ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

ISAC use only: Protocol Number Date submitted		**IMPORTANT** **If you have any queries, please contact ISAC Secretariat:** ISAC@cprd.com

1. Study Title

PRJ2282: CHESS: CPRD-COPD Hawthorn 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. Principal Investigator (full name, job title, organisation & e-mail address for correspondence regarding this protocol)

Matthew Sperrin, Lecturer in Health Data Science, University of Manchester, Matthew.sperrin@manchester.ac.uk

3. Affiliation (full address)

Centre for Health Informatics, Institute of Population Health, University of Manchester,
Vaughan House, Portsmouth St, Manchester, M13 9PL

4. Protocol's Author (if different from the principal investigator)

N/A

5. List of all investigators/collaborators (*please list the names, affiliations and e-mail addresses* of all collaborators*, other than the principal investigator)

Tjeerd Van Staa, Professor, University of Manchester, tjeerd.vanstaa@manchester.ac.uk
Kourtney Davis, Senior Director, Worldwide Epidemiology, GlaxoSmithKline, kourtney.j.davis@gsk.com
Jeanne Pimenta, Director, Worldwide Epidemiology, GlaxoSmithKline, jeanne.m.pimenta@gsk.com
Rachael Williams, CPRD, Rachael.Williams@mhra.gsi.gov.uk

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

6. Type of Institution (please tick one box below)

Academia	☒	Research Service Provider	☐	Pharmaceutical Industry	☐
NHS	☐	Government Departments	☐	Others	☐

7. Financial Sponsor of study

Pharmaceutical Industry *(please specify)*	☒ GlaxoSmithKline	Academia *(please specify)*	☐
Government / NHS *(please specify)*	☐	None	☐
Other *(please specify)*	☐		

8. Data source *(please tick one box below)*

Sponsor has on-line access	☒	Purchase of ad hoc dataset	☐
Commissioned study	☐		
Other	☐ *(please specify)*		

9. Has this protocol been peer reviewed by another Committee?

Yes* ☒ No ☐

Reviewing Committee: The protocol was reviewed by GSK Worldwide Epidemiology Protocol Review Forum (GSK WWEpi PRF).
Committee review process: GSK WWEpi PRF review and approval is required for all studies conducted under the sponsorship of GSK Worldwide Epidemiology and is a binding procedure within GSK under SOP_72625(3.0). The review committee is chaired by the Vice-President (VP) of WWEpi (or their delegate) and the committee is composed of GSK staff from the following roles: 2 Epidemiologists; 1 Observational Data Analyst; 1 Medically Qualified Member; 1 Health Outcomes Advisor (optional); 1 Statistician and 1 Secretary. All members (excluding secretary) are expected to review the protocol and provide written comments to the protocol author within pre-specified timelines. These are addressed by authors and discussed at a PRF meeting. The PRF makes recommendations to the protocol authors and assigns a decision outcome.
Committee decision: Following review and discussion on 23rd January 2015, this study (PRJ2282) was approved.

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

Adverse Drug Reaction/Drug Safety	☐	Drug Use	☐	Disease Epidemiology	☒
Drug Effectiveness	☐	Pharmacoeconomic	☐	Other	☒

11. This study is intended for:

Publication in peer reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☒	Other	

12. Does this protocol also seek access to data held under the CPRD Data Linkage Scheme?

Yes ☒ No ☐

13. If you are seeking access to data held under the CPRD Data Linkage Scheme*, please select the source(s) of linked data being requested.

☒ Hospital Episode Statistics ☐ Cancer Registry Data**
☐ MINAP ☒ ONS Mortality Data
☒ Index of Multiple Deprivation/ Townsend Score
☐ Mother Baby Link ☐ Other: (please specify)

** As part of the ISAC review of linkages, the protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.*

***Please note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss this requirement further.*

14. If you are seeking access to data held under the CPRD Data Linkage Scheme, have you already discussed your request with a member of the Research team?

Yes ☒ No* ☐

**Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss your requirements before submitting your application.*

Please list below the name of the person/s at the CPRD with whom you have discussed your request. Rachael Williams (CPRD) is a co-investigator. Tim Williams (Head of Research, CPRD) is a member of the Scientific Steering Committee.

15. If you are seeking access to data held under the CPRD Data Linkage Scheme, please provide the following information:

The number of linked datasets requested: 3

A synopsis of the purpose(s) for which the linkages are required:

Hospital Episode Statistics: two of our primary endpoints are COPD exacerbation and severe pneumonia. We therefore require information on hospital admissions for these two conditions.

Index of Multiple Deprivation: We are comparing the demographics of Salford with the rest of the UK, and have identified deprivation as an important demographic to consider. This is also a potential confounding factor in our models.

ONS Mortality Data: While mortality data is not an endpoint of primary interest it will be important to appropriately account for mortality as a censoring event/competing risk.

Is linkage to a local dataset with <1 million patients being requested?

Yes* ☐ No ☒

** If yes, please provide further details:*

16. If you have requested linked data sets, please indicate whether the Principal Investigator or any of the collaborators listed in response to question 5 above, have access to any of the linked datasets in a patient identifiable form, or associated with a patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

17. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

* *Please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐

Provision of anonymised records (e.g. hospital discharge summaries) Yes ☐ No ☐

Other (please describe)

[ψ] *Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.*

18. Does this protocol describe a purely observational study using CPRD data (this may include the review of anonymised free text)?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*
*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

19. Does this study involve linking to patient *identifiable* data from other sources?

Yes ☐ No ☒

20. Does this study require contact with patients in order for them to complete a questionnaire?

Yes ☐ No ☒

N.B. Any questionnaire for completion by patients must be approved by ISAC before circulation for completion.

21. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected*

22. Experience/expertise available

Please complete the following questions to indicate the experience/expertise available within the team of researchers actively involved in the proposed research, including analysis of data and interpretation of results

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☐	☐
> 3	☒	☒

	Yes	No
Is statistical expertise available within the research team?	☒	☐

If yes, please outline level of experience

All applicants have advanced statistical expertise – e.g. all have PhDs or equivalent with statistical component.

	Yes	No
Is experience of handling large data sets (>1 million records) available within the research team?	☒	☐

If yes, please outline level of experience

The study will be based within the Centre for Health Informatics at the University of Manchester, which has substantial infrastructure and experience for handling large data sets. Both University of Manchester and GSK already have CPRD

licences and applicants have been using CPRD actively.

Is UK primary care experience available within the research team? ☒ ☐

If yes, please outline level of experience

All applicants are actively researching in primary care.

23. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study.

1. New JP, Bakerly ND, Leather D, Woodcock A. Obtaining real-world evidence: the Salford Lung Study. Thorax. 2014 Apr 26 e pub ahead of print.
2. van Staa T-P, Goldacre B, Gulliford M, Cassell J, Pirmohamed M, Taweel A, Delaney B, Smeeth L. Pragmatic randomised trials using routine electronic health records: putting them to the test. BMJ 2012, 344: e55 doi: 10.1136.
3. French J.R.P. Experiments in field settings. In: Festinger L., Katz D., editors. Research methods in the behavioral sciences. Holt, Rinehart & Winston; New York, NY: 1953

PROTOCOL CONTENT CHECKLIST

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced instructions on the content of protocols for research using CPRD data. These instructions are available on the CPRD website (www.cprd.com/ISAC). All protocols using CPRD data which are submitted for review by ISAC must contain information on the areas detailed in the instructions. IF you do not feel that a specific area required by ISAC is relevant for your protocol, you will need to justify this decision to ISAC.

Applicants must complete the checklist below to confirm that the protocol being submitted includes all the areas required by ISAC, or to provide justification where a required area is not considered to be relevant for a specific protocol. Protocols will not be circulated to ISAC for review until the checklist has been completed by the applicant.

Please note, your protocol will be returned to you if you do not complete this checklist, or if you answer 'no' and fail to include justification for the omission of any required area.

	Included in protocol?		
Required area	Yes	No	If no, reason for omission
Lay Summary (max.200 words)	☒	☐	
Background	☒	☐	
Objective, specific aims and rationale	☒	☐	
Study Type *Descriptive* *Hypothesis Generating* *Hypothesis Testing*	 ☒ ☐ ☐	 ☐ ☐ ☐	
Study Design	☒	☐	
Sample size/power calculation (Please provide justification of sample size in the protocol)	☒	☐	
Study population (including estimate of expected number of relevant patients in the CPRD)	☒	☐	
Selection of comparison group(s) or controls	☒	☐	
Exposures, outcomes and covariates *Exposures are clearly described* *Outcomes are clearly described*	☒ ☒ ☒	☐ ☐ ☐	
Use of linked data (if applicable)	☒	☐	
Data/ Statistical Analysis Plan *There is plan for addressing confounding* *There is a plan for addressing missing data*	☒ ☒ ☒	☐ ☐ ☐	
Patient/ user group involvement †	☐	☒	This is a purely observational study, and quality of life will not be evaluated.
Limitations of the study design, data sources and analytic methods	☒	☐	
Plans for disseminating and communicating study results	☒	☐	

† It is expected that many studies will benefit from the involvement of patient or user groups in their planning and refinement, and/or in the interpretation of the results and plans for further work. This is particularly, but not exclusively true of studies with interests in the impact on quality of life. Please indicate whether or not you intend to engage patients in any of the ways mentioned above.

Voluntary registration of ISAC approved studies:

Epidemiological studies are increasingly being included in registries of research around the world, including those primarily set up for clinical trials. To increase awareness amongst researchers of ongoing research, ISAC encourages voluntary registration of epidemiological research conducted using MHRA databases. This

will not replace information on ISAC approved protocols that may be published in its summary minutes or annual report. It is for the applicant to determine the most appropriate registry for their study. Please inform the ISAC secretariat that you have registered a protocol and provide the location.

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

Lay Summary

The Salford Lung Study (SLS) is an evaluation of a new drug, RELVAR, taking place in Salford, UK. RELVAR is a drug that treats chronic obstructive pulmonary disease (COPD). The study is unique in that it is taking place in routine care, so it is hoped that the results will show how effective the drug is in the 'real world'.

However, one issue with a study of this kind is that the fact that the study is taking place raises awareness of COPD in both patients and clinicians taking part. This could lead to the 'Hawthorne effect', in which patients in both the group receiving RELVAR, and the group receiving usual care, do better than the general population.

In this study we aim to compare outcomes for patients in the SLS with other COPD patients in the UK who are not in the study, to see whether the Hawthorne effect occurs and its severity. We will also assess whether the COPD patients in the SLS are similar to the rest of the UK. The conclusions will help us understand the extent to which the findings of the SLS can be generalised to the rest of the UK.

Background

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. GPRD has also been used previously for descriptive drug utilization studies for prescription medications in respiratory diseases [16, 17, 18]. 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 SLS is an ongoing Phase 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 via their neighbourhood pharmacy, and followed for safety and effectiveness via linked primary care/secondary routine care with the 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 of the medicine against the most relevant standard of care.

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].

Additionally, 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.

Objectives

Co-primary objectives:

PO1: To characterize the patients enrolled in the SOC arm of the SLS compared with the UK population of COPD patients (using CPRD linked data), including the distribution of deprivation levels, 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 the SOC arm of the SLS compared with the SOC recorded in the CPRD linked data, in order to detect a potential Hawthorne effect as a result of potentially increased attention paid by GPs and nurses to patients with COPD during the SLS study period.

PO3: To compare the rate of severe pneumonia over the 12 months in the SOC arm of the SLS compared with the SOC recorded in the CPRD linked data. Severe pneumonia is a safety signal being assessed in the SLS.

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.

Study Type

The study will primarily be descriptive.

Study Design

This will be an observational COPD cohort study that will utilize the CPRD linked data and the Salford EHR system to compare selected cohorts with SLS.

For SLS, the reference/index date is study entry. This will be matched in the CPRD cohort by the following algorithm:

1. Draw up a long-list of potentially eligible individuals in the CPRD linked data (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, otherwise, they will be excluded.

First, the COPD populations in both Salford and in the wider CPRD cohort (excluding Greater Manchester area) will be compared. Second, we will focus on comparisons between all patients enrolled in the SLS versus the larger CPRD defined COPD cohort "eligible for RELVAR prescription" (target patient population per label). Third, we will compare the COPD exacerbation response between eligible CPRD population, and the Salford population in SLS receiving SOC, in a multilevel model – i.e. evaluating Hawthorne effect.

Sample Size

The target sample size for the number of COPD patients enrolled in the SLS is 2,800. A preliminary feasibility count using the February 2015 version of the CPRD GOLD database identified 265,076 patients with a Read code for COPD in their clinical or referral files (see Annex 1 for codelist), with at least one day of up-to-standard registration aged 40+, and eligible for linkage to Hospital Episode Statistics (HES), ONS mortality data and deprivation data. This is a large number of cases and as the study is primarily descriptive, a power calculation is not required.

Data Linkage

Linkages to inpatient HES data, Index of Multiple Deprivation (IMD) data and ONS mortality data will be used in this study. HES will be used to identify two of the primary endpoints - hospital admissions for COPD exacerbation and severe pneumonia. IMD data will be used adjust for confounding due to deprivation. ONS mortality data will be used to censor at death. The entire study will be undertaken among linked practices only.

Fully linked data will only be available up to a certain date when analyses are undertaken (currently March 2014), 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.

Study Population

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
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). 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. Patients will be included according to the following 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. The SLS is described in [14]. In brief, it is a pragmatic trial, carried out in Salford, UK, to evaluate the relative effectiveness of RELVAR compared with SOC.

Subjects meeting any of the following criteria will be excluded from the restricted cohorts:

1. Patients with any life threatening condition or uncontrolled/clinically significant disease
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.
3. Chronic user of oral corticosteroids: Subjects who are considered to be a chronic user of oral corticosteroids for respiratory or other indications
4. In the Salford population only, those patients who are entered in the SLS and randomised to the RELVAR arm.

Exposures

This is a binary comparison of COPD patients enrolled in the SLS and COPD patients in the CPRD cohort. 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.

Outcomes

Primary outcomes/endpoint:

- Rate of COPD exacerbation: 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 the ongoing study being conducted by Jenny Quint et al. (collaborative project between London School of Hygiene and Tropical Medicine and GSK). The 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) will also be compared.
- Pneumonia: To be defined as per the codelist used in SLS – see Annex 2 and 3

Secondary outcomes/endpoints:

- Healthcare utilisation: All GP visits/encounters and all hospital admissions during the 12 month follow-up.
- 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 Jenni Quint's study.

Covariates

Covariates will include :

- demographic variables (sex, age, IMD)
- current exposure to LAMA, LABA and ICD
- comorbidities (heart failure, myocardial infarction, stroke, depression, anxiety, asthma, pneumonia, gastro-oesophageal reflux and peptic ulcer disease, Charlson score (COPD will be removed from score), disability)
- markers of COPD severity (previous COPD exacerbation, FEV1 % predicted, FEV1/FVC ratio, GOLD stage, MRC Dyspnoea score)
- co-medications and vaccinations
- lifestyle behaviours (smoking status, BMI)

Analysis

All analyses will be conducted using SAS.

For PO1, distributions of the confounders and effect modifiers 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 deprivation 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.

There are a range of subsets and derivations of the data sources that will be considered for this study, listed here for clarity.

CPRD:	all CPRD COPD patients
CPRD-GM:	CPRD COPD patients registered in practices in Greater Manchester
CPRD-xGM:	CPRD COPD patients registered in non-Greater Manchester practices
CPRD-GM-IC:	CPRD COPD patients registered in practices in Greater Manchester meeting the SLS inclusion criteria
CPRD-xGM-IC:	CPRD COPD patients registered in non-Greater Manchester practices meeting the SLS inclusion criteria
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

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 the CPRD cohort 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.

Missing data in confounders and effect modifiers will be imputed using multiple imputation for the primary analysis, with complete case analysis included as sensitivity analysis.

For PO2, we will commence with exploratory analyses, similar to described above, to explore the distributions of the primary and secondary endpoints. The 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. As above, confounders and effect modifiers will be imputed using multiple imputation for the primary analysis, with complete case analysis included as sensitivity analysis.

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, SO1 and SO2 (which pertain to comparing other endpoints and sensitivity analyses of endpoint definition) will be carried out using the same approach as for 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 the CPRD cohort to control for UK-wide secular trends. This acts as sensitivity analysis to support PO2 (using controls distinct in time rather than in geography).

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. Wherever feasible, all statistical programming will be independently reviewed by a second analyst, with oversight by a senior statistician.

Limitations

The 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 outside the scope of this protocol.

While GP data are the same, some data (hospital validated COPD diagnoses, pharmacy data) for participants in SLS are collected using a different mechanism to CPRD GOLD. 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 GOLD data from within Greater Manchester.

Plans for Dissemination

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, including a submission to Thorax in Q2 2016 based on interim results, and followed by a subsequent manuscript containing the final analyses of the data (planned for Q4 2016). 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.

References

4. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, GOLD Executive Summary. Am J Respir Crit Care Med 2013, 187: 347-365.
5. Mathers CD, Loncar D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. PLoS Med 2006, 3(11): e442.
6. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL. Held LS, Schmid V, Buist S. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006, 27: 397–412.
7. Bellamy D, Bouchard J, Henrichsen S, Johansson G, Langhammer A, Reid J, van Weel C, Buist S. International Primary Care Respiratory Group (IPCRG) Guidelines: Management of Chronic Obstructive Pulmonary Disease (COPD). Prim Care Respir 2006, 15:48-57.
8. Sobradillo-Peña V, Miravitlles M, Gabriel R, Jiménez-Ruiz CA, Villasante C, Masa JF, Viejo JL, Fernández-Fau L. Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest 2000, 118: 981-9.
9. Soriano JB, Miravitlles M, Borderías L, Duran-Tauleria E, García Río F, Martínez J, Montemayor T, Muñoz L, Piñeiro L, Sánchez G, Serra J, Soler-Cataluña JJ, Torres A, Viejo JL, Sobradillo-Peña V, Ancochea J. Geographical Variations in the Prevalence of COPD in Spain: Relationship to Smoking, Death Rates and other Determining Factors. Arch Bronconeumol. 2010, 46: 522-530.
10. Aisanov Z, Bai C, Bauerle O, Colodenco FD, Feldman C, Hashimoto S, Jardim J, Lai CKW, Laniado-Laborin R, Nadeau G, Sayiner A, Shim JJ, Tsai YH, Walters RD, Waterer G. Primary care physician perceptions on the diagnosis and management of chronic obstructive pulmonary disease in diverse regions of the world. Int J Chron Obstruct Pulmon Dis 2012, 7: 271–282.
11. Corrado A, Rossi A. How far is real life from COPD therapy guidelines? An Italian observational study. Respir Med. 2012, 106: 989-97.
12. Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). Thorax 1999, 54: 413–419.
13. Soriano JB, Maier WC, Egger P, Visick G, Thakrar B, Sykes J, Pride NB. Recent trends of physician-diagnosed COPD in women and men in the UK. Thorax 2000, 55: 789–794.
14. Hansell AL, Lam KA, Richardson S, Visick G, Soriano JB. Medical event profiling of COPD patients. Pharmacoepidemiol Drug Saf 2004, 13: 547–555.
15. van Staa T-P, Goldacre B, Gulliford M, Cassell J, Pirmohamed M, Taweel A, Delaney B, Smeeth L. Pragmatic randomised trials using routine electronic health records: putting them to the test. BMJ 2012, 344: e55 doi: 10.1136.
16. Department of Health (Research and Development Directorate) policy paper: Best research for best health: a new national health research strategy. 25 January 2006. Last accessed 06 June 2013 www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4127127.

17. New JP, Bakerly ND, Leather D, Woodcock A. Obtaining real-world evidence: the Salford Lung Study. Thorax. 2014 Apr 26 e pub ahead of print.
18. French J.R.P. Experiments in field settings. In: Festinger L., Katz D., editors. Research methods in the behavioral sciences. Holt, Rinehart & Winston; New York, NY: 1953
19. DiSantostefano RL, Sampson T, Le HV, Hinds D, Davis KJ, Bakerly ND. Risk of Pneumonia with Inhaled Corticosteroid versus Long-Acting Bronchodilator Regimens in Chronic Obstructive Pulmonary Disease: A New-User Cohort Study. PLoS One. 2014; 9(5):e97149.
20. Ashworth M, Latinovic R, Charlton J, Cox K, Rowlands G, Gulliford M. Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database. *J Public Health (Oxf)*. 2004; 26(3):268-274.
21. van Staa TP, Cooper C, Leufkens HG, Lammers JW, Suissa S. The use of inhaled corticosteroids in the United Kingdom and the Netherlands. Respir Med. 2003; 97(5):578-585.

Annex 1 : Read codes to be used to identify COPD

Read Code	Read Term
66YB.00	Chronic obstructive pulmonary disease monitoring
66YB000	Chronic obstructive pulmonary disease 3 monthly review
66YB100	Chronic obstructive pulmonary disease 6 monthly review
66Yd.00	COPD accident and emergency attendance since last visit
66YD.00	Chronic obstructive pulmonary disease monitoring due
66Ye.00	Emergency COPD admission since last appointment
66Yf.00	Number of COPD exacerbations in past year
66Yg.00	Chronic obstructive pulmonary disease disturbs sleep
66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep
66YI.00	COPD self-management plan given
66Yi.00	Multiple COPD emergency hospital admissions
66YL.00	Chronic obstructive pulmonary disease follow-up
66YL.11	COPD follow-up
66YM.00	Chronic obstructive pulmonary disease annual review
66YS.00	Chronic obstructive pulmonary disease monitoring by nurse
66YT.00	Chronic obstructive pulmonary disease monitoring by doctor
8BMW.00	Issue of chronic obstructive pulmonary disease rescue pack
8BP8.00	Antibiotic therapy for acute pulmonary exacerbation
8CE6.00	Chronic obstructive pulmonary disease leaflet given
8CR1.00	Chronic obstructive pulmonary disease clini management plan
8H2R.00	Admit COPD emergency
9h52.00	Excepted from COPD quality indicators: Informed dissent
9kf..00	COPD - enhanced services administration
9kf0.00	COPD patient unsuitable for pulmonary rehab - enh serv admin
9kf0.11	COPD patient unsuitable for pulmonary rehabilitation
9kf1.00	Refer COPD structured smoking assessment - enhanc serv admin
9kf1.11	Referred for COPD structured smoking assessment
9kf2.00	COPD structured smoking assessment declined - enh serv admin
9kf2.11	COPD structured smoking assessment declined
9Oi..00	Chronic obstructive pulmonary disease monitoring admin
9Oi0.00	Chronic obstructive pulmonary disease monitoring 1st letter
9Oi1.00	Chronic obstructive pulmonary disease monitoring 2nd letter
9Oi2.00	Chronic obstructive pulmonary disease monitoring 3rd letter
9Oi3.00	Chronic obstructive pulmonary disease monitoring verb invite
9Oi4.00	Chronic obstructive pulmonary disease monitor phone invite
H3...00	Chronic obstructive pulmonary disease
H3...11	Chronic obstructive airways disease
H30..00	Bronchitis unspecified
H30..11	Chest infection - unspecified bronchitis
H30..12	Recurrent wheezy bronchitis
H300.00	Tracheobronchitis NOS
H301.00	Laryngotracheobronchitis
H302.00	Wheezy bronchitis
H30z.00	Bronchitis NOS
H31..00	Chronic bronchitis
H310.00	Simple chronic bronchitis
H310000	Chronic catarrhal bronchitis

H310100	Smokers' cough
H310z00	Simple chronic bronchitis NOS
H311.00	Mucopurulent chronic bronchitis
H311000	Purulent chronic bronchitis
H311100	Fetid chronic bronchitis
H311z00	Mucopurulent chronic bronchitis NOS
H312.00	Obstructive chronic bronchitis
H312000	Chronic asthmatic bronchitis
H312011	Chronic wheezy bronchitis
H312100	Emphysematous bronchitis
H312200	Acute exacerbation of chronic obstructive airways disease
H312300	Bronchiolitis obliterans
H312z00	Obstructive chronic bronchitis NOS
H313.00	Mixed simple and mucopurulent chronic bronchitis
H31y.00	Other chronic bronchitis
H31y000	Chronic tracheitis
H31y100	Chronic tracheobronchitis
H31yz00	Other chronic bronchitis NOS
H31z.00	Chronic bronchitis NOS
H32..00	Emphysema
H320.00	Chronic bullous emphysema
H320000	Segmental bullous emphysema
H320100	Zonal bullous emphysema
H320200	Giant bullous emphysema
H320300	Bullous emphysema with collapse
H320311	Tension pneumatocoele
H320z00	Chronic bullous emphysema NOS
H321.00	Panlobular emphysema
H322.00	Centrilobular emphysema
H32y.00	Other emphysema
H32y000	Acute vesicular emphysema
H32y100	Atrophic (senile) emphysema
H32y111	Acute interstitial emphysema
H32y200	MacLeod's unilateral emphysema
H32yz00	Other emphysema NOS
H32z.00	Emphysema NOS
H36..00	Mild chronic obstructive pulmonary disease
H37..00	Moderate chronic obstructive pulmonary disease
H38..00	Severe chronic obstructive pulmonary disease
H39..00	Very severe chronic obstructive pulmonary disease
H3A..00	End stage chronic obstructive airways disease
H3y..11	Other specified chronic obstructive pulmonary disease
H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn
H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec
H3z..00	Chronic obstructive airways disease NOS
H3z..11	Chronic obstructive pulmonary disease NOS

Annex 2 : ICD-10 codes to be used to identify pneumonia

ICD-10 code	ICD-10 description
A06.5	Amoebic lung abscess
A15*	Respiratory TB bacteriologically and histologically confirmed
A16*	Respiratory TB not confirmed bacteriologically or histologically
A19*	Miliary tuberculosis
A20.2	Pneumonic plague
A21.2	Pulmonary tularaemia
A22.1	Pulmonary anthrax
A31.0	Pulmonary mycobacterial infection
A42.0	Pulmonary actinomycosis
A43.0	Pulmonary nocardiosis
A48.1	Legionnaires' disease
B01.2	Varicella pneumonia
B05.2	Measles complicated by pneumonia
B20.6	HIV disease resulting in Pneumocystis carinii pneumonia
B25.0	Cytomegaloviral pneumonitis
B37.1	Pulmonary candidiasis
B38*	Coccidioidomycosis
B39*	Histoplasmosis
B40*	Blastomycosis
B41.0	Pulmonary paracoccidioidomycosis
B42.0	Pulmonary sporotrichosis
B44*	Aspergillosis
B45.0	Pulmonary cryptococcosis
B46.0	Pulmonary mucormycosis
B58.3	Pulmonary toxoplasmosis
B59*	Pneumocystosis
B67.1	Echinococcus granulosus infection of lung
J10.0	Influenza with pneumonia, influenza virus identified
J11.0	Influenza with pneumonia, virus not identified
J12*	Viral pneumonia, not elsewhere classified
J13*	Pneumonia due to Streptococcus pneumoniae
J14*	Pneumonia due to Haemophilus influenzae
J15*	Bacterial pneumonianot elsewhere classified
J16*	Pneumonia due to other infectious organisms NEC
J17*	Pneumonia in diseases classified elsewhere
J18*	Pneumoniaorganism unspecified
J85*	Abscess of lung and mediastinum
J86.0	Pyothorax with fistula
J86.9	Pyothorax without fistula

Annex 3 : Read codes to be used to identify pneumonia

Read Code	Read Term
A022200	Salmonella pneumonia
A054.00	Amoebic lung abscess
A10..00	Primary tuberculous infection
A100.00	Primary tuberculous complex
A101.00	Tuberculous pleurisy in primary progressive tuberculosis
A10y.00	Other primary progressive tuberculosis
A10z.00	Primary tuberculous infection NOS
A11..00	Pulmonary tuberculosis
A11..11	Lung tuberculosis
A110.00	Infiltrative lung tuberculosis
A111.00	Nodular lung tuberculosis
A112.00	Tuberculosis of lung with cavitation
A113.00	Tuberculosis of bronchus
A114.00	Tuberculous fibrosis of lung
A115.00	Tuberculous bronchiectasis
A116.00	Tuberculous pneumonia
A117.00	Tuberculous pneumothorax
A11y.00	Other specified pulmonary tuberculosis
A11z.00	Pulmonary tuberculosis NOS
A12..00	Other respiratory tuberculosis
A120.00	Tuberculous pleurisy
A120000	Tuberculosis of pleura
A120100	Tuberculous empyema
A120200	Tuberculous hydrothorax
A120z00	Tuberculous pleurisy NOS
A121.00	Tuberculosis of intrathoracic lymph nodes
A121000	Tuberculosis of hilar lymph nodes
A121100	Tuberculosis of mediastinal lymph nodes
A121200	Tuberculosis of tracheobronchial lymph nodes
A121z00	Tuberculosis of intrathoracic lymph nodes NOS
A122.00	Isolated tracheal or bronchial tuberculosis
A122000	Isolated tracheal tuberculosis
A122100	Isolated bronchial tuberculosis
A122z00	Isolated tracheal or bronchial tuberculosis NOS
A123.00	Tuberculous laryngitis
A124.00	Resp TB bacteriologically and histologically confirmed
A124000	TB lung confirm sputum microscopy with or without culture
A124100	Tuberculosis of lung, confirmed by culture only
A124200	Tuberculosis of lung, confirmed histologically
A124300	Tuberculosis of lung, confirmed by unspecified means
A124400	TB intrathoracic lymph nodes confirm bact histologically
A124500	Tuberculosis of larynx, trachea & bronchus conf bact/hist'y
A124600	Tuberculous pleurisy, conf bacteriologically/histologically
A124700	Primary respiratory TB confirm bact and histologically
A125.00	Respiratory TB not confirmed bact or histologically
A125000	Tuberculosis of lung, bacteriologically & histolog'y neg
A125100	Tuberculosis lung bact and histological examin not done

A125200	Prim respiratory TB without mention of bact or hist confirm
A125X00	Resp TB unspcf,w'out mention/bacterial or histol confrmtn
A12y.00	Other specified respiratory tuberculosis
A12y000	Tuberculosis of mediastinum
A12y100	Tuberculosis of nasopharynx
A12y200	Tuberculosis of nasal septum
A12y300	Tuberculosis of nasal sinus
A12yz00	Other specified respiratory tuberculosis NOS
A18..00	Miliary tuberculosis
A180.00	Acute miliary tuberculosis
A180000	Acute miliary tuberculosis of a single specified site
A180100	Acute miliary tuberculosis of multiple sites
A18y.00	Other specified miliary tuberculosis
A18z.00	Miliary tuberculosis NOS
A203.00	Primary pneumonic plague
A205.00	Pneumonic plague, unspecified
A221.00	Pulmonary anthrax
A221.11	Woolsorters' disease
A310.00	Pulmonary mycobacterial infection
A310000	Pulmonary mycobacterium avium-intracellulare infection
A391.00	Pulmonary actinomycosis
A39y000	Pulmonary nocardiosis
A54x400	Herpes simplex pneumonia
A551.00	Postmeasles pneumonia
A730.00	Ornithosis with pneumonia
A785000	Cytomegaloviral pneumonitis
A789300	HIV disease resulting in Pneumocystis carinii pneumonia
A789311	HIV disease resulting in Pneumocystis jirovecii pneumonia
AB24.00	Candidiasis of lung
AB24.11	Pneumonia - candidal
AB3..00	Coccidioidomycosis
AB30.00	Primary pulmonary coccidioidomycosis
AB31.00	Primary extrapulmonary coccidioidomycosis
AB32.00	Coccidioidal meningitis
AB33.00	Other progressive coccidioidomycosis
AB33000	Coccidioidal granuloma
AB3z.00	Coccidioidomycosis NOS
AB4..00	Histoplasmosis
AB40.11	American histoplasmosis
AB40100	Histoplasma capsulatum with meningitis
AB40200	Histoplasma capsulatum with retinitis
AB40300	Histoplasma capsulatum with pericarditis
AB40500	Histoplasma capsulatum with pneumonia
AB40600	Acute pulmonary histoplasmosis capsulati
AB40700	Chronic pulmonary histoplasmosis capsulati
AB40800	Disseminated histoplasmosis capsulati
AB41200	Histoplasma duboisii with retinitis
AB41300	Histoplasma duboisii with pericarditis
AB41400	Histoplasma duboisii with endocarditis
AB41500	Histoplasma duboisii with pneumonia

AB42.00	Pulmonary histoplasmosis
AB4z200	Histoplasmosis with retinitis
AB4zz00	Unspecified histoplasmosis NOS
AB50.00	Blastomycosis
AB50.13	North American blastomycosis
AB50000	Cutaneous blastomycosis
AB50100	Primary pulmonary blastomycosis
AB50200	Disseminated blastomycosis
AB50300	Blastomycosis liver
AB50z00	Blastomycosis NOS
AB51.13	South American blastomycosis
AB52.11	Keloidal blastomycosis
AB62.00	Chromoblastomycosis
AB62100	Phaeomycotic brain abscess
AB62200	Subcutaneous phaeomycotic abscess and cyst
AB62X00	Chromomycosis, unspecified
AB63.00	Aspergillosis
AB63000	Invasive pulmonary aspergillosis
AB63100	Tonsillar aspergillosis
AB63200	Disseminated aspergillosis
AB63300	Allergic bronchopulmonary aspergillosis
AB63400	Pulmonary aspergillus disease
AB63500	Aspergilloma
AB63600	Aspergillus bronchitis
AB63X00	Aspergillosis, unspecified
AB65000	Pulmonary cryptococcosis
AC21.00	Lung echinococcus granulosus
AD63.00	Pneumocystosis
AE00.00	Late effects of respiratory tuberculosis
Ayu1000	[X]Other resp tubercul,confirmd bacteriologicly+histologicly
Ayu1100	[X]Resp tuberculos unspcfd,confirmd bacteriolog+histologicly
Ayu1300	[X]Resp TB unspcf,w'out mention/bacterial or histol confrmtn
Ayu1800	[X]Other miliary tuberculosis
Ayu1900	[X]Miliary tuberculosis, unspecified
AyuEK00	[X]Other forms of aspergillosis
AyuEU00	[X]Other pulmonary aspergillosis
AyuJ400	[X]Sequelae of respiratory and unspecified tuberculosis
F501B00	Chronic otitis externa due to aspergillosis
H20..00	Viral pneumonia
H20..11	Chest infection - viral pneumonia
H200.00	Pneumonia due to adenovirus
H201.00	Pneumonia due to respiratory syncytial virus
H202.00	Pneumonia due to parainfluenza virus
H203.00	Pneumonia due to human metapneumovirus
H20y.00	Viral pneumonia NEC
H20y000	Severe acute respiratory syndrome
H20z.00	Viral pneumonia NOS
H21..00	Lobar (pneumococcal) pneumonia
H21..11	Chest infection - pneumococcal pneumonia
H22..00	Other bacterial pneumonia

H22..11	Chest infection - other bacterial pneumonia
H220.00	Pneumonia due to klebsiella pneumoniae
H221.00	Pneumonia due to pseudomonas
H222.00	Pneumonia due to haemophilus influenzae
H222.11	Pneumonia due to haemophilus influenzae
H223.00	Pneumonia due to streptococcus
H223000	Pneumonia due to streptococcus, group B
H224.00	Pneumonia due to staphylococcus
H22y.00	Pneumonia due to other specified bacteria
H22y000	Pneumonia due to escherichia coli
H22y011	E.coli pneumonia
H22y100	Pneumonia due to proteus
H22y200	Pneumonia - Legionella
H22yX00	Pneumonia due to other aerobic gram-negative bacteria
H22yz00	Pneumonia due to bacteria NOS
H22z.00	Bacterial pneumonia NOS
H23..00	Pneumonia due to other specified organisms
H23..11	Chest infection - pneumonia organism OS
H230.00	Pneumonia due to Eaton's agent
H231.00	Pneumonia due to mycoplasma pneumoniae
H232.00	Pneumonia due to pleuropneumonia like organisms
H233.00	Chlamydial pneumonia
H23z.00	Pneumonia due to specified organism NOS
H24..00	Pneumonia with infectious diseases EC
H24..11	Chest infection with infectious disease EC
H240.00	Pneumonia with measles
H241.00	Pneumonia with cytomegalic inclusion disease
H242.00	Pneumonia with ornithosis
H243.00	Pneumonia with whooping cough
H243.11	Pneumonia with pertussis
H244.00	Pneumonia with tularaemia
H246.00	Pneumonia with aspergillosis
H247000	Pneumonia with candidiasis
H247100	Pneumonia with coccidioidomycosis
H247z00	Pneumonia with systemic mycosis NOS
H24y.00	Pneumonia with other infectious diseases EC
H24y000	Pneumonia with actinomycosis
H24y100	Pneumonia with nocardiasis
H24y200	Pneumonia with pneumocystis carinii
H24y300	Pneumonia with Q-fever
H24y400	Pneumonia with salmonellosis
H24y500	Pneumonia with toxoplasmosis
H24y600	Pneumonia with typhoid fever
H24y700	Pneumonia with varicella
H24yz00	Pneumonia with other infectious diseases EC NOS
H24z.00	Pneumonia with infectious diseases EC NOS
H25..00	Bronchopneumonia due to unspecified organism
H25..11	Chest infection - unspecified bronchopneumonia
H26..00	Pneumonia due to unspecified organism
H26..11	Chest infection - pnemonia due to unspecified organism

H260.00	Lobar pneumonia due to unspecified organism
H260000	Lung consolidation
H261.00	Basal pneumonia due to unspecified organism
H262.00	Postoperative pneumonia
H263.00	Pneumonitis, unspecified
H27..11	
H270.00	Influenza with pneumonia
H270.11	Chest infection - influenza with pneumonia
H270000	Influenza with bronchopneumonia
H270100	Influenza with pneumonia, influenza virus identified
H270z00	Influenza with pneumonia NOS
H28..00	Atypical pneumonia
H2B..00	Community acquired pneumonia
H2C..00	Hospital acquired pneumonia
H470.11	Aspiration pneumonia
H470312	Aspiration pneumonia due to vomit
H471000	Lipoid pneumonia (exogenous)
H501600	Pyothorax
H53..00	Abscess of lung and mediastinum
H530.00	Abscess of lung
H530000	Single lung abscess
H530100	Multiple lung abscess
H530200	Gangrenous pneumonia
H530300	Abscess of lung with pneumonia
H530z00	Abscess of lung NOS
H531.00	Abscess of mediastinum
H53z.00	Abscess of lung and mediastinum NOS
H540000	Hypostatic pneumonia
H540100	Hypostatic bronchopneumonia
H564.00	Bronchiolitis obliterans organising pneumonia
H564.11	Cryptogenic organising pneumonia
H56y000	Endogenous lipoid pneumonia
H56y100	Interstitial pneumonia
H571.00	Rheumatic pneumonia
Hyu0800	[X]Other viral pneumonia
Hyu0A00	[X]Other bacterial pneumonia
Hyu0B00	[X]Pneumonia due to other specified infectious organisms
Hyu0D00	[X]Pneumonia in viral diseases classified elsewhere
Hyu0H00	[X]Other pneumonia, organism unspecified
SP13100	Other aspiration pneumonia as a complication of care