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Protocol for non-interventional studies based on existing data

Document Number:	c25002535-01
BI Study Number:	0205-0537
BI Investigational Product(s):	Spiriva Respimat
Title:	Characteristics of patients initiating Spiriva Respimat in Asthma in the UK: a cross-sectional study based on the Clinical Practice Research Datalink
Brief Lay Title	Characteristics of patients who start to use the Spiriva Respimat® to treat their Asthma: a study based on the Clinical Practice Research Datalink in the UK
Protocol version identifier:	1.1
Date of last version of protocol:	Not applicable
PASS:	No
EU PAS register number:	Not applicable
Active substance:	Tiotropium bromide (ATC code R03B B04)
Medicinal product:	Tiotropium® Respimat®
Product reference:	Not applicable
Procedure number:	Not applicable
Joint PASS:	No
Research question and objectives:	The main objective of the study is to describe the clinical and socio-demographic characteristics of asthma patients prior to the initiation of Spiriva Respimat for the treatment of Asthma within a general clinical population using the Clinical Practice Research Database (CPRD). A secondary objective will be to describe and compare the characteristics of asthma patients who initiated Spiriva Respimat to asthma patients who initiated a higher dose of ICS/LABA FDC, or leukotriene receptor antagonist (LTRA), or alternatively those who switched from the previous ICS/LABA FDC to a new ICS/LABA FDC.
Country(-ies) of study:	United Kingdom

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Author:	Tel.: Fax: E-mail:
Marketing authorisation holder(s):	
MAH contact person:	Not applicable
In case of PASS, add: **<EU-QPPV:>**	Not applicable
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Date:	Aug 3, 2018
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2. LIST OF ABBREVIATIONS

A&E	Accident and Emergency
BI	Boehringer Ingelheim
BMI	Body mass index
BTS	British Thoracic Society
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Database
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GP	General practitioner
GPP	Guideline for Good Pharmacoepidemiology Practices
HES	Hospital Episode Statistics
HES-APC	Hospital Episode Statistics Admitted Patient Care
HES A&E	Hospital Episode Statistics Accident and Emergency
ICS	Inhaled corticosteroids
IQR	Interquartile range
ISAC	Independent Scientific Advisory Committee
LABA	Long-acting beta agonists
LAMA	Long-acting muscarinic antagonists
LTRA	Leukotriene receptor antagonist
NIS	Non-interventional study
NISed	Non-interventional study based on existing data
OCS	oral corticosteroids
PSD	Program specification document
RCP	Royal College of Physicians
RMP	Risk management plan
SIGN	Scottish Intercollegiate Guidelines Network
UTS	Up-to-standard

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3. RESPONSIBLE PARTIES

The study investigators (Global Epidemiology) at Boehringer Ingelheim International GmbH (BI) are responsible for the design and conduct of the study. The study protocol has been written following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [R15-4870]. The investigators are responsible for conducting the study in a manner that meets regulatory standards. The study shall be conducted as described in the approved protocol. All revisions to the protocol will be properly documented as protocol amendments.

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva® Respimat®			
Name of active ingredient: Tiotropium bromide (ATC code R03B B04)			
Protocol date: 3 Aug, 2018	**Study number:** 0205-0537	**Version/Revision:** 1.0	**Version/Revision date:** 3 Aug, 2018
Title of study:	Characteristics of patients initiating Spiriva Respimat in Asthma in the UK: a cross-sectional, non-interventional study based on the Clinical Practice Research Datalink		
Rationale and background:	Asthma is a respiratory condition that causes symptoms of wheezing, shortness of breath, chest tightness and cough. [P18-03927] According to treatment guidelines, asthma patients at treatment step 3 and above treated with inhaled corticosteroids, often in combination with long-acting beta agonists. However, many patients continue to have symptoms despite the use of these agents. [P10-08936] In late 2014, Spiriva Respimat (tiotropium bromide), a long acting anticholinergic, was approved for treatment of asthma in the UK. Since this time, it has been approved for use in asthma patients in other countries including Japan and the United States. The current BTS/SIGN Guideline for the management of asthma recommends tiotropium by soft-mist inhaler as an alternate controller therapy at steps three, four and five of the asthma treatment paradigm, on top of inhaled corticosteroid (ICS)/LABA. [P18-03927] As tiotropium is the first of its class approved for the use in the treatment of asthma, it is important to identify patient clinical and socio-demographic characteristics of those who initiate this treatment as opposed to other available treatments. This type of study will allow us to evaluate potential channeling of prescribing to different patient populations.		
Research question and objectives:	The main objective of the study is to describe the clinical and socio-demographic characteristics of asthma patients prior to the initiation of Spiriva Respimat for the treatment of Asthma within a general clinical population using the Clinical Practice Research Database (CPRD). A secondary objective will be to describe and compare the characteristics of asthma patients who initiated Spiriva Respimat to asthma patients who initiated a higher dose of ICS/LABA FDC, or leukotriene receptor antagonist (LTRA), or alternatively those who switched from the previous ICS/LABA FDC to a new ICS/LABA FDC.		
Study design:	A cross-sectional assessment of asthma patients who initiated Spiriva Respimat, who initiated leukotriene receptor antagonist (LTRA), who received a higher dose of ICS/LABA FDC, or who switched to a new ICS/LABA FDC in asthma in the UK		

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Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva® Respimat®			
Name of active ingredient: Tiotropium bromide (ATC code R03B B04)			
Protocol date: 3 Aug, 2018	**Study number:** 0205-0537	**Version/Revision:** 1.0	**Version/Revision date:** 3 Aug, 2018
	during the study period (September, 2014-December 31, 2017). (Non-interventional study based on existing data, NISed)		
Population:	All adult patients who had a diagnosis of asthma before the index date, who received ICS/LABA FDC treatment and who were new initiators of Spiriva Respimat or those who initiated a higher dose of ICS/LABA FDC, a LTRA, or alternatively, those switched to a new ICS/LABA FDC. The index date will be defined as the date of new initiation of Spiriva Respimat or the date of initiation of, or switch to, the treatments specified above. Patients with a diagnosis of COPD as well as patients on any LAMA prior to the index date will be excluded from the main analysis. A history in the database of at least 1 year of continuous up-to-standard (UTS) registration in the CPRD prior to index date will be required to determine indications of use and previous treatments.		
Variables:	As stated above the patients will be grouped by type of treatment initiated or switched to. This will include Spiriva Respimat, a higher dose of ICS/LABA FDC, a new ICS/LABA FDC or an LTRA. Patient characteristics will be identified based on data recorded on the index date (date of dispensing/initiation of the exposure), or when a characteristic was not recorded on the index date, during the pre-index period (the one closest to the index date), unless otherwise specified. The outcome is whether a patient has a cardiac arrhythmias diagnosis on the index date or in the year prior to the index date. The secondary outcome is whether a patient has a cardiac failure diagnosis on the index date or in the year prior to the index date. In addition, the following covariates will be assessed in this study: • Demographic characteristics • Lifestyle factors • Asthma history and lab tests • Comorbidities • Concomitant prescriptions (both asthma related and non-asthma related prescriptions)		
Data sources:	United Kingdom's Clinical Practice Research Datalink (CPRD) GOLD database		

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Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva® Respimat®			
Name of active ingredient: Tiotropium bromide (ATC code R03B B04)			
Protocol date: 3 Aug, 2018	**Study number:** 0205-0537	**Version/Revision:** 1.0	**Version/Revision date:** 3 Aug, 2018

Study size:

The study size is dependent on the uptake of Spiriva Respimat for asthma in the CPRD. Table 1 provides a range of estimates for different prevalence estimates of disease (or characteristics). The numerator represents the number of patients with the comorbidity of interest and the denominator represents the number of new users in the population. With 500 patients we would have adequate confidence intervals around these estimates.

Table 1. Precision of estimates for proportion measures

Number of New Users	95% Confidence Intervals for Various Prevalences of Diseases (%)				
	1%	2%	5%	7%	10%
500	0.4-2.3	1.1-3.6	3.4-7.3	5.1-9.6	7.7-12.9
800	0.5-2.0	1.2-3.2	3.7-6.7	5.4-9.0	8.1-12.3
2,000	0.6-1.5	1.5-2.7	4.1-6.0	6.0-8.2	8.8-11.3
5,000	0.8-1.3	1.6-2.4	4.4-5.6	6.3-7.7	9.2-10.9

A feasibility check was conducted to assess the number of patients in the tiotropium group, after application of the study inclusion and exclusion criteria. The result indicated that between September 2014 and December 2017, the number of patients in the tiotropium group was around 935, which is sufficient for the study aims, as per the described precision estimates.

Data analysis:

For the primary objective of the study, patient characteristics will be tabulated and summarized for all new users of Spiriva Respimat.

For the secondary objectives patient characteristics will be tabulated for the patients that initiated or switched to the other available treatments. Patient characteristics will be compared among patients who initiated Spiriva Respimat and patients in other treatment groups. Analyses will be conducted in unmatched cohorts and differences between Spiriva Restinmat and each of the other exposure groups will be assessed using absolute standardized differences (ASD), where an ASD of at least 10% will be considered a meaningful difference [R16-1227].

Milestones:

Start of data collection: September 1, 2018

End of data collection: September 30, 2018

Final report of study results: December 31, 2018

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5. AMENDMENTS AND UPDATES

None.

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6. MILESTONES

Milestone	**Planned Date**
Start of data collection	September 1, 2018
End of data collection	September 30, 2018
Final report of study results:	December 31, 2018

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7. RATIONALE AND BACKGROUND

Asthma is a respiratory condition that causes symptoms of wheezing, shortness of breath, chest tightness and cough [P18-03927]. According to treatment guidelines, asthma patients at treatment step 3 and above should be treated with inhaled corticosteroids often in combination with long-acting beta agonists. However, many patients continue to have symptoms despite the use of these agents [P10-08936].

In late 2014, Spiriva Respimat (tiotropium), a long acting anticholinergic, was approved for treatment of asthma in the UK. Since this time, it has been approved for use in asthma patients in other countries including Japan and the United States. In the U.K., Spiriva® Respimat® is indicated as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (⩾800µg budesonide/day or equivalent) and long-acting beta2-agonists and who experienced one or more severe exacerbations in the previous year.

The current BTS/SIGN Guideline for the management of asthma recommends tiotropium by soft-mist inhaler as an alternate controller therapy at steps three, four and five of the asthma treatment paradigm, on top of inhaled corticosteroid (ICS)/LABA [P18-03927]. Alternatively, these patients could also be treated with a higher dose of ICS or ICS/LABA or MART, addition of leukotriene receptor antagonist (LTRA), addition of theophylline, beta agonist tablet, or switching to a different ICS/LABA, as shown in figure 1.

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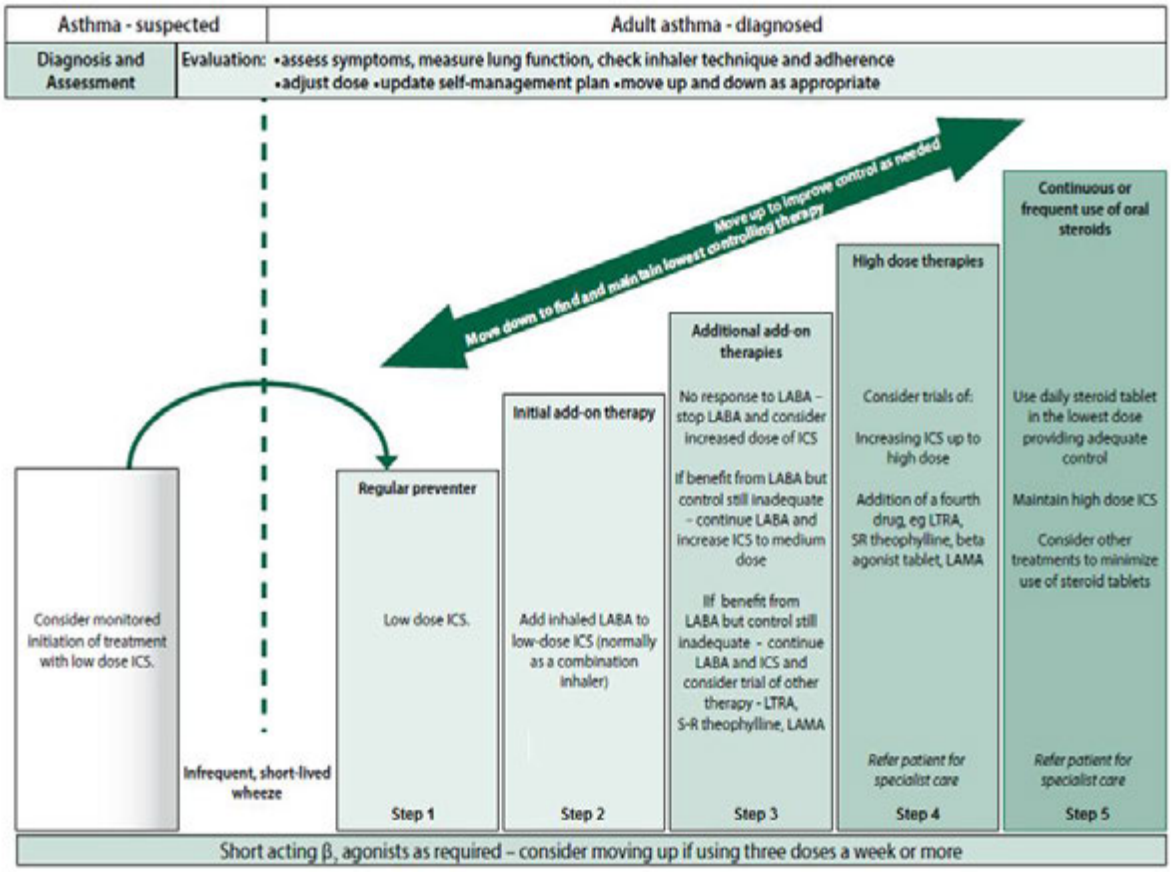


Figure 1 Summary of asthma management in adults.

Tiotropium is the first of its class approved for the use in the treatment of asthma. After a drug is launched in the market, it is important to identify patient clinical and socio-demographic characteristics of patients who initiate this treatment as opposed to other available treatments for patients at the same stage of disease. This type of study will allow us to evaluate potential channeling of prescribing to different patient populations. The results of the current study can also be used to determine the variables included in the calculation of propensity scores in future studies.

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8. RESEARCH QUESTION AND OBJECTIVES

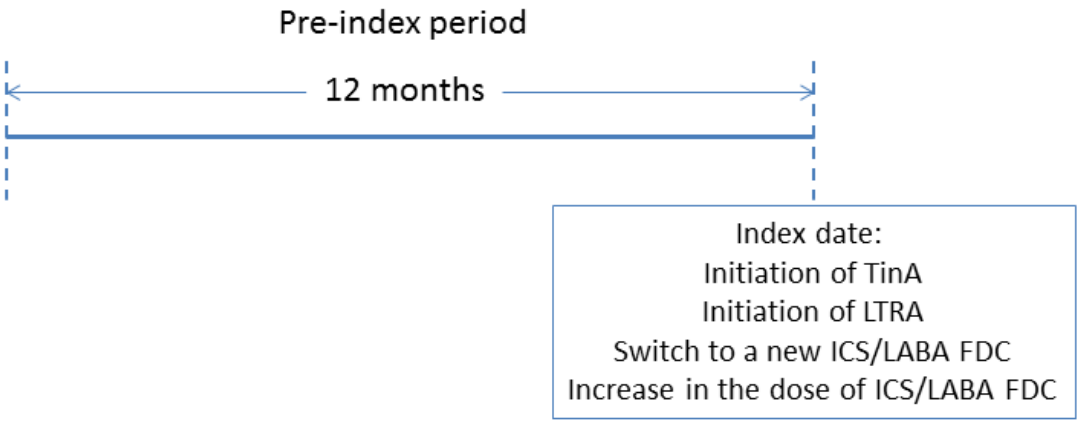
The primary objective of the study is to describe the clinical and socio-demographic characteristics of asthma patients at the time of the initial prescription of Spiriva Respimat for the treatment of Asthma within a general clinical population using the GOLD database within Clinical Practice Research Datalink (CPRD).
A secondary objective will be to describe and compare the characteristics of asthma patients who initiated Spiriva Respimat to asthma patients who initiated a higher dose of ICS/LABA FDC, or LTRA, or alternatively those who switched to a new ICS/LABA FDC.

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9. RESEARCH METHODS

9.1 STUDY DESIGN

This study is a cross-sectional, non-interventional study based on existing data (NISed). The UK CPRD data will be used to assess the characteristics of asthma patients who were prescribed ICS/LABA FDC before the index date and who initiated Spiriva Respimat, or received a higher dose of ICS/LABA FDC, or initiated LTRA, or switched to a new ICS/LABA FDC in the UK during the study period (September 2014-December 2017). This will allow us to assess potential channeling of prescribing to different patient populations.



Note: Study period: September 2014-December 2017.

This is a cross-sectional study and patients will not be followed up after the index date.

Patient characteristics will be evaluated on the index date, or when a characteristic was not recorded on the index date, during the pre-index period (the one closest to the index date).

In the UK, nearly all residents are registered in a general medical practice that uses electronic medical records. Some of those records are available for research purposes in the CPRD. CPRD contains diagnostic and prescribing information recorded by general practitioners (GPs) as part of their routine clinical practice in the UK. The database currently contains data for over 13.2 million patients with research-quality data from 680 UK practices; 5.69 million of these patients are active (still registered with a contributing GP practice) [R14-5257]. Patients registered are representative of the whole UK population in terms of age and sex. More detailed description of the CPRD data is provided in section 9.4.

9.2 SETTING

The study population will be asthmatic patients who were prescribed ICS/LABA FDC before the index date and who initiated Spiriva Respimat, or received a higher dose of ICS/LABA FDC, or initiated LTRA, or switched to a new ICS/LABA FDC from the previous ICS/LABA FDC in the UK during the study period (September, 2014-December 31, 2017). Selection of the above therapies is based on the BTS/SIGN guideline (see figure 1 in section 7). These therapies are all options at adult asthma treatment steps 3 or 4. Although theophylline and

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beta-agonist tablet are also options for add-on therapy at steps 3 and 4, we will not include these two in the current study because they are not widely used in the U.K.

The index prescription will be one of the follows:
- The first prescription of Spiriva Respimat during the study period;
- The first prescription of ICS/LABA FDC with a higher daily dose (any higher dose) (compared to the last prescription) during the study period (if there are more than 1 dose increase during the study period, only the first dose increase will be used in the analyses);
- The first prescription of LTRA during the study period;
- The first prescription of a new ICS/LABA FDC during the study period.

The index date is defined as the date of the index prescription.

In this study, all patients will be required to have at least 1 year of continuous up-to-standard (UTS) registration in the CPRD prior to index date to determine indications of use and previous treatments.

The in- and exclusion criteria of this study are as follows:

Inclusion criteria:
- Aged 18 years and above at the index date
- At least 12 months of continuous registration prior to the index date in a practice contributing up to standard (UTS) data to the CPRD
- Had a diagnosis of asthma before the index date (In this study, an asthma diagnosis is defined as at least one medcode for asthma prior to the index date. Please refer to annex 3 for the detailed medcodes for asthma and the related Read terms)
- Being treated with ICS/LABA FDC before the index date (at least one prescription within 3 months before the index date)
- Patients who were new users of Spiriva Respimat, or LTRA, or patients who were prescribed a higher dose of ICS/LABA FDC, or patients who switched to a new ICS/LABA FDC from the previous ICS/LABA FDC

Exclusion criteria:
- Patients who were prescribed other LAMA any time before or on the index date
- In the primary analysis, patients who were diagnosed with COPD before or on the index date will be excluded from the study.

  (In this study, a COPD diagnosis is defined as at least one Readcode for COPD before or on the index date. Please refer to annex 4 for the detailed medcodes for COPD and the related readterms)

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9.3 VARIABLES

All the variables will be identified based on data recorded on the index date (date of dispensing/initiation of the exposure), or when a characteristic was not recorded on the index date, during the pre-index period (the one closest to the index date), unless otherwise specified.

9.3.1 Exposures

The study drug of interest is Spiriva Respimat. The exposure in the Spiriva group will be initiation of Spiriva Respimat. The exposure in the comparator group will include: 1) initiation of LTRA; 2) an increase in daily dose of ICS/LABA FDC; and 3) switching to a new ICS/LABA FDC.

To make sure that patients who initiated Spiriva Respimat or LTRA are new users of these drugs, patients who initiated Spiriva Respimat must have no exposure to tiotropium before the index date, and patients who initiated LTRA must have no exposure to LTRA before the index date.

An increase in daily dose of ICS/LABA FDC refers to any increase in the daily dose. If there was more than 1 dose increase during the study period, only the first dose increase will be included in the analysis.

Switching to a new ICS/LABA FDC refers to patients who switched to a new ICS/LABA FDC with different drug ingredient that was not prescribed during the pre-index period. If there was more than 1 switch during the study period, only the first switch will be used in the analysis.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary outcome is whether patient has Cardiac arrhythmias on the index date or in the year prior to the index date. Cardiac arrhythmias is defined as having the following readcode in the above mentioned time period:

medcode	readcode	readterm
17597	327..00	ECG: supraventricular arrhythmia
19707	328..00	ECG: ventricular arrhythmia
29371	328Z.00	ECG: ventricular arrhythmia NOS
97780	G559.00	Arrhythmogenic right ventricular cardiomyopathy
6503	G57..11	Cardiac arrhythmias
426	G577.00	Sinus arrhythmia
31690	G57yA00	Re-entry ventricular arrhythmia
53893	Gyu5a00	[X]Other specified cardiac arrhythmias
26670	2432.00	O/E - pulse irregularly irreg.
18746	662S.00	Atrial fibrillation monitoring
45773	6A9..00	Atrial fibrillation annual review

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9479	7936A00	Implant intravenous pacemaker for atrial fibrillation
92361	793M000	Perc translum ablat pulmon vein to lft atrium conduct system
105554	8CMW200	Atrial fibrillation care pathway
57832	9Os..00	Atrial fibrillation monitoring administration
90187	9Os0.00	Atrial fibrillation monitoring first letter
90188	9Os1.00	Atrial fibrillation monitoring second letter
90189	9Os2.00	Atrial fibrillation monitoring third letter
90190	9Os3.00	Atrial fibrillation monitoring verbal invite
90191	9Os4.00	Atrial fibrillation monitoring telephone invite
63350	9hF..00	Exception reporting: atrial fibrillation quality indicators
39114	9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
2212	G573.00	Atrial fibrillation and flutter
1664	G573000	Atrial fibrillation
35127	G573300	Non-rheumatic atrial fibrillation
96277	G573400	Permanent atrial fibrillation
96076	G573500	Persistent atrial fibrillation
23437	G573z00	Atrial fibrillation and flutter NOS

9.3.2.2 Secondary outcomes

The secondary outcome is whether patient has Cardiac failure on the index date or in the year prior to the index date. Cardiac failure is defined as having the following readcode in the above mentioned time period:

medcode	readcode	readterm
15058	14A6.00	H/O: heart failure
46912	14AM.00	H/O: Heart failure in last year
21235	1J60.00	Suspected heart failure
9913	1O1..00	Heart failure confirmed
46672	388D.00	New York Heart Assoc classification heart failure symptoms
106198	661M500	Heart failure self-management plan agreed
83502	662p.00	Heart failure 6 month review
12366	662T.00	Congestive heart failure monitoring
30779	662W.00	Heart failure annual review
95835	679X.00	Heart failure education
60099	67D4.00	Heart failure information given to patient
46636	68B6.00	Heart failure screen
105542	8CeC.00	Preferred place of care for next exacerbation heart failure
32945	8CL3.00	Heart failure care plan discussed with patient
103732	8CMK.00	Has heart failure management plan
106008	8CMW800	Heart failure clinical pathway
32898	8H2S.00	Admit heart failure emergency
17851	8HBE.00	Heart failure follow-up
91288	8Hg8.00	Discharge from practice nurse heart failure clinic
102585	8HgD.00	Discharge from heart failure nurse service
26115	8HHb.00	Referral to heart failure nurse
70619	8HHz.00	Referral to heart failure exercise programme

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71235	8Hk0.00	Referred to heart failure education group
48897	8HTL.00	Referral to heart failure clinic
106894	8IE1.00	Referral to heart failure exercise programme declined
90935	9hH..00	Exception reporting: heart failure quality indicators
30749	9hH0.00	Excepted heart failure quality indicators: Patient unsuitabl
64062	9hH1.00	Excepted heart failure quality indicators: Informed dissent
106545	9m5..00	High risk of heart failure screening invitation
12627	9N0k.00	Seen in heart failure clinic
19002	9N2p.00	Seen by community heart failure nurse
95021	9N4s.00	Did not attend practice nurse heart failure clinic
83481	9N4w.00	Did not attend heart failure clinic
69062	9N6T.00	Referred by heart failure nurse specialist
32911	9Or..00	Heart failure monitoring administration
19380	9Or0.00	Heart failure review completed
90193	9Or1.00	Heart failure monitoring telephone invite
90192	9Or2.00	Heart failure monitoring verbal invite
72965	9Or3.00	Heart failure monitoring first letter
72386	9Or4.00	Heart failure monitoring second letter
89650	9Or5.00	Heart failure monitoring third letter
21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
28684	G233.00	Hypertensive heart and renal disease with renal failure
57987	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
2062	G58..00	Heart failure
1223	G58..11	Cardiac failure
398	G580.00	Congestive heart failure
2906	G580.11	Congestive cardiac failure
10079	G580.12	Right heart failure
10154	G580.13	Right ventricular failure
9524	G580.14	Biventricular failure
23707	G580000	Acute congestive heart failure
32671	G580100	Chronic congestive heart failure
27884	G580200	Decompensated cardiac failure
11424	G580300	Compensated cardiac failure
94870	G580400	Congestive heart failure due to valvular disease
884	G581.00	Left ventricular failure
23481	G581.11	Asthma - cardiac
43618	G581.12	Pulmonary oedema - acute
5942	G581.13	Impaired left ventricular function
5255	G581000	Acute left ventricular failure
27964	G582.00	Acute heart failure
101138	G583.00	Heart failure with normal ejection fraction
101137	G583.11	HFNEF - heart failure with normal ejection fraction
106897	G583.12	Heart failure with preserved ejection fraction
104275	G584.00	Right ventricular failure
4024	G58z.00	Heart failure NOS
12590	G58z.11	Weak heart

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17278	G58z.12	Cardiac failure NOS
96799	G5y4z00	Post cardiac operation heart failure NOS
8966	G5yy900	Left ventricular systolic dysfunction
12550	G5yyA00	Left ventricular diastolic dysfunction
104876	G5yyB00	Right ventricular diastolic dysfunction
104333	G5yyC00	Diastolic dysfunction
20822	Q48y100	Congenital cardiac failure
66306	SP11111	Heart failure as a complication of care
26242	ZRad.00	New York Heart Assoc classification heart failure symptoms

9.3.3 Covariates

The following patient characteristics will be assessed in this study:

Demographic characteristics:
- Age on the index date (continuous variable in years)
- Age on the index date (categorical variable: 18-34 years, 35-49 years, 50-64 years, 65 years and above)
- Gender (male, female)
- Ethnicity (if available)
- Patient level Index of Multiple Deprivation (IMD)

Lifestyle factors
- Smoking status (closest to index date; if available)
- Alcohol consumption (closest to index date; if available)
- Body mass index (BMI) (closest to index date; if available)
- Systolic and Diastolic Blood pressure measurement (closest to index date; if available)

Asthma history and lab tests
- Number of asthma exacerbations in the year prior to the index date. This is defined as as ≤300 mg oral corticosteroids (OCS) (not prescribed during an annual asthma review), or an Accident and Emergency (A&E) visit, or hospital admission. Exacerbations recorded within 14 days after the index 1 were considered part of the same exacerbation.
- Royal College of Physicians (RCP) 3 Questions for Asthma score on the index date, or when it was not recorded on the index date, during the pre-index period (the one closest to the index date) (each question scored 0 (no) or 1 (yes) for the following three questions: "Have you had difficulty sleeping because of your asthma symptoms (including cough)?" "Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?" and "Has your asthma interfered with your usual activities (e.g., housework, work, school, etc)?"[R18-1720]).
- Number of all-cause hospitalization in the year prior to the index date
- Number of respiratory disease related hospitalization in the year prior to the index date

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- Eosinophil count on the index date, or when it was not recorded on the index date, during the pre-index period (the one closest to the index date) (if available)

Comorbidities
- Respiratory
  - Pneumonia
  - Bronchiectasis
- Cardiovascular
  - Ischaemic heart disease
    - Myocardial infarction (MI)
    - Angina pectoris
  - Aneurysm
  - Hypertension,
- Renal failure
- Diabetes mellitus (any type)
- Psychiatric disorders
  - Dementia
  - Delerium
  - Depression
- Stroke
- Allergic rhinitis
- Sinusitis
- Charlson comorbidity index [R08-1584]
- Cataract
- Osteoporosis
- Obesity

Concomitant prescriptions
- Asthma-related prescriptions in the year prior to index date
  - Short-acting beta agonists
  - Inhaled long-acting beta agonists (on top of ICS/LABA FDC)
  - Inhaled corticosteroid (ICS) (on top of ICS/LABA FDC)
  - Oral corticosteroid
  - Theophylline
  - Leukotriene Receptor Antagonist (LTRA)
  - Azithromycin,
  - Mucolytics
- Cardiovascular medications
  - Cardiac Glycosides
  - Thiazides
  - Loop diuretics
  - Antiarrhythmics
  - Beta blocker
  - Vasodilator Antihypertensive Drug
  - Centrally Acting Antihypertensive Drugs
  - Alpha-adrenoceptor Blocking Drugs
  - Drugs affecting the renin-angiotensin system

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  - Angiotensin Converting Enzyme Inhibitors
  - Angiotensin II receptor blockers
  - Renin Inhibitors
  - Other antihypertensives
  - Nitrates
  - Calcium channel blockers
  - Oral anticoagulants
  - Heparin and other low molecular weight heparins
  - Aspirin
  - Antiplatelet
- Lipid-regulating Drugs
  - Bile Acid Sequestrants (lipid-regulating Drugs) - including Colesevelam
  - Ezetimibe (only in combination with Statin)
  - Fibrates
  - Statins
  - Nicotinic Acid Group
  - Omega-3 Fatty Acid Compounds
  - Other lipid-regulating drugs
- Glucose-lowering agents
- Non-steroidal anti-inflammatory drugs
- Psycholeptics
- Antipsychotics
- Antidepressants
- Agents for dementia

For concomitant medications used for diseases other than asthma the look-back time period will be limited to 180 days prior to the index date to increase the likelihood that the medications were used concomitantly. Concomitant medications will be categorized as current use (up to and including 60 days before index date) and past use (use any time prior to the 60 days before index date).

9.4 DATA SOURCES

In the UK, nearly all residents are registered in a general medical practice that uses electronic medical records. Some of those records are available for research purposes in the CPRD. CPRD contains diagnostic and prescribing information recorded by general practitioners (GPs) as part of their routine clinical practice in the UK. The database currently contains data for over 13.2 million patients with research-quality data from 680 UK practices; 5.69 million of these patients are active (still registered with a contributing GP practice) [R14-5257]. Patients registered are representative of the whole UK population in terms of age and sex.

Data collection happens as part of normal clinical care of patients in participating practices on a daily basis. Patients are included in the primary care dataset from their first until their last contact with the participating practice. Data are collected by practices and usually uploaded to the CPRD secure servers on a monthly basis.

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The CPRD contains data on demographic information, prescription details, clinical events (symptoms, diagnoses), preventive care provided, tests, immunisations, specialist referrals, hospital admissions and their major outcomes, and details relating to death. It should be noted that the CPRD only has prescription data but not the actual dispensing data. Data are largely recorded by general practice staff using version 2 Read codes, a hierarchical clinical classification system containing over 96, 000 codes. Numerical data on additional clinical measures (e.g. height, weight, blood pressure, alcohol intake) can also be recorded during consultations. Prescriptions issued by the GP are automatically recorded with a product name and British National Formulary code, alongside the dosage instructions and quantity. Results of laboratory tests ordered by the GP are commonly added to the patient record via electronic links to laboratories. Data fed back to the GP from other sources may also be entered into the patient record by practice staff; this might include information from secondary care such as key diagnoses, discharge data from hospitals, or follow-up information from specialist clinics. [R16-1231]

In addition, the following CPRD-linked data will be used in this study:

- Hospital Episode Statistics (HES) Admitted Patient Care (HES APC) data
- HES Accident and Emergency (HES A&E) data
- Patient Level Index of Multiple Deprivation

HES APC data are collected on all admissions to National Health Service (NHS) hospitals in England. HES APC also covers admissions to independent sector providers (private or charitable hospitals) paid for by the NHS. HES APC does not cover accident and emergency (A&E, emergency department) attendances or outpatient bookings. In the financial year 2014/15 (April to March), 18,731,987 hospital episodes from 451 different NHS hospital trusts (known as 'providers') were recorded in HES APC. HES APC provides detailed clinical, demographic and organizational information for each Finished Consultant Episode. Data on drugs prescribed through hospital pharmacies to inpatients are not available in HES APC [R18-0523]. In this study, HES APC will be used to assess hospitalization (all-cause, respiratory disease related, or asthma or lower respiratory condition related) in the year prior to the index date among patients who were treated at English NHS health care providers.
HES A&E data consist of individual records of patient care administered in the accident and emergency setting in England. These data are a subset of national A&E data collected by NHS England to monitor the national standard that 95% of patients attending A&E should wait no longer than 4 hours from arrival to admission, transfer or discharge. A&E data are submitted by A&E providers of all types in England. Data collected includes details about patients' attendance, outcomes of attendance, waiting times, referral source, A&E diagnosis, A&E treatment (drugs prescribed not recorded), A&E investigations and Health Resource Group [R18-0524]. In this study, HES A&E will be used to ascertain A&E attendance for asthma or low respiratory conditions, which will be used to calculate the number of asthma exacerbation in the year prior to the index date.
Patient Level Index of Multiple Deprivation (IMD) data are small area level measures of relative deprivation that are available for linkage to CPRD GOLD data through the patient and/or practice postcode. These measures can be used as a proxy to socio-demographic and socio-economic data which are generally poorly recorded in the primary care data as they do not directly relate to a patient's care. Data is provided as quintiles or deciles of the deprivation

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score or rank to prevent disclosure of patient or practice area. The postcode of the practice or patient residence is mapped to lower layer Super Output Area (LSOA) using a postcode lookup file [R18-0524]. In this study, Patient Level Index of Multiple Deprivation data will be used to ascertain patient level IMD.

9.5 STUDY SIZE

The study size is dependent on the uptake of Spiriva Respimat for asthma in the CPRD. Table 1 provides a range of estimates for different prevalence estimates of disease (or characteristics). The numerator represents the number of patients with the comorbidity of interest and the denominator represents the number of new users in the population. With 500 patients we would have adequate confidence intervals around these estimates.

Table 1 Precision of estimates for proportion measures

Number of New Users	95% Confidence Intervals for Various Prevalences of Diseases (%)				
	1%	2%	5%	7%	10%
500	0.4-2.3	1.1-3.6	3.4-7.3	5.1-9.6	7.7-12.9
800	0.5-2.0	1.2-3.2	3.7-6.7	5.4-9.0	8.1-12.3
2,000	0.6-1.5	1.5-2.7	4.1-6.0	6.0-8.2	8.8-11.3
5,000	0.8-1.3	1.6-2.4	4.4-5.6	6.3-7.7	9.2-10.9

A feasibility check was conducted to assess the number of patients in the tiotropium group, after application of the study inclusion and exclusion criteria. The result indicated that between September 2014 and December 2017, the number of patients in the tiotropium group was 935.

9.6 DATA MANAGEMENT

This study will use the in-house CPRD data set. Data management, tabulations, and graphics will be carried out with SAS 9.4 (SAS Institute, Cary NC). Source code of data management and data analyses will be kept for inspection at least for five years after publication of the results.

9.7 DATA ANALYSIS

All the analyses will be conducted with SAS 9.4 (SAS Institute, Cary NC).

9.7.1 Main analysis

The primary objective of this study is to describe the clinical and socio-demographic characteristics of asthma patients prior to the initiation of Spiriva Respimat for the treatment of Asthma. For this objective, patient baseline characteristics (as described in the “outcomes” and “covariates” section) will be tabulated and summarized for all new users of Spiriva Respimat. Means, standard deviations, medians, minimum, maximum, and interquartile range

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(IQR) will be used to present continuous variables, counts and percentages will be used to present categorical variables.

The secondary objective of this study is to describe and compare the characteristics of asthma patients who initiated Spiriva Respimat to asthma patients who initiated a higher dose of ICS/LABA FDC, or LTRA, or alternatively those who switched from the previous ICS/LABA FDC to a new ICS/LABA FDC. For this objective, patient characteristics (as described in the "outcomes" and "covariates" section) will be tabulated for the patients that initiated or switched to the other available treatments separately, using measures as described for the patient baseline characteristics of Spiriva.

Patient characteristics (as described in the "outcomes" and "covariates" section) will be compared among patients who initiated Spiriva Respimat and patients in other treatment groups. Analyses will be conducted in unmatched cohorts and differences between spiriva restinmat and each of the other exposure groups will be assessed using absolute standardized differences (ASD), where an ASD of at least 10% will be considered a meaningful difference [R16-1227].

9.7.3 Missing values

No imputation will be done for missing values. For all covariates, missing values will be presented as a separate category.

9.8 QUALITY CONTROL

This protocol will be strictly followed in the study. All changes to this protocol will be documented in protocol amendments.

The study protocol has been written following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [R15-4870] that provides a set of rules and principles for post-authorisation studies with regard to the best practices and transparency, thereby promoting scientific independence of such studies. The study will be registered to the ENCePP's E-register and the results will also be published on the same site.

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The study protocol also follows the key elements of the Guideline for Good Pharmacoepidemiology Practices (GPP) by International Society for Pharmacoepidemiology [R11-4318], and the recent draft Guidance for Industry and FDA Staff "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets" [R15-4859].

The statistical analytic approach will be reviewed/repeated by a second analyst to ensure quality control.

The study report will be reviewed, approved and archived per BI SOP and conducted upon ISAC approval.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The main analysis will exclude patients with other respiratory disease (e.g., COPD). This will exclude asthma-COPD overlap patients and some other patients and the results may not be representative to all asthma patients. However, Spiriva has both asthma and COPD indications. Therefore, for asthma-COPD overlap patients, the reason for initiating Spiriva Respimat can be unclear in existing data. Since the primary objective is to describe the characteristics of asthma patients prior to the initiation of Spiriva Respimat for the treatment of Asthma, it would be reasonable to exclude asthma-COPD overlap patients,

This study is based on existing data. It is possible that misclassification may happen for the measurement of comorbidities. However, we will use all the available data before the index date to minimize the possibility of misclassification.

Some covariates such as smoking status, alcohol use, BMI, pulmonary function, and eosinophil count may not be well recorded in CPRD. In the analyses we will present missing data as a separate category.

Some information may be recorded very infrequently or not at all in CPRD, e.g., number of people in a household, over-the-counter medication use, prescriptions in secondary care. These variables will not be assessed in this study.

The CPRD only includes patient data captured from general practitioners. Although some information about patient contacts with secondary care could be manually entered into the patient record, details about these specialty visits and hospital admissions (including dates, diagnoses, tests performed, length of stay) may be incomplete.

The CPRD may not be representative of all practices in the UK based on geography and size. There are certain patient groups that are missing from primary care records, such as prisoners, private patients, some residential homes and the homeless. Thus, selection bias cannot be ruled out. However, studies suggested that CPRD patients are broadly representative of the UK population in terms of age and sex. Patients are also comparable to the UK census in

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terms of ethnicity, and comparable to the Health Survey for England for body mass index distribution in most patient subgroups.

The HES APC data and HES A&E data only have data for patients from England.

9.10 OTHER ASPECTS

None.

9.11 SUBJECTS

Not applicable.

9.11.1 Cases

Not applicable.

9.11.2 Controls

Not applicable.

9.12 BIAS

None.

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10. PROTECTION OF HUMAN SUBJECTS

This study is a non-interventional study based on existing data and does not require patient informed consent. All the data used in this study will be anonymized. Study results will be presented at aggregate level. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

BI will submit the final study protocol for approval to the Independent Scientific Advisory Committee (ISAC) (http://www.cprd.com/ISAC). The CPRD has obtained ethical approval from a Multicentre Research Ethics Committee for all observational research using CPRD data without patient involvement; however, ISAC may recommend that the Multicentre Research Ethics Committee review the study documentation if any ethical issues arise.

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11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on current guidelines from the International Society for Pharmacoepidemiology [R11-4318] and the EMA [R13-1970], non-interventional studies such as the one described in this protocol, conducted using health care records, do not require expedited reporting of suspected adverse events/reactions. Data is anonymized and extracted, analyzed, validated and reported in aggregate. There is no potential that any employee of BI or agent working on behalf of BI will access individual patient data in which the patient may be identified during data compilation, data reporting or data analysis.

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12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study report will be prepared using the BI non-interventional study report template. Final study results will be posted on the ENCePP website. A scientific manuscript will be published in a peer-reviewed journal. Authorship and publication will follow the corresponding BI SOP 001-MCS-00-002 and guidelines of good scientific practice. The study results may also be submitted to scientific conferences for presentation.

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13. REFERENCES

13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

None.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

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ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS





Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

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Study title:

Characteristics of patients initiating Spiriva Respimat in Asthma in the UK

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	N/A
1.1.4 Interim progress report(s)	☐	☐	☒	N/A
1.1.5 Registration in the EU PAS register	☐	☐	☒	N/A
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	N/A

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

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Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7.1
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	N/A
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:	☒	☐	☐	9.2
4.2.1 Study time period?	☒	☐	☐	9.2
4.2.2 Age and sex?	☒	☐	☐	9.2
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☐	☐	☒	N/A
4.2.5 Duration of follow-up?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	N/A

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Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	N/A
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	N/A

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	N/A
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	N/A

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	N/A
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	N/A
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	N/A

Comments:

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Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	N/A

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.3.2
9.1.3 Covariates?	☒	☐	☐	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	NA

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7

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Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.3 Are stratified analyses included?	☒	☐	☐	N/A 9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	N/A
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/	☒	☐	☐	10

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Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
Institutional Review Board been described?				
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol:
Date: Aug/31/2017
Signature: _____

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ANNEX 3. CPRD MEDCODES INDICATING ASTHMA

A) Specific asthma codes

medcode	readterm
78	asthma
81	asthma monitoring
185	acute exacerbation of asthma
232	asthma attack
233	severe asthma attack
1555	bronchial asthma
2290	allergic asthma
3018	mild asthma
3366	severe asthma
3458	occasional asthma
3665	late onset asthma
4442	asthma unspecified
4606	exercise induced asthma
4892	status asthmaticus nos
5267	intrinsic asthma
5627	hay fever with asthma
5798	chronic asthmatic bronchitis
5867	exercise induced asthma
6707	extrinsic asthma with asthma attack
7058	emergency admission, asthma
7146	extrinsic (atopic) asthma
7191	asthma limiting activities
7378	asthma management plan given
7416	asthma disturbing sleep
7731	pollen asthma
8335	asthma attack nos
8355	asthma monitored

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9018	number of asthma exacerbations in past year
9552	change in asthma management plan
9663	step up change in asthma management plan
10043	asthma annual review
10274	asthma medication review
10487	asthma - currently active
11370	asthma confirmed
12987	late-onset asthma
13064	asthma severity
13065	moderate asthma
13175	asthma disturbs sleep frequently
13176	asthma follow-up
14777	extrinsic asthma without status asthmaticus
15248	hay fever with asthma
16070	asthma nos
16667	asthma control step 2
16785	asthma control step 1
18223	step down change in asthma management plan
18224	asthma control step 3
18323	intrinsic asthma with asthma attack
19167	asthma monitoring by nurse
19519	asthma treatment compliance unsatisfactory
19520	asthma treatment compliance satisfactory
20860	asthma control step 5
20886	asthma control step 4
21232	allergic asthma nec
22752	occupational asthma
24479	emergency asthma admission since last appointment
24506	further asthma - drug prevent.
24884	asthma causes daytime symptoms 1 to 2 times per week
25181	asthma restricts exercise

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25791	asthma clinical management plan
26501	asthma never causes daytime symptoms
26503	asthma causes daytime symptoms most days
26504	asthma never restricts exercise
26506	asthma severely restricts exercise
26861	asthma sometimes restricts exercise
27926	extrinsic asthma with status asthmaticus
29325	intrinsic asthma without status asthmaticus
30458	asthma monitoring by doctor
30815	asthma causing night waking
31167	asthma night-time symptoms
31225	asthma causes daytime symptoms 1 to 2 times per month
38143	asthma never disturbs sleep
38144	asthma limits walking up hills or stairs
38145	asthma limits walking on the flat
38146	asthma disturbs sleep weekly
39478	wood asthma
39570	asthma causes night symptoms 1 to 2 times per month
40823	brittle asthma
41017	aspirin induced asthma
41020	absent from work or school due to asthma
42824	asthma daytime symptoms
45073	intrinsic asthma nos
45782	extrinsic asthma nos
46529	attends asthma monitoring
47337	asthma accident and emergency attendance since last visit
47684	detergent asthma
58196	intrinsic asthma with status asthmaticus
73522	work aggravated asthma
93353	sequoiosis (red-cedar asthma)
93736	royal college of physicians asthma assessment

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98185	asthma control test
99793	patient has a written asthma personal action plan
100107	health education - asthma self management
100397	asthma control questionnaire
100509	under care of asthma specialist nurse
100740	health education - structured asthma discussion
102170	asthma review using roy colleg of physicians three questions
102209	mini asthma quality of life questionnaire
102301	asthma trigger - seasonal
102341	asthma trigger - pollen
102395	asthma causes symptoms most nights
102400	asthma causes night time symptoms 1 to 2 times per week
102449	asthma trigger - respiratory infection
102713	asthma limits activities 1 to 2 times per month
102871	asthma trigger - exercise
102888	asthma limits activities 1 to 2 times per week
102952	asthma trigger - warm air
103318	health education - structured patient focused asthma discuss
103321	asthma trigger - animals
103612	asthma never causes night symptoms
103631	royal college physician asthma assessment 3 question score
103813	asthma trigger - cold air
103944	asthma trigger - airborne dust
103945	asthma trigger - damp
103952	asthma trigger - emotion
103955	asthma trigger - tobacco smoke
103998	asthma limits activities most days
105420	asthma self-management plan review
105674	asthma self-management plan agreed
106805	chronic asthma with fixed airflow obstruction
107167	number days absent from school due to asthma in past 6 month

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B) Non-specific asthma codes

medcode	readterm
719	h/o: asthma
1208	childhood asthma
5138	patient in asthma study
5515	seen in asthma clinic
7229	asthma prophylactic medication used
11022	asthma trigger
11387	refuses asthma monitoring
11673	excepted from asthma quality indicators: patient unsuitable
11695	excepted from asthma quality indicators: informed dissent
13066	asthma - currently dormant
13173	asthma not disturbing sleep
13174	asthma not limiting activities
16655	asthma monitoring admin.
18141	asthma monitoring due
18692	exception reporting: asthma quality indicators
18763	referral to asthma clinic
19539	asthma monitoring check done
20422	asthma clinic administration
25705	asthma monitor 3rd letter
25706	asthma monitor 2nd letter
25707	asthma monitor 1st letter
25796	mixed asthma
26496	health education - asthma
29645	asthma control step 0
30308	dna - did not attend asthma clinic
30382	asthma monitoring admin.nos
31135	asthma monitor phone invite
35927	asthma leaflet given
37943	asthma monitor verbal invite

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41554	asthma monitor offer default
43770	asthma society member
92109	asthma outreach clinic

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ANNEX 4. CPRD MEDCODES INDICATING COPD

medcode	readterm
18476	COPD follow-up
45771	Chronic obstructive pulmonary disease does not disturb sleep
4084	Airways obstructn irreversible
794	Emphysema
998	Chronic obstructive airways disease
1001	Chronic obstructive pulmonary disease
5710	Chronic obstructive airways disease NOS
9520	Chronic obstructive pulmonary disease monitoring
9876	Severe chronic obstructive pulmonary disease
10802	Moderate chronic obstructive pulmonary disease
10863	Mild chronic obstructive pulmonary disease
10980	Centrilobular emphysema
11287	Chronic obstructive pulmonary disease annual review
14798	Emphysematous bronchitis
18621	Chronic obstructive pulmonary disease follow-up
18792	Chronic obstructive pulmonary disease monitoring admin
23492	Chronic bullous emphysema NOS
26018	Chronic obstructive pulmonary disease monitoring by nurse
26306	Chronic bullous emphysema
28755	Chronic obstructive pulmonary disease monitoring 1st letter
33450	Emphysema NOS
34202	Chronic obstructive pulmonary disease monitoring 2nd letter
34215	Chronic obstructive pulmonary disease monitoring 3rd letter
37247	Chronic obstructive pulmonary disease NOS
37371	Chronic obstructive pulmonary disease monitoring due
44525	Obstructive chronic bronchitis NOS
45998	Chronic obstructive pulmonary disease monitoring by doctor
93568	Very severe chronic obstructive pulmonary disease
12166	Other specified chronic obstructive airways disease
38074	Chronic obstructive pulmonary disease monitor phone invite
42258	Chronic obstructive pulmonary disease monitoring verb invite
42313	Health education - chronic obstructive pulmonary disease
45770	Chronic obstructive pulmonary disease disturbs sleep
45777	Chronic obstructive pulmonary disease clini management plan

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval- of Global Epidemiology		09 Aug 2018 20:09 CEST
Approval-Team Member Medicine		10 Aug 2018 16:28 CEST
Approval- Safety Evaluation Therapeutic Area		13 Aug 2018 08:56 CEST
Approval-Other		14 Aug 2018 09:25 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**