

STATISTICAL ANALYSIS PLAN FOR NON-INTERVENTIONAL STUDIES BASED ON EXISTING DATA

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ABBREVIATIONS

A&E	Accident and Emergency
BI	Boehringer Ingelheim
BMI	Body mass index
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Database
Dx	Diagnosis Record
FDC	Fixed Dose Combination
HES	Hospital Episode Statistics
HES A&E	Hospital Episode Statistics Accident and Emergency
HES APC	Hospital Episode Statistics Admitted Patient Care
ICS	Inhaled corticosteroids
IMD	Patient level Index of Multiple Deprivation
IQR	Interquartile range
ISAC	Independent Scientific Advisory Committee
LABA	Long-acting beta agonists
LAMA	Long-acting muscarinic antagonists
LTRA	Leukotriene receptor antagonist
OCS	oral corticosteroids
RCP	Royal College of Physicians
Rx	Prescription Record
SmPC	Summary of Product Characteristics
TinA	Tiotropium in Asthmatic Patients
UTS	Up-to-standar

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1. PURPOSE AND SCOPE

The purpose of this document is to provide further details to the planned analysis described in the related study protocol. Details are given on implementation of study cohort build, definition of all variables and covariates (via code lists and/or algorithms), as well as report table shells.

The actual implementation and data analysis will be executed upon ISAC approval.

2. CHANGES IN THE PLANNED ANALYSIS OF THE STUY

The protocol mentions the patient characterisation by the Royal College of Physicians (RCP) 3 Questions for Asthma score. During covariate review it was observed that the conduct of this questionnaire might be recorded in CPRD GOLD, but not the results. Therefore the covariate was removed from the list of baseline characteristics.

The protocol planned for reporting BMI and under comorbidities Obesity. During SAP development it was regared sufficient to have BMI, therefore Obesity was removed from the comorbidity list.

3. STUDY DESIGN

This cross-sectional, non-interventional study will describe baseline characteristics of asthmatic patients of four treatment groups. They are characterized at treatment initiation or at time of treatment change of their ICS/LABA FDC. Baseline characteristics will be compared pairwise against the one of Spiriva Respimat Initiators and difference will be reported as absolute standardized differences.

The study will be conducted using CPRD GOLD data. Some linkage data sets will be requested in addition to refine some patient characteristics. Further details are given in the next chapters.

In this chapter the build of the treatment cohorts will be further described.

From CPRD online platform (Define and Extract tools) a source cohort will be extracted from CPRD GOLD containing all potential patients, which will be further processed in SAS to identify the final four treatment cohorts. This two stage approach is required, because the CPRD online tools only allows extraction by code lists, whereas the two ICS/LABA cohorts can only be identified through an algorithm.

The source cohort is defined as:

All patients with at least one of the following prescriptions during study period (from 01-Sep-2014 to 31-Dec-2017) will be selected:

- Spiriva Respimat,
- LTRA,
- ICS/LABA FDC

and will require to be of gender male or female.

This source cohort will be further limited to only “acceptable” patients. The acceptable flag in CPRD GOLD is a quality flag on patient’s record level, identifying patient with data quality sufficient to be used for research purposes.

Table 1 lists the final study cohorts which will be identified in a consecutive step from patients in the source cohort. Details to their build are given in chapter 3.

Table 1 - Study Cohorts (Main Definition)

<u>MAIN</u>	
Asthmatic Patients treated w ICS/LABA FDC (w/o COPD co-diagnosis)	
Cohort_1	Initiator of Spiriva Respimat
Cohort_2	Initiator of LTRA
Cohort_3	Switchers (different ICS/LABA FDC)
Cohort_4	Initiator higher ICS dose (ICS/LABA FDC)

3.1 STUDY COHORTS

Patients are only allowed to contribute to one cohort (cohorts are mutually exclusive). The four treatment cohorts are identified as such, that first “Initiator of Spiriva Respimat” cohort is identified, the remaining three will be build upon the first qualifying event of the corresponding definition. Priority is given to “Initiator of Spiriva Respimat” cohort to allow sufficient number of patients.

3.1.1 Cohort: Initiator of Spiriva Respimat

The first Spiriva Respimat prescription record during study period qualifies for cohort entry and its event date will be set as index date.

Patients will be excluded if they fulfill any of the following exclusion criteria:

- prior Spiriva Respimat use (*)
- no ICS/LABA FDC Rx within 3 months before index date
- no prior asthma Dx (*)
- age on index date less than 18 years
- on index date less than 365 days prior UTS registration
- prior COPD Dx (**)
- any prior LAMA use (**)

(*) prior means here any time before index date (**) prior means here any time before index date (incl. index date)

3.1.2 Cohort: Initiator of Leukotriene Receptor Antagonist (LTRA)

The first LTRA prescription record during study period qualifies for cohort entry and its event date will be set as index date.

Patients will be excluded if they fulfill any of the following exclusion criteria:

- prior LTRA use (*)
- no ICS/LABA FDC Rx within 3 months before index date
- no prior asthma Dx (*)
- age on index date less than 18 years
- on index date less than 365 days prior UTS registration
- prior COPD Dx (**)
- any prior LAMA use (**)

(*) prior means here any time before index date (**) prior means here any time before index date (incl. index date)

3.1.3 Identifying ICS/LABA FDC cohorts

Figure 1 shows how patients may qualify for one of the ICS/LABA FDC cohorts during study period. Further exclusion criteria are applied as described in the following sub-chapters.



Figure 1- Schematic illustration on how patients may qualify for inclusion into one of the ICS/LABA FDC cohorts

For the last decision node in above flow chart, the prescribed daily dose needs to be calculated considering number of puffs per day as given with the prescription in patient record (table therapy; variable ndd) in combination with the dose per puff given in the drug dictionary (harmonized entries during code list review).

1 Calculation of ICS Dose per Rx

$$\text{ICS Daily Dose} = \text{Dose per puff} * \text{Number of puffs per day}$$

Dose per puff – from harmonized product list (see details below – field “mcg ICS per dose”)
Number of puffs per day – from patient data file (table: therapy), consider only valid entries. Unrealistic entries are substituted.

Figure 2 - ICS daily dose calculation per Rx

Valid entries for “number of puffs per day” are the following: 1,2,3,4,5,6,7,8. Missing or any other entries are substituted by the valid NDD from previous prescription (“last observation carried forward” approach). Otherwise the NDD (e.g. two inhalations/puffs twice daily → 4) given in the Summary of Product Characteristics (SmPC) (online on webpage: <https://www.medicines.org.uk/emc/>) is used. If multiple option given in SmPC, the largest maintenance related number of puffs were selected as replacement value.

Product dictionary entries are not in a fully structured and consistent format provided. During code list preparation and review the following harmonized columns were prepared to allow correct processing:

- ICS drug substance name
- ICS strength per dose/puff
- LABA drug substance name
- LABA strength per dose/puff
- Device (DPI / pMDI)
- Daily dose as per SmPC (SPC_NDD)

3.1.3.1 Cohort: Initiator of new ICS/LABA FDC (switchers)

The first ICS/LABA FDC prescription record during study period with different ICS and/or LABA drug substance component as compared to the preceding FDC prescription qualifies for cohort entry and its event date will be set as index date. Same ICS/LABA FDC, but different device (e.g. switch from DPI to pMDI) will trigger cohort entry to this cohort as well.

Patients will be excluded if they fulfil any of the following exclusion criteria:

- prior use of the same ICS/LABA FDC (evaluated on drug substance and device level) (*)
- preceding ICS/LABA FDC Rx not within 3 months before index date
- no prior asthma Dx (*)
- age on index date less than 18 years
- on index date less than 365 days prior UTS registration
- prior COPD Dx (**)
- any prior LAMA use (**)

(*) prior means here any time before index date (**) prior means here any time before index date (incl. index date)

3.1.3.2 Cohort: ICS dose increase of ICS/LABA FDC user

The first ICS/LABA FDC prescription record during study period which represent a dose increase of ICS daily dose as compared to the preceding FDC prescription qualifies for cohort entry and its event date will be set as index date.

Patients will be excluded if they fulfill any of the following exclusion criteria:

- preceding ICS/LABA FDC Rx within 3 months before index date
- no prior asthma Dx (*)
- age on index date less than 18 years
- on index date less than 365 days prior UTS registration
- prior COPD Dx (**)
- any prior LAMA use (**)

(*) prior means here any time before index date (**) prior means here any time before index date (incl. index date)

3.2 SETTING

All patients will be required to have the status at least 1 year (365 days) of continuous up-to-standard (UTS) registration in CPRD GOLD prior to index. The start of the up-to-standard registration period per patient is set to the latest date of the following dates:

- practice's Up-to-standard date
- patient's current registration date

4. VARIABLES

All variables will be derived based on data recorded on the index date or during the pre-index period (the one closest to the index date), unless otherwise specified. Most variables are defined by code lists (Read codes for diagnosis or Product codes for prescribed medications) or can be directly extracted from CPRD GOLD table fields (e.g. gender). Algorithms are applied if information of interest are not readily available e.g. combination of code lists and/or other database fields e.g. entity type including some data cleaning logic.

Where available previously prepared code lists and algorithms were re-used. The majority were originally prepared for another BI study (study ID: 1245.122). Treatment code lists for cohort build were all newly developed using the latest version of the product dictionary. All codelists and algorithms were reviewed by experienced clinicians ().

4.1.1 Exposures / Cohort entry variable / Cohort build variables

For cohort build the following variables will be identified via medical or product (drug) code lists. Related codelists are provided in the appendix of this document or in the study protocol.

Prescription related code lists

- ICS/LABA FDC (incl. harmonised entries e.g. drug substance names)
- Spiriva Respimat
- LTRA
- LAMA (for exclusion criteria)

For extracting the source cohort the first three listed codelists will be combined to one.

Disease related code lists:

- Asthma (Read code list provided in the study protocol)
- COPD (Read code list provided in the study protocol)

4.1.2 Outcomes

4.1.2.1 Primary outcomes

Cardiac arrhythmias (Read code list provided in the study protocol)

Assessment period: on the index date or in the year prior to the index date

4.1.2.2 Secondary outcomes

Cardiac failure arrhythmias (Read code list provided in the study protocol)

Assessment period: on the index date or in the year prior to the index date

4.1.3 Covariates

Patient characteristics will be evaluated on the index date and/or during the pre-index period (the one closest to the index date).

In the following tables the column “definition” indicates how covariate are identified:

- A = algorithm
- C = code list (Read or product)
- D = data field
- O = other

Details to the algorithm based definition are given in subchapters to this chapter. Code lists are provided in the appendix. Diagnosis records based on Read code lists will be extracted from table CLINICAL if not otherwise specified. Data field are not further defined as they used directly as provided in database fields.

Table 2 - Baseline Characteristics – Demographics, Life style factors, Comorbidities

	Lookback Period	Definition	Data Source
Demographic characteristics			
Age in years	on idt	A	CPRD GOLD
Gender		D	
Ethnicity		A	CPRD GOLD + HES APC
Patient level Index of Multiple Deprivation	<i>not applicable</i>	O	IMD
Life style factors *			
Smoking status	within 3y prior to idt (incl idt)	A	CPRD GOLD
Alcohol consumption	within 3y prior to idt (incl idt)	A	
Body mass index (BMI)	within 365d prior to idt (incl idt)	A	
Systolic blood pressure (SBP)	within 365d prior to idt (incl idt)	A	
Diastolic blood pressure (DBP)	within 365d prior to idt (incl idt)	A	
Asthma history and lab tests		A	
Number of asthma exacerbations	within 365d prior to idt (<u>excl</u> idt)	A	HES APC + HES A&E
Number of all-cause hospitalization		A	HES APC
Number of respiratory disease related hospitalization		A	HES APC
Eosinophil count (units of 10 ⁹ /L)	within 365d prior to idt (<u>excl</u> idt)	A	
Comorbidities			
Charlson comorbidity	within 365d prior to idt (incl idt)	A	CPRD GOLD + HES APC
Respiratory			
Pneumonia	within 365d prior to idt (incl idt)	C	CPRD GOLD
Bronchiectasis	within 365d prior to idt (incl idt)	C	
Cardiovascular			
Ischaemic heart disease	within 365d prior to idt (incl idt)	C	CPRD GOLD
Myocardial infarction (MI)		C	
Angina pectoris		C	
Abdominal Aneurysm		C	
Hypertension		C	
Chronic Kidney		C	
End Stage		C	
Dialysis		C	
Diabetes mellitus (any Type)		C	
Psychiatric disorders			
Dementia	within 365d prior to idt (incl idt)	C	CPRD GOLD
Delirium		C	
Depression		C	
Stroke		C	
Allergic rhinitis		C	
Sinusitis		C	
Cataract		C	
Osteoporosis		C	

d = days, idt = index date; * closest to index date will be reported

Table 3 - Asthma-related prescriptions and potential combination prescriptions

<i>All definition based on product codelists</i>	overall	past use	current use	concurrent use
Short-acting beta agonists	365 d lookback (<u>excl</u> idt)	365 upto 61 d prior to idt	60 d prior upto idt	
Inhaled LABA mono				30 d prior upto 30 d after idt
ICS mono				30 d prior upto 30 d after idt
Oral corticosteroid				
Theophylline				
Leukotriene Receptor Antagonist (LTRA)				
Azithromycin				
Mucolytics				

d = days, idt = index date;

Table 4 - Other concomitant medications

<i>All definition based on product codelists</i>	Overall	past use	current use
Cardiovascular medications			
Cardiac Glycosides	180 d lookback (incl idt)	180 upto 61 d prior to idt	60 d prior upto idt (incl idt)
Thiazides			
Loop diuretics			
Antiarrhythmics			
Beta blocker			
Vasodilator Antihypertensive Drug			
Centrally Acting Antihypertensive Drugs			
Alpha-adrenoceptor Blocking Drugs			
Drugs affecting the renin-angiotensin system			
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 (oral and insulin)			
Non-steroidal anti-inflammatory drugs			
Psycholeptics			
Antipsychotics			
Antidepressants			
Agents for dementia			

d = days, idt = index date;

4.1.3.1 Age

Age on index date will be approximated because only patient's year of birth is provided. The day and month of birth are set midway through the year to 01-Jul.

4.1.3.2 Ethnicity

Ethnicity is well recorded in HES APC data, therefore corresponding records are taken from this data set where HES APC data are available. For the remaining patients information will be retrieved via Read code list from CPRD GOLD.

The following ethnicity groups will be reported:

- 0 - White
- 1 - Black
- 2 - Asian
- 3 - other (incl. mixed)
- <missing>

Related code lists are provided in the appendix.

In case CPRD GOLD records result in multiple, contradicting ethnicity records the most frequent record (consolidated from all records) will be kept. In case this does not solve the issue, ethnicity will be set to missing/unknwon.

Original definition from CALIBER research with some modification done (grouping categories and extending the concept to consider CPRD GOLD records in addition)

https://www.caliberresearch.org/portal/show/ethnic_hes

4.1.3.3 Patient level index of multiple deprivation

2015 English Index of Multiple Deprivation (with 2011 LSOA boundries) will be requested on patient level in quintile. The 2015 data are the closest to the study period.

Quintiles ranging from quintile 1 = least deprived to quintile 5 = most deprived.

There are IMD data sets on practice level as well with more coverage beyond England (+ Scotland + Wales), but the scores are not comparable across countries as they are calculated on different levels e.g. for England: IMD score calculated on a lower super output area (LSOA) level. Where as Scotland's IMD score is calculated on data zones which are slightly smaller than LSOAs.

4.1.3.4 Smoking status

Smoking status will be evaluated using an algorithm considering diagnosis, treatment and health status records.

The following status categories will be reported:

- 0 – unknown
- 1 – Smoker
- 2 – Non-Smoker
- 3 – Ex-Smoker

As the information is not expected to be regularly reported in patient record (especially for non-smokers), a so called base table will be prepared considering all patient records reported over time related to smoking status with some logic build in to handling contradicting information. From this table the status record prior to and closest to index date will be extracted to report patient's status at baseline.

Algorithm details

Table: Additional
Enttype = 4

Tables: Clinical and Referral
Read code list with classification into the different status - see appendix

Table: Therapy
Product code list - see appendix (patients with any of those medications prescribed is consider a smoker)

Preparing Smoking “base” table - data handling and processing steps:

- 1) Extract from each data table records which fulfil the selection criteria (either entity type or read/product code lists)
- 2) Combine the data to one big data set, keeping Patient number (Patid), Diagnose Date (Eventdate), Smoking status
- 3) If patient ever had a status of being “smoker” or “ex-smoker” and a current record of “non-smoker”, the current status is reset “ex-smoker”
- 4) In case multiple contradicting records per patient on the same date:
 - a. If “Non smoker” occurs along with a status of “Ex smoker”, keep only “Ex smoker”
 - b. Otherwise set status to “Unknown” for that date

4.1.3.5 Alcohol consumption

Drinking status will be evaluated using an algorithm considering diagnosis, treatment and health status records.

The following status categories will be reported:

- 0 – unknown
- 1 – Drinker
- 2 – Non-Drinker
- 3 – Ex-Drinker

Drinking related information are not expected to be regularly document in patient records (especially for non-drinker – if at all). Therefore a so called base table will be prepared considering all dinking status related records with some logic build in to handling contradicting information. From this table the status record prior to and closest to index date will be extracted to report patient’s status at baseline.

Algorithm details

Table: Additional
Enttype = 5

Tables: Clinical and Referral
Read code list with classification into the different status - see appendix

Table: Therapy
Product code list - see appendix (patients with any of those medications prescribed is consider a drinker)

Preparing Dinking “base” table - data handling and processing steps:

- 1) Extract from each data table records which fulfil the selection criteria (either entity type, read code or product code lists)
- 2) Combine the data to one big data set, keeping Patient number (Patid), Diagnose Date (Eventdate), Drinking status
- 3) If patient had a previous status of being a “drinker” or “ex-drinker” and a current status of “non-drinker”, its status will be reset to “ex-drinker”
- 4) In case multiple contradicting records per patient on the same date:
 - a. If “Non Drinker” occures along with a status of “Ex Drinker”, keep only “Ex Drinker”
 - b. Otherwise set status to “Unknown” for that date

4.1.3.6 Body mass index

Body mass index (BMI) will be evaluated using an algorithm considering diagnosis and actual BMI records.

A so called “base” table will be prepared considering all BMI records with some logic build in to handling multiple recordings per day and during pregnancy. From this table the BMI record prior to and closest to index date will be extracted to report patient’s BMI at baseline.

Algorithm details

Table: Additional

Enttype = 13

Data field = Data3 (this is the field were the actual value is recorded).

Tables: Clinical

Read code list to identify pregnancies.

Preparing BMI “base” table - data handling and processing steps:

- a. Extract BMI records from additional table (enttype 13, variable: data3 = BMI)
memo: merge with clinical table to get the corresponding event date
- b. Exclude records with no value entered or values equal to 0.
- c. Rounded values down to the next integer (e.g. 24,7 becomes 24).
- d. Drop duplicate records on the same date.
- e. Exclude records not within the range of 10 to 60.
- f. If there are still multiple records on the same date left, exclude all records of that date.
- g. Drop BMI records with event date within 4,5 month (1month = 30 days) of date of pregnancy event (identify in Clinical table via pregnancy code list).

Table 5 - BMI - Example of data handling

Patid	Eventdate	BMI (original value)	BMI (rounded to the next lower integer value)	Record in basedata._base_bmi	Comment
				No	Two ambiguous records on the same date.
				No	
				Yes	Two records available, after rounding duplicate records. Only one is kept and stored in base data set.
				Yes	
					No

4.1.3.7 Systolic blood pressure

SBP records are extracted from CPRD GOLD fulfilling the following conditions:

Table: Additional

Enttype = 1

Data field = Data2 (this is the field where the actual value is recorded).

The following data processing steps are taken to clean the extracted raw SBP values:

- (1) round value to nearest integer
- (2) keep only records with values with the limit: 0 to 300 (inclusive)
- (3) if multiple distinct values per day, check time (data field 4)
 - if time available for all records, keep last record.
 - otherwise drop all records of that date (because discrepancy can't be solved).

4.1.3.8 Diastolic blood pressure

DBP records processing follows the same approach as for SBP with limits set to 0 to 150.

4.1.3.9 Asthma Exacerbation

Count asthma exacerbation per patients over the baseline period (1 year prior to index date) will be extracted with an algorithm. Its definition consists of three components, which are described below. The algorithm considers a logic to collapse records to one exacerbation if multiple occur within 14 days of each other.

Algorithm details

Component: oral steroid Rx (≤ 300mg) during non asthma review visit

Table: Therapy in combination with table clinical

Product code list for oral steroid Rx (≤ 300mg) - see code list in appendix

Limit to those prescription not recorded during asthma review visit [CPRD GOLD]

Calculating daily dose per patient considering patient level information

"during non asthma review visit" is defined as no concurrent record (on same date) with read code "66YJ.00" in CLINICAL table.

OR Component: hospitalisations for asthma or lower respiratory conditions [HES APC]

Table: HES APC – any record with ICD10: J45* (for asthma and any subcode)

OR Component: A&E attendance for asthma or lower [HES A&E]

Table: HES A&E – any records with the following diagnosis code:

25 = respiratory condition

OR 251 = respiratory conditions - bronchial asthma

4.1.3.10 All-cause hospitalisation

On patient level, count any record in HES APC data set in the year prior to index date. Multiple records on one date will be counted as one.

4.1.3.11 Respiratory disease related hospitalisation

Defined as ICD10: J* (including any subcode)

On patient level, count any record with above ICD10 code in the year prior to index date. Multiple records on one date will be counted as one.

4.1.3.12 Eosinophil count

Eosinophil count (unit $10^9/L$) are extracted from CPRD GOLD table using an algorithm considering Read codes and applying range of valid values as well as selection of records by valid units. The algorithm handles multiple records on the same date. Details are provided further below.

This algorithm is a modified version of the one from CALIBER research group (URL: https://www.caliberresearch.org/portal/show/eosinophils_gprd).

A so called base table will be prepared considering all Eosinophil count records. From this table the Eosinophil count record closest to index date within 365 days prior to index date (including index date) will be extracted to report patient's Eosinophil count at baseline.

Algorithm details

Table: Test

Record selection by:

- Read code:
 - 42K..00 Eosinophil count
 - 42K3.00 Eosinophil count raised
 - 42KZ.00 Eosinophil count NOS
 - 42K1.00 Eosinophil count normal
- AND event date not missing (not equal .)
- AND entity type number 186 (Eosinophil Count)
- AND data2 (value) between 0 and 10 (inclusive)
- AND data3 (units) in (0 [no data entered], 37 [$10^9/L$], 153 [10^9], 17 [$/L$])

Introduce column with harmonised unit with “ $10^9/L$ ” for all entries.

Handling multiple recordings on the same date:

- If same Eosinophil count value reported multiple times, keep only one record
- If different Eosinophil count values reported, remove all records of that date.

4.1.3.13 Charlson comorbidity index

Charlson comorbidity index will be implemented following the definition of the CALIBER research (URL: https://www.caliberresearch.org/portal/show/charlson_composite), which considers CPRD GOLD (table: clinical) and HES APC records. Correspondingly for each condition two code lists are defined: one Read code list and one ICD10 code lists – see appendix.

In the table below the condition with its related weights and potential rules are given.

Table 6 - Charlson comorbidity index - conditions and weights

Conditions	Weight	Rules
Myocardial infarction	1	
Heart Failure	1	
Peripheral vascular disease	1	
Cerebrovascular disease	1	
Dementia	1	
Pulmonary Disease	1	
Connective Tissue Disease	1	
Peptic ulcer disease	1	
Mild liver disease	1	
Diabetes	1	
Diabetes with complications	2	If “diabetes with complications”, set diabetes weight to 0.
Hemiplegia	2	
Renal disease	2	
Cancer/All tumours	2	
Metastatic tumour	6	If “metastatic tumor”, set cancer weight to 0.
Severe Liver Disease	3	
Acquired Immune Deficiency Syndrome (AIDS/HIV)	6	

Each condition is considered with its respective weight if an event is retrieved in either data set (CPRD GOLD and/or HES APC) in the year prior to index date (incl. index date). For each patient the sum over all weights are calculated to build the Charlson score on patient level.

5. DATA SOURCES

The latest CPRD GOLD data base version online available will be used to define and extract the source cohort and all related data.

Once the study cohorts are identified in CPRD GOLD, additional data for linkage will be requested for English patients eligible for linkage:

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

Linkage is conducted by a trusted-third party on behalf of CPRD. No personal identifiers will become available neither for CPRD nor for Boehringer Ingelheim.

All data base and data cut version related documentation (data dictionary, user guide etc.) will be stored along with the study documentation in IDEA for GEN.

6. DATA MANAGEMENT

The source cohort will be defined and extracted via CPRD GOLD online portal. All further data preparation steps are conducted using SAS 9.4 (SAS Institute, Cary NC).

Linkage data sets will be requested for the sub-set of patient which are eligible following CPRD process.

All related data files and records are stored on the BI inhouse server (“Epi SAS Server”).

Documentation of study conduct will be stored in IDEA for CON.

7. DATA ANALYSIS

This study is fully descriptive and will report baseline characterisations for each of the treatment cohorts. Differences in characteristics will be compared pairwise and reported as absolute standardized difference (ASD). Details are given below.

Analyses will be conducted in unmatched cohorts.

Table shells of planned report tables are given in appendix.

For compliance with ISAC requirements, any covariate resulting in cell counts less than 5 will be reported as “<5” without any further reporting of proportions or ASD.

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

7.1.1 Main analysis

Continuous variables will be reported by mean, standard deviation, median, minimum and maximum values and interquartile range (IQR). Categorical variables will be summarized by numbers and proportion. Proportions which will result to 0.00% due to rounding will be replaced by <0.01% value.

Differences in characteristics will be compared pairwise - each of the treatment group (reference) against the exposure group Spiriva Respimat initiator. The absolute standardized difference is calculated as follows:

For categorical variables:

$$ASD = \left| \frac{PE - PR}{\sqrt{\frac{PE * (1 - PE) + PR * (1 - PR)}{2}}} \right|$$

PE = Prevalence of past users of exposure group
PR = Prevalence of past users of referent group

For continuous variables:

$$ASD = \left| \frac{mean.E - mean.R}{\sqrt{\frac{var.E + var.R}{2}}} \right|$$

Mean.E, var.E from continuous variable of exposure group
Mean.R, var.R from continuous variable of referent group

7.1.3 Handling of Missing Values

Imputation is only done for cohort entry related prescriptions of ICS/LABA FDC. If daily number of puffs is missing or implausible, a valid value will be derived by carrying forward the value from proceeding prescription (if value was plausible then) or by imputing from SmPC recommendations. See algorithm description in previous chapter for details. For all other variables no imputation is applied.

7.1.4 Handling of Inconsistencies in Data

Rules to handle inconsistencies are applied as needed. Details are provided in previous chapters on algorithms.

8. QUALITY CONTROL

The SAS programs, outputs and all other related documents to prepare the report tables will be reviewed and as needed re-programmed by a second data analyst to ensure quality control.

9. REFERENCES

9.1 PUBLISHED REFERENCES

The CALIBER Data Portal.

webpage: <https://www.caliberresearch.org/portal/>

Last Accessed 4-Jan-2019

for e.g. code lists and algorithms e.g. HES ethnicity code list

Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; 28 (25): 3083 – 3107.

The electronic Medicines Compendium (eMC)

webpage: <https://www.medicines.org.uk/emc/>

Last Accessed 4-Jan-2019

for e.g. access to Summary of Product Characteristics (SmPC)

9.2 UNPUBLISHED REFERENCES

None.

ANNEX 1. CODE LISTS

All Read code and Product code lists, which are not already listed in the study protocol, are provided in the following stand-alone excel files:

- 1) Study_0205_0537_Codelists_CCI.xlsx
- 2) Study_0205_0537_Codelists_allExceptCCI.xlsx containing:

A_01_ICSLABA	E2_234_CKD_DIALYSIS
A_02_SPIRIVARESP	E2_260_ANYDMTYPE
A_03_LTRA	E2_275_DEMENTIA_CALIBER
A_40_LAMA	E2_280_DELIRIUM
B_30_ETHNICITY_READ	E2_290_DEPRESSION
C_10_SMOKING_PRODUCT	E2_300_STROKE
C_10_SMOKING_READ	E2_310_ALLERGICRHINITIS
C_20_DRINKING_PRODUCT	E2_320_SINUSITIS
C_20_DRINKING_READ	E2_330_CATARACT
C_30_BMI	E2_340_OSTEOPOROSIS
D_50_EOSINOPHIL	F_400_SABAMONO
E2_120_PNEUMONIA	F_405_LABAMONO
E2_140_BRONCHIECTASIS	F_410_ICSMONO
E2_160_IHD	F_415_OCS
E2_170_MI	F_420_THEO
E2_180_UNSTABLEANGINA	F_452_AZI
E2_210_ABDOMINALANEURYSM	F_454_MUCO
E2_220_HTN	F_460_TO_640_CVMED
E2_231_CKD_AcuteRenal	F_650_TO_730_LIPIDREGDRUGS
E2_232_CKD_CKD	F_730_GLUCOSELOWERINGAGENTS
E2_233_CKD_ENDSTAGE	F_740_TO_810_ALLOTHERMED

ANNEX 2. REPORT TABLE SHELLS

Report Table Shell 1 - Consort Table for Cohort Build per Cohort (illustrated for cohort build of Cohort_1 “Initiator of Spiriva Respimat”)

Criteria	N of excluded Patients	N of remaining Patients
Source cohort		xxx
Incl: first Spiriva Respimat Rx in study period	- xxx	xxx
Excl: prior Spiriva Respimat use	- xxx	xxx
Excl. no ICS/LABA FDC Rx within 3 months before index date	- xxx	xxx
Excl: no prior asthma Dx	- xxx	xxx
Excl: age on index date less than 18 years	- xxx	xxx
Excl: on index date less than 365 days prior UTS registration	- xxx	xxx
Excl: prior COPD Dx	- xxx	xxx
Excl: any prior LAMA use	- xxx	xxx
Final Cohort: Total Number of Patients		xxxxx

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Report Table Shell 2 - Baseline Characteristics

		Spiriva Respimat Initiator	LTRA Initiator	ASD	Switchers	ASD	Dose Increaser	ASD
Number of patients	N	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Demographic characteristics								
Age in years on the index date	Mean (SD)							
	Median (IQR)							
	Min, Max							
Age category								
>> 18-34	N (%)							
>> 35-49	N (%)							
>> 50-64	N (%)							
>> 65+	N (%)							
Gender								
>> male	N (%)							
>> female	N (%)							
Ethnicity								
>> missing	N (%)							
>> 0 - white	N (% of non missings)							
>> 1 - black	N (% of non missings)							
>> 2 - Asian	N (% of non missings)							
>> 3 - other (incl. mixed)	N (% of non missings)							
Patient level Index of Multiple Deprivation								
>> missing	N (%)							
>> quintile 1 (least deprived)	N (% of non missings)							
>> quintile 2	N (% of non missings)							
>> quintile 3	N (% of non missings)							
>> quintile 4	N (% of non missings)							
>> quintile 5 (most deprived)	N (% of non missings)							

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Life style factors								
Smoking status								
>> missing	N (%)							
>> Non-Smoker	N (% of non missings)							
>> Ex-Smoker	N (% of non missings)							
>> Smoker	N (% of non missings)							
Alcohol consumption								
>> missing	N (%)							
>> Non-Drinker	N (% of non missings)							
>> Ex-Drinker	N (% of non missings)							
>> Drinker	N (% of non missings)							
Body mass index (BMI)								
>> missing	N (%)							
>> BMI measurement of non-missing	Mean (SD)							
Systolic blood pressure (SBP)								
>> missing	N (%)							
>> SBP measurement of non-missing	Mean (SD)							
Diastolic blood pressure (DBP)								
>> missing	N (%)							
>> DBP measurement of non-missing	Mean (SD)							
Asthma history and lab tests								
Number of asthma exacerbations	Mean (SD)							
Number of all-cause hospitalization	Mean (SD)							
Number of respiratory disease related hospitalization	Mean (SD)							
Eosinophil count (units of 10⁹/L)								
>> missing	N (%)							
>> Eosinophil count	Mean (SD)							

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Comorbidities								
Charlson comorbidity index	--							
>> CCI = 1	N (%)							
>> CCI = 2	N (%)							
>> CCI = 3	N (%)							
>> CCI = 4	N (%)							
>> CCI = 5+	N (%)							
Respiratory	--							
Pneumonia	N (%)							
Bronchiectasis	N (%)							
Cardiovascular	--							
Ischaemic heart disease	N (%)							
Myocardial infarction (MI)	N (%)							
Angina pectoris	N (%)							
Abdominal Aneurysm	N (%)							
Hypertension	N (%)							
Chronic Kidney	N (%)							
End Stage	N (%)							
Dialysis	N (%)							
Diabetes mellitus (any Type)	N (%)							
Psychiatric disorders	--							
Dementia	N (%)							
Delirium	N (%)							
Depression	N (%)							
Stroke	N (%)							
Allergic rhinitis	N (%)							
Sinusitis	N (%)							
Cataract	N (%)							
Osteoporosis	N (%)							

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Concomitant prescriptions								
Asthma-related Rx								
Short-acting beta agonists		N (%)						
current use		N (%)						
past use		N (%)						
Inhaled LABA mono								
concurrent use		N (%)						
current use		N (%)						
past use		N (%)						
ICS mono								
concurrent use		N (%)						
current use		N (%)						
past use		N (%)						
Oral corticosteroid		N (%)						
current use		N (%)						
past use		N (%)						
Theophylline		N (%)						
current use		N (%)						
past use		N (%)						
Leukotriene Receptor Antagonist (LTRA)		N (%)						
current use		N (%)						
past use		N (%)						
Azithromycin		N (%)						
current use		N (%)						
past use		N (%)						
Mucolytics		N (%)						
current use		N (%)						
past use		N (%)						

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Cardiovascular medications								
Cardiac Glycosides	N (%)							
current use	N (%)							
past use	N (%)							
Thiazides	N (%)							
current use	N (%)							
past use	N (%)							
Loop diuretics	N (%)							
current use	N (%)							
past use	N (%)							
Antiarrhythmics	N (%)							
current use	N (%)							
past use	N (%)							
Beta blocker	N (%)							
current use	N (%)							
past use	N (%)							
Vasodilator Antihypertensive Drug	N (%)							
current use	N (%)							
past use	N (%)							
Centrally Acting Antihypertensive Drugs	N (%)							
current use	N (%)							
past use	N (%)							
Alpha-adrenoceptor Blocking Drugs	N (%)							
current use	N (%)							
past use	N (%)							
Drugs affecting the renin-angiotensin system	N (%)							
current use	N (%)							
past use	N (%)							
Angiotensin Converting Enzyme Inhibitors	N (%)							
current use	N (%)							
past use	N (%)							

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Lipid-regulating Drugs	N (%)							
current use	N (%)							
past use	N (%)							
Bile Acid Sequestrants (lipid-regulating Drugs) - including Colesevelam	N (%)							
current use	N (%)							
past use	N (%)							
Ezetimibe (only in combination with Statin)	N (%)							
current use	N (%)							
past use	N (%)							
Fibrates	N (%)							
current use	N (%)							
past use	N (%)							
Statins	N (%)							
current use	N (%)							
past use	N (%)							
Nicotinic Acid Group	N (%)							
current use	N (%)							
past use	N (%)							
Omega-3 Fatty Acid Compounds	N (%)							
current use	N (%)							
past use	N (%)							
Other lipid-regulating drugs	N (%)							
current use	N (%)							
past use	N (%)							
Glucose-lowering agents (oral and insulin)	N (%)							
current use	N (%)							
past use	N (%)							
Non-steroidal anti-inflammatory drugs	N (%)							
current use	N (%)							
past use	N (%)							

Report Table Shell 3 - Primary and Secondary Outcomes

		Spiriva Respimat Initiator	LTRA Initiator	ASD	Switchers	ASD	Dose Incraser	ASD
Number of patients	N	xxx	xxx	xxx	xxx	xxx	xxx	x
Outcomes								
Cardiac arrhythmias	N (%)							
Cardiac failure	N (%)							