compared with the SLS SOC arm.
- **Deaths:** All cause, pneumonia death, COPD-attributed death during the 12 month follow-up. For the CPRD, deaths will be determined using Office of National Statistics (ONS) linked mortality data.
- **Other definitions of COPD exacerbation:** Other definitions will be described as per the outputs of study WEUSKOP5893.

8.3.2. Exposure definitions

This is a binary comparison of COPD patients enrolled in the SLS and COPD patients in the CPRD. Hence the primary exposure of interest is whether a patient is enrolled in SLS (yes/no). A third grouping, COPD patients in Salford (who are not in SLS) will also be examined.

8.3.3. Confounders and effect modifiers

- Sex
- Age
- Socio-economic status (SES)
- Current/SOC COPD Medication group:

- LAMA or LABA only
- LAMA+LABA
- LABA+ICS (combination product or two inhalers)
- LABA+ICS+LAMA

- Comorbidities
  - Cardio-and cerebrovascular diseases (heart failure, myocardial infarction, stroke)
  - Depression
  - Anxiety
  - Asthma
  - History of pneumonia
  - Gastro-oesophageal reflux and peptic ulcer disease
  - Diabetes
  - Charlson score (COPD will be removed from score)
- Markers of COPD severity
  - Previous COPD exacerbation
  - FEV1 % predicted
  - FEV1/FVC ratio
  - GOLD stage
  - MRC Dyspnoea score
- Comedications: major medication classes for each comorbidity of interest
- Smoking
- BMI
- Vaccinations
- Disability status

Further information on the definitions for the variables above will be provided in the SAP.

8.4. Data sources

The three main data sources are SLS, CPRD and SIR.

The Salford Lung Study (SLS) is described in [14]. In brief, it is a pragmatic trial, carried out in Salford, UK, to evaluate the relative effectiveness and safety of RELVAR compared with SOC. There are two separate studies within the SLS; one for COPD and the other for asthma. For this protocol, the SLS data refers to SLS for COPD only.

The CPRD is a primary care database consisting of a subset of GP practices across the UK. This will be linked to Hospital Episode Statistics (HES), socio-economic status (SES) and Office of National Statistics (ONS) datasets. For brevity, the linked dataset will henceforth be referred to as CPRD.

The SIR is a comprehensive primary and secondary care database detailing healthcare contacts, diagnostic tests and prescriptions of all patients registered with a GP in Salford, UK.

There are a range of subsets and derivations of the data sources that will be considered for this study, listed here for clarity.

CPRD: CPRD – all practices, all COPD patients

CPRD-GM: CPRD – practices/patients in Greater Manchester only, all COPD patients

CPRD-xGM: CPRD – excluding practices/patients in Greater Manchester, all COPD patients

CPRD-GM-IC: CPRD – practices/patients in Greater Manchester only, COPD patients meeting SLS inclusion criteria only

CPRD-xGM-IC: CPRD – excluding practices/patients in Greater Manchester, COPD patients meeting SLS inclusion criteria only

SLS-E: SLS – all eligible. Not all of these are enrolled (some decline)

SLS: SLS – all enrolled

SLS-SOC: SLS – SOC arm only

SIR: SIR – all COPD patients

SIR-IC: SIR - COPD patients meeting SLS inclusion criteria only

In the CPRD, data linkage will be subject to a lag due to the delayed availability of HES and ONS data. Fully linked data will only be available up to a certain date when analyses are undertaken, and as such, primary analyses will be restricted to include SLS enrolled patients up to that date. Subsequent analyses will be conducted once linkage is available for the entire recruitment period. As capture of events of serious pneumonia (as defined in the context of this study) is dependent on records of hospitalisation, PO3 will be analysed when fully linked CPRD-HES data are available.

8.5. Study size

The target sample size for the number of COPD patients enrolled in the SLS is 2,800. Study size in CPRD will be based on the prevalence of COPD diagnosis codes; this will be a minimum 2,800 to match but is expected to be considerably larger (x5-10).

8.6. Data management

8.6.1. Data handling conventions

Data handling within University of Manchester will be governed by the System Level Security Policy for the study (see Annex 1a). Quality control programming will be conducted by within GSK, following data handling SOPs.

8.6.2. Resourcing needs

Staff resources required for the project are outlined in section 2 (responsible parties).

8.6.3. Timings of Assessment during follow-up

As per SLS protocol for SLS patients. CPRD and SIR patients are observational only.

8.7. Data analysis

8.7.1. Essential analysis

All analyses will be conducted using SAS.

For PO1, distributions of the confounders and effect modifiers (as listed in Section 8.3.3) will be tabulated – summarised as proportions in each category for binary and categorical variables, and means/medians and standard deviations for continuous variables. Graphical visualisations will also be produced to aid interpretation (for example, boxplots to characterise age distributions in each population, stacked bar charts to visualise SES by population). This will be done for a series of the derived populations to separate out true differences in demographics in Salford and differences that arise as a consequence of data quality issues etc. The following comparisons will be of interest:

- CPRD-GM v CPRD-xGM: to give an indication of true demographic difference from the same data source.
- CPRD-GM-IC v CPRD-xGM-IC: as above, but restricted to patients meeting the inclusion criteria.
- SIR v CPRD-GM: to give an indication of differences arising as a consequence of selection bias of CPRD practices, and through data quality issues etc.
- SIR-IC v CPRD-GM-IC: as above, but restricted to patients meeting the inclusion criteria.
- SIR-IC v SLS-E: to give an indication of recruitment bias and physician researcher bias (at the approach stage).
- SIR-IC v SLS: to give an indication of recruitment bias (at recruitment stage).
- **SLS v CPRD-xGM-IC**: to indicate the difference between trial recruited, and those meeting the inclusion criteria outside of Salford. This is the key comparison for addressing PO1.

We will then move on to explicit modelling of regional variation of the characteristics within CPRD for the emboldened comparison (**SLS v CPRD-xGM-IC)** to ascertain whether the characteristics observed within Salford are unusual by comparison with CPRD-xGM-IC. We will take local authority regional level (anonymised) as the comparable unit to the study region for SLS. SLS will be considered unusual on a given demographic if an appropriately chosen summary statistic for that demographic (mean for continuous variables) falls outside the 2.5-97.5 percentile range.

For PO2, we will commence with exploratory analyses, similar to described above, to explore the distributions of the primary and secondary endpoints.

Hawthorne effect will be evaluated in two different ways.

Firstly, for descriptive purposes, we will measure the prevalence of the endpoints in a series of subgroups. For example, we will compare the COPD exacerbations in CPRD-xGM-IC with SLS, stratified by SES, gender, etc.

Secondly, we will take a multilevel modelling approach. For this we will combine the SLS and CPRD into one dataset (retaining an indicator of SLS membership). The hierarchies of the model will be patient -> GP practice -> local authority region (with SLS members being treated as a single distinct region) -> strategic health authority region. Strategic health authorities (population threshold of 1 million) are non-anonymised (named) regions. Local authority regions are below the population threshold so an anonymised LA marker will be available.

We will include all confounders and effect modifiers as covariates, with outcomes corresponding to the primary and secondary study outcomes (a separate model for each). Important fixed effects at the local authority level (for example, existence of community teams) will be incorporated into the model if these can be ascertained.

A final model will be selected via backward selection using AIC (Akaike Information Criterion). We will then examine the random effect of the SLS region in the context of the random effects for the other regions. Similar to the above, if the random effect of the SLS region falls outside the 2.5-97.5 percentile range, we will conclude that SOC SLS behaves unusually compared with the rest of the UK, and hence evidence of a Hawthorne effect.

PO3 will be carried out using the same approach as for PO2.

SO1 and SO2 (which pertain to comparing other endpoints, and sensitivity analyses of endpoint definition) will be carried out in the same way as PO2.

SO3 makes explicit the possible change in outcomes at commencement of SLS. We will compare outcome rates within Salford before and after the commencement of SLS, in a self-controlling case design. We will do the same thing within CPRD to control for UK-wide secular trends. This acts as sensitivity analysis to support PO2 (using controls distinct in time rather than in geography).

Additional work will take place exploring the development of methods for a framework of measuring representativeness; this is not within scope of this protocol and is described in Annex 2.1.

8.7.2. Exploratory analysis

8.7.3. General considerations for data analyses

The main identified risks are:

- How linkable the SLS and CPRD datasets are – e.g. can variables be extracted from both with the same (or very similar) definitions for all outcomes and potential confounders.
- Linkage of CPRD to HES and SES is not possible over the calendar dates that SLS has run as there is a lag time until these are released. Hence it may be necessary to restrict some analyses to data from earlier time periods.

8.8. Quality control

CPRD-GOLD has been used previously for descriptive drug utilization studies for prescription medications in respiratory diseases [16, 17, 18].

The standard operating procedures of University of Manchester 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.

The QC of analysis will be performed by GSK, 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 standardized 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

Hawthorne effect can only be evaluated for the SOC comparison. This does not give definite evidence about whether the prognostic or predictive effect of RELVAR would differ in the general population. This information could only truly be obtained following use of RELVAR in the general population.

There is no direct metric by which 'representativeness' of the Salford cohort can be measured. Early explorations of this will be made in a companion project – see Annex 2.1.

While both the SLS and CPRD use GP data, some data (hospital validated COPD diagnoses, pneumonia data, pharmacy data) for participants in SLS are collected using a different mechanism to CPRD. In this study protocol, only serious pneumonia defined by hospitalization will be assessed, which is a subset of total pneumonia cases recorded in the SLS. Hence any differences (either in representativeness or treatment response) observed between the SLS and non-SLS cohorts could be attributed to differences in data quality and the data collection mechanism. This will be mitigated by an additional comparison of SLS data with CPRD data from within Greater Manchester.

8.9.1. Study closure/uninterpretability of results

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

Individual subject consent is not required as this work is using research data. Internal ethical approval will be sought from the University of Manchester.

Linkage of the CPRD 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). In addition to ISAC approval, the protocol will be reviewed by GSK Worldwide Epidemiology Protocol Review Forum.

9.2. Subject confidentiality

The SLS data will be anonymised at source by the SLS team, before this is passed to University of Manchester.

The CPRD only contains 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 study partners 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

This is a retrospective study. From the CPRD, free text data will not be available to allow causality determination of any potential adverse events. Adverse events arising from the SLS trial will have previously been reported appropriately during the trial period.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

This work is targeted 1) internally at GSK, 2) regulators and 3) the wider scientific community; in order to understand the SLS in wider context. Results will be disseminated externally primarily by manuscripts.

11.2. Study reporting and publications

Reporting and publications according to the following table:

Deliverable	Timelines
Agreed Protocol for GSK protocol-review forum	November, 2014
Completion of Statistical analyses plan. Development of programs for analyses.	November 2014 – 1st October 2015
Analyses of PO2 (COPD exacerbation data) using final SLS data: First report with PO1/PO2 to GSK	By 29th April 2016
Share output from Primary Objectives with SLS Scientific Committee; and CHESS Steering Committee	9-10th May 2016
First manuscript developed and ready for submission with SLS paper to Thorax based PO1 and PO2 data	June-July 2016
Analysis for P03 and draft tables circulated	November 2016
Draft complete study report with PO1/PO2/PO3 to GSK	December 2016
Regulatory reporting of PO3	Q1 2017

Final follow-up manuscript	Q1-2 2017

In addition, we will present the results of the study at international respiratory conferences as appropriate. The study protocol and results will be posted to GSK Clinical Study Register as per GSK SOPs.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Annex 1a: System Level Security Policy (SLSP) for Study

System Details

1. **The System shall be known as**

   CHESS: CPRD-COPD Hawthorne Effect Study in Salford: A UK cohort study to characterise patients enrolled in the Salford Lung Study and to evaluate a potential Hawthorne effect

2. **The System's responsible owner shall be** PPD

3. **The System's Caldicott Guardian or Data Controller shall be** PPD PPD

System Security

4. **Security of the system shall be governed by the corporate security policy of University of Manchester**

   http://documents.manchester.ac.uk/display.aspx?DocID=6525 (policy)

   http://documents.manchester.ac.uk/display.aspx?DocID=8039 (responsibilities)

5. **The System's responsible security manager shall be:**

   PPD University IT Security Coordinator

6. **The security manager duties shall include**:

   Devise, implement, enforce and review the University's IT security and data handling policies.
   Being the first point of contact for any security related queries or concerns.
   Being consulted on and providing the final sign-off for any requests for change to any aspects of IT security for the system.

7. **The System shall incorporate the following security countermeasures**:

   - **Physical Security – Data Processing**: The researchers are based within Vaughan House which is swipe card access only from reception into the building. Staff and Postgraduate students must have their University swipe cards enabled for access to the building. The offices are also locked when vacant.
   - **Physical Security – Data Hosting**: The data will be stored within Personal Drives (P: Drives) hosted on the University's network storage infrastructure which is the recommended location for storing sensitive or critical University

data. The storage infrastructure is hosted across two data centres (approx. 2KM apart) for resilience and disaster recovery purposes. Physical access to the data centres is strictly limited to data centre staff and a limited number of authorised IT Services staff. The data centres are protected by physical and electronic access security systems, swipe card access in and out of the data centres and CCTV coverage. The data centres are locked down out of hours and access is discouraged, but can be arranged by prior agreement with the data centre manager.

- **Access Control and Privilege Management:** The data will be hosted on authorised system user's P: drives which are strictly controlled data shares within the University's network storage infrastructure to which only the owner of the P: Drive has access permissions. The data share will only be accessed via a mapped network drive from PCs identified for research data processing.
- **Network Security Measures:** Network access control lists prevent PCs outside of the campus LAN from accessing the network storage infrastructure.
- **Other – Data Processing:** Four PCs have been identified for processing the research data. Once the PC has loaded the operating system a local, password protected computer account is required to login to the PC. This account is unique to the primary user of the computer and only the account owner knows the password. The PC has the Windows firewall enabled and configured to prevent remote access. The PCs have been configured to automatically update their antivirus signatures daily and have been configured to download and install any Microsoft operating system and application security patches automatically from the Microsoft update service.

System Management

8. **The System shall be developed / provided by:**

   University of Manchester, Faculty of Medical & Human Sciences, Information Services
   University of Manchester, IT Services Division

9. **The System shall be implemented & maintained by:**

   University of Manchester, Faculty of Medical & Human Sciences, Information Services will configure and maintain the security aspects of the PC, user accounts and access controls for the data share on the network storage infrastructure.

   University of Manchester, IT Services Division (ITSD) will be responsible for providing secure, reliable data hosting on the network storage infrastructure.

   Servers procured by ITSD include maintenance on either 3 or 5 year agreements depending on the Service requirements. Supplier engineers replace any defectives items and may request access to the Data Centre. In addition Data centre staff are trained and able to carry out component replacements on behalf of the suppliers.

Storage arrays are procured with support and maintenance included as part of a 3 year package. The SAN Arrays in the central ITS Data Centres are supplied by EMC and have allocated engineers who are familiar with our site configuration and conversant in maintaining the equipment and advising on future changes.

To ensure the security of University hosted infrastructure systems, all system changes must be authorised via the change management process. Any proposed system changes are recorded as requests for change (RFC's) and authorised by the change advisory board (CAB).

10. **The System shall be shared or used by the following organisations:**

GSK will have direct access to the system for quality checking purposes.

System Design

11. **The System shall comprise:**

The research PCs connect to the University's network via access switches which are located in data cabinets within secure, dedicated comms rooms. The switches are logically segregated into separate VLAN's for network efficiency and security. The access switches then connect to the University's core router and onto perimeter routers via multiple paths for resilient access to the data centres where the network storage infrastructure is hosted. The perimeter routers connect onto the JANET network and the wider internet. The perimeter routers are configured with access control lists which provide security for incoming network traffic. A network diagram can be found at the end of this SLSP.

The operating system on the PCs identified for data processing require local username and password authentication for access. The P: drives on the network require username and password authentication also.

Operational Processes

12. **The patient identifiable / sensitive data will be collected:**

Datasets will be pseudonymised at source by providers. No patient identifiable or sensitive information will be processed.

13. **The data will be stored:**

The data will be stored electronically in R and SAS file formats. The data will be made available to authorised members of research staff via P: drives hosted on the University's network storage infrastructure housed in the University's data centres.

14. **The data will be processed**:

Four University approved desktop PCs will be used to process the data. The PCs will not cache copies of the data and all data will be stored on the network storage infrastructure.

The University's Information Handling Policy sets out how digital information should be handled. This includes confidentiality, integrity and availability and the use of encryption tools for the protection of sensitive information and communications.

http://www.itservices.manchester.ac.uk/medialibrary/pdf/secureguidance/GP-InformationHandling.pdf

15. **The System's authorised users shall be** :

University of Manchester:

- PPD
-
-
- 1 x Research Associate, to be appointed.

GSK

- TBA by GSK.

The system's authorised users are all University members of staff and individuals designated by GSK. The data will not be accessible by any other third party organisations

16. **When the system or its data has completed its purpose / has become redundant or is no longer needed, the following methods will be adopted to dispose of equipment, back-up media or other stored data**:

Sensitive material on removable media are deleted as soon as possible. Printed materials and CD/DVDs containing sensitive information are shredded when no longer required. When the analysis is completed the researcher will delete files. All items of equipment containing storage media shall be checked to ensure that any sensitive data and licensed software has been removed or securely overwritten.

Desktop PCs are disposed of when replaced via a recognised disposal company, Computer Disposals LTD (CDL). CDL erase the hard drives to Government Restricted Standard SEAP (UK), which is three overwrites plus an additional verification pass. A certificate is produced for every successfully data erased hard drive to include the make, model and serial number of the hard drive. Any hard drive that fails the data erase process is degaussed on site at CDL using the latest CESG approved degausses and forwarded for recycling.

University IT Services has a policy of securely wiping network storage infrastructure arrays onsite prior to disposal. Disks are securely erased by software aligned to the DoD5220-22M standard and are then disposed of via CDL who also wipe the disks as per their procedure outlined above.

System Audit

17. **The System shall benefit from the following internal / external audit arrangements:**

In 2006, the University's IT Services undertook (in conjunction with KPMG) a comprehensive IT Risk Management Benchmarking exercise to appraise the University's approach to the management of IT-related risks. The review was intended to provide a benchmark upon which to build the maturity of IT Services activities over a number of years. Whilst the exercise found a number of positive areas within IT, it also identified a number of areas for development and agreed management action plans to address the issues raised.

A follow-up review was conducted during 2009 by UNIAC, the University's internal auditing body. This review: (i) revisited each original recommendation, ascertaining progress to date (supported by testing where appropriate) and its ongoing relevance; (ii) commented on the adequacy of the actions to date; (iii) proposed revised action plans for previous actions remaining outstanding; (iv) made additional suggestions over and above the agreed action.

The original KPMG report contained over thirty high and medium level recommendations and, realistically, a number of them would take a considerable period to fully implement. The follow-up review in 2009 concluded that: (i) recommendations had been fully implemented with no further action required in seven areas; (ii) good progress had been made towards implementing a further fifteen recommendations; (iii) some progress had been made towards implementing a further six recommendations; (iv) limited progress had been made towards implementing a final four recommendations.

Overall, the report concluded that progress has been encouraging and indicated that IT Services management had provided adequate focus to improving the management of IT risks.

Future auditing arrangements include regular audits agreed with internal and external auditors. The Director of IT Services meets the UNIAC Director annually to agree the internal programme; the external programme is agreed via the University's Audit Committee.

18. **The System shall be risk assessed every 12 months**

The University's Compliance and Risk Officer (CRO) is responsible for ensuring that the University is meeting its many statutory and regulatory compliance obligations. The CRO is responsible for supporting the University's risk management process, all aspects of risk management and has developed a risk management framework.

All major University functional areas (including IT Services) are required to conduct annual risk assessments and to review risk registers on a quarterly basis. Risk registers are submitted to the University's CRO for reporting to the

University's Risk Management Committee. Risk management is a specific responsibility of heads of operational areas.

System Protection

19. **The System shall benefit from the following resilience / contingency / disaster recovery arrangements:**

    The University's storage infrastructure is hosted and replicated across two data centres (approx. 2KM apart) for resilience and disaster recovery purposes.

    The University's IT Services Division (ITSD) utilises Legato Networker Backup domains. Supporting infrastructure comprises disk libraries and both physical and virtual tape libraries. Cross data centre backup is performed, so services hosted within data centre 1 (Kilburn) are backed up to data centre 2 (Reynold) and vice versa.

    Backup/recovery plans are documented as part of the service install process during the commissioning of a specific service. Each Service is responsible for its business continuity and disaster recovery plans, to which ITSD feed in its technical recovery plans

    ITSD operates a change management process. All proposed changes to infrastructure hosted, maintained and administered by ITSD are recorded via the RFC process with changes being authorised by a Change Advisory Board (CAB).

20. **In the event of serious disruption or total system failure, business continuity shall be provided by the following means:**

    The University's geographically dispersed, replicated, twin data centre approach with cross site backup has been designed to be as fault tolerant as possible and to provide business continuity in the event of a data centre failure. Should a situation arise where both data centres became unavailable then the University's disaster recovery plans relating to the failed system would be implemented.

21. **In the event of a security or confidentiality breach occurring the following procedure shall be followed:**

    Information on the procedure for reporting a security or confidentiality breach is available from the following link on the University's Secure-IT website: http://www.itservices.manchester.ac.uk/secure-it/reporting/

SSP Ownership

22. **This SLSP shall be the responsibility of:**

    PPD

22.1 - Shall be reviewed on an annual basis for its completeness and for relevant update.

23. **The SLSP shall be available / distributed to:**

Authorised GSK and University of Manchester staff involved in research activities or members of IT staff assisting with the completion of SLSP forms.

- Through which secure means:

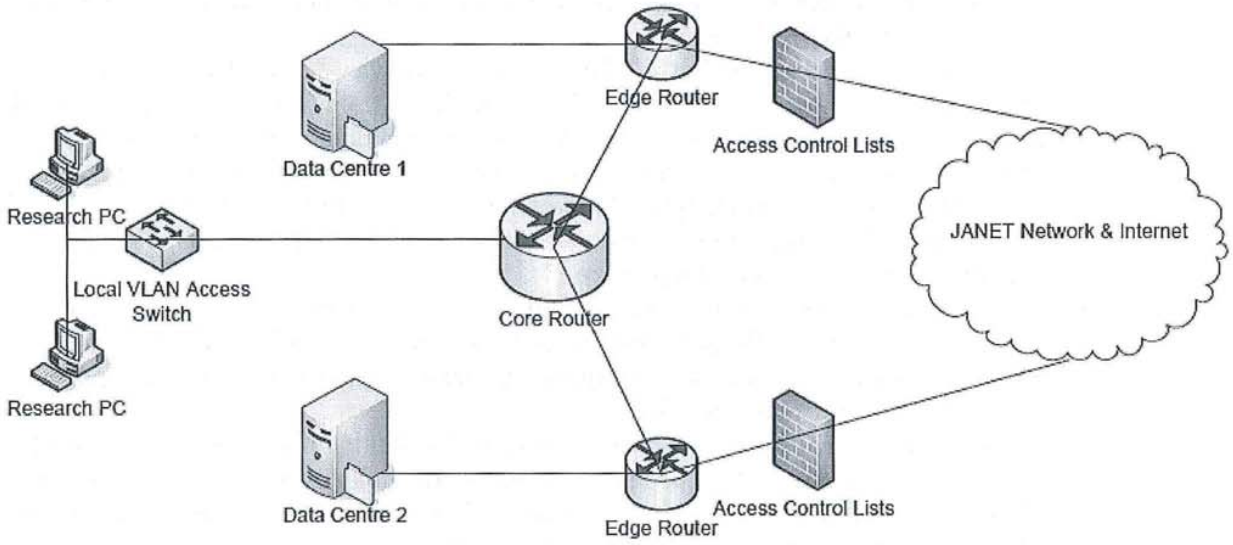
The SLSP document will be distributed to authorised GSK and University of Manchester staff via the internal email system.

Data Protection Registration

24. **Please confirm that your organisation has Data Protection Registration to cover the purposes of analysis and for the classes of data requested.**

http://www.ico.gov.uk/ESDWebPages/search.asp - . Registration No: Z6787610

Network diagram as referenced in the System Design section of the SLSP



ANNEX 2. ADDITIONAL INFORMATION

A2.1 Development of methods for the measurements of representativeness

This part of the project will deal with the development of methods for measuring representativeness of trials and evaluating potential effects of non-representativeness. It will be explorative and focused on methods. The concept of representativeness of trials is widely known but it is less known how to actually measure representativeness. This project will evaluate RELVAR use as an exemplar case study. These results will be compared to a historic case study of selective Cox-2 inhibitors (comparing the registration trials); the Cox-2 analyses will be conducted and funded as part of the GetReal IMI project. The RELVAR project will include the following activities:

(i) Review of literature for methods that can measure level of representativeness and evaluate the effects of non-representativeness. These methods may include multilevel models (including levels of clinician, practice, patient, disease and exposure characteristics.

(ii) Risk prediction models will be developed in CPRD for the outcomes of interest (to be defined). This analysis will determine the risk factors for the outcomes of interest. In addition, experts will be asked to provide likely effect modifiers of RELVAR. The analyses will focus on risk factors and effect modifiers.

(iii) Three populations will be identified in CPRD:

a. the first population will be based on the inclusion and exclusion criteria of the SLS trial. In case that information is missing in the EHR, methods will be evaluated to possibly impute these criteria.

b. the second population will be based on expert views of the likely possible use of RELVAR, and will be compared to Cox-2 inhibitors (from GetReal) in actual clinical practice. As an example, the trials for selective Cox-2 inhibitors were conducted in narrowly defined populations while later used in very broad population (replacing traditional NSAIDs). Any analysis of representativeness would have showed a considerable difference between the populations potentially eligible for a trial and potential users in actual clinical practice.

c. the third population will consist of all COPD patients aged 40 years or older alive at the index date. The propensity score for recruitment into SLS (as based on the Salford data) will be applied to this population, estimating the probability that a patient could have been recruited into SLS.

(iv) The analyses will include comparisons of the distribution of risk factors and effect modifiers between these three populations and the trial populations. Also, a comparison of incidence rates for the outcomes of interest will be conducted across these populations. Methods will be developed to integrate these results.

This project will be conducted in collaboration with GetReal partners, including NICE.

13. TABLES

13.1. Table 1: Pneumonia definition/codes used in SLS

Within the SLS, these codes are used assess pneumonia from hospital discharge records.

ICD-10 code	ICD-10 description	Comment
B67.1	Other B67.1 Echinococcus granulosus infection of lung	Other
J17.3	Other J17.3 Pneumonia in parasitic diseases	Other
J16	Pneumonia due to other infectious organisms NEC	unspecified
J16.8	Pneumonia due to other specified infectious organisms	unspecified
J17	Pneumonia in diseases classified elsewhere	unspecified
J17.8	Pneumonia in other diseases classified elsewhere	unspecified
J18	Pneumoniaorganism unspecified	unspecified
J18.0	Bronchopneumonia, unspecified	unspecified
J18.1	Lobar pneumonia, unspecified	unspecified
J18.8	Other pneumonia, organism unspecified	unspecified
J18.9	Pneumonia, unspecified	unspecified
A06.5	Amoebic lung abscess	Lung abscess
J85	Abscess of lung and mediastinum	Lung abscess
J85.0	Gangrene and necrosis of lung	Lung abscess
J85.1	Abscess of lung with pneumonia	Lung abscess
J85.2	Abscess of lung without pneumonia	Lung abscess
B20.6	HIV disease resulting in Pneumocystis carinii pneumonia	Fungal
B37.1	Pulmonary candidiasis	Fungal
B38.0	Acute pulmonary coccidioidomycosis	Fungal
B38.1	Chronic pulmonary coccidioidomycosis	Fungal
B38.2	Pulmonary coccidioidomycosis, unspecified	Fungal
B39.0	Acute pulmonary histoplasmosis capsulation	Fungal
B39.2	Pulmonary histoplasmosis capsulati, unspecified	Fungal
B40.0	Acute pulmonary blastomycosis	Fungal
B40.2	Pulmonary blastomycosis, unspecified	Fungal
B41.0	Pulmonary paracoccidioidomycosis	Fungal
B42.0	Pulmonary sporotrichosis	Fungal
B44.0	Invasive pulmonary aspergillosis	Fungal

B44.1	Other pulmonary aspergillosis	Fungal
B45.0	Pulmonary cryptococcosis	Fungal
B46.0	Pulmonary mucormycosis	Fungal
B58.3	Pulmonary toxoplasmosis	Fungal
B59.X	Pneumocystosis	Fungal
J17.2	Pneumonia in mycoses	Fungal
A15	Respiratory TB bacteriologically and histologically confirmed	Mycobacterial
A15.0	TB lung confirm sputum microscopy with or without culture	Mycobacterial
A15.1	Tuberculosis of lung, confirmed by culture only	Mycobacterial
A15.2	Tuberculosis of lung, confirmed histologically	Mycobacterial
A15.3	Tuberculosis of lung, confirmed by unspecified means	Mycobacterial
A15.4	TB intrathoracic lymph nodes confirm bact histologically	Mycobacterial
A15.5	Tuberculosis of larynx, trachea & bronchus conf bact/hist'y	Mycobacterial
A15.6	Tuberculous pleurisy, conf bacteriologically/his'y	Mycobacterial
A15.7	Primary respiratory TB confirm bact and histologically	Mycobacterial
A15.8	Other respiratory TB confirm bact and histologically	Mycobacterial
A15.9	Respiratory TB unspec confirm bact and histologically	Mycobacterial
A16	Respiratory TB not confirmed bacteriologically or histologically	Mycobacterial
A16.0	Tuberculosis of lung, bacteriologically & histolog'y neg	Mycobacterial
A16.1	Tuberculosis lung bact and histological examin not done	Mycobacterial
A16.2	TB lung without mention of bact or histological confirm	Mycobacterial
A16.5	TB pleurisy without mention of bact or histological confirm	Mycobacterial
A16.7	Prim respiratory TB without mention of bact or hist confirm	Mycobacterial
A16.8	Oth respiratory TB without mention of bact or hist confirm	Mycobacterial
A16.9	Resp TB unspec without mention of bact or hist confirm	Mycobacterial
A19	Miliary tuberculosis	Mycobacterial
A19.0	Acute miliary tuberculosis of a single specified site	Mycobacterial

A19.1	Acute miliary tuberculosis of multiple sites	Mycobacterial
A19.2	Acute miliary tuberculosis, unspecified	Mycobacterial
A19.8	Other miliary tuberculosis	Mycobacterial
A19.9	Miliary tuberculosis, unspecified	Mycobacterial
A31.0	Pulmonary mycobacterial infection	Mycobacterial
B01.2	Varicella pneumonia	Viral
B05.2	Measles complicated by pneumonia	Viral
J10.0	Influenza with pneumonia, influenza virus identified	Viral
J11.0	Influenza with pneumonia, virus not identified	Viral
J12	Viral pneumonia, not elsewhere classified	Viral
J12.0	Adenoviral pneumonia	Viral
J12.1	Respiratory syncytial virus pneumonia	Viral
J12.2	Parainfluenza virus pneumonia	Viral
J12.8	Other viral pneumonia	Viral
J12.9	Viral pneumonia, unspecified	Viral
J17.1	Pneumonia in viral diseases classified elsewhere	Viral
A20.2	Pneumonic plague	Bacterial
A21.2	Pulmonary tularaemia	Bacterial
A22.1	Pulmonary anthrax	Bacterial
A42.0	Pulmonary actinomycosis	Bacterial
A43.0	Pulmonary nocardiosis	Bacterial
A48.1	Legionnaires' disease	Bacterial
J13	Pneumonia due to Streptococcus pneumoniae	Bacterial
J13.0	Pneumonia due to Streptococcus pneumoniae	Bacterial
J13X	Pneumonia due to Streptococcus pneumoniae	Bacterial
J14	Pneumonia due to Haemophilus influenzae	Bacterial
J14.0	Pneumonia due to Haemophilus influenzae	Bacterial
J14X	Pneumonia due to Haemophilus influenzae	Bacterial
J15	Bacterial pneumonianot elsewhere classified	Bacterial
J15.0	Pneumonia due to Klebsiella pneumoniae	Bacterial
J15.1	Pneumonia due to Pseudomonas	Bacterial
J15.2	Pneumonia due to staphylococcus	Bacterial
J15.3	Pneumonia due to streptococcus, group	Bacterial

	B	
J15.4	Pneumonia due to other streptococci	Bacterial
J15.5	Pneumonia due to Escherichia coli	Bacterial
J15.6	Pneumonia due to other aerobic Gram-negative bacteria	Bacterial
J15.7	Pneumonia due to Mycoplasma pneumoniae	Bacterial
J15.8	Other bacterial pneumonia	Bacterial
J15.9	Bacterial pneumonia, unspecified	Bacterial
J16.0	Chlamydial pneumonia	Bacterial
J17.0	Pneumonia in bacterial diseases classified elsewhere	Bacterial
B25.0	Cytomegaloviral pneumonitis	No
B38	Coccidioidomycosis	No
B38.9	Coccidioidomycosis, unspecified	No
B39	Histoplasmosis	No
B39.4	Histoplasmosis capsulati, unspecified	No
B39.5	Histoplasmosis duboisii	No
B39.9	Histoplasmosis, unspecified	No
B40	Blastomycosis	No
B409	Blastomycosis, unspecified	No
B44	Aspergillosis	No
B44.9	Aspergillosis, unspecified	No
J18.2	Hypostatic pneumonia, unspecified	No
J86.0	Pyothorax with fistula	No
J86.9 Pyothorax without fistula	Pyothorax without fistula	No
'X' denotes that all subcodes under the 3-digit main number are included		
"No" in category denotes not assigned to a major category		

Annex 2: Code lists for key definitions using in study PRJ2282/201491

1. Medical codes considered to identify those with COPD in the CPRD
2. Code lists for moderate/severe COPD exacerbation used in CPRD and SLS-EHR
3. Code list to define Hospitalised pneumonia (PO3 and SO2) in CPRD

1. COPD: MEDICAL CODES CONSIDERED TO IDENTIFY THOSE WITH COPD IN THE CPRD

Description	CPRD Medcode	Read Code
Airways obstructn irreversible	4084	663K.00
COPD accident and emergency attendance since last visit	19106	66Yd.00
COPD follow-up	18476	66YL.11
COPD patient unsuitable for pulmonary rehab - enh serv admin	99948	9kf0.00
COPD self-management plan agreed	104117	661M300
COPD self-management plan review	104169	661N300
Centrilobular emphysema	10980	H322.00
Chronic bullous emphysema	26306	H320.00
Chronic bullous emphysema NOS	23492	H320z00
Chronic obstructiv pulmonary disease medication optimisation	103678	8BMa000
Chronic obstructive airways disease	998	H3...11
Chronic obstructive airways disease NOS	5710	H3z..00
Chronic obstructive pulmonary disease	1001	H3...00
Chronic obstructive pulmonary disease 3 monthly review	102685	66YB000
Chronic obstructive pulmonary disease 6 monthly review	103007	66YB100
Chronic obstructive pulmonary disease NOS	37247	H3z..11
Chronic obstructive pulmonary disease annual review	11287	66YM.00
Chronic obstructive pulmonary disease clini management plan	45777	8CR1.00
Chronic obstructive pulmonary disease disturbs sleep	45770	66Yg.00
Chronic obstructive pulmonary disease does not disturb sleep	45771	66Yh.00
Chronic obstructive pulmonary disease follow-up	18621	66YL.00
Chronic obstructive pulmonary disease monitor phone invite	38074	9Oi4.00
Chronic obstructive pulmonary disease monitoring	9520	66YB.00
Chronic obstructive pulmonary disease monitoring 1st letter	28755	9Oi0.00
Chronic obstructive pulmonary disease monitoring 2nd letter	34202	9Oi1.00
Chronic obstructive pulmonary disease monitoring 3rd letter	34215	9Oi2.00
Chronic obstructive pulmonary disease monitoring admin	18792	9Oi..00

Description	CPRD Medcode	Read Code
Chronic obstructive pulmonary disease monitoring by doctor	45998	66YT.00
Chronic obstructive pulmonary disease monitoring by nurse	26018	66YS.00
Chronic obstructive pulmonary disease monitoring due	37371	66YD.00
Chronic obstructive pulmonary disease monitoring verb invite	42258	9Oi3.00
Emergency COPD admission since last appointment	19003	66Ye.00
Emphysema	794	H32..00
Emphysema NOS	33450	H32z.00
Emphysematous bronchitis	14798	H312100
End stage chronic obstructive airways disease	104608	H3A..00
Has chronic obstructive pulmonary disease care plan	104481	8CMV.00
Health education - chronic obstructive pulmonary disease	42313	679V.00
Issue of chronic obstructive pulmonary disease rescue pack	101042	8BMW.00
Mild chronic obstructive pulmonary disease	10863	H36..00
Moderate chronic obstructive pulmonary disease	10802	H37..00
Multiple COPD emergency hospital admissions	46036	66Yi.00
Number of COPD exacerbations in past year	28743	66Yf.00
Obstructive chronic bronchitis	27819	H312.00
Obstructive chronic bronchitis NOS	44525	H312z00
Other specified chronic obstructive airways disease	12166	H3y..00
Referred for COPD structured smoking assessment	103400	9kf1.11
Severe chronic obstructive pulmonary disease	9876	H38..00
Very severe chronic obstructive pulmonary disease	93568	H39..00
Acute exacerbation of chronic obstructive airways disease	1446	H312200
Admit COPD emergency	11019	8H2R.00
Chron obstruct pulmonary dis wth acute exacerbation, unspec	7884	H3y1.00
Chronic obstruct pulmonary dis with acute lower resp infectn	21061	H3y0.00

2. CODE LISTS FOR MODERATE/SEVERE COPD EXACERBATION

The definition of a COPD exacerbation was identified using a validated algorithm based on medical and treatment codes in primary care data that have been shown to result in a positive predictive value of 86% and 63% ([1]). The algorithm defined any of the following as exacerbation events:

- (1) Prescription of pre-specified antibiotics (ABx) and oral corticosteroid (OCS) for 5-14 days both on the same day,
- (2) Exacerbation symptom definition (Exacerbation symptoms are codes suggesting increase in two or more of: breathlessness, cough, or sputum volume and/or purulence) and use of pre-specified antibiotics, where medical code is on the same day as prescription, OR
  Exacerbation symptom definition and oral corticosteroids, where medical code is on the same day as prescription,
- (3) Lower respiratory tract infection (LRTI) code (not including pneumonia codes, but including acute bronchitis and other lower respiratory tract infection diagnosis codes),
- (4) Definite Acute Exacerbation of COPD (AECOPD) medical diagnosis code.

When secondary care episode data was available the following notes from secondary care were also considered as representing exacerbations.

- (5) "Probable" AECOPD as the primary diagnosis within a Hospital Episode OR
- (6) "Definite" AECOPD recorded as any diagnosis within a Hospital Episode

Events of type (1) or (2) were not considered as exacerbations when the date of prescribing coincided with the issue of a rescue pack for AECOPD or a formal review of the patient's COPD status by the GP.

Events of type (3) or (4) were not considered as exacerbations when the events were recorded on the same data as a formal review of the patient's COPD status.

For the analyses comparing CPRD to the Salford EHR were only primary care data was used, events of type (1) were identified by the following relaxed definition:

- (1) Prescription of pre-specified antibiotics (ABx) and oral corticosteroid (OCS) both on the same day

The sets of codes used to identify prescription for ABx or OCS, exacerbation symptoms, LRTIs, AECOPDs, rescue packs for COPD exacerbations and reviews for COPD are listed.

[1] Rothnie KJ, Müllerová 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 Records. PLoS One. 2016 Mar 9;11(3):e0151357.

Moderate/severe COPD exacerbation coding definition

Prescriptions of pre-specified antibiotics (ABx)

CPRD Prodcode	Description
18685	achromycin 125mg/5ml oral solution (wyeth pharmaceuticals)
4579	achromycin 250mg capsules (wyeth pharmaceuticals)
15513	achromycin 250mg tablet (wyeth pharmaceuticals)
32233	achromycin powder (wyeth pharmaceuticals)
15407	achromycin v 250mg capsule (wyeth pharmaceuticals)
54152	acnamino mr 100mg capsules (almus pharmaceuticals ltd)
14984	acnamino mr 100mg capsules (dexcel-pharma ltd)
18728	aknemin 100mg capsules (almirall ltd)
18684	aknemin 50 capsules (almirall ltd)
22016	almodan 125mg/5ml oral solution (berk pharmaceuticals ltd)
17282	almodan 125mg/5ml syrup (teva uk ltd)
21799	almodan 250mg capsule (berk pharmaceuticals ltd)
21845	almodan 250mg/5ml oral solution (berk pharmaceuticals ltd)
21963	almodan 250mg/5ml oral solution (berk pharmaceuticals ltd)
21827	almodan 500mg capsule (berk pharmaceuticals ltd)
22029	amiclav 250mg/125mg tablets (ashbourne pharmaceuticals ltd)
11634	amix 125 oral suspension (ashbourne pharmaceuticals ltd)
11613	amix 250 capsules (ashbourne pharmaceuticals ltd)
21844	amix 250 oral suspension (ashbourne pharmaceuticals ltd)
18786	amix 500 capsules (ashbourne pharmaceuticals ltd)
29697	amopen 125mg/5ml liquid (yorkshire pharmaceuticals ltd)
30498	amopen 250mg capsule (yorkshire pharmaceuticals ltd)
31423	amopen 250mg/5ml liquid (yorkshire pharmaceuticals ltd)
17711	amopen 500mg capsule (yorkshire pharmaceuticals ltd)
12378	amoram 125mg/5ml oral suspension (lpc medical (uk) ltd)
9243	amoram 250mg capsules (lpc medical (uk) ltd)
22438	amoram 250mg/5ml oral suspension (lpc medical (uk) ltd)
22415	amoram 500mg capsules (lpc medical (uk) ltd)
8906	amoxicillin 125mg / clavulanic acid 31mg/5ml oral suspension
13285	amoxicillin 125mg / clavulanic acid 31mg/5ml oral suspension
53942	amoxicillin 125mg / clavulanic acid 62.5mg/5ml oral suspension
41835	amoxicillin 125mg powder (ivax pharmaceuticals uk ltd)
3742	amoxicillin 125mg sugar free chewable tablets
13848	amoxicillin 125mg sugar free powder
485	amoxicillin 125mg/1.25ml oral suspension paediatric
42822	amoxicillin 125mg/5ml mixture (celltech pharma europe ltd)
28872	amoxicillin 125mg/5ml mixture (crosspharma ltd)
41818	amoxicillin 125mg/5ml oral solution (berk pharmaceuticals ltd)
42240	amoxicillin 125mg/5ml oral solution (co-pharma ltd)
29337	amoxicillin 125mg/5ml oral solution (neo laboratories ltd)
62	amoxicillin 125mg/5ml oral suspension
33690	amoxicillin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)

CPRD Prodcode	Description
34857	amoxicillin 125mg/5ml oral suspension (actavis uk ltd)
42545	amoxicillin 125mg/5ml oral suspension (almus pharmaceuticals ltd)
50002	amoxicillin 125mg/5ml oral suspension (bristol laboratories ltd)
32622	amoxicillin 125mg/5ml oral suspension (generics (uk) ltd)
23238	amoxicillin 125mg/5ml oral suspension (ivax pharmaceuticals uk ltd)
48038	amoxicillin 125mg/5ml oral suspension (kent pharmaceuticals ltd)
52685	amoxicillin 125mg/5ml oral suspension (phoenix healthcare distribution ltd)
28875	amoxicillin 125mg/5ml oral suspension (ranbaxy (uk) ltd)
43229	amoxicillin 125mg/5ml oral suspension (sandoz ltd)
55047	amoxicillin 125mg/5ml oral suspension (sandoz ltd)
28870	amoxicillin 125mg/5ml oral suspension (teva uk ltd)
56561	amoxicillin 125mg/5ml oral suspension (waymade healthcare plc)
503	amoxicillin 125mg/5ml oral suspension sugar free
33696	amoxicillin 125mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
34679	amoxicillin 125mg/5ml oral suspension sugar free (actavis uk ltd)
53078	amoxicillin 125mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
36054	amoxicillin 125mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
52122	amoxicillin 125mg/5ml oral suspension sugar free (bristol laboratories ltd)
31014	amoxicillin 125mg/5ml oral suspension sugar free (generics (uk) ltd)
24150	amoxicillin 125mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
34384	amoxicillin 125mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)
52857	amoxicillin 125mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)
29858	amoxicillin 125mg/5ml oral suspension sugar free (sandoz ltd)
34638	amoxicillin 125mg/5ml oral suspension sugar free (teva uk ltd)
55626	amoxicillin 125mg/5ml oral suspension sugar free (waymade healthcare plc)
1391	amoxicillin 250mg / clavulanic acid 125mg tablets
7636	amoxicillin 250mg / clavulanic acid 62mg/5ml oral suspension
13262	amoxicillin 250mg / clavulanic acid 62mg/5ml oral suspension
42809	amoxicillin 250mg capsule (c p pharmaceuticals ltd)
31661	amoxicillin 250mg capsule (co-pharma ltd)
28882	amoxicillin 250mg capsule (crosspharma ltd)
34435	amoxicillin 250mg capsule (ddsa pharmaceuticals ltd)
33222	amoxicillin 250mg capsule (lagap)
32872	amoxicillin 250mg capsule (mepra-pharm)
34714	amoxicillin 250mg capsule (neo laboratories ltd)
45267	amoxicillin 250mg capsule (regent laboratories ltd)
9	amoxicillin 250mg capsules
25484	amoxicillin 250mg capsules (a a h pharmaceuticals ltd)
33343	amoxicillin 250mg capsules (actavis uk ltd)
54796	amoxicillin 250mg capsules (boston healthcare ltd)
54491	amoxicillin 250mg capsules (bristol laboratories ltd)
30745	amoxicillin 250mg capsules (generics (uk) ltd)
34042	amoxicillin 250mg capsules (ivax pharmaceuticals uk ltd)

CPRD Prodcode	Description
30528	amoxicillin 250mg capsules (kent pharmaceuticals ltd)
54271	amoxicillin 250mg capsules (mawdsley-brooks & company ltd)
51536	amoxicillin 250mg capsules (milpharm ltd)
30743	amoxicillin 250mg capsules (ranbaxy (uk) ltd)
48006	amoxicillin 250mg capsules (sandoz ltd)
23967	amoxicillin 250mg capsules (teva uk ltd)
54185	amoxicillin 250mg capsules (wockhardt uk ltd)
870	amoxicillin 250mg sugar free chewable tablets
42815	amoxicillin 250mg/5ml mixture (celltech pharma europe ltd)
33570	amoxicillin 250mg/5ml mixture (crosspharma ltd)
40238	amoxicillin 250mg/5ml mixture (mepra-pharm)
45317	amoxicillin 250mg/5ml oral solution (neo laboratories ltd)
427	amoxicillin 250mg/5ml oral suspension
33165	amoxicillin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
34760	amoxicillin 250mg/5ml oral suspension (actavis uk ltd)
41090	amoxicillin 250mg/5ml oral suspension (almus pharmaceuticals ltd)
55018	amoxicillin 250mg/5ml oral suspension (bristol laboratories ltd)
33689	amoxicillin 250mg/5ml oral suspension (generics (uk) ltd)
32640	amoxicillin 250mg/5ml oral suspension (ivax pharmaceuticals uk ltd)
51382	amoxicillin 250mg/5ml oral suspension (phoenix healthcare distribution ltd)
55499	amoxicillin 250mg/5ml oral suspension (ranbaxy (uk) ltd)
37755	amoxicillin 250mg/5ml oral suspension (sandoz ltd)
56223	amoxicillin 250mg/5ml oral suspension (sandoz ltd)
53924	amoxicillin 250mg/5ml oral suspension (sigma pharmaceuticals plc)
27725	amoxicillin 250mg/5ml oral suspension (teva uk ltd)
585	amoxicillin 250mg/5ml oral suspension sugar free
34232	amoxicillin 250mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
40243	amoxicillin 250mg/5ml oral suspension sugar free (actavis uk ltd)
54222	amoxicillin 250mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
42732	amoxicillin 250mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
49065	amoxicillin 250mg/5ml oral suspension sugar free (bristol laboratories ltd)
31535	amoxicillin 250mg/5ml oral suspension sugar free (generics (uk) ltd)
33699	amoxicillin 250mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
34855	amoxicillin 250mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)
34775	amoxicillin 250mg/5ml oral suspension sugar free (teva uk ltd)
17746	amoxicillin 375mg soluble tablets
1140	amoxicillin 3g oral powder sachets sugar free
33383	amoxicillin 3g oral powder sachets sugar free (a a h pharmaceuticals ltd)
40168	amoxicillin 3g oral powder sachets sugar free (kent pharmaceuticals ltd)
28130	amoxicillin 3g oral powder sachets sugar free (teva uk ltd)
41734	amoxicillin 3g powder (actavis uk ltd)
15192	amoxicillin 400mg / clavulanic acid 57mg/5ml sugar free oral suspension
13216	amoxicillin 500mg / clavulanic acid 125mg tablets
38684	amoxicillin 500mg capsule (c p pharmaceuticals ltd)

CPRD Prodcode	Description
35570	amoxicillin 500mg capsule (crosspharma ltd)
34885	amoxicillin 500mg capsule (ddsa pharmaceuticals ltd)
44854	amoxicillin 500mg capsule (lagap)
34912	amoxicillin 500mg capsule (neo laboratories ltd)
48	amoxicillin 500mg capsules
33692	amoxicillin 500mg capsules (a a h pharmaceuticals ltd)
53627	amoxicillin 500mg capsules (accord healthcare ltd)
26157	amoxicillin 500mg capsules (actavis uk ltd)
52820	amoxicillin 500mg capsules (alliance healthcare (distribution) ltd)
47640	amoxicillin 500mg capsules (almus pharmaceuticals ltd)
55527	amoxicillin 500mg capsules (boston healthcare ltd)
52771	amoxicillin 500mg capsules (bristol laboratories ltd)
23740	amoxicillin 500mg capsules (generics (uk) ltd)
29463	amoxicillin 500mg capsules (ivax pharmaceuticals uk ltd)
33706	amoxicillin 500mg capsules (kent pharmaceuticals ltd)
52058	amoxicillin 500mg capsules (medreich plc)
54725	amoxicillin 500mg capsules (milpharm ltd)
34852	amoxicillin 500mg capsules (ranbaxy (uk) ltd)
31801	amoxicillin 500mg capsules (sandoz ltd)
34001	amoxicillin 500mg capsules (teva uk ltd)
55394	amoxicillin 500mg capsules (wockhardt uk ltd)
1722	amoxicillin 500mg dispersible tablets
2281	amoxicillin 500mg sugar free chewable tablets
4582	amoxicillin 750mg soluble tablets
9343	amoxicillin 750mg sugar free powder
439	amoxicillin with clavulanic acid dispersible tablets
2171	amoxil 125mg/1.25ml paediatric oral suspension (glaxosmithkline uk ltd)
2153	amoxil 125mg/5ml syrup sucrose free (glaxosmithkline uk ltd)
133	amoxil 250mg capsules (glaxosmithkline uk ltd)
1812	amoxil 250mg/5ml syrup sucrose free (glaxosmithkline uk ltd)
2174	amoxil 3g oral powder sachets sucrose free (glaxosmithkline uk ltd)
847	amoxil 500mg capsules (glaxosmithkline uk ltd)
49590	amoxil 500mg capsules (lexon (uk) ltd)
51436	amoxil 500mg capsules (mawdsley-brooks & company ltd)
56700	amoxil 500mg capsules (necessity supplies ltd)
15148	amoxil 500mg dispersible tablet (smithkline beecham plc)
4010	amoxil 750mg sachets (glaxosmithkline uk ltd)
4154	amoxil fiztab 125mg tablet (bencard)
1637	amoxil fiztab 250mg tablet (bencard)
7737	amoxil fiztab 500mg tablet (bencard)
27897	amoxycillin
31571	amoxycillin
32505	amoxycillin
7592	amoxycillin 125 mg cap
22469	amoxycillin 125mg/31mg clavulanic acid

CPRD Prodcode	Description
25034	amoxycillin 125mg/62mg clavulanic acid
7581	amoxycillin 125mg/62mg clavulanic acid syr
27886	amoxycillin 250/clavulanic acid 125 disp
19795	amoxycillin 250mg/clavulanic acid 125mg
1570	amoxycillin 500 mg tab
2902	amoxycillin fiztab 125 mg tab
1393	amoxycillin fiztab 250 mg tab
21982	amoxycillin trihydrate sachet
22293	amoxycillin trihydrate sachet
31286	amoxymed 125mg/5ml oral solution (medipharma ltd)
3669	amoxymed 250mg capsule (medipharma ltd)
33109	amrit 125mg/5ml liquid (bhr pharmaceuticals ltd)
27714	amrit 250mg capsule (bhr pharmaceuticals ltd)
33110	amrit 250mg/5ml liquid (bhr pharmaceuticals ltd)
33112	amrit 500mg capsule (bhr pharmaceuticals ltd)
27495	arpimycin 125mg/5ml liquid (rosemont pharmaceuticals ltd)
36544	arpimycin 125mg/5ml oral suspension (rosemont pharmaceuticals ltd)
24220	arpimycin 250mg/5ml liquid (rosemont pharmaceuticals ltd)
36514	arpimycin 250mg/5ml oral suspension (rosemont pharmaceuticals ltd)
37022	arpimycin 500mg/5ml liquid (rosemont pharmaceuticals ltd)
415	augmentin 125/31 sf oral suspension (glaxosmithkline uk ltd)
50595	augmentin 125/31 sf oral suspension (mawdsley-brooks & company ltd)
51164	augmentin 125/31 sf oral suspension (waymade healthcare plc)
569	augmentin 250/62 sf oral suspension (glaxosmithkline uk ltd)
52666	augmentin 250/62 sf oral suspension (sigma pharmaceuticals plc)
2507	augmentin 375mg dispersible tablets (glaxosmithkline uk ltd)
49063	augmentin 375mg tablets (doncaster pharmaceuticals ltd)
399	augmentin 375mg tablets (glaxosmithkline uk ltd)
48683	augmentin 375mg tablets (lexon (uk) ltd)
49374	augmentin 375mg tablets (mawdsley-brooks & company ltd)
49048	augmentin 375mg tablets (waymade healthcare plc)
50279	augmentin 625mg tablets (doncaster pharmaceuticals ltd)
509	augmentin 625mg tablets (glaxosmithkline uk ltd)
49656	augmentin 625mg tablets (lexon (uk) ltd)
52207	augmentin 625mg tablets (mawdsley-brooks & company ltd)
49321	augmentin 625mg tablets (sigma pharmaceuticals plc)
49683	augmentin 625mg tablets (waymade healthcare plc)
5341	augmentin-duo 400/57 oral suspension (glaxosmithkline uk ltd)
56591	augmentin-duo 400/57 oral suspension (lexon (uk) ltd)
51194	augmentin-duo 400/57 oral suspension (sigma pharmaceuticals plc)
2127	aureomycin 250mg capsule (wyeth pharmaceuticals)
31007	aureomycin powder (wyeth pharmaceuticals)
25127	avelox 400mg tablets (bayer plc)
26289	bacticlor mr 375mg tablets (ranbaxy (uk) ltd)
4895	benzoyl peroxide 5% / erythromycin 3% gel

CPRD Prodcode	Description
21802	berkmycen 250mg tablet (berk pharmaceuticals ltd)
17093	bisolvomycin capsule (boehringer ingelheim ltd)
21978	blemix 100mg tablets (ashbourne pharmaceuticals ltd)
21865	blemix 50mg tablets (ashbourne pharmaceuticals ltd)
13910	cefaclor 125mg/5ml liquid (generics (uk) ltd)
14607	cefaclor 125mg/5ml liquid (lagap)
1038	cefaclor 125mg/5ml oral suspension
39703	cefaclor 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
34913	cefaclor 125mg/5ml oral suspension (genus pharmaceuticals ltd)
32235	cefaclor 125mg/5ml oral suspension (ranbaxy (uk) ltd)
7526	cefaclor 125mg/5ml oral suspension sugar free
56610	cefaclor 125mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)
9520	cefaclor 250mg capsule (lagap)
366	cefaclor 250mg capsules
30772	cefaclor 250mg capsules (ranbaxy (uk) ltd)
20420	cefaclor 250mg/5ml liquid (generics (uk) ltd)
20409	cefaclor 250mg/5ml liquid (lagap)
3737	cefaclor 250mg/5ml oral suspension
46973	cefaclor 250mg/5ml oral suspension (genus pharmaceuticals ltd)
48025	cefaclor 250mg/5ml oral suspension (ranbaxy (uk) ltd)
9293	cefaclor 250mg/5ml oral suspension sugar free
3180	cefaclor 375mg modified-release tablets
34838	cefaclor 375mg modified-release tablets (a a h pharmaceuticals ltd)
20881	cefaclor 375mg modified-release tablets (ranbaxy (uk) ltd)
4689	cefaclor 500mg capsule (lagap)
2976	cefaclor 500mg capsules
43425	cefaclor 500mg capsules (a a h pharmaceuticals ltd)
55211	cefaclor 500mg capsules (kent pharmaceuticals ltd)
30771	cefaclor 500mg capsules (ranbaxy (uk) ltd)
8051	cefaclor 500mg modified-release tablets
12248	cefalexin 125mg/1.25ml paediatric drops
1693	cefalexin 125mg/5ml oral suspension
29748	cefalexin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
32181	cefalexin 125mg/5ml oral suspension (actavis uk ltd)
53945	cefalexin 125mg/5ml oral suspension (alliance healthcare (distribution) ltd)
39417	cefalexin 125mg/5ml oral suspension (generics (uk) ltd)
32642	cefalexin 125mg/5ml oral suspension (kent pharmaceuticals ltd)
36578	cefalexin 125mg/5ml oral suspension (ranbaxy (uk) ltd)
33329	cefalexin 125mg/5ml oral suspension (teva uk ltd)
6651	cefalexin 125mg/5ml oral suspension sugar free
19144	cefalexin 125mg/5ml oral suspension sugar free (teva uk ltd)
1384	cefalexin 125mg/5ml suspension
18451	cefalexin 1g tablets
33802	cefalexin 250mg capsule (berk pharmaceuticals ltd)

CPRD Prodcode	Description
155	cefalexin 250mg capsules
34253	cefalexin 250mg capsules (a a h pharmaceuticals ltd)
19152	cefalexin 250mg capsules (actavis uk ltd)
54864	cefalexin 250mg capsules (alliance healthcare (distribution) ltd)
52283	cefalexin 250mg capsules (arrow generics ltd)
19160	cefalexin 250mg capsules (generics (uk) ltd)
19133	cefalexin 250mg capsules (ivax pharmaceuticals uk ltd)
41736	cefalexin 250mg capsules (kent pharmaceuticals ltd)
52282	cefalexin 250mg capsules (milpharm ltd)
24090	cefalexin 250mg capsules (pliva pharma ltd)
36599	cefalexin 250mg capsules (ranbaxy (uk) ltd)
9690	cefalexin 250mg capsules (teva uk ltd)
40747	cefalexin 250mg chewable tablets
1146	cefalexin 250mg tablets
33334	cefalexin 250mg tablets (a a h pharmaceuticals ltd)
36330	cefalexin 250mg tablets (actavis uk ltd)
47163	cefalexin 250mg tablets (arrow generics ltd)
36701	cefalexin 250mg tablets (generics (uk) ltd)
31825	cefalexin 250mg tablets (ivax pharmaceuticals uk ltd)
9698	cefalexin 250mg tablets (teva uk ltd)
41825	cefalexin 250mg/5ml oral solution (c p pharmaceuticals ltd)
1860	cefalexin 250mg/5ml oral suspension
42008	cefalexin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
45221	cefalexin 250mg/5ml oral suspension (actavis uk ltd)
29464	cefalexin 250mg/5ml oral suspension (generics (uk) ltd)
41192	cefalexin 250mg/5ml oral suspension (ranbaxy (uk) ltd)
41968	cefalexin 250mg/5ml oral suspension (teva uk ltd)
6671	cefalexin 250mg/5ml oral suspension sugar free
34133	cefalexin 250mg/5ml oral suspension sugar free (teva uk ltd)
1713	cefalexin 250mg/5ml suspension
44755	cefalexin 500mg capsule (berk pharmaceuticals ltd)
400	cefalexin 500mg capsules
32643	cefalexin 500mg capsules (a a h pharmaceuticals ltd)
19138	cefalexin 500mg capsules (actavis uk ltd)
52851	cefalexin 500mg capsules (alliance healthcare (distribution) ltd)
19184	cefalexin 500mg capsules (generics (uk) ltd)
9664	cefalexin 500mg capsules (ivax pharmaceuticals uk ltd)
36569	cefalexin 500mg capsules (kent pharmaceuticals ltd)
54955	cefalexin 500mg capsules (milpharm ltd)
19161	cefalexin 500mg capsules (ranbaxy (uk) ltd)
29281	cefalexin 500mg capsules (teva uk ltd)
865	cefalexin 500mg tablets
29202	cefalexin 500mg tablets (a a h pharmaceuticals ltd)
22321	cefalexin 500mg tablets (generics (uk) ltd)
31827	cefalexin 500mg tablets (ivax pharmaceuticals uk ltd)

CPRD Prodcode	Description
9689	cefalexin 500mg tablets (teva uk ltd)
2227	cefalexin 500mg/5ml oral suspension
17150	ceporex 125mg/1.25ml drops (glaxo laboratories ltd)
7560	ceporex 125mg/5ml liquid (galen ltd)
3609	ceporex 125mg/5ml oral solution (galen ltd)
41106	ceporex 125mg/5ml syrup (co-pharma ltd)
12235	ceporex 1g tablet (galen ltd)
192	ceporex 250mg capsule (galen ltd)
40884	ceporex 250mg capsules (co-pharma ltd)
8019	ceporex 250mg tablet (galen ltd)
41049	ceporex 250mg tablets (co-pharma ltd)
8625	ceporex 250mg/5ml liquid (galen ltd)
8008	ceporex 250mg/5ml oral solution (galen ltd)
40945	ceporex 250mg/5ml syrup (co-pharma ltd)
2661	ceporex 500mg capsule (galen ltd)
40915	ceporex 500mg capsules (co-pharma ltd)
8085	ceporex 500mg tablet (galen ltd)
40914	ceporex 500mg tablets (co-pharma ltd)
5859	ceporex 500mg/5ml oral solution (galen ltd)
41230	ceporex 500mg/5ml syrup (co-pharma ltd)
7881	chlortetracycline 250mg capsules
36689	chlortetracycline hcl syr
17284	chlortetracycline hyd./demeclocycline hy 115.4 mg tab
738	chlortetracycline with demeclocycline with tetracycline tablets
27016	ciprofloxacin
498	ciprofloxacin 100mg tablets
42507	ciprofloxacin 100mg tablets (a a h pharmaceuticals ltd)
48031	ciprofloxacin 100mg tablets (almus pharmaceuticals ltd)
54555	ciprofloxacin 100mg tablets (doncaster pharmaceuticals ltd)
54674	ciprofloxacin 100mg tablets (phoenix healthcare distribution ltd)
39913	ciprofloxacin 100mg tablets (sandoz ltd)
52309	ciprofloxacin 100mg tablets (sigma pharmaceuticals plc)
52945	ciprofloxacin 200mg/100ml solution for infusion vials
56439	ciprofloxacin 200mg/100ml solution for infusion vials (a a h pharmaceuticals ltd)
34647	ciprofloxacin 250mg tablet (neo laboratories ltd)
281	ciprofloxacin 250mg tablets
29343	ciprofloxacin 250mg tablets (a a h pharmaceuticals ltd)
50601	ciprofloxacin 250mg tablets (accord healthcare ltd)
34308	ciprofloxacin 250mg tablets (actavis uk ltd)
51537	ciprofloxacin 250mg tablets (alliance healthcare (distribution) ltd)
54393	ciprofloxacin 250mg tablets (arrow generics ltd)
54701	ciprofloxacin 250mg tablets (bristol laboratories ltd)
56381	ciprofloxacin 250mg tablets (co-pharma ltd)
43814	ciprofloxacin 250mg tablets (dr reddy's laboratories (uk) ltd)

CPRD Prodcode	Description
33989	ciprofloxacin 250mg tablets (generics (uk) ltd)
41561	ciprofloxacin 250mg tablets (ivax pharmaceuticals uk ltd)
54302	ciprofloxacin 250mg tablets (medreich plc)
34448	ciprofloxacin 250mg tablets (niche generics ltd)
34694	ciprofloxacin 250mg tablets (pliva pharma ltd)
34559	ciprofloxacin 250mg tablets (sandoz ltd)
34478	ciprofloxacin 250mg tablets (teva uk ltd)
34655	ciprofloxacin 250mg tablets (wockhardt uk ltd)
4091	ciprofloxacin 250mg/5ml oral suspension
10304	ciprofloxacin 2mg/ml infusion
45341	ciprofloxacin 500mg tablet (neo laboratories ltd)
34322	ciprofloxacin 500mg tablet (niche generics ltd)
583	ciprofloxacin 500mg tablets
29458	ciprofloxacin 500mg tablets (a a h pharmaceuticals ltd)
52501	ciprofloxacin 500mg tablets (accord healthcare ltd)
34605	ciprofloxacin 500mg tablets (actavis uk ltd)
49445	ciprofloxacin 500mg tablets (almus pharmaceuticals ltd)
56789	ciprofloxacin 500mg tablets (apc pharmaceuticals & chemicals (europe) ltd)
52616	ciprofloxacin 500mg tablets (arrow generics ltd)
53641	ciprofloxacin 500mg tablets (co-pharma ltd)
50055	ciprofloxacin 500mg tablets (doncaster pharmaceuticals ltd)
53088	ciprofloxacin 500mg tablets (dr reddy's laboratories (uk) ltd)
30707	ciprofloxacin 500mg tablets (generics (uk) ltd)
42174	ciprofloxacin 500mg tablets (ivax pharmaceuticals uk ltd)
55917	ciprofloxacin 500mg tablets (medreich plc)
43557	ciprofloxacin 500mg tablets (pliva pharma ltd)
53878	ciprofloxacin 500mg tablets (ranbaxy (uk) ltd)
43797	ciprofloxacin 500mg tablets (sandoz ltd)
45285	ciprofloxacin 500mg tablets (teva uk ltd)
34494	ciprofloxacin 500mg tablets (wockhardt uk ltd)
34973	ciprofloxacin 750mg tablet (niche generics ltd)
1837	ciprofloxacin 750mg tablets
29472	ciprofloxacin 750mg tablets (a a h pharmaceuticals ltd)
43517	ciprofloxacin 750mg tablets (actavis uk ltd)
52099	ciprofloxacin 750mg tablets (bristol laboratories ltd)
56856	ciprofloxacin 750mg tablets (ranbaxy (uk) ltd)
28544	ciprofloxaxin 400mg/200ml in glucose 5% infusion
9154	ciproxin 100mg tablets (bayer plc)
1202	ciproxin 250mg tablets (bayer plc)
52353	ciproxin 250mg tablets (doncaster pharmaceuticals ltd)
53519	ciproxin 250mg tablets (lexon (uk) ltd)
163	ciproxin 250mg/5ml oral suspension (bayer plc)
728	ciproxin 500mg tablets (bayer plc)
52807	ciproxin 500mg tablets (mawdsley-brooks & company ltd)
52177	ciproxin 500mg tablets (sigma pharmaceuticals plc)

CPRD Prodcode	Description
49839	ciproxin 500mg tablets (waymade healthcare plc)
7752	ciproxin 750mg tablets (bayer plc)
45591	clarie xl 500mg tablets (teva uk ltd)
10326	clarithromycin 125mg granules straws
331	clarithromycin 125mg/5ml oral suspension
45795	clarithromycin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
54903	clarithromycin 125mg/5ml oral suspension (alliance healthcare (distribution) ltd)
51831	clarithromycin 125mg/5ml oral suspension (phoenix healthcare distribution ltd)
41453	clarithromycin 125mg/5ml oral suspension (ranbaxy (uk) ltd)
53168	clarithromycin 125mg/5ml oral suspension (sandoz ltd)
26059	clarithromycin 187.5mg granules straws
765	clarithromycin 250mg granules sachets
17645	clarithromycin 250mg granules straws
537	clarithromycin 250mg tablets
34650	clarithromycin 250mg tablets (a a h pharmaceuticals ltd)
54472	clarithromycin 250mg tablets (accord healthcare ltd)
48163	clarithromycin 250mg tablets (actavis uk ltd)
52158	clarithromycin 250mg tablets (alliance healthcare (distribution) ltd)
54882	clarithromycin 250mg tablets (almus pharmaceuticals ltd)
52719	clarithromycin 250mg tablets (apotex uk ltd)
53086	clarithromycin 250mg tablets (doncaster pharmaceuticals ltd)
34394	clarithromycin 250mg tablets (generics (uk) ltd)
51154	clarithromycin 250mg tablets (kent pharmaceuticals ltd)
53153	clarithromycin 250mg tablets (phoenix healthcare distribution ltd)
53688	clarithromycin 250mg tablets (ranbaxy (uk) ltd)
47582	clarithromycin 250mg tablets (sandoz ltd)
50946	clarithromycin 250mg tablets (sigma pharmaceuticals plc)
54269	clarithromycin 250mg tablets (somex pharma)
34533	clarithromycin 250mg tablets (teva uk ltd)
54897	clarithromycin 250mg tablets (tillomed laboratories ltd)
53144	clarithromycin 250mg tablets (wockhardt uk ltd)
5357	clarithromycin 250mg/5ml oral suspension
54241	clarithromycin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
55148	clarithromycin 250mg/5ml oral suspension (alliance healthcare (distribution) ltd)
34811	clarithromycin 250mg/5ml oral suspension (ranbaxy (uk) ltd)
53179	clarithromycin 250mg/5ml oral suspension (sandoz ltd)
54208	clarithromycin 250mg/5ml oral suspension (sigma pharmaceuticals plc)
55428	clarithromycin 250mg/5ml oral suspension (waymade healthcare plc)
54529	clarithromycin 500mg modified-release tablet (hillcross pharmaceuticals ltd)
6803	clarithromycin 500mg modified-release tablets
681	clarithromycin 500mg tablets
38163	clarithromycin 500mg tablets (a a h pharmaceuticals ltd)
51426	clarithromycin 500mg tablets (accord healthcare ltd)

CPRD Prodcode	Description
48023	clarithromycin 500mg tablets (actavis uk ltd)
49939	clarithromycin 500mg tablets (alliance healthcare (distribution) ltd)
53715	clarithromycin 500mg tablets (almus pharmaceuticals ltd)
53776	clarithromycin 500mg tablets (doncaster pharmaceuticals ltd)
34608	clarithromycin 500mg tablets (generics (uk) ltd)
53703	clarithromycin 500mg tablets (kent pharmaceuticals ltd)
46488	clarithromycin 500mg tablets (ranbaxy (uk) ltd)
40784	clarithromycin 500mg tablets (sandoz ltd)
53109	clarithromycin 500mg tablets (somex pharma)
34974	clarithromycin 500mg tablets (teva uk ltd)
53875	clarithromycin 500mg tablets (tillomed laboratories ltd)
28349	clarosip 125mg granules for oral suspension straws (grunenthal ltd)
31689	clarosip 187.5mg granules for oral suspension straws (grunenthal ltd)
31690	clarosip 250mg granules for oral suspension straws (grunenthal ltd)
9925	clavulanic acid 125mg with amoxicillin 250mg tablets
13239	clavulanic acid 125mg with amoxicillin 500mg tablets
24006	clavulanic acid 31mg with amoxcillin 125mg/5ml oral suspension
21775	clavulanic acid 31mg with amoxicillin 125mg/5ml sugar free oral suspension
20432	clavulanic acid 57mg with amoxicillin 400mg/5ml sugar free suspension
42485	clavulanic acid 62mg with amoxicillin 250mg/5ml oral suspension
16612	clavulanic acid 62mg with amoxicillin 250mg/5ml sugar free suspension
24093	clavulanic acid with amoxicillin dispersible tablets
12504	clomocycline 170mg capsules
10200	co-amoxiclav 125mg/31mg/5ml oral suspension
54052	co-amoxiclav 125mg/31mg/5ml oral suspension (a a h pharmaceuticals ltd)
54732	co-amoxiclav 125mg/31mg/5ml oral suspension (generics (uk) ltd)
1638	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free
43548	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
54324	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (actavis uk ltd)
54452	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
54808	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
28874	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
56884	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)
34680	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (ranbaxy (uk) ltd)
34972	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (sandoz ltd)
829	co-amoxiclav 250mg/125mg dispersible tablets sugar free
545	co-amoxiclav 250mg/125mg tablets
30786	co-amoxiclav 250mg/125mg tablets (a a h pharmaceuticals ltd)
19209	co-amoxiclav 250mg/125mg tablets (actavis uk ltd)
51623	co-amoxiclav 250mg/125mg tablets (alliance healthcare (distribution) ltd)
48147	co-amoxiclav 250mg/125mg tablets (almus pharmaceuticals ltd)
34297	co-amoxiclav 250mg/125mg tablets (generics (uk) ltd)

CPRD Prodcode	Description
28871	co-amoxiclav 250mg/125mg tablets (ivax pharmaceuticals uk ltd)
33693	co-amoxiclav 250mg/125mg tablets (kent pharmaceuticals ltd)
50446	co-amoxiclav 250mg/125mg tablets (phoenix healthcare distribution ltd)
30783	co-amoxiclav 250mg/125mg tablets (ranbaxy (uk) ltd)
19414	co-amoxiclav 250mg/125mg tablets (sandoz ltd)
34734	co-amoxiclav 250mg/125mg tablets (teva uk ltd)
55312	co-amoxiclav 250mg/125mg tablets (waymade healthcare plc)
46915	co-amoxiclav 250mg/125mg tablets (zentiva)
7364	co-amoxiclav 250mg/62mg/5ml oral suspension
54708	co-amoxiclav 250mg/62mg/5ml oral suspension (a a h pharmaceuticals ltd)
54780	co-amoxiclav 250mg/62mg/5ml oral suspension (generics (uk) ltd)
524	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free
42227	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
51678	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
37304	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
40320	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (ranbaxy (uk) ltd)
46918	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (sandoz ltd)
34234	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (teva uk ltd)
56578	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (waymade healthcare plc)
6687	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free
51637	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
641	co-amoxiclav 500mg/125mg tablets
33701	co-amoxiclav 500mg/125mg tablets (a a h pharmaceuticals ltd)
50742	co-amoxiclav 500mg/125mg tablets (actavis uk ltd)
50341	co-amoxiclav 500mg/125mg tablets (alliance healthcare (distribution) ltd)
53609	co-amoxiclav 500mg/125mg tablets (apc pharmaceuticals & chemicals (europe) ltd)
53996	co-amoxiclav 500mg/125mg tablets (aurobindo pharma ltd)
30705	co-amoxiclav 500mg/125mg tablets (generics (uk) ltd)
29356	co-amoxiclav 500mg/125mg tablets (ivax pharmaceuticals uk ltd)
40148	co-amoxiclav 500mg/125mg tablets (kent pharmaceuticals ltd)
49610	co-amoxiclav 500mg/125mg tablets (medreich plc)
54591	co-amoxiclav 500mg/125mg tablets (phoenix healthcare distribution ltd)
34493	co-amoxiclav 500mg/125mg tablets (ranbaxy (uk) ltd)
32910	co-amoxiclav 500mg/125mg tablets (sandoz ltd)
29353	co-amoxiclav 500mg/125mg tablets (teva uk ltd)
44154	co-amoxiclav 500mg/125mg tablets (zentiva)
21860	cyclodox 100mg capsule (berk pharmaceuticals ltd)
24245	cyclomin 100mg tablet (berk pharmaceuticals ltd)
21837	cyclomin 50mg tablet (berk pharmaceuticals ltd)
9131	demeclocycline 150mg capsules
8694	demeclocycline 300mg tablets

CPRD Prodcode	Description
50765	demeclocycline 300mg/5ml oral solution
24643	demeclocycline with chlortetracycline with tetracycline tablets
21878	demix 100 capsules (ashbourne pharmaceuticals ltd)
21828	demix 50 capsules (ashbourne pharmaceuticals ltd)
2256	deteclo 300mg tablet (wyeth pharmaceuticals)
13327	deteclo 300mg tablets (mercury pharma group ltd)
2428	distaclor 125mg/5ml liquid (dista products ltd)
25384	distaclor 125mg/5ml oral suspension (flynn pharma ltd)
4576	distaclor 250mg capsule (dista products ltd)
9219	distaclor 250mg/5ml liquid (dista products ltd)
22042	distaclor 250mg/5ml oral suspension (flynn pharma ltd)
7889	distaclor 375mg modified-release tablet (dista products ltd)
319	distaclor 500mg capsule (dista products ltd)
18243	distaclor 500mg capsules (flynn pharma ltd)
3523	distaclor 500mg modified-release tablet (dista products ltd)
20992	distaclor mr 375mg tablets (flynn pharma ltd)
21038	doxatet 100mg tablet (manufacturer unknown)
2884	doxycycline (as hyclate) 100mg dispersible tablets
970	doxycycline (as hyclate) 100mg tablets
12987	doxycycline (as hyclate) 50mg capsules with microgranules
23819	doxycycline (as hyclate) 50mg capsules with microgranules
8724	doxycycline (as hyclate) 50mg/5ml oral solution
41560	doxycycline 100mg capsule (ivax pharmaceuticals uk ltd)
34594	doxycycline 100mg capsule (neo laboratories ltd)
34423	doxycycline 100mg capsule (pliva pharma ltd)
41605	doxycycline 100mg capsule (sandoz ltd)
1046	doxycycline 100mg capsules
24149	doxycycline 100mg capsules (a a h pharmaceuticals ltd)
34300	doxycycline 100mg capsules (actavis uk ltd)
49737	doxycycline 100mg capsules (alliance healthcare (distribution) ltd)
46807	doxycycline 100mg capsules (almus pharmaceuticals ltd)
32066	doxycycline 100mg capsules (generics (uk) ltd)
24126	doxycycline 100mg capsules (ivax pharmaceuticals uk ltd)
33671	doxycycline 100mg capsules (kent pharmaceuticals ltd)
53310	doxycycline 100mg capsules (sigma pharmaceuticals plc)
30739	doxycycline 100mg capsules (teva uk ltd)
55519	doxycycline 100mg capsules (waymade healthcare plc)
6396	doxycycline 100mg dispersible tablets sugar free
26747	doxycycline 100mg tablet (neo laboratories ltd)
40796	doxycycline 40mg modified-release capsules
264	doxycycline 50mg capsules
34175	doxycycline 50mg capsules (a a h pharmaceuticals ltd)
48095	doxycycline 50mg capsules (actavis uk ltd)
53973	doxycycline 50mg capsules (alliance healthcare (distribution) ltd)
34765	doxycycline 50mg capsules (generics (uk) ltd)

CPRD Prodcode	Description
40391	doxycycline 50mg capsules (ivax pharmaceuticals uk ltd)
32419	doxycycline 50mg capsules (teva uk ltd)
23405	doxylar 100mg capsules (sandoz ltd)
23432	doxylar 50mg capsules (sandoz ltd)
17226	economycin 250mg capsule (ddsa pharmaceuticals ltd)
26111	economycin 250mg tablet (ddsa pharmaceuticals ltd)
40980	efracea 40mg modified-release capsules (galderma (uk) ltd)
4489	erycen 250mg tablet (berk pharmaceuticals ltd)
23017	erycen 500mg tablet (berk pharmaceuticals ltd)
318	erymax 250mg capsule (elan pharma)
10190	erymax 250mg gastro-resistant capsules (teva uk ltd)
14511	erymax sprinkle 125mg capsule (elan pharma)
9434	erymin 250mg/5ml oral suspension (elan pharma)
48017	erythoden 125mg/5ml liquid (stevenden healthcare)
41389	erythoden 250mg/5ml liquid (stevenden healthcare)
39616	erythrocin 250 tablets (amdipharm plc)
480	erythrocin 250mg tablet (abbott laboratories ltd)
1072	erythrocin 500 500mg tablet (abbott laboratories ltd)
39613	erythrocin 500 tablets (amdipharm plc)
53449	erythrocin 500 tablets (lexon (uk) ltd)
51984	erythrocin 500 tablets (mawdsley-brooks & company ltd)
53004	erythrocin 500 tablets (necessity supplies ltd)
50693	erythrocin 500 tablets (sigma pharmaceuticals plc)
50223	erythrocin 500 tablets (stephar (u.k.) ltd)
27768	erythrolar 250mg tablet (lagap)
50205	erythrolar 250mg tablets (ennogen pharma ltd)
4153	erythrolar 250mg/5ml liquid (lagap)
23954	erythrolar 500mg tablet (lagap)
49301	erythrolar 500mg tablets (ennogen pharma ltd)
3209	erythromid 250mg tablet (abbott laboratories ltd)
9148	erythromid ds 500mg tablet (abbott laboratories ltd)
1376	erythromycin 100 mg syr
7792	erythromycin 12 mg syr
14429	erythromycin 125mg sprinkle capsules
34231	erythromycin 125mg/5ml liquid (berk pharmaceuticals ltd)
33248	erythromycin 125mg/5ml liquid (ivax pharmaceuticals uk ltd)
397	erythromycin 125mg/5ml oral suspension
9656	erythromycin 2% gel
1969	erythromycin 250 mg mix
29154	erythromycin 250mg capsule (actavis uk ltd)
103	erythromycin 250mg gastro-resistant capsules
33686	erythromycin 250mg gastro-resistant capsules (a a h pharmaceuticals ltd)
50580	erythromycin 250mg gastro-resistant capsules (actavis uk ltd)
50694	erythromycin 250mg gastro-resistant capsules (alliance healthcare (distribution) ltd)

CPRD Prodcode	Description
55133	erythromycin 250mg gastro-resistant capsules (kent pharmaceuticals ltd)
49952	erythromycin 250mg gastro-resistant capsules (phoenix healthcare distribution ltd)
34512	erythromycin 250mg gastro-resistant capsules (teva uk ltd)
55397	erythromycin 250mg gastro-resistant capsules (waymade healthcare plc)
34837	erythromycin 250mg gastro-resistant tablet (co-pharma ltd)
63	erythromycin 250mg gastro-resistant tablets
24127	erythromycin 250mg gastro-resistant tablets (a a h pharmaceuticals ltd)
33703	erythromycin 250mg gastro-resistant tablets (abbott laboratories ltd)
29344	erythromycin 250mg gastro-resistant tablets (actavis uk ltd)
52906	erythromycin 250mg gastro-resistant tablets (alliance healthcare (distribution) ltd)
42661	erythromycin 250mg gastro-resistant tablets (almus pharmaceuticals ltd)
52952	erythromycin 250mg gastro-resistant tablets (co-pharma ltd)
42296	erythromycin 250mg gastro-resistant tablets (dr reddy's laboratories (uk) ltd)
34334	erythromycin 250mg gastro-resistant tablets (generics (uk) ltd)
24129	erythromycin 250mg gastro-resistant tablets (ivax pharmaceuticals uk ltd)
53986	erythromycin 250mg gastro-resistant tablets (medreich plc)
55483	erythromycin 250mg gastro-resistant tablets (milpharm ltd)
52428	erythromycin 250mg gastro-resistant tablets (phoenix healthcare distribution ltd)
31530	erythromycin 250mg gastro-resistant tablets (ranbaxy (uk) ltd)
34479	erythromycin 250mg gastro-resistant tablets (sovereign medical ltd)
33685	erythromycin 250mg gastro-resistant tablets (teva uk ltd)
34873	erythromycin 250mg tablet (berk pharmaceuticals ltd)
34189	erythromycin 250mg tablet (c p pharmaceuticals ltd)
553	erythromycin 250mg.5ml oral suspension
47242	erythromycin 250mg/5ml liquid (c p pharmaceuticals ltd)
41584	erythromycin 250mg/5ml liquid (ivax pharmaceuticals uk ltd)
3408	erythromycin 500 mg cap
401	erythromycin 500mg ec gastro-resistant tablets
34869	erythromycin 500mg tablet (c p pharmaceuticals ltd)
41604	erythromycin 500mg tablet (hillcross pharmaceuticals ltd)
26365	erythromycin 500mg tablet (ivax pharmaceuticals uk ltd)
55300	erythromycin 500mg tablet (teva uk ltd)
47676	erythromycin 500mg/5ml liquid (c p pharmaceuticals ltd)
2326	erythromycin 500mg/5ml oral suspension
37796	erythromycin estolate 125mg/5ml suspension
9903	erythromycin estolate 250mg capsules
40073	erythromycin estolate 250mg/5ml suspension
37694	erythromycin estolate 500mg tablets
2429	erythromycin ethyl succinate 125mg/5ml oral suspension
13167	erythromycin ethyl succinate 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
49978	erythromycin ethyl succinate 125mg/5ml oral suspension (focus pharmaceuticals ltd)
50948	erythromycin ethyl succinate 125mg/5ml oral suspension (phoenix healthcare

CPRD Prodcode	Description
	distribution ltd)
47126	erythromycin ethyl succinate 125mg/5ml oral suspension (pinewood healthcare)
34779	erythromycin ethyl succinate 125mg/5ml oral suspension (sandoz ltd)
4672	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free
33697	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
42659	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (abbott laboratories ltd)
55589	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
48101	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (focus pharmaceuticals ltd)
33695	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (generics (uk) ltd)
34795	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
45870	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (pinewood healthcare)
33705	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (teva uk ltd)
2376	erythromycin ethyl succinate 250mg/5ml oral suspension
13120	erythromycin ethyl succinate 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
32902	erythromycin ethyl succinate 250mg/5ml oral suspension (kent pharmaceuticals ltd)
46696	erythromycin ethyl succinate 250mg/5ml oral suspension (sandoz ltd)
2225	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free
32898	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
46154	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (abbott laboratories ltd)
52860	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
33694	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (generics (uk) ltd)
30177	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
34853	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (teva uk ltd)
733	erythromycin ethyl succinate 500mg tablets
2226	erythromycin ethyl succinate 500mg/5ml oral suspension
30980	erythromycin ethyl succinate 500mg/5ml oral suspension (kent pharmaceuticals ltd)
14171	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free
31514	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (abbott laboratories ltd)
25595	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
27203	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (teva uk ltd)
25751	erythromycin ethylsuccinate (coated) 250mg/5ml oral suspension sugar free
30234	erythromycin ethylsuccinate 125mg sachets

CPRD Prodcode	Description
12330	erythromycin ethylsuccinate 1g sachets
13635	erythromycin ethylsuccinate 250mg sachets
15713	erythromycin ethylsuccinate 500mg sachets
1037	erythromycin ethylsuccinate sf 125 mg/5ml sus
3907	erythromycin sf sach 250 mg
438	erythromycin stearate 250mg tablets
2350	erythromycin stearate 500mg tablets
3572	erythroped 250mg powder (abbott laboratories ltd)
16747	erythroped 250mg sachets (abbott laboratories ltd)
105	erythroped 250mg/5ml liquid (abbott laboratories ltd)
532	erythroped 250mg/5ml oral suspension (abbott laboratories ltd)
4596	erythroped a 1g sachets (abbott laboratories ltd)
327	erythroped a 500mg tablet (abbott laboratories ltd)
39632	erythroped a 500mg tablets (amdipharm plc)
54098	erythroped a 500mg tablets (lexon (uk) ltd)
56203	erythroped a 500mg tablets (sigma pharmaceuticals plc)
4372	erythroped forte 500mg sachets (abbott laboratories ltd)
993	erythroped forte 500mg/5ml liquid (abbott laboratories ltd)
4610	erythroped forte 500mg/5ml oral suspension (abbott laboratories ltd)
39642	erythroped forte sf 500mg/5ml oral suspension (amdipharm plc)
3042	erythroped pi 125mg sachets (abbott laboratories ltd)
997	erythroped pi 125mg/5ml liquid (abbott laboratories ltd)
825	erythroped pi 125mg/5ml oral suspension (abbott laboratories ltd)
39623	erythroped pi sf 125mg/5ml oral suspension (amdipharm plc)
39669	erythroped sf 250mg/5ml oral suspension (amdipharm plc)
18930	flemoxin 375mg soluble tablet (paines & byrne ltd)
24396	flemoxin 750mg soluble tablet (paines & byrne ltd)
14386	galenamox 125mg/5ml oral suspension (galen ltd)
14371	galenamox 250mg capsules (galen ltd)
14407	galenamox 250mg/5ml oral suspension (galen ltd)
14396	galenamox 500mg capsules (galen ltd)
18682	ilosone 125mg/5ml liquid (dista products ltd)
17207	ilosone 250mg capsule (dista products ltd)
19330	ilosone 250mg/5ml liquid (dista products ltd)
18643	ilosone 500mg tablet (dista products ltd)
23244	ilotycin 250mg tablet (eli lilly and company ltd)
12541	imperacin 250mg tablet (astrazeneca uk ltd)
7485	keflex 125mg/5ml liquid (eli lilly and company ltd)
27072	keflex 125mg/5ml oral suspension (flynn pharma ltd)
7430	keflex 250mg capsule (eli lilly and company ltd)
11989	keflex 250mg capsules (flynn pharma ltd)
9157	keflex 250mg tablet (eli lilly and company ltd)
830	keflex 250mg tablets (flynn pharma ltd)
10455	keflex 250mg/5ml liquid (eli lilly and company ltd)
28722	keflex 250mg/5ml oral suspension (flynn pharma ltd)

CPRD Prodcode	Description
12276	keflex 500mg capsule (eli lilly and company ltd)
24618	keflex 500mg capsules (flynn pharma ltd)
9603	keflex 500mg tablet (eli lilly and company ltd)
31110	keflex 500mg tablets (flynn pharma ltd)
26233	keftid 125mg/5ml oral suspension (co-pharma ltd)
26207	keftid 250mg capsules (co-pharma ltd)
41853	keftid 250mg/5ml oral suspension (co-pharma ltd)
26236	keftid 500mg capsules (co-pharma ltd)
33304	kerymax 250mg gastro-resistant capsules (kent pharmaceuticals ltd)
26989	kiflone 125mg/5ml oral solution (berk pharmaceuticals ltd)
21835	kiflone 250mg capsule (berk pharmaceuticals ltd)
21979	kiflone 250mg/5ml oral solution (berk pharmaceuticals ltd)
27017	kiflone 500mg capsule (berk pharmaceuticals ltd)
26992	kiflone 500mg tablet (berk pharmaceuticals ltd)
3736	klaricid 125mg/5ml oral suspension (abbott laboratories ltd)
2719	klaricid 250mg tablets (abbott laboratories ltd)
52411	klaricid 250mg tablets (necessity supplies ltd)
9583	klaricid 250mg/5ml oral suspension (abbott laboratories ltd)
6623	klaricid 500 tablets (abbott laboratories ltd)
14816	klaricid adult 250mg granules sachets (abbott laboratories ltd)
38997	klaricid paediatric 125mg/5ml oral suspension (abbott laboratories ltd)
39010	klaricid paediatric 250mg/5ml oral suspension (abbott laboratories ltd)
6121	klaricid xl 500mg tablets (abbott laboratories ltd)
7439	ledermycin 150mg capsule (wyeth pharmaceuticals)
16613	ledermycin 150mg capsules (mercury pharma group ltd)
22076	ledermycin 300mg tablet (wyeth pharmaceuticals)
6295	levofloxacin 250mg tablets
55708	levofloxacin 250mg tablets (actavis uk ltd)
56012	levofloxacin 250mg tablets (dr reddy's laboratories (uk) ltd)
5238	levofloxacin 500mg tablets
53673	levofloxacin 500mg/100ml infusion bags
453	lymecycline 408mg capsules
19001	megaclor 170mg capsule (pharmax ltd)
3413	minocin 100mg tablets (wyeth pharmaceuticals)
164	minocin 50mg tablets (wyeth pharmaceuticals)
1039	minocin mr 100mg capsules (meda pharmaceuticals ltd)
9380	minocycline 100mg capsules
2578	minocycline 100mg modified-release capsules
34077	minocycline 100mg modified-release capsules (a a h pharmaceuticals ltd)
46954	minocycline 100mg tablet (lagap)
1532	minocycline 100mg tablets
34926	minocycline 100mg tablets (a a h pharmaceuticals ltd)
40383	minocycline 100mg tablets (actavis uk ltd)
429	minocycline 50mg capsules
43700	minocycline 50mg tablet (lagap)

CPRD Prodcode	Description
2999	minocycline 50mg tablets
46947	minocycline 50mg tablets (actavis uk ltd)
6306	moxifloxacin 400mg tablets
1013	mysteclin capsule (bristol-myers squibb pharmaceuticals ltd)
17222	mysteclin oral solution (bristol-myers squibb pharmaceuticals ltd)
1828	mysteclin tablet (bristol-myers squibb pharmaceuticals ltd)
15071	nordox 100mg capsule (sankyo pharma uk ltd)
8393	novobiocin/tetracycline 125 mg cap
25752	nystatin with tetracycline hc capsule
9361	oxymycin 250mg tablets (dr reddy's laboratories (uk) ltd)
2458	oxytetracycline 100 mg tab
9034	oxytetracycline 125mg/5ml syrup
8285	oxytetracycline 250 mg syr
132	oxytetracycline 250mg capsules
34888	oxytetracycline 250mg tablet (c p pharmaceuticals ltd)
77	oxytetracycline 250mg tablets
34044	oxytetracycline 250mg tablets (a a h pharmaceuticals ltd)
34040	oxytetracycline 250mg tablets (actavis uk ltd)
34336	oxytetracycline 250mg tablets (ivax pharmaceuticals uk ltd)
40483	oxytetracycline 250mg tablets (sandoz ltd)
34141	oxytetracycline 250mg tablets (teva uk ltd)
3025	oxytetracycline 500 mg tab
17703	oxytetramix 250 tablets (ashbourne pharmaceuticals ltd)
30520	primacine 125mg/5ml liquid (pinewood healthcare)
39118	primacine 250mg/5ml liquid (pinewood healthcare)
27504	primacine 500mg/5ml liquid (pinewood healthcare)
27681	ranclav 125mg/31mg/5ml sf oral suspension (ranbaxy (uk) ltd)
25370	ranclav 375mg tablets (ranbaxy (uk) ltd)
22015	respillin 125mg/5ml oral solution (opd pharm)
22017	respillin 125mg/5ml oral solution (opd pharm)
24203	respillin 250mg capsule (opd pharm)
24200	respillin 500mg capsule (opd pharm)
31428	retcin 250mg tablet (ddsa pharmaceuticals ltd)
21808	rommix 125mg/5ml oral suspension sugar free (ashbourne pharmaceuticals ltd)
11611	rommix 250 ec tablets (ashbourne pharmaceuticals ltd)
25278	rommix 500mg tablet (ashbourne pharmaceuticals ltd)
24097	rondomycin 150mg capsule (pfizer ltd)
18109	sebomin mr 100mg capsules (actavis uk ltd)
37440	sebren mr 100mg capsules (teva uk ltd)
19693	sustamycin 250mg capsule (boehringer mannheim uk ltd)
17693	tavanic 250mg tablets (sanofi)
6206	tavanic 500mg tablets (sanofi)
27254	tenkorex 500mg capsule (opd pharm)
7455	terramycin 250mg capsule (pfizer ltd)

CPRD Prodcode	Description
17467	terramycin 250mg tablets (pfizer ltd)
9014	tetrabid-organon 250mg capsule (organon laboratories ltd)
8219	tetrachel 250mg capsule (berk pharmaceuticals ltd)
3816	tetrachel 250mg tablet (berk pharmaceuticals ltd)
25017	tetracycline
56044	tetracycline 125mg/5ml oral solution
8284	tetracycline 125mg/5ml syrup
21804	tetracycline 125mg/5ml syrup
41547	tetracycline 250mg capsule (berk pharmaceuticals ltd)
121	tetracycline 250mg capsules
34011	tetracycline 250mg capsules
56181	tetracycline 250mg tablet (celltech pharma europe ltd)
45271	tetracycline 250mg tablet (numark management ltd)
386	tetracycline 250mg tablets
43538	tetracycline 250mg tablets (a a h pharmaceuticals ltd)
41636	tetracycline 250mg tablets (actavis uk ltd)
54214	tetracycline 250mg tablets (alliance healthcare (distribution) ltd)
53117	tetracycline 250mg tablets (almus pharmaceuticals ltd)
48100	tetracycline 250mg tablets (teva uk ltd)
2922	tetracycline 250mg with nystatin 250000units tablets
2636	tetracycline 500 mg cap
3528	tetracycline 500 mg tab
21654	tetracycline ear/eye
21629	tetracycline eye
31425	tetracycline hcl/pancreatic concentrate cap
28736	tetracycline hydrochloride/amphotericin syr
15355	tetracycline with chlortetracycline & demeclocycline tablets
25071	tetracycline with nystatin capsules
4951	tetralysal 300 capsules (galderma (uk) ltd)
20054	tetralysal 408mg capsule (pharmacia ltd)
25280	tiloryth 250mg gastro-resistant capsules (tillomed laboratories ltd)
268	vibramycin 100mg capsules (pfizer ltd)
3152	vibramycin 100mg dispersible tablet (pfizer ltd)
2202	vibramycin 50 capsules (pfizer ltd)
10454	vibramycin 50mg/5ml oral solution (pfizer ltd)
9267	vibramycin acne pack 50mg capsules (pfizer ltd)
56198	vibramycin-d 100mg dispersible tablets (mawdsley-brooks & company ltd)
14904	vibramycin-d 100mg dispersible tablets (pfizer ltd)
52967	vibramycin-d 100mg dispersible tablets (stephar (u.k.) ltd)
53135	vibramycin-d 100mg dispersible tablets (waymade healthcare plc)
26392	vibrox 100mg capsules (kent pharmaceuticals ltd)
21829	zoxycil 250mg capsule (trinity pharmaceuticals ltd)
26262	zoxycil 500mg capsule (trinity pharmaceuticals ltd)

Prescriptions of pre-specified oral corticosteroid (OCS)

CPRD Prodcode	Description
30971	decortisyl 25 mg tab
21833	decortisyl 5mg tablet (roussel laboratories ltd)
27962	deltastab 1mg tablet (waymade healthcare plc)
30390	deltastab 2 mg tab
28859	deltastab 5mg tablet (waymade healthcare plc)
54432	lodotra 1mg modified-release tablets (napp pharmaceuticals ltd)
44803	lodotra 2mg modified-release tablets (napp pharmaceuticals ltd)
44802	lodotra 5mg modified-release tablets (napp pharmaceuticals ltd)
25272	precortisyl 1mg tablet (hoechst marion roussel)
23512	precortisyl 5mg tablet (hoechst marion roussel)
20095	precortisyl forte 25mg tablet (aventis pharma)
1063	prednesol 5mg tablet (sovereign medical ltd)
27889	prednisolone
27959	prednisolone
2799	prednisolone 10 mg tab
7710	prednisolone 15 mg tab
34914	prednisolone 1mg tablet (celltech pharma europe ltd)
34631	prednisolone 1mg tablet (co-pharma ltd)
13522	prednisolone 2 mg tab
28376	prednisolone 2.5mg gastro-resistant tablet (biorex laboratories ltd)
2368	prednisolone 2.5mg tablet
38407	prednisolone 20mg tablet
7584	prednisolone 4 mg tab
34109	prednisolone 5 mg gastro-resistant tablet
3059	prednisolone 50 mg tab
9727	prednisolone 50mg tablets
33691	prednisolone 5mg gastro-resistant tablet (biorex laboratories ltd)
47142	prednisolone 5mg soluble tablet (amdipharm plc)
45302	prednisolone 5mg tablet (biorex laboratories ltd)
33988	prednisolone 5mg tablet (co-pharma ltd)
33990	prednisolone 5mg tablet (ivax pharmaceuticals uk ltd)
95	prednisolone 5mg tablets
20670	prednisolone e/c
24716	prednisolone e/c
2390	prednisolone e/c 1 mg tab
31327	prednisolone steaglate 6.65mg tablet
13615	prednisone 10 mg tab
44380	prednisone 1mg modified-release tablets
3557	prednisone 1mg tablets
2044	prednisone 2.5 mg tab
46711	prednisone 2mg modified-release tablets
7934	prednisone 30 mg tab
16724	prednisone 50 mg tab

CPRD Prodcode	Description
44723	prednisone 5mg modified-release tablets
43544	prednisone 5mg tablet (knoll ltd)
2949	prednisone 5mg tablets
3345	sintisone tablet (pharmacia ltd)

Exacerbation symptoms

CPRD Medcode	Description	Symptom
735	[d]breathlessness	breathless
3092	[d]dyspnoea	breathless
2563	[d]respiratory distress	breathless
9297	[d]respiratory insufficiency	breathless
741	[d]shortness of breath	breathless
31143	breathless - at rest	breathless
7683	breathless - lying flat	breathless
7932	breathless - mild exertion	breathless
6326	breathless - moderate exertion	breathless
24889	breathless - strenuous exertion	breathless
1429	breathlessness	breathless
21801	breathlessness nos	breathless
5175	breathlessness symptom	breathless
2931	difficulty breathing	breathless
5896	dyspnoea - symptom	breathless
53771	dyspnoea on exertion	breathless
18116	nocturnal dyspnoea	breathless
7000	o/e - dyspnoea	breathless
7534	o/e - respiratory distress	breathless
6434	paroxysmal nocturnal dyspnoea	breathless
2737	respiratory distress syndrome	breathless
22094	short of breath dressing/undressing	breathless
2575	short of breath on exertion	breathless
4822	shortness of breath	breathless
5349	shortness of breath symptom	breathless
40813	Unable to complete a sentence in one breath	breathless
1160	[d]cough	cough
8239	[d]cough with haemorrhage	cough
1025	bronchial cough	cough
1273	c/o - cough	cough
292	chesty cough	cough
92	cough	cough
60903	cough aggravates symptom	cough
100515	cough swab	cough
7707	cough symptom nos	cough
18907	cough with fever	cough
3645	coughing up phlegm	cough
22318	difficulty in coughing up sputum	cough
4931	dry cough	cough
29318	evening cough	cough
4070	morning cough	cough
3068	night cough present	cough
4836	nocturnal cough / wheeze	cough
7706	productive cough -clear sputum	cough

CPRD Medcode	Description	Symptom
7773	productive cough -green sputum	cough
1234	productive cough nos	cough
7708	productive cough-yellow sputum	cough
1251	[d]abnormal sputum	sputum
36515	[d]abnormal sputum - tenacious	sputum
23582	[d]abnormal sputum nos	sputum
8760	[d]positive culture findings in sputum	sputum
20086	[d]sputum abnormal - amount	sputum
15430	[d]sputum abnormal - colour	sputum
44214	[d]sputum abnormal - odour	sputum
11072	acute purulent bronchitis	sputum
1025	bronchial cough	sputum
100931	brown sputum	sputum
292	chesty cough	sputum
100647	copious sputum	sputum
3645	Coughing up phlegm	sputum
22318	difficulty in coughing up sputum	sputum
36880	green sputum	sputum
103209	grey sputum	sputum
100524	moderate sputum	sputum
7706	productive cough -clear sputum	sputum
7773	productive cough -green sputum	sputum
1234	productive cough nos	sputum
7708	productive cough-yellow sputum	sputum
101782	profuse sputum	sputum
9807	sputum - symptom	sputum
14273	sputum appearance	sputum
14804	sputum appears infected	sputum
18964	sputum clearance	sputum
14271	sputum culture	sputum
43270	sputum evidence of infection	sputum
16026	sputum examination: abnormal	sputum
14272	sputum microscopy	sputum
23252	sputum microscopy nos	sputum
8287	sputum sample obtained	sputum
3727	sputum sent for c/s	sputum
30904	sputum sent for examination	sputum
54177	sputum: excessive - mucoid	sputum
24181	sputum: mucopurulent	sputum
49694	sputum: organism on gram stain	sputum
49144	sputum: pus cells present	sputum
100484	volume of sputum	sputum
100629	white sputum	sputum
30754	yellow sputum	sputum

Lower respiratory tract infections (LRTIs)

CPRD Medcode	Read Code	Description
99214	Hyu1100	[x]acute bronchiolitis due to other specified organisms
73100	Hyu1000	[x]acute bronchitis due to other specified organisms
98257	Hyu0400	[x]flu+oth respiratory manifestations,'flu virus identified
97605	Hyu0600	[x]influenza+oth respiratory manifestatns,virus not identifd
97279	Hyu0700	[x]influenza+other manifestations, virus not identified
97936	Hyu0500	[x]influenza+other manifestations,influenza virus identified
66397	Hyu1.00	[x]other acute lower respiratory infections
24800	H060x00	acute bacterial bronchitis unspecified
1019	H061.00	acute bronchiolitis
66228	H061600	acute bronchiolitis due to other specified organisms
18451	H061500	acute bronchiolitis due to respiratory syncytial virus
17917	H061z00	acute bronchiolitis nos
17185	H061200	acute bronchiolitis with bronchospasm
312	H060.00	acute bronchitis
29669	H06..00	acute bronchitis and bronchiolitis
54830	H460000	acute bronchitis due to chemical fumes
93153	H060B00	acute bronchitis due to coxsackievirus
65916	H060F00	acute bronchitis due to echovirus
29273	H060C00	acute bronchitis due to parainfluenza virus
48593	H060D00	acute bronchitis due to respiratory syncytial virus
64890	H060E00	acute bronchitis due to rhinovirus
20198	H060z00	acute bronchitis nos
41137	H06z.00	acute bronchitis or bronchiolitis nos
54533	H061000	acute capillary bronchiolitis
21145	H060400	acute croupous bronchitis
69192	H061300	acute exudative bronchiolitis
50396	H060000	acute fibrinous bronchitis
21492	H060800	acute haemophilus influenzae bronchitis
6124	H062.00	acute lower respiratory tract infection
37447	H06z112	acute lower respiratory tract infection
101775	H060100	acute membranous bronchitis
49794	H060900	acute neisseria catarrhalis bronchitis
41589	H061100	acute obliterating bronchiolitis
9043	H060600	acute pneumococcal bronchitis
71370	H060200	acute pseudomembranous bronchitis
11072	H060300	acute purulent bronchitis
43362	H060700	acute streptococcal bronchitis
11101	H060500	acute tracheobronchitis
1382	H060w00	acute viral bronchitis unspecified
5978	H060.11	acute wheezy bronchitis
18207	H33zz13	allergic bronchitis nec
100650	AB63600	aspergillus bronchitis
94930	H29..00	avian influenza
63697	43jQ.00	avian influenza virus nucleic acid detection
26125	H312300	bronchiolitis obliterans

CPRD Medcode	Read Code	Description
3480	H30z.00	bronchitis nos
148	H30..00	bronchitis unspecified
2476	H07..00	chest cold
68	H06z011	chest infection
17359	H30..11	chest infection - unspecified bronchitis
2581	H06z000	chest infection nos
24316	H24..11	chest infection with infectious disease ec
15626	H310000	chronic catarrhal bronchitis
21061	H3y0.00	chronic obstruct pulmonary dis with acute lower resp infectn
14798	H312100	emphysematous bronchitis
2157	H27z.11	flu like illness
96286	4JUF.00	human parainfluenza virus detected
556	H27..00	influenza
98102	H2A..11	influenza a (h1n1) swine flu
98143	4J3L.00	influenza a virus h1n1 subtype detected
97062	4JU4.00	influenza a virus, other or untyped strain detected
96017	4JU5.00	influenza b virus detected
98129	H2A..00	influenza due to influenza a virus subtype h1n1
96019	4JU0.00	influenza h1 virus detected
102918	4JU1.00	influenza h2 virus detected
96018	4JU2.00	influenza h3 virus detected
98156	4JU3.00	influenza h5 virus detected
5947	H27z.12	influenza like illness
16388	H27z.00	influenza nos
46157	H27y000	influenza with encephalopathy
14791	H27y100	influenza with gastrointestinal tract involvement
15774	H271000	influenza with laryngitis
47472	H27y.00	influenza with other manifestations
31363	H27yz00	influenza with other manifestations nos
43625	H271.00	influenza with other respiratory manifestation
29617	H271100	influenza with pharyngitis
23488	H271z00	influenza with respiratory manifestations nos
8980	16L..00	influenza-like symptoms
1934	H301.00	laryngotracheobronchitis
3358	H06z100	lower resp tract infection
24248	H313.00	mixed simple and mucopurulent chronic bronchitis
11150	H311.00	mucopurulent chronic bronchitis
61513	H311z00	mucopurulent chronic bronchitis nos
6181	H061400	obliterating fibrous bronchiolitis
63216	H464100	obliterative bronchiolitis due to chemical fumes
94130	43jx.00	parainfluenza type 1 nucleic acid detection
94858	43jy.00	parainfluenza type 2 nucleic acid detection
91123	43jz.00	parainfluenza type 3 nucleic acid detection
98103	1W0..00	possible influenza a virus h1n1 subtype
40159	H311000	purulent chronic bronchitis
4899	H06z200	recurrent chest infection

CPRD Medcode	Read Code	Description
7092	H30..12	recurrent wheezy bronchitis
55391	H060v00	subacute bronchitis unspecified
98125	1J72.00	suspected influenza a virus subtype h1n1 infection
98115	1J72.11	suspected swine influenza
3163	H300.00	tracheobronchitis nos
152	H302.00	wheezy bronchitis

Acute Exacerbation of COPD (AECOPD) – primary care

CPRD Medcode	Read Code	Description
1446	H312200	acute exacerbation of chronic obstructive airways disease
7884	H3y1.00	chron obstruct pulmonary dis wth acute exacerbation, unspec

Acute Exacerbation of COPD (AECOPD) – secondary care

ICD10 Code	Description	Classify
J44.1	Chronic obstructive pulmonary disease with acute exacerbation, unspecified	Definite
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection	Definite
J43.2	Centrilobular emphysema	Possible
J44.9	Chronic obstructive pulmonary disease, unspecified	Possible
J43	Emphysema	Possible
J43.9	Emphysema, unspecified	Possible
J43.0	MacLeod's syndrome	Possible
J41.8	Mixed simple and mucopurulent chronic bronchitis	Possible
J41.1	Mucopurulent chronic bronchitis	Possible
J44	Other chronic obstructive pulmonary disease	Possible
J43.8	Other emphysema	Possible
J44.8	Other specified chronic obstructive pulmonary disease	Possible
J43.1	Panlobular emphysema	Possible
J41	Simple and mucopurulent chronic bronchitis	Possible
J41.0	Simple chronic bronchitis	Possible
J22	Unspecified acute lower respiratory infection	Possible
J42	Unspecified chronic bronchitis	Possible

Rescue packs for COPD exacerbations

CPRD Medcode	Read Code	Description
25997	8BP0.00	Deferred antibiotic therapy
100459	8B32.00	Advance supply of steroid medication
101042	8BMW.00	Issue of chronic obstructive pulmonary disease rescue pack

Patient COPD reviews

CPRD Medcode	Read Code	Description
10043	66YJ.00	Asthma annual review
11287	66YM.00	Chronic obstructive pulmonary disease annual review
9520	66YB.00	Chronic obstructive pulmonary disease monitoring
28743	66Yf.00	Number of COPD exacerbations in past year

3. CODE LIST TO DEFINE HOSPITALISED PNEUMONIA (PO3 AND SO2)

Episodes of Pneumonia during the study were identified by a record for a diagnosis of pneumonia while hospitalised using the set of ICD-10 diagnosis codes that follows.

Pneumonia (as outcome) coding definition

ICD10 Code	Description	Classification
J15.9	Bacterial pneumonia, unspecified	Bacterial
J15	Bacterial pneumonianot elsewhere classified	Bacterial
J16.0	Chlamydial pneumonia	Bacterial
A48.1	Legionnaires' disease	Bacterial
J15.8	Other bacterial pneumonia	Bacterial
J15.5	Pneumonia due to Escherichia coli	Bacterial
J14	Pneumonia due to Haemophilus influenzae	Bacterial
J14.0	Pneumonia due to Haemophilus influenzae	Bacterial
J14X	Pneumonia due to Haemophilus influenzae	Bacterial
J15.0	Pneumonia due to Klebsiella pneumoniae	Bacterial
J15.7	Pneumonia due to Mycoplasma pneumoniae	Bacterial
J15.1	Pneumonia due to Pseudomonas	Bacterial
J13	Pneumonia due to Streptococcus pneumoniae	Bacterial
J13.0	Pneumonia due to Streptococcus pneumoniae	Bacterial
J13X	Pneumonia due to Streptococcus pneumoniae	Bacterial
J15.6	Pneumonia due to other aerobic Gram-negative bacteria	Bacterial
J15.4	Pneumonia due to other streptococci	Bacterial
J15.2	Pneumonia due to staphylococcus	Bacterial
J15.3	Pneumonia due to streptococcus, group B	Bacterial
J17.0	Pneumonia in bacterial diseases classified elsewhere	Bacterial
A20.2	Pneumonic plague	Bacterial
A42.0	Pulmonary actinomycosis	Bacterial
A22.1	Pulmonary anthrax	Bacterial
A43.0	Pulmonary nocardiosis	Bacterial
A21.2	Pulmonary tularaemia	Bacterial
B40.0	Acute pulmonary blastomycosis	Fungal
B38.0	Acute pulmonary coccidioidomycosis	Fungal
B39.0	Acute pulmonary histoplasmosis capsulation	Fungal
B38.1	Chronic pulmonary coccidioidomycosis	Fungal
B20.6	HIV disease resulting in Pneumocystis carinii pneumonia	Fungal
B44.0	Invasive pulmonary aspergillosis	Fungal
B44.1	Other pulmonary aspergillosis	Fungal
B59.X	Pneumocystosis	Fungal
J17.2	Pneumonia in mycoses	Fungal
B40.2	Pulmonary blastomycosis, unspecified	Fungal
B37.1	Pulmonary candidiasis	Fungal
B38.2	Pulmonary coccidioidomycosis, unspecified	Fungal

ICD10 Code	Description	Classification
B45.0	Pulmonary cryptococcosis	Fungal
B39.2	Pulmonary histoplasmosis capsulati, unspecified	Fungal
B46.0	Pulmonary mucormycosis	Fungal
B41.0	Pulmonary paracoccidioidomycosis	Fungal
B42.0	Pulmonary sporotrichosis	Fungal
B58.3	Pulmonary toxoplasmosis	Fungal
J85	Abscess of lung and mediastinum	Lung abscess
J85.1	Abscess of lung with pneumonia	Lung abscess
J85.2	Abscess of lung without pneumonia	Lung abscess
A06.5	Amoebic lung abscess	Lung abscess
J85.0	Gangrene and necrosis of lung	Lung abscess
A19.0	Acute miliary tuberculosis of a single specified site	Mycobacterial
A19.1	Acute miliary tuberculosis of multiple sites	Mycobacterial
A19.2	Acute miliary tuberculosis, unspecified	Mycobacterial
A19	Miliary tuberculosis	Mycobacterial
A19.9	Miliary tuberculosis, unspecified	Mycobacterial
A16.8	Oth respiratory TB without mention of bact or hist confirm	Mycobacterial
A19.8	Other miliary tuberculosis	Mycobacterial
A15.8	Other respiratory TB confirm bact and histologically	Mycobacterial
A16.7	Prim respiratory TB without mention of bact or hist confirm	Mycobacterial
A15.7	Primary respiratory TB confirm bact and histologically	Mycobacterial
A31.0	Pulmonary mycobacterial infection	Mycobacterial
A16.9	Resp TB unspec without mention of bact or hist confirm	Mycobacterial
A15	Respiratory TB bacteriologically and histologically confirmed	Mycobacterial
A16	Respiratory TB not confirmed bacteriologically or histologically	Mycobacterial
A15.9	Respiratory TB unspec confirm bact and histologically	Mycobacterial
A15.4	TB intrathoracic lymph nodes confirm bact histologically	Mycobacterial
A15.0	TB lung confirm sputum microscopy with or without culture	Mycobacterial
A16.2	TB lung without mention of bact or histological confirm	Mycobacterial
A16.5	TB pleurisy without mention of bact or histological confirm	Mycobacterial
A16.1	Tuberculosis lung bact and histological examin not done	Mycobacterial
A15.5	Tuberculosis of larynx, trachea & bronchus conf bact/hist'y	Mycobacterial
A16.0	Tuberculosis of lung, bacteriologically & histolog'y neg	Mycobacterial
A15.1	Tuberculosis of lung, confirmed by culture only	Mycobacterial
A15.3	Tuberculosis of lung, confirmed by unspecified means	Mycobacterial
A15.2	Tuberculosis of lung, confirmed histologically	Mycobacterial
A15.6	Tuberculous pleurisy, conf bacteriologically/his'y	Mycobacterial
B67.1	Other B67.1 Echinococcus granulosus infection of lung	Other
J17.3	Other J17.3 Pneumonia in parasitic diseases	Other
J12.0	Adenoviral pneumonia	Viral
J10.0	Influenza with pneumonia, influenza virus identified	Viral
J11.0	Influenza with pneumonia, virus not identified	Viral
B05.2	Measles complicated by pneumonia	Viral
J12.8	Other viral pneumonia	Viral
J12.2	Parainfluenza virus pneumonia	Viral

ICD10 Code	Description	Classification
J17.1	Pneumonia in viral diseases classified elsewhere	Viral
J12.1	Respiratory syncytial virus pneumonia	Viral
B01.2	Varicella pneumonia	Viral
J12	Viral pneumonia, not elsewhere classified	Viral
J12.9	Viral pneumonia, unspecified	Viral
J18.0	Bronchopneumonia, unspecified	unspecified
J18.1	Lobar pneumonia, unspecified	unspecified
J18.8	Other pneumonia, organism unspecified	unspecified
J16	Pneumonia due to other infectious organisms NEC	unspecified
J16.8	Pneumonia due to other specified infectious organisms	unspecified
J17	Pneumonia in diseases classified elsewhere	unspecified
J17.8	Pneumonia in other diseases classified elsewhere	unspecified
J18.9	Pneumonia, unspecified	unspecified
J18	Pneumoniaorganism unspecified	unspecified

INVESTIGATOR SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge Study PRJ2282/201491 was carried out as described in this GlaxoSmithKline Report

Name of Investigator: Matthew Sperrin

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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 PRJ2282/201491.

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