Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	**document number**
BI Study Number:	1237-0091
BI Investigational Product(s):	Sp(t)iolto® Respimat®
Title:	Characteristics and Treatment Patterns of Patients with Chronic Obstructive Pulmonary Disease (COPD), Initiating Tio+Olo or Other Maintenance Therapies in the US and the UK: A Retrospective Claims Database Study.
Protocol version identifier:	1.0
Date of last version of protocol:	N/A
PASS:	No
EU PAS register number:	Study not registered
Active substance:	Olodaterol and Tiotropium Bromide (ATC R03AL06)
Medicinal product:	
Product reference:	N/A
Procedure number:	N/A
Joint PASS:	No
Research question and objectives:	The primary objectives of the study are to use US and UK data to describe the characteristics of COPD patients according to various demographic, lifestyle, clinical, and concomitant medication use at the following times: ● Date of COPD claim confirming diagnosis. ● Date of initiation of Tio+Olo or any other mono, dual, or triple combination of LAMA, LABA, or ICS as first maintenance therapy after May 21, 2015 or July 1, 2015. ● Date of initiation of Tio+Olo or any other mono, dual, or triple combination of LAMA, LABA, or ICS as second maintenance

	therapy after first maintenance therapy. The secondary objectives of the study are as follows: ● To estimate the time between the following events among COPD patients, overall and stratified by maintenance therapy type: ○ COPD claim confirming diagnosis and first maintenance therapy ○ COPD claim confirming diagnosis and second maintenance therapy ○ First and second maintenance therapy ● To estimate the number of COPD exacerbations overall and stratified by maintenance therapy type during the year prior to the following: ○ Date of first maintenance therapy. ○ Date of second maintenance therapy. ● To describe COPD patients at the time of COPD claim confirming diagnosis according to various demographic, lifestyle, clinical, and medication use, stratified by calendar year. ● To describe the characteristics of COPD patients stratified by therapy category at the following times: ○ Date of initiation of Tio+Olo or other maintenance therapies as first maintenance therapy. ○ Date of initiation of Tio+Olo or other maintenance therapies as second maintenance therapy. To estimate the proportion of patients who used each combination of therapy class at first vs. second maintenance therapy.
Country(-ies) of study:	United States; United Kingdom
Author:	[redacted] Tel: [redacted] Email: [redacted] [redacted] Tel: [redacted] Email: [redacted]
Marketing authorisation	[redacted]

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In case of PASS, add: **<EU-QPPV:>**	N/A
In case of PASS, add: <**Signature of EU-QPPV:>**	N/A
Date:	22 Feb 2019
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2. LIST OF ABBREVIATIONS

ACEi	Angiotensin Converting Enzyme Inhibitor
ACOS	Asthma COPD Overlap Syndrome
AIDS	Acquired Immune Deficiency Syndrome
BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
DPP-4	Dipeptidyl peptidase-4
EMR	Electronic Medical Record
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FVC	Forced Vital Capacity
FEV	Forced Expiratory Volume
GLP-1	Glucagon-like Peptide-1
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases
ICS	Inhaled Corticosteroid
IP	Inpatient
IQR	Interquartile Range
IRB	Institutional Review Board
LABA	Long-Acting Beta-Agonists
LAMA	Long-Acting Muscarinic Antagonists
NOA	Non-obstructive Asthma
NSAID	Nonsteroidal Anti-inflammatory Drug
OP	Outpatient
PDE-4	Phosphodiesterase-4
SABA	Short-acting Beta Agonist
SAMA	Short-acting Muscarinic Antagonist
SD	Standard Deviation
SGLT2	Sodium-glucose Cotransporter 2
TIA	Transient Ischemic Attack

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Name of company: Boehringer Ingelheim International GmbH			
Name of finished medicinal product:			
Name of active ingredient: Olodaterol and Tiotropium Bromide *(ATC R03AL06)*			
Protocol date: 22 February 2019	**Study number:**	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	Characteristics and Treatment Patterns of Patients with Chronic Obstructive Pulmonary Disease (COPD), Initiating Tiotropium+Olodaterol or Other Maintenance Therapies in the US and the UK: A Retrospective Claims Database Study		
Rationale and background:	Chronic obstructive pulmonary disease (COPD) is a common disease characterized by airway obstruction confirmed by spirometry, often including small airway obstruction and emphysema. For patients who are diagnosed with COPD, maintenance treatments often include bronchodilators, primarily long-acting muscarinic antagonists (LAMA), long-acting beta agonists (LABA), and inhaled corticosteroids (ICS) alone or in combination with each other and corticosteroids. Sp(t)iolto® Respimat®, a LAMA+LABA combination, was approved in May 21, 2015 in the US and July 1, 2015 in the EU (marketed as Stiolto in the US and Spiolto in the EU, referred to here as Tio+Olo). Selective prescribing according to patient characteristics, known as channeling, can lead to bias in comparative studies where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences. Claimed advantages of a new drug may be distorted if they are channeled to patients with special pre-existing morbidity, with the consequence that disease states can be incorrectly attributed to use of the drug. Therefore, it is important to identify clinical and socio-demographic characteristics of patients who initiate each treatment as opposed to other available maintenance treatments in COPD patients.		
Research question and objectives:	The primary objectives of the study are to use US and UK data to describe the characteristics of COPD patients according to various demographic, lifestyle, clinical, and medication use at the following times: ● Date of COPD claim confirming diagnosis (at any time). ● Date of initiation of Tio+Olo or other maintenance therapies as first maintenance therapy (after date of Spiolto launch). ● Date of initiation of Tio+Olo or other maintenance therapies as second maintenance therapy (after date of Spiolto launch).		

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Name of active ingredient: Olodaterol and Tiotropium Bromide *(ATC R03AL06)*			
Protocol date: 22 February 2019	**Study number:**	**Version/Revision:** 1.0	**Version/Revision date:**
	The secondary objectives of the study are as follows: ● To estimate the time between the following events among COPD patients, overall and stratified by maintenance therapy type: ○ COPD claim confirming diagnosis and first maintenance therapy. ○ COPD claim confirming diagnosis and second maintenance therapy. ○ First and second maintenance therapy in patients receiving second maintenance therapy. ● To estimate the number of COPD exacerbations overall and stratified by maintenance therapy type during the year prior to the following: ○ Date of first maintenance therapy. ○ Date of second maintenance therapy. ● To describe COPD patients at the time of COPD claim confirming diagnosis according to various demographic, lifestyle, clinical, and medication use, stratified by calendar year. ● To describe the characteristics of COPD patients stratified by therapy category at the following times: ○ Date of COPD claim confirming diagnosis. ○ Date of initiation of Tio+Olo or other maintenance therapies as first maintenance therapy. ○ Date of initiation of Tio+Olo or other maintenance therapies as second maintenance therapy. ● To estimate the proportion of patients who used each combination of therapy class at first vs. second maintenance therapy		
Study design:	Retrospective cohort study using previously collected administrative healthcare data.		
Population:	**COPD ("Parent") Cohort:** The study population for the analysis will consist of all patients with at least one medical claim with a diagnosis code of COPD identified (ICD-9-CM code 491.*, 492.*, 496.*, ICD-10-CM J41.*, J43.*, J44.*, or the appropriate READ codes) between date of first availability of Tio+Olo (launch date May 21, 2015 in the United States and July 1, 2015 in the UK) and last date of available data (March 31, 2017 for MarketScan and June 6, 2018 for CPRD).		

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	Patients will be required to be >= age 40 at cohort entry date and have at least 12 months of enrolment in the health plan prior to COPD claim confirming diagnosis. Patients with previous use of any maintenance medication in the 12 months before index will be excluded. **Child Cohort:** Among the COPD ("Parent") cohort, includes all patients of the parent cohort who initiated first maintenance therapy with any combination of LAMA, LABA, or ICS after the date of Spiolto approval. **Grandchild Cohort:** Among the Child cohort, includes all patients of the Child cohort who initiated second maintenance therapy with any combination of LAMA, LABA, or ICS that is different from the first maintenance therapy.		
Variables:	**Therapy Classes** ● Mutually exclusive maintenance therapy categories: **Monotherapy** ○ LAMA ○ LABA ○ ICS **Dual Therapy** ○ Tio+Olo (LAMA + LABA) ○ LAMA + LABA that is not Tio+Olo ○ LAMA + ICS ○ LABA + ICS **Triple Therapy** ○ LAMA + LABA + ICS ● First maintenance therapy is defined as first occurrence after Spiolto approval date. ● Second maintenance therapy is defined as any subsequent maintenance therapy category that differs from the first maintenance therapy category. **Outcome** • Time between COPD claim confirming diagnosis and first		

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maintenance therapy.
- Time between COPD claim confirming diagnosis and second maintenance therapy.
- Time between first and second maintenance therapy.
- Duration of first maintenance therapy.
- Number of COPD exacerbations prior to index therapy.

Covariates
A series of baseline variables will be created as covariates. All variables will be assessed in the 365-day baseline period before COPD claim confirming diagnosis, except for comorbidities, which will be assessed from the start of all available data to the cohort entry date:

Demographics
- Age on cohort entry date
- Sex
- Region (MarketScan)
- Practice Region (CPRD)

Concomitant Medications in Previous 365 days
- Corticosteroids
- Short acting muscarinic antagonist (SAMA)
- Short acting beta agonist (SABA)
- NSAIDs
- Antihistamines
- Oral antibiotics
- Diabetes mellitus medications
- Insulin
- Methotrexate
- Statins
- Antihypertensives
- Anticoagulants
- Anti-psychotic/anti-depressives/anxiolytic
- Opioids
- Oxygen therapy

<table>
<tr><td colspan="2">Name of company:
Boehringer Ingelheim International GmbH</td><td></td><td></td></tr>
<tr><td colspan="2">Name of finished medicinal product:</td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td colspan="2">Name of active ingredient:
Olodaterol and Tiotropium Bromide (ATC R03AL06)</td></tr>
<tr><td>Protocol date:
22 February 2019</td><td>Study number:</td><td>Version/Revision:
1.0</td><td>Version/Revision date:</td></tr>
<tr><td></td><td colspan="3">Comorbidities Since Start of All Data
● All-Cause Hospitalization (MarketScan only)
● All-Cause Emergency Department Visits (MarketScan only)
● Respiratory-related Hospitalization (MarketScan only)
● Peripheral Vascular Disease
● Cerebrovascular Disease
● Myocardial Infarction
● Cardiac Arrhythmia
● Heart Failure
● Angina Pectoris
● Hypertension
● Osteoporosis
● Anxiety
● Depression
● Type 2 Diabetes
● Upper respiratory tract infection
● Lower respiratory tract infection
● Pneumonia
● Bronchiectasis
● Asthma
● Allergic Rhinitis
● Chronic Sinusitis
● Chronic Bronchitis
● Lung Fibrosis
● Exertional breathlessness
● Impaired Cognitive Function/Dementia
● Charlson Deyo Comorbidity Score
● Cancer (any except non-melanoma skin cancer)
● Lung Cancer
● Lung Transplant
● Rheumatologic Disease
● Hepatic Failure/Injury
● Hemiplegia or Paraplegia
● Chronic Kidney Disease (CKD) without ESRD
● End Stage Renal Disease (ESRD)
● AIDS/HIV</td></tr>
</table>

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Protocol date: 22 February 2019	**Study number:**	**Version/Revision:** 1.0	**Version/Revision date:**
	● Peptic Ulcer Disease (PUD) ● Gastroesophageal Reflux Disease (GERD) **Lifestyle** ● Smoking-related Claim (MarketScan only) ● Vaccination for Influenza or Pneumococcus ● Body mass index (BMI) (last recorded) (CPRD only) ● Smoking status (last recorded) (CPRD only) ● Alcohol consumption (last recorded) (CPRD only) **Other Variables of Interest** ● Calendar year of cohort entry date ● FEV1/FVC (last recorded) (CPRD only)		
Data sources:	**MarketScan**: a claims database that captures longitudinal, individual-level administrative claims data from the United States. **CPRD:** administrative database based on standardized electronic medical records (EMR) systems in primary care practices in the United Kingdom (UK). This database represents over 700 contributing general practices in the UK, and includes approximately 17.8 million patients.		
Study size:	Among approximately 1,487,765 patients with COPD in MarketScan who did not use maintenance therapy before May 21, 2015, there were about 1,269 with at least 1 claim for Stiolto Respimat in follow-up. Among approximately 98,537 patients with COPD in CPRD who did not use maintenance therapy before July 1, 2015, there are 332 with at least 1 claim for Spiolto Respimat in follow-up.		

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Data analysis:	Baseline Covariates • All covariates will be reported as mean (SD) and/or median (IQR) for continuous variables and counts and frequency (%) for categorical variables. • Descriptions of baseline variables will be done for all three cohorts at the cohort entry date. • For the parent cohort of COPD patients, will be further stratified by whether COPD claim confirming diagnosis took place before or after date of Spiolto approval. Maintenance Therapy Use • In the child and grandchild cohorts, absolute and relative frequencies of use for each therapy class will be reported on the date of initiation. Time between COPD claim confirming diagnosis and first maintenance therapy. • In the child cohort, will be reported as mean and median time to initiation. • Will be stratified by therapy class Time between COPD claim confirming diagnosis and second maintenance therapy. • In the grandchild cohort, will be reported as mean and median time to initiation. • Will be stratified by therapy class Time between first and second maintenance therapy. • In the grandchild cohort, will be reported as mean and median time to initiation. • Will be stratified by therapy class Number of COPD exacerbations • Will be reported in the baseline period for the child and grandchild cohorts as mean (SD) and median (IQR) for continuous variables and frequency (%) for categories (0, 1, 2, 3, 4, 5+) • Will be stratified by therapy class [redacted]		

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Milestones:	
Sept 2018	Descriptive - Kick-off meeting
Dec 2018	Draft Protocol development for Marketscan and CPRD implementation
Feb 2019	Revised Protocol for Marketscan and CPRD implementation
April 2019	Preliminary Result Table
May 2019	Revised Result Tables
May 2019	Final Result Tables, any final revisions, and Final Aetion Implementation Report

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
<1>	DD Month YYYY	None	None	None

6. MILESTONES

Milestone	Planned Date
Start of data collection	DD Month YYYY
End of data collection	DD Month YYYY
<Study progress report 1>	DD Month YYYY
<Study progress report 2>	DD Month YYYY
<Study progress report n>	DD Month YYYY
<Interim report 1>	DD Month YYYY
<Interim report 2>	DD Month YYYY
<Interim report n>	DD Month YYYY
<Registration in the EU PAS register>	DD Month YYYY
Final report of study results:	DD Month YYYY

7. RATIONALE AND BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by airway obstruction confirmed by spirometry, often including small airway obstruction and emphysema (Barnes 2015). Patients may experience exacerbations, defined as acute onset, short but sustained worsening of patient's condition beyond normal levels. Exacerbations often lead to hospitalization and/or change in medication, as they negatively impact long-term health outcomes (Pavord 2016). Asthma COPD Overlap Syndrome (ACOS) is another complication that consists of concurrent COPD and asthma. Most studies have reported that patients with ACOS have worse prognosis than patients with only COPD in terms of more frequent and severe exacerbations, worsened symptoms, and decreased quality of life (Barnes 2016). Scant information exists on appropriate therapy for ACOS, because these patients are often excluded from clinical trials of asthma or COPD (Barnes 2016).
No known medications can reverse COPD, but use of rescue medications in the form of short acting muscarinic antagonists (SAMA), short acting beta agonists (SABA), and also regular maintenance treatments can help manage symptoms and improve quality of life. The Global Initiative for Chronic Obstructive Disease (GOLD 2017) recommends classifying patients for treatment based on assessment of existing symptoms and history of exacerbations. For patients who are diagnosed with COPD, maintenance treatments often include bronchodilators, primarily long-acting muscarinic antagonists (LAMA), long-acting beta agonists (LABA), and inhaled corticosteroids (ICS) alone or in combination with each other and corticosteroids. Sp(t)iolto® Respimat®, a LAMA+LABA combination, was approved in May 21, 2015 in the US and July 1, 2015 in the EU (marketed as Stiolto in the US and Spiolto in the EU, referred to here as Sp(t)iolto). Currently the product is sold in 46 countries, including the UK and most of the EU countries, US, Japan, Canada and several other 1st wave countries. Respimat is a device that aerates the Tio+Olo drug into a mist that may be more effective in reaching the lungs. Compared with LAMA or LABA alone, LAMA+LABA has demonstrated improved lung function, patient-reported outcomes, and quality of life measures in clinical trials (Calzetta 2017). Furthermore, the classic side effects of weight gain, osteoporosis, and community-acquired pneumonia associated with ICS use do not appear to be as severe for LAMA+LABA use (Tariq 2017).
Selective prescribing according to patient characteristics, known as channeling, can lead to allocation bias in comparative studies, where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences (Petri 1991). Claimed advantages of a new drug may be distorted if they are channeled to patients with special pre-existing morbidity, with the consequence that disease states can be incorrectly attributed to use of the drug. Therefore, it is important to identify clinical and socio-demographic characteristics of patients who initiate each treatment as opposed to other available maintenance treatments in COPD patients.
This study will allow us to evaluate patient characteristics by first and second maintenance therapy and to identify factors potentially driving prescriptions to different patient populations in the US and UK.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objectives of the study are to use US and UK data to describe the characteristics of COPD patients according to various demographic, lifestyle, clinical, and medication use at the following times:

- Date of COPD claim confirming diagnosis.
- Date of initiation of Tio+Olo or other as first maintenance therapy, after Spiolto approval date.
- Date of initiation of Tio+Olo or other as second maintenance therapy, after Spiolto approval date.

The secondary objectives of the study are as follows:

- To estimate the time between the following events among COPD patients, overall and stratified by maintenance therapy type:
    - COPD claim confirming diagnosis and first maintenance therapy.
    - COPD claim confirming diagnosis and second maintenance therapy.
    - First and second maintenance therapy.
- To estimate the number of COPD exacerbations overall and stratified by maintenance therapy type during the year prior to the following:
    - Date of first maintenance therapy.
    - Date of second maintenance therapy.
- To describe COPD patients at the time of COPD claim confirming diagnosis according to various demographic, lifestyle, clinical, and medication use, stratified by pre vs. post Spiolto approval.
- To describe the characteristics of COPD patients stratified by therapy category at the following times:
    - Date of initiation of Tio+Olo or other maintenance therapies as first maintenance therapy.
    - Date of initiation of Tio+Olo or other maintenance therapies as second maintenance therapy.
- To estimate the proportion of patients who used each combination of therapy class at first vs. second maintenance therapy.

9. RESEARCH METHODS

9.1 STUDY DESIGN

MarketScan:
The proposed study is a non-interventional retrospective study based on existing data from the Truven Health MarketScan, a US claims database. Data from Jan 1, 2008 *(earliest data available)* to March 31, 2017 *(latest data available)* will be used to characterize COPD patients who initiated first and/or second maintenance treatment in three different cross sections: at COPD claim confirming diagnosis date, at date of first maintenance therapy, and at date of second maintenance therapy. Details of the study design are provided below.

CPRD:
The proposed study is a non-interventional retrospective study based on existing data from the CPRD, a UK-based administrative database. Data from November 21, 1987 *(earliest data available)* to June 30, 2018 *(latest data available)* will be used to characterize COPD patients who initiated first and/or second maintenance treatment in three different cross sections: at COPD claim confirming diagnosis date, at date of first maintenance therapy, and at date of second maintenance therapy. Details of the study design are provided below.

9.2 SETTING

9.2.1 Definitions

Study Period: The period of time that includes the baseline, cohort entry date, and follow-up period for the study population. This period is the same for all patients.

The study period will be from January 1, 2008 to March 31, 2017 in MarketScan and November 21, 1987 to June 30, 2018 in the CPRD, encompassing the date of earliest follow-up availability to the date of the latest follow-up availability.

Patient Selection Period: the period of time for which patients are eligible to enter the cohort. The earliest date of the patient selection period is January 1, 2009 for MarketScan and November 21, 1988 for CPRD, corresponding to 12 months after the date of first data availability to allow for a sufficient enrollment and washout period.

Cohort Entry Date: Date of entry to the initial cohort of COPD patients.

1st Treatment Index Date: Date of initiation of Tio+Olo or other as first maintenance therapy.

2nd Treatment Index Date: Date of initiation of Tio+Olo or other as second maintenance therapy.

Baseline Period: The 365-day period prior to the cohort entry date or treatment index date used to assess concomitant medication use and lifestyle variables. The baseline period will vary between patients depending on these dates.

Follow-Up Period: For patients who were diagnosed with COPD before May 21, 2015 (MarketScan) or July 1, 2015 (CPRD), the follow-up period will be May 22, 2015 (MarketScan) or July 2, 2015 (CPRD) to the earliest occurrence of death, disenrolment, or end of data. For patients diagnosed after those dates in their respective dataset, the follow-up period will be 1 day after their cohort entry date to the earliest occurrence of death, disenrolment, or end of data. Occurrence of first and second maintenance treatment will be assessed during this period.

For entry into the study population, patients will be required to have 365 days of continuous enrolment with both medical and pharmacy coverage, as well as no occurrence of COPD in the previous 365 days. The follow-up period will be used for capturing first and second maintenance therapies. This is illustrated in **Figure 1**.

Figure 1a. Study timeline for MarketScan for the Primary Study Population (Parent Cohort)_

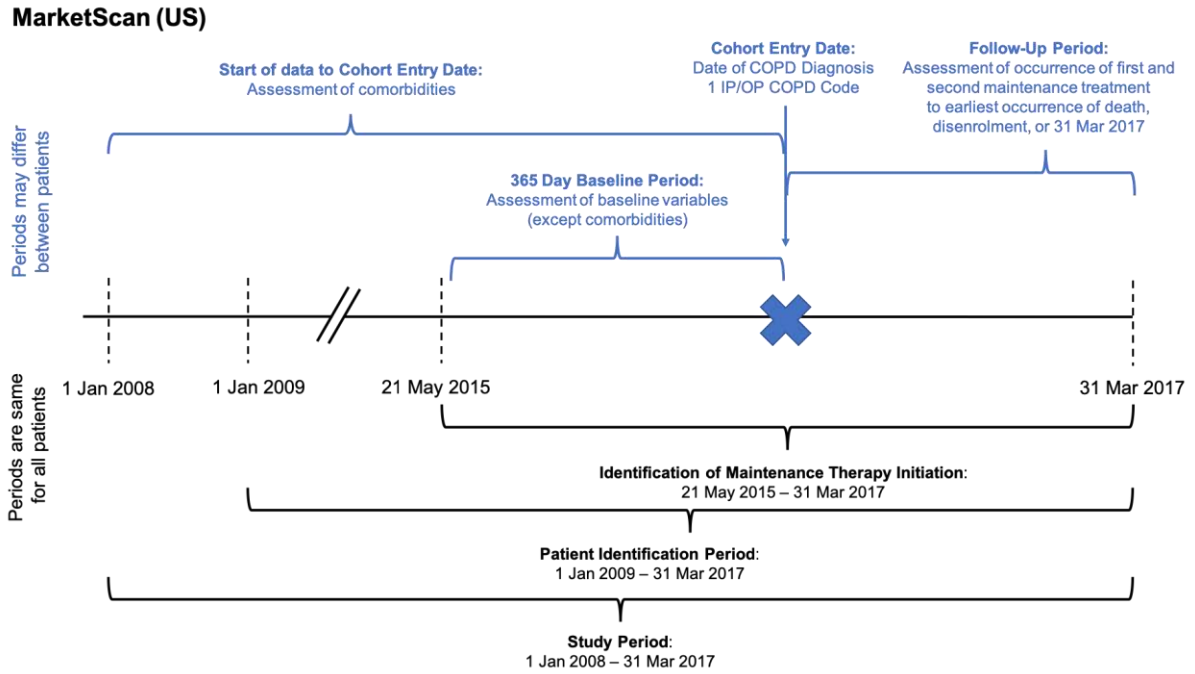
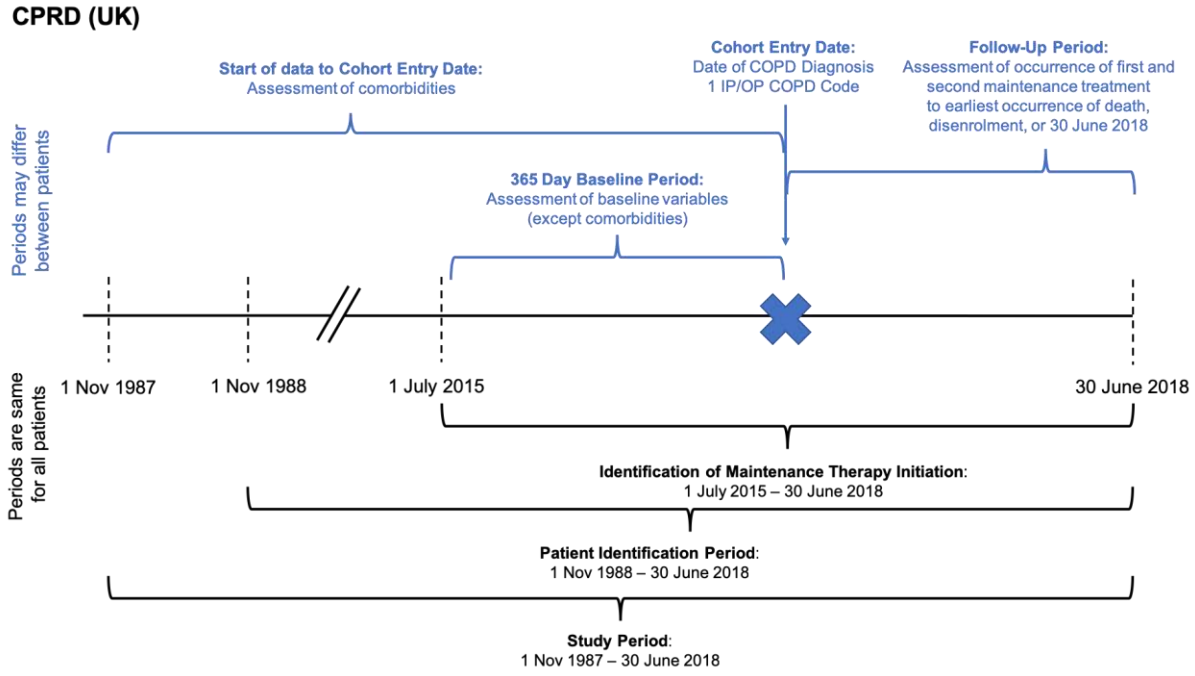


Figure 1b**.** Study timeline for CPRD for the Primary Study Population (Parent Cohort)



9.2.2 Study population

The overall flow chart for the study population is depicted in **Figure 2.**

Figure 2a. Flow chart of the study population in MarketScan.

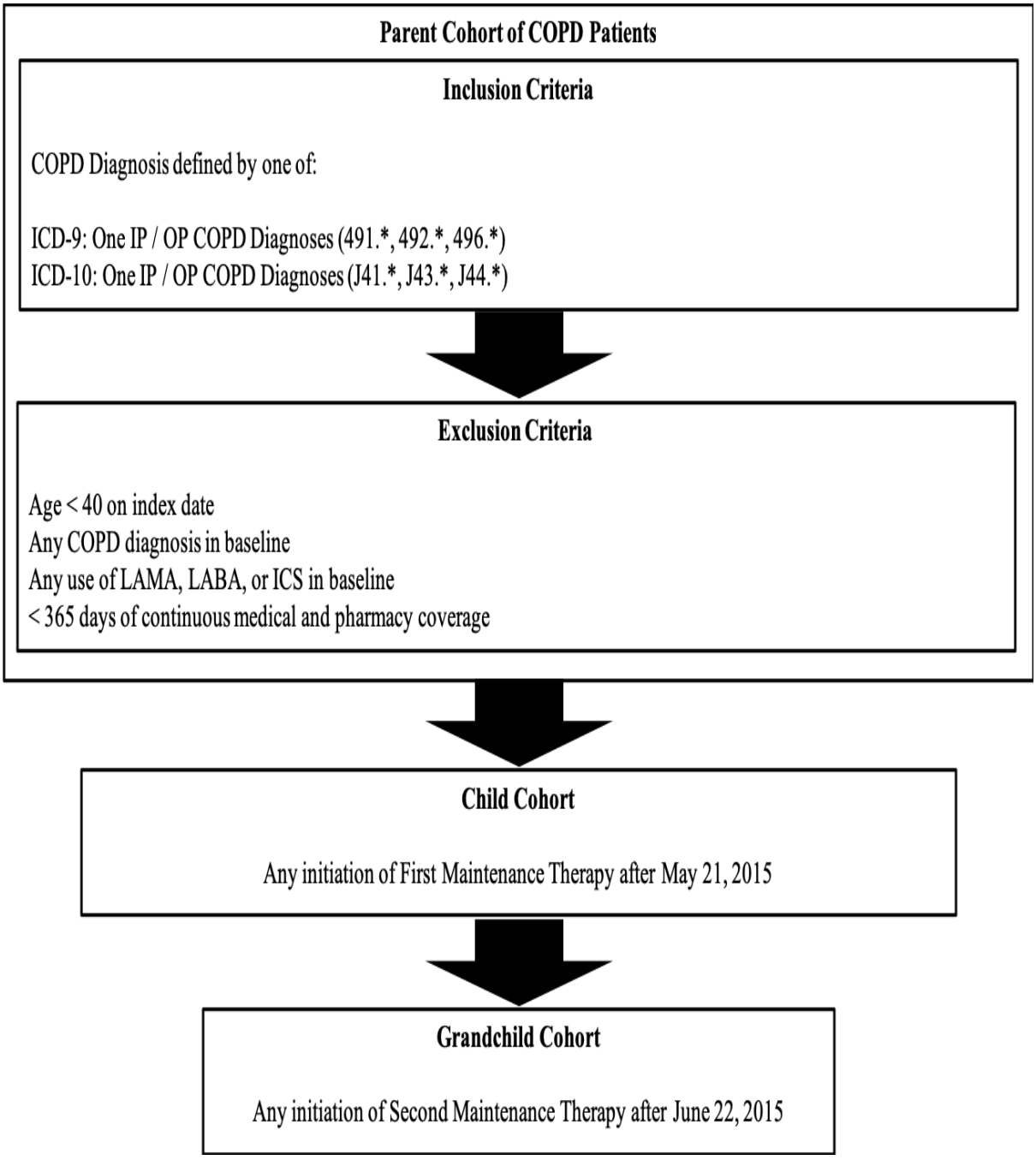
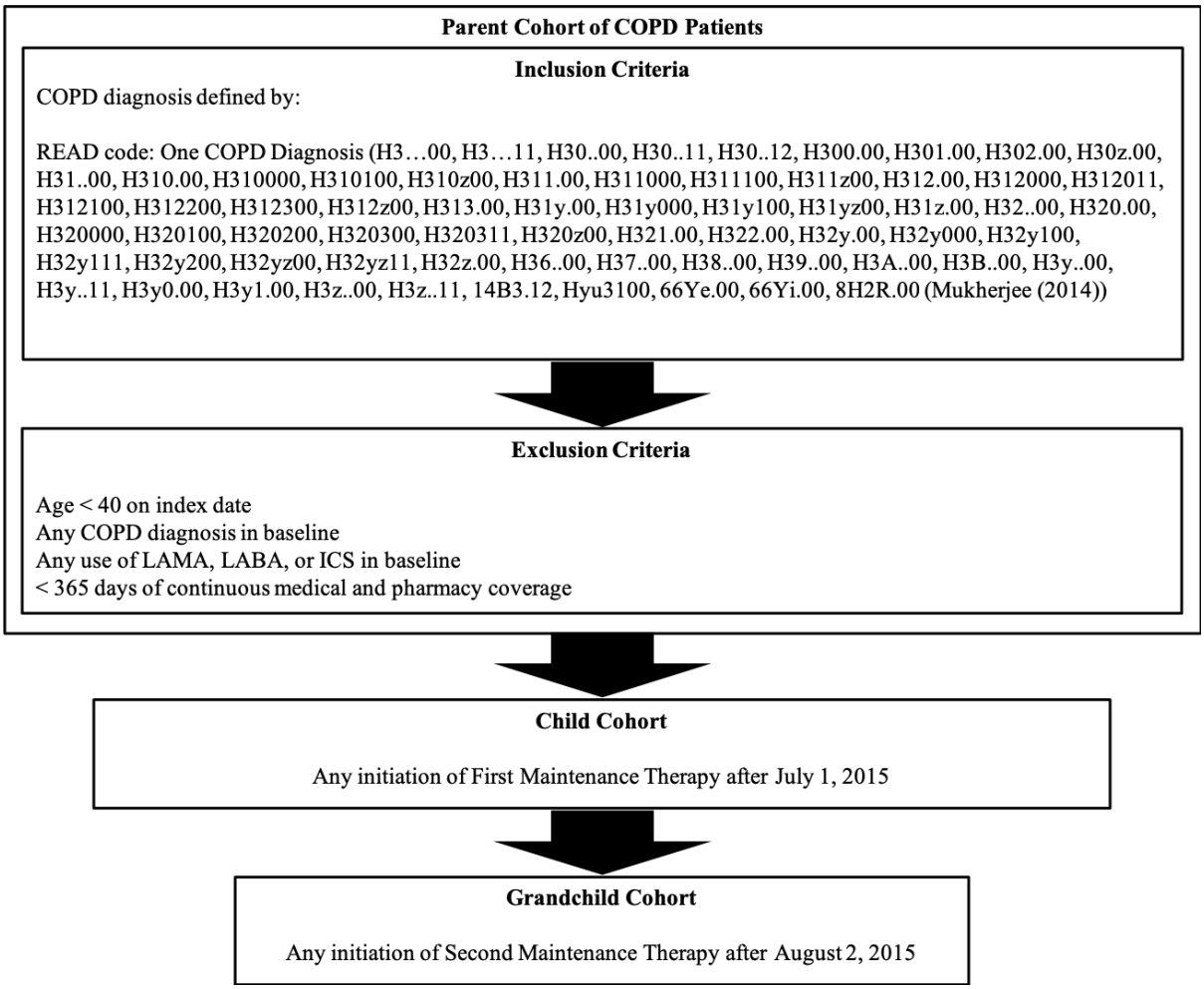


Figure 2b. Flow chart of the study population in CPRD.



Three cohorts will be used to address the study objectives: 1) a parent cohort of COPD patients with no previous maintenance medication use; 2) a child cohort of first maintenance therapy users; 3) a grandchild cohort of second maintenance therapy users. All analyses will include patients who are aged 40 years or older on the cohort entry date, and who have at least 365 days of continuous enrolment before these dates. For the parent cohort, patients who had maintenance medication use in the 365 days before index will be excluded (i.e. parent cohort will include only incident COPD cases).

Table 1 indicates the study periods for each of the three cohorts.

Table 1a. Study Periods for each Cohort in MarketScan.

	Parent Cohort	**Child Cohort**	**Grandchild Cohort**
MarketScan (US)			
Case Definition	COPD (1 IP/OP ICD-9 or 1 IP/OP ICD-10 Code)	First Maintenance Therapy (See Section 9.3.2.1)	Second Maintenance Therapy (See Section 9.3.2.1)
Cohort Entry or Index Date	Date of diagnosis	Date of Initiation of First Maintenance Therapy	Date of Initiation of Second Maintenance Therapy
Study Period	1 Jan 08 - 31 Mar 17	1 Jan 08 - 31 Mar 17	1 Jan 08 - 31 Mar 17
Patient Selection Period	1 Jan 09 - 31 Mar 17	21 May 15 - 31 Mar 17	22 Jun 15 - 31 Mar 17
Baseline Period	365 days before Cohort Entry Date	365 days before Treatment Index Date	365 days before Treatment Date
Comorbidity Assessment Period	1 Jan 08 – Cohort Entry Date	1 Jan 08 – Cohort Entry Date	1 Jan 08 – Cohort Entry Date
Follow-up Period	Cohort Entry Date to Earliest Occurrence of Death, Disenrolment, or 31 Mar 17	Index Date to Earliest Occurrence of Death, Disenrolment, or 31 Mar 17	N/A

Table 1b. Study Periods for each Cohort in CPRD.

CPRD (UK)			
Case Definition	COPD (1 READ Code)	First Maintenance Therapy (See Section 9.3.2.1)	Second Maintenance Therapy (See Section 9.3.2.1)
Cohort Entry or Index Date	Date of diagnosis date	Date of Initiation of First Maintenance Therapy	Date of Initiation of Second Maintenance Therapy
Study Period	21 Nov 87 - 30 Jun 18	21 Nov 87 - 31 Mar 17	21 Nov 87 - 31 Mar 17
Patient Selection Period	21 Nov 88 - 30 Jun 18	1 Jul 15 - 31 Mar 17	2 Aug 15 - 31 Mar 17
Baseline Period	365 days before Cohort Entry Date	365 days before Treatment Index Date	365 days before Treatment Index Date
Comorbidity Assessment Period	21 Nov 87 – Cohort Entry Date	21 Nov 87 – Cohort Entry Date	21 Nov 87 – Cohort Entry Date
Follow-up Period	Cohort Entry Date to Earliest Occurrence of Death, Disenrolment, or 30 Jun 18	Index Date to Earliest Occurrence of Death, Disenrolment, or 30 Jun 18	N/A

9.2.2.1 Primary Study Population

The study population will consist of patients diagnosed with COPD, defined as at least one inpatient or outpatient diagnosis of COPD (MarketScan: ICD-9 codes 491.*, 492.*, 496.* or ICD-10 codes J41.*, J43.*, J44.*; CPRD: READ codes “H3…00”, “H3…11”, “H30..00”, “H30..11”, “H30..12”, “H300.00”, “H301.00”, “H302.00”, “H30z.00”, “H31..00”, “H310.00”, “H310000”, “H310100”, “H310z00”, “H311.00”, “H311000”, “H311100”, “H311z00”, “H312.00”, “H312000”, “H312011”, “H312100”, “H312200”, “H312300”, “H312z00”, “H313.00”, “H31y.00”, “H31y000”, “H31y100”, “H31yz00”, “H31z.00”, “H32..00”, “H320.00”, “H320000”, “H320100”, “H320200”, “H320300”, “H320311”, “H320z00”, “H321.00”, “H322.00”, “H32y.00”, “H32y000”, “H32y100”, “H32y111”, “H32y200”, “H32yz00”, “H32yz11”, “H32z.00”, “H36..00”, “H37..00”, “H38..00”, “H39..00”, “H3A..00”, “H3B..00”, “H3y..00”, “H3y..11”, “H3y0.00”, “H3y1.00”, “H3z..00”, “H3z..11”, “14B3.12”, “Hyu3100”, “66Ye.00”, “66Yi.00”, “8H2R.00” (Mukherjee (2014)) identifiable in the database. The identification period of this primary cohort of COPD patients will be from date of earliest available data to date of latest available data.

As the objective is to study the first and second prescription for maintenance therapy, patients receiving maintenance treatment at study entry or up to 365 days prior to study entry will be excluded. In order to ensure that the first prescriptions are captured, at least 1 year of continuous data available prior to COPD claim confirming diagnosis will be required. All patients must also be age 40 years or more on the date of COPD claim confirming diagnosis. The study timelines for this primary study population are depicted in **Figures 1** and **2**.

9.2.2.2 Child Cohort for First Maintenance Therapy

A child (i.e. nested) cohort will be created consisted solely of individuals who ever initiated first maintenance therapy. The parent cohort is the population of COPD patients described above. The date of initiation of first maintenance therapy will be set as the index date, and the 365-day period before index will be used to provide descriptive analyses and number of COPD exacerbations. **Importantly, the date of initiation of first maintenance therapy must occur on or after May 21, 2015 (MarketScan) or July 1, 2015 (CPRD), the Spiolto approval date.**

For entry into this child cohort, patients will be required to have 365 days of continuous insurance enrolment with both medical and pharmacy coverage prior to initiation of the maintenance therapy. Data in this baseline period will be used to provide descriptive statistics and number of COPD exacerbations. This is illustrated in **Figure 3**.

Figure 3a. Study timeline for MarketScan for the Child Cohort (Initiation of First Maintenance Therapy as Index)

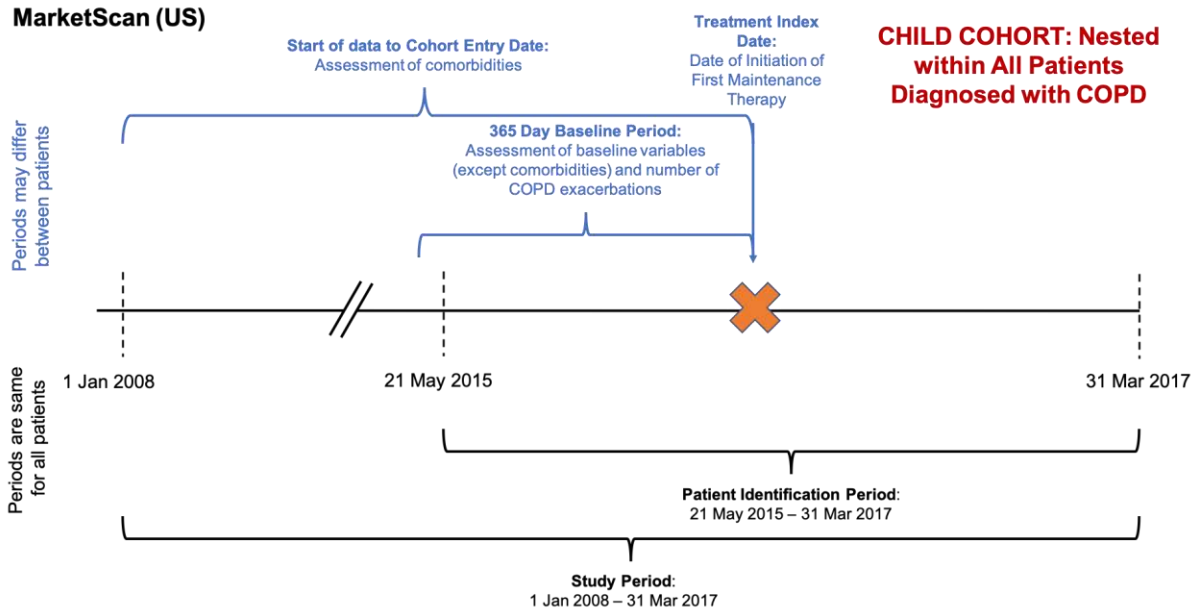
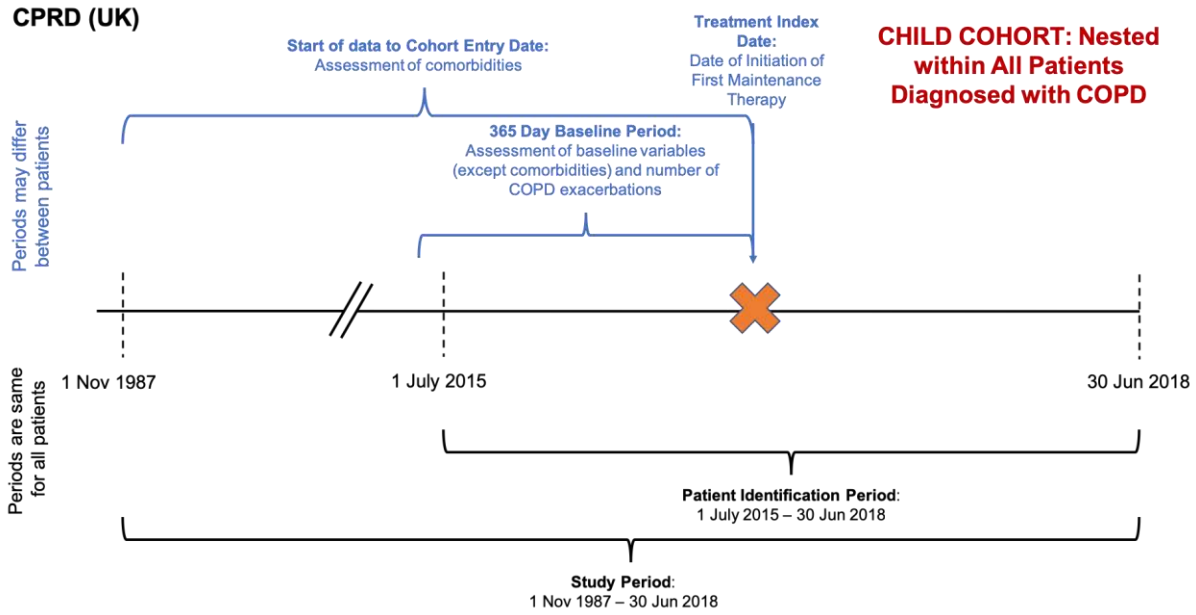


Figure 3b. Study timeline for CPRD for the Child Cohort (Initiation of First Maintenance Therapy as Index)



9.2.2.3 Grandchild Cohort for Second Maintenance Therapy

A grandchild cohort will be created consisted solely of individuals who ever initiated second maintenance therapy. The grandchild cohort will be nested within the child cohort described above consisting of patients who ever initiated first maintenance therapy and had COPD diagnosis. The date of initiation of second maintenance therapy will be set as the index date, and the 365-day period before index will be used to provide descriptive analyses, number of COPD exacerbations, and proportion of patients who used each combination of therapy category at first vs. second maintenance.

For entry into this child cohort, patients will be required to have 365 days of continuous insurance enrolment with both medical and pharmacy coverage. This is illustrated in **Figure 4**. Note that the study period and patient identification periods are shifted forward by 31 days compared to the child cohort because the shortest possible time between initiation of first and initiation of second maintenance therapy is 31 days by definition (30 days of use of previous therapy + 1 day).

Figure 4a. Study timeline for MarketScan for the Grandchild Cohort (Initiation of Second Maintenance Therapy as Index)

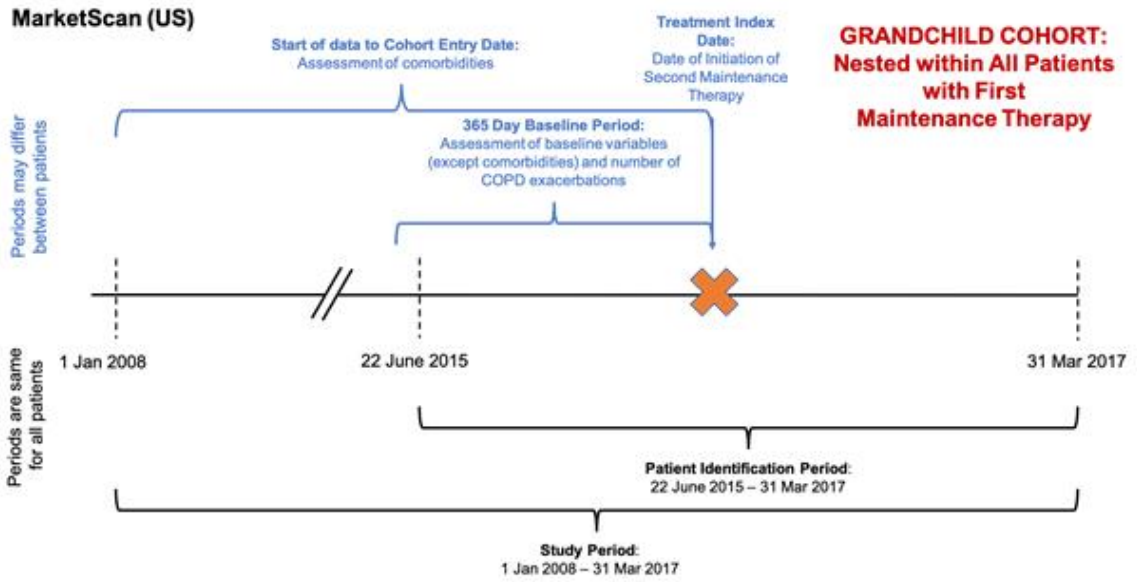
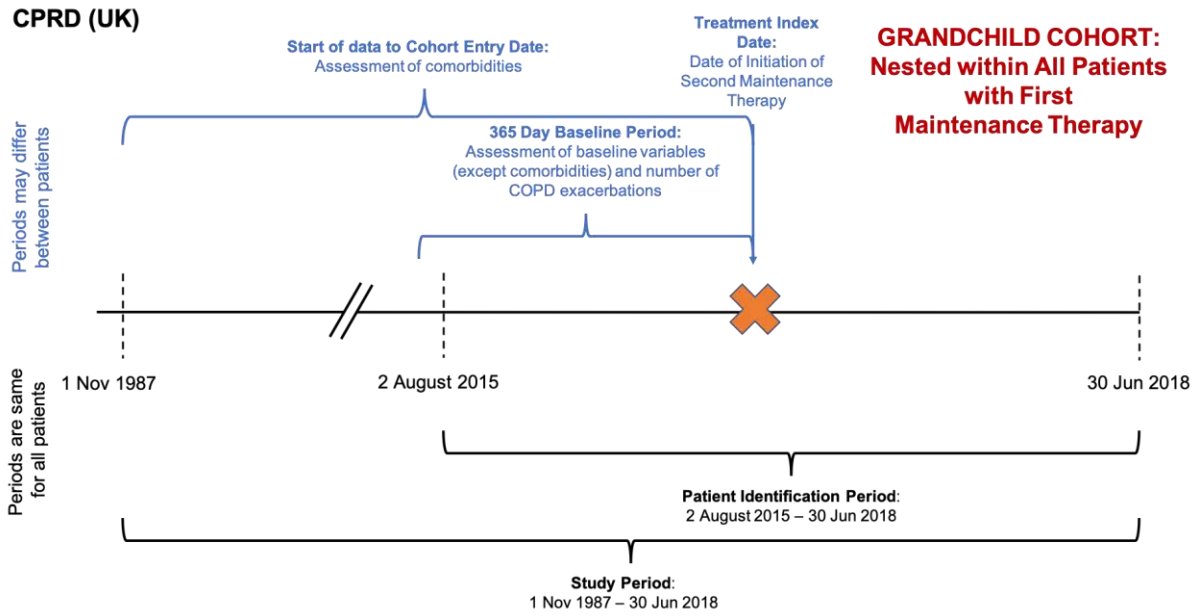


Figure 4b. Study timeline for CPRD for the Grandchild Cohort (Initiation of Second Maintenance Therapy as Index)



9.3 VARIABLES

9.3.1 Exposures

Specific drug class definitions are defined herein. A list of drug definitions, formulations, and brands is provided in Annex 5.

Mutually exclusive maintenance therapy categories:
Monotherapy
- LAMA
- LABA
- ICS

Dual Therapy
- Tio+Olo (LAMA + LABA)
- LAMA + LABA that is not Tio+Olo
- LAMA + ICS
- LABA + ICS
- SAMA + SABA

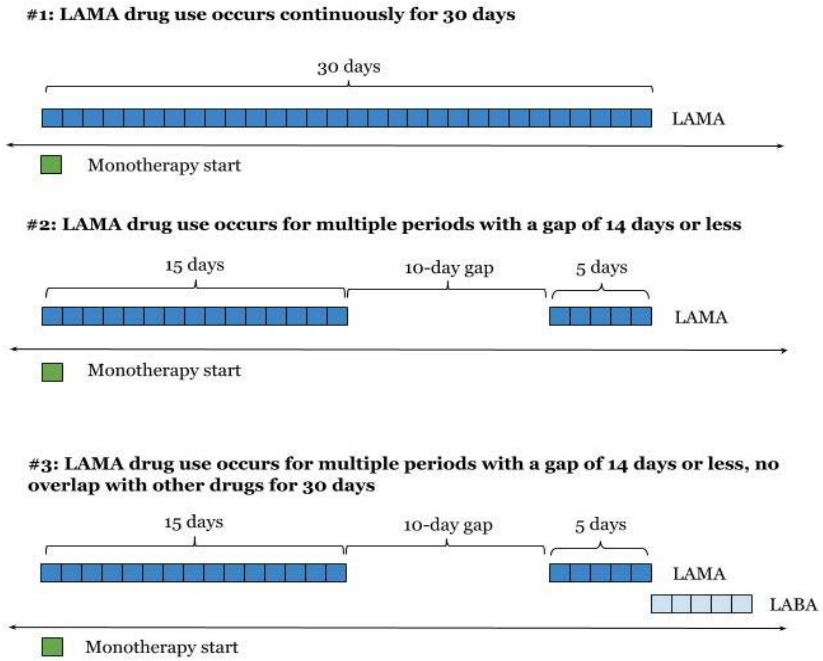
Triple Therapy
- Tio+Olo + ICS
- LAMA + LABA + ICS

The two medication-related outcomes in this non-interventional study are as follows:
1. First maintenance therapy is defined as first occurrence of any of the categories listed above after cohort entry date.
2. Second maintenance therapy is defined as any subsequent maintenance therapy category that differs from the first maintenance therapy category. The earliest date of initiation of second maintenance therapy is 30 days after date of initiation of first maintenance therapy.

Classification of individuals to different therapy categories will be based on the continuous use of a single drug (defined by the supply of the drug over the number of treatment days) for at least 30 days (monotherapy), a combination therapy for at least 30 days (dual therapy), an overlap of two different mono-formulations (e.g. LAMA overlapping with LABA) for at least 30 days (dual therapy), or different combination formulations and mono-formulations together for at least 30 days (triple therapy). We will employ a 14-day allowable gap for continuous drug use to account for possible under-dosing of maintenance therapies (analogous to splitting pills) and skipping or forgetting to take doses. The specific definitions for therapy classification are detailed below.

Monotherapy is defined as at least 30 days of continuous drug use (with a 14-day allowable gap), without use of either of the other two drug classes during that 30-day period. For illustrations of three possible cases that would be classified as monotherapy, see Figure 5 below.

Figure 5. Three possible monotherapy scenarios.

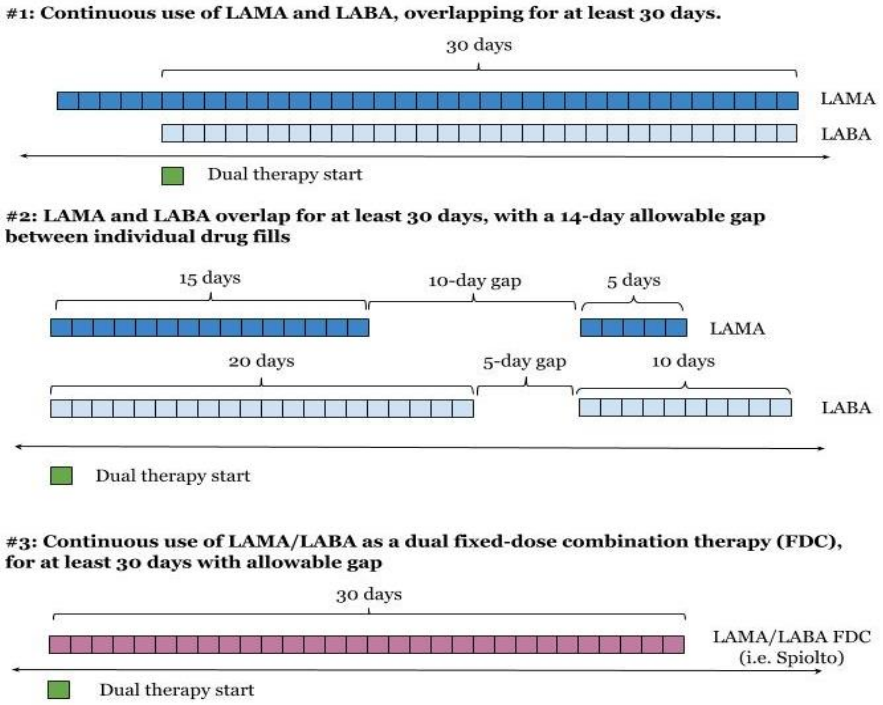


Dual therapy is defined as:

- At least 30 days of overlap of continuous drug use of separate prescriptions for two drug classes, OR
- At least 30 days of continuous drug use of a fixed-dose combination formulations.
- In both cases, there is a 14-day allowable gap between individual drug fills.

For illustrations of three possible cases that would be classified as dual therapy, see **Figure 6** below.

Figure 6. Three possible dual therapy scenarios.

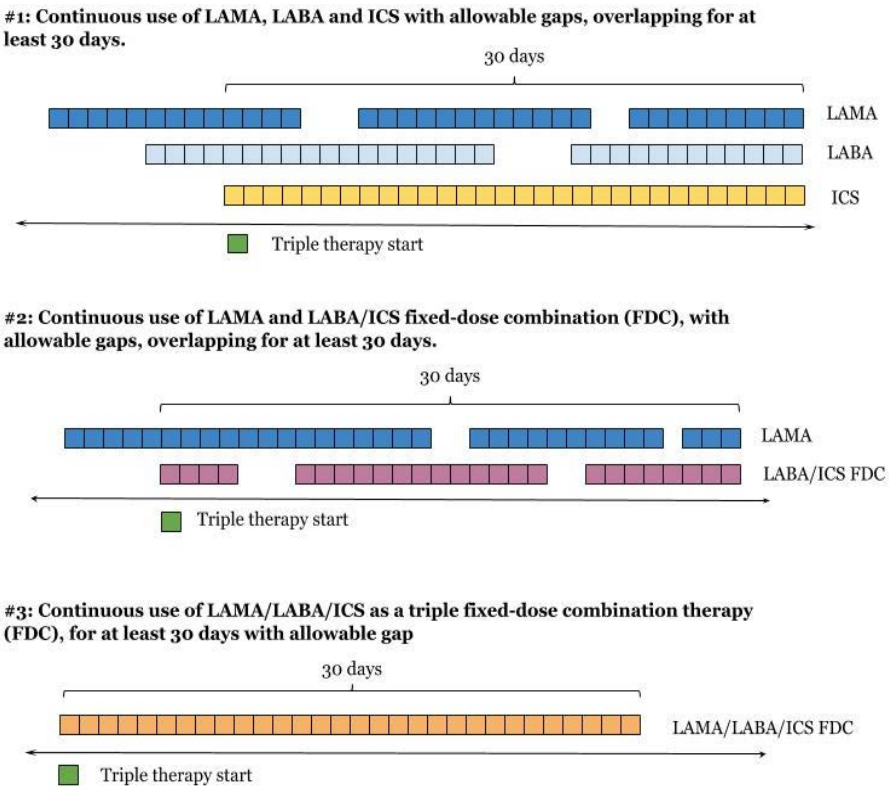


Triple therapy is defined as:

- At least 30 days of overlap of continuous drug use of separate prescriptions for three drug classes, OR
- At least 30 days of overlap of a dual fixed-dose combination formulations paired with a mono-formulation for the third drug class, OR
- At least 30 days of continuous drug use of a triple fixed-dose combination formulations.
- In all cases, there is a 14-day allowable gap between individual drug fills.

For illustrations of three possible cases that would be classified as triple therapy, see **Figure 7** below.

Figure 7. Three possible triple therapy scenarios.



9.3.2 Outcomes

9.3.2.1 Primary outcomes

Patient characteristics, include various demographic, lifestyle, clinical, and medication characteristics will be reported at three points in time: 1) COPD claim confirming diagnosis date (Cohort Entry Date), overall and stratified by before or after Spiolto approval date; 2) Date of initiation of first maintenance therapy (1st Treatment Index Date), overall and stratified by therapy category; 3) Date of initiation of second maintenance therapy (2nd Treatment Index Date), overall and stratified by therapy category.

9.3.2.2 Secondary outcomes

We will also examine two clinical outcomes over follow-up among individuals among individuals who had first and/or second maintenance therapy:

- Exacerbations in the year prior to the start of first maintenance therapy.
- Exacerbations in the year prior to the start of second maintenance therapy (if available).

For MarketScan, there are specific ICD-10 codes to identify exacerbations, but no ICD-9 code. COPD exacerbations will be defined as any of the following:

- An acute COPD exacerbation diagnosis (ICD-10 J44.0, J44.1);
- A claim for an antibiotic or a corticosteroids on the same day or within 7 days following an outpatient COPD diagnosis;
- An inpatient diagnosis of COPD in any position;
- A hospitalization due to respiratory condition;
- An emergency department visit with a COPD diagnosis in any position;
- Lower respiratory tract infection diagnosis (ICD-9 466, ICD-10 J20.9, J21.0, J21.8, J22) (Rothnie 2016);

For CPRD, COPD exacerbations will be defined as any of the following:

- An acute COPD exacerbation diagnosis or respiratory failure (READ code “H312200”, “8BP8.00”, “H3y1.00”, “H590.00”, “H59..00”, “R2y1.00”, “R2y1z00”);
- A lower respiratory tract infection diagnosis (READ code “H060.00”, “H060.11”, “H060300”, “H060500”, “H060w00”, “H060x00”, “H060z00”, “H062.00”, “H06z000”, “H06z011”, “H06z100”, “H06z112”, “H20..11”, “H20y.00”, “H20z.00”, “H22..00”, “H22..11”, “H22y.00”, “H22yz00”, “H22z.00”, “H23..11”, “H24..00”, “H24y.00”, “H24yz00”, “H24z.00”, “H25..00”, “H25..11”, “H26..00”, “H26..11”, “H260.00”, “H261.00”, “H2B..00”, “H2z..00”, “H30..11”, “H300.00”, “H301.00”, “H30z.00”, “H3y0.00”, “H540000”, “H540100”, “Hyu0800”, “Hyu0A00”, “Hyu0B00”, “Hyu0H00”, “Hyu1.00”);
- Antibiotic or oral corticosteroids prescription on the same or within 7 days following a COPD diagnosis (Chalmers 2018).

Exacerbations occurring within 14 days of one another will be considered a single event.

The mean (SD) and median (IQR) number of COPD exacerbations will be reported. Categories of COPD exacerbations will also be reported as: 0, 1, 2, 3, 4, 5+ exacerbations.

[redacted]

9.3.3 Covariates

Patient characteristics will be identified based on data recorded within one year prior to or on the index date (date of dispensing/initiation of the exposure), unless otherwise specified. If multiple measurements are made in the baseline period, then the most recent measurement prior to index date will be used.

Demographics (Last Recorded Value)

- Age on index date (Mean, Median, Categories: 40 – 54, 55 – 64, 65 – 74, 75 – 84, 85+)
- Sex
- Region (MarketScan): Northeast, North Central, South, West, Unknown, Missing
- Practice Region (CPRD): North East, North West, Yorkshire & The Humber, East Midlands, West Midlands, East of England, South West, South Central, London, South East Coast, Northern Ireland, Scotland, Wales, Missing

Recent Concomitant Medications (365-day Baseline Period)

- Corticosteroids
- Short acting muscarinic antagonist (SAMA)
- Short acting beta agonist (SABA)
- NSAIDs
- Antihistamines
- Oral antibiotics
- Diabetes mellitus medications
- Insulin
- Methotrexate
- Statins
- Antihypertensives
- Anticoagulants
- Anti-psychotic/anti-depressives/anxiolytic
- Opioids
- Oxygen therapy

Comorbidities (All Available Data)

- All-Cause Hospitalization
- All-Cause Emergency Department Visits
    - Respiratory-related Hospitalization

  - Cardiovascular Disease
    - Peripheral Vascular Disease
    - Cerebrovascular Disease
    - Myocardial Infarction
    - Cardiac Arrhythmia
    - Heart Failure
    - Angina Pectoris
    - Hypertension
- Exertional breathlessness
- Osteoporosis
- Anxiety
- Depression
- Type 2 Diabetes
  - Diabetic Retinopathy/Nephropathy/Neuropathy
- Upper/lower respiratory tract infection
  - Pneumonia
- Bronchiectasis
- Asthma
- Allergic Rhinitis
- Sinusitis
- Chronic Bronchitis
- Chronic Cough
- Impaired Cognitive Function/Dementia
- Gastroesophageal Reflux Disease (GERD)
- Deyo Charlson Comorbidity Score
- Cancer (any except non-melanoma skin cancer)
  - Lung Cancer
- Lung Transplant
- Rheumatic Disease (any kind)
- Hepatic Failure/Injury
- Hemiplegia or Paraplegia
- Renal Disease
  - Chronic Kidney Disease (CKD)
  - Acute Renal Failure
  - End Stage Renal Disease (ESRD)
- AIDS/HIV
- Peptic Ulcer Disease (PUD)
- Lung Fibrosis

Lifestyle

- Smoking-related Claim
- Vaccination for Influenza or Pneumococcus
- Body mass index (Categories: < 18.5, 18.5 - 24.9, 25.0 - 29.9, 30.0 - 34.9, 35+ kg/m^2) (last recorded) (CPRD Only)
- Smoking status (Categories: Never smoker, Past smoker, Current smoker, Unknown) (last recorded) (CPRD Only)
- Alcohol consumption (last recorded) (Categories: Never drinker, Past drinker, Current drinker, Unknown) (CPRD Only)

Other Variables of Interest

- Calendar year of index date (Categories: 1987, …, 2018)
- FEV1/FVC (last recorded) (CPRD Only)

9.4 DATA SOURCES

The proposed study will utilize data from two separate data sources: the Truven MarketScan data (US) and The Clinical Practice Research Datalink (CPRD) (UK).

MarketScan

The Truven MarketScan databases capture longitudinal, individual-level administrative claims data from the United States. The data available for study included three components of MarketScan: the Commercial Claims and Encounters (CCAE) Database, the Medicare Supplemental and Coordination of Benefits Database (MDCR), and the Medicaid Database. Patients in the databases are active employees, dependents, retirees, COBRA recipients, and Medicare or Medicaid enrollees. Data were drawn from large employers, health plans, and public organizations in the United States. The following tables of the MarketScan databases were available for analysis: Enrolment Detail, Inpatient Admissions, Inpatient Services, Outpatient Services, Outpatient Pharmaceutical Claims, and Long Term Care. These tables provide information on plan enrolment, healthcare utilization and expenditures, demographics, and integrated records for inpatient events, outpatient events, and pharmacy dispensings. Data were available from January 1, 2008 to March 31, 2017, and represent approximately 155.8 million patients.

CPRD

Clinical Practice Research Datalink (CPRD) is based on standardized electronic medical records (EMR) systems in primary care practices in the United Kingdom (UK). This database represents over 700 contributing general practices in the UK, and includes approximately 17.8 million patients. The geographical distribution of the practices has been shown to be representative of the UK population, and age and sex distributions of patients in the databases are similar to those reported by the national population census (Walley 1997). Participating general practitioners have been trained to record medical information, including demographic

data, medical diagnoses, procedures, and deaths using a standardized form (Garcia Rodriguez 1998). The EMR system records conditions, interventions and diagnostics using READ codes and medication prescribing is recorded using the British National Formulary (BNF). The EMR system records the prescribing of medications, including over-the-counter medications, but it does not verify whether patients fill the medications at the pharmacy. The system records laboratory test results and lifestyle measures like smoking, alcohol use, and body mass index with varying degrees of completeness. The database is limited to recordings by the primary care physician including the transferred notes from specialists and some information on hospitalization. Linkage to other datasets is possible, including the Hospital Episodes Statistics (HES), which is a data warehouse containing records of all patients admitted to NHS hospitals in England (Walley 1997). In the current study, event dates spanned from November 21, 1987 through June 30, 2018.

9.5 STUDY SIZE

Among approximately 1,487,765 patients with COPD in MarketScan who did not use maintenance therapy before May 21, 2015, there were about 1,269 with at least 1 claim for Stiolto Respimat in follow-up.
Among approximately 98,537 patients with COPD in CPRD who did not use maintenance therapy before July 1, 2015, there are 332 with at least 1 claim for Spiolto Respimat in follow-up.

9.6 DATA MANAGEMENT

MarketScan
The Truven Health MarketScan database is comprised of fully adjudicated and paid claims records of integrated longitudinal enrolment, inpatient, outpatient and drug data from multiple payers, that has been standardized and de-identified prior to use for the analysis. The statistical analysis will be conducted using the Aetion Evidence Platform.

Drug Duration
For MarketScan, unless otherwise noted, drug event duration was calculated from the "Days Supply" field, and in cases where this field was 0, the duration was assumed to be 1 day.

Handling of Missing Data
Missing data that occurs in covariates or descriptive variables will be classified as own category. In addition, a feasibility assessment before beginning the analyses will be done, and variables with >75 % missing values will be excluded from all analyses, other than baseline characteristics. If a variable is left with only one category other than missing, the variable will be excluded completely from all analyses. The percentage of patients with missing data for both categorical and continuous variables will be reported.

CPRD

Drug Duration
For CPRD, drug events' duration was calculated from the provided number of days field. In the case where this field was zero and a dosage identifier was present in the text field, the days supplied was determined from the quantity field and the numeric daily dose from the associated dosage metadata. In the case where this field was zero and no numeric daily dose could be determined, the default duration will be set to thirty days.

Handling of Missing Data
Missing data that occurs in covariates or descriptive variables will be classified as its own level. In addition, a feasibility assessment before beginning the analyses will be done, and variables with >75 % missing values will be excluded from all analyses, other than baseline characteristics. If a variable is left with only one level other than missing, the variable will be excluded completely from all analyses.

For clinical variables (FEV1/FVC, BMI), distributions of observed values will be evaluated and clinically feasible ranges will be applied. Following implementation of reasonable ranges, a final assessment of outliers will be tested visually using histograms to understand the distribution of these variables. Any potential effects of skewed distributions will be presented in results and revised approaches will be considered where necessary.

9.7 DATA ANALYSIS

9.7.1 Main analysis

For all analyses, variables will be reported as follows:

- Continuous variables (e.g., age) will be presented as means (with standard deviation, SD) and/or medians (with interquartile range, IQR).
- Categorical variables (e.g., sex) will be presented as absolute and relative frequencies.
- All results will have two digits following the decimal point.

9.7.1.1 Descriptive Analysis

- Descriptive Analysis at Cohort Entry Date

All variables specified in section 9.3.3 will be reported. For demographic and lifestyle variables, the value recorded on the cohort entry date will be reported, otherwise the most recent known value will be reported. Presence of concomitant medication use will be determined based whether they ever occurred within the 365-day baseline period preceding the cohort entry date. Presence of comorbidities will be determined based on whether they ever occurred within all data preceding cohort entry. In CPRD, BMI, alcohol use, smoking status, and FEV1/FVC will be reported based on the last recorded value.

- Descriptive Analysis at First Maintenance Therapy

The child cohort described in section 9.2.2.2 will be used for this analysis.
All variables specified in section 9.3.3 will be reported. For demographic and lifestyle variables, the value recorded on the date of initiation of first maintenance therapy will be reported, otherwise the most recent known value will be reported. Presence of concomitant medication use will be determined based whether they ever occurred within the 365-day baseline period preceding the cohort entry date. Presence of comorbidities will be determined based on whether they ever occurred within all data preceding date of initiation of first maintenance therapy. In CPRD, BMI, alcohol use, smoking status, and FEV1/FVC will be reported based on the last recorded value.

- Descriptive Analysis at Second Maintenance Therapy

The grandchild cohort described in section 9.2.2.3 will be used for this analysis.
All variables specified in section 9.3.3 will be reported. For demographic and lifestyle variables, the value recorded on the date of initiation of second maintenance therapy will be reported, otherwise the most recent known value will be reported. Presence of concomitant medication use will be determined based whether they ever occurred within the 365-day baseline period preceding the cohort entry date. Presence of comorbidities will be determined based on whether they ever occurred within all data preceding date of initiation of second maintenance therapy. In CPRD, BMI, alcohol use, smoking status, and FEV1/FVC will be reported based on the last recorded value.

- Treatment Patterns at First vs. Second Maintenance Therapy

The grandchild cohort described in section 9.2.2.3 will be used for this analysis.
A table will be constructed cross tabulating proportions of patients using a specific medication class at first maintenance vs. a specific medication class at second maintenance. We will present two proportions, a conditional and a marginal proportion: 1) For the conditional proportion, the numerator will be the number of patients who used that specific combination, and the denominator will include all patients who used the first maintenance drug for that combination. Using arbitrary values as an example, if the number of patients who switched from LABA → LAMA was 400 and the number of patients who used LABA as first maintenance therapy was 1000, then the conditional proportion would be: 400 / 1000 = 0.4; 2) For the marginal proportion, the numerator will be the number of patients who used the specific combination, and the denominator will include all patients in the grandchild cohort. Using arbitrary values as an example, if the number of patients who switched from LABA → LAMA was 400 and all patients who used any second maintenance therapy was 5,000, then the marginal proportion would be: 400 / 5000 = 0.08.
Sankey plots will also be generated to visually illustrate the flow of patients from first to second maintenance therapy according to therapy category.

9.7.1.2 Time to Initiation of Therapy

- Time Between Cohort Entry Date and First Maintenance Therapy

Among patients with first maintenance therapy, the mean (SD) and median (IQR) time (days) between index date and first maintenance therapy will be reported in tabular form.

- Time Between Cohort Entry Date and Second Maintenance Therapy

Among patients with second maintenance therapy, the mean (SD) and median (IQR) time (days) between cohort entry date and second maintenance therapy will be reported in tabular form.

- Time Between First and Second Maintenance Therapy

Among patients with second maintenance therapy, the mean (SD) and median (IQR) time (days) between date of initiation of first to the date of initiation of second maintenance therapy will be reported in tabular form.

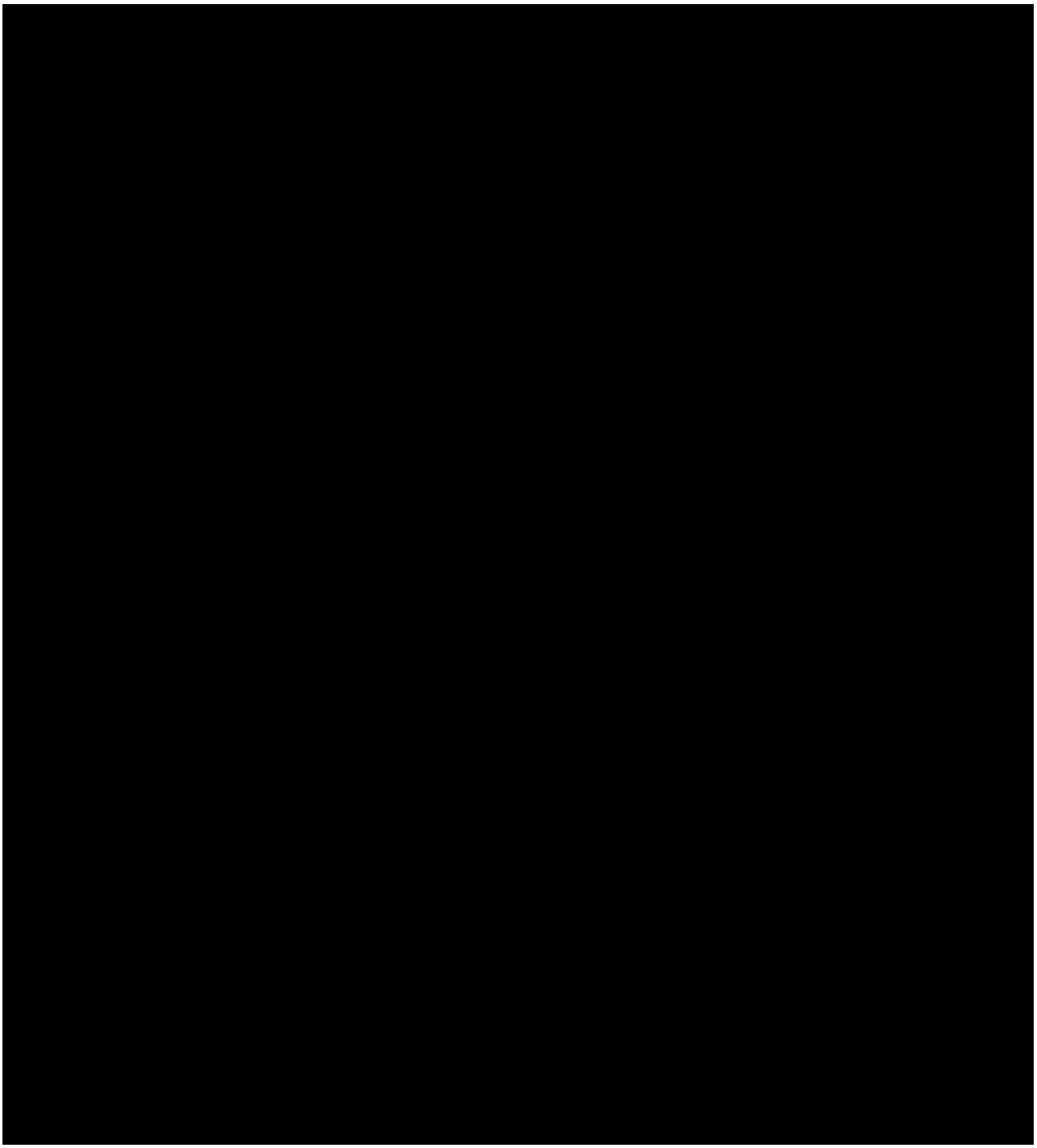
9.7.1.3 Number of COPD Exacerbations

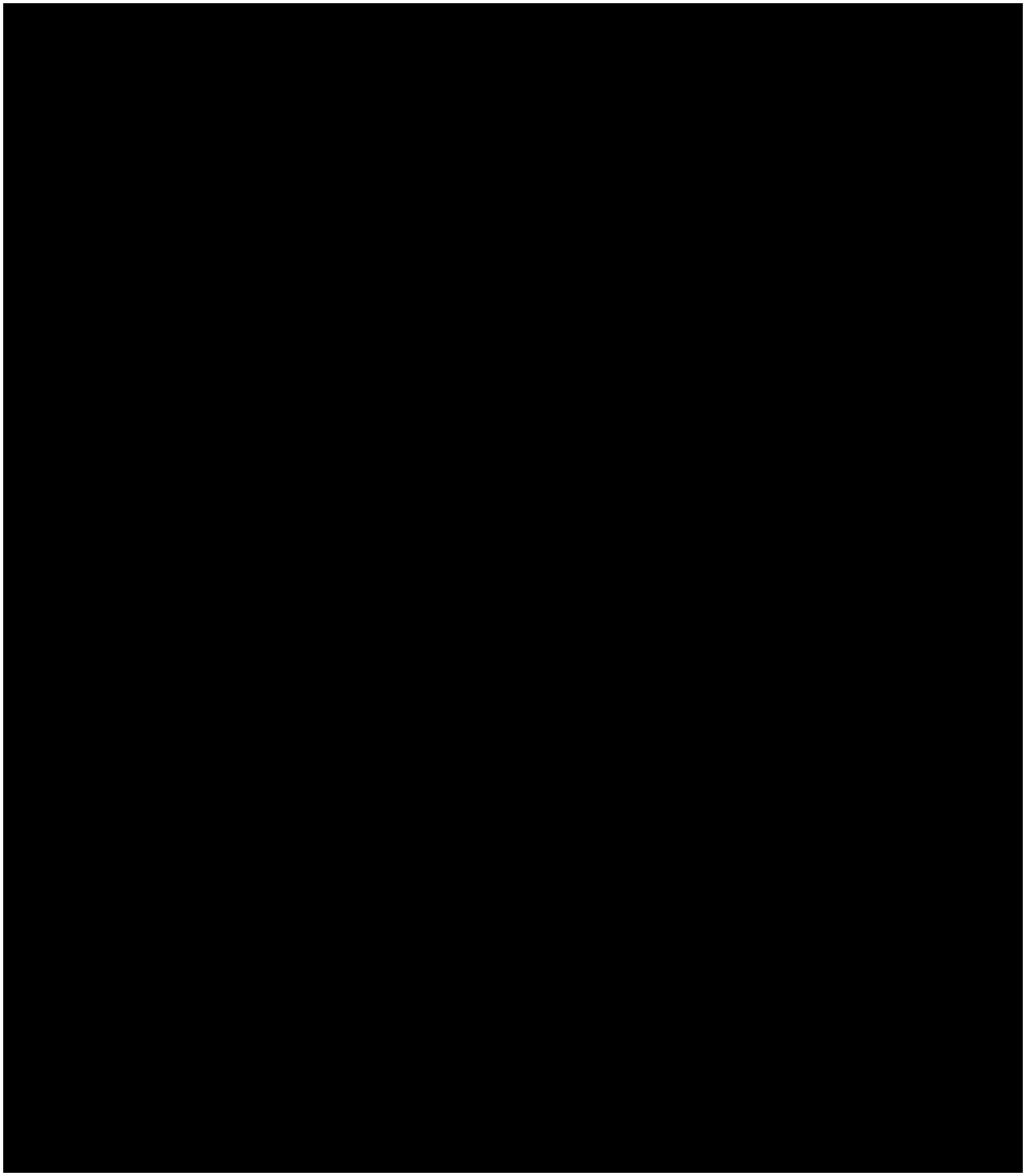
- Number of COPD Exacerbations in the Year Before First Maintenance Therapy

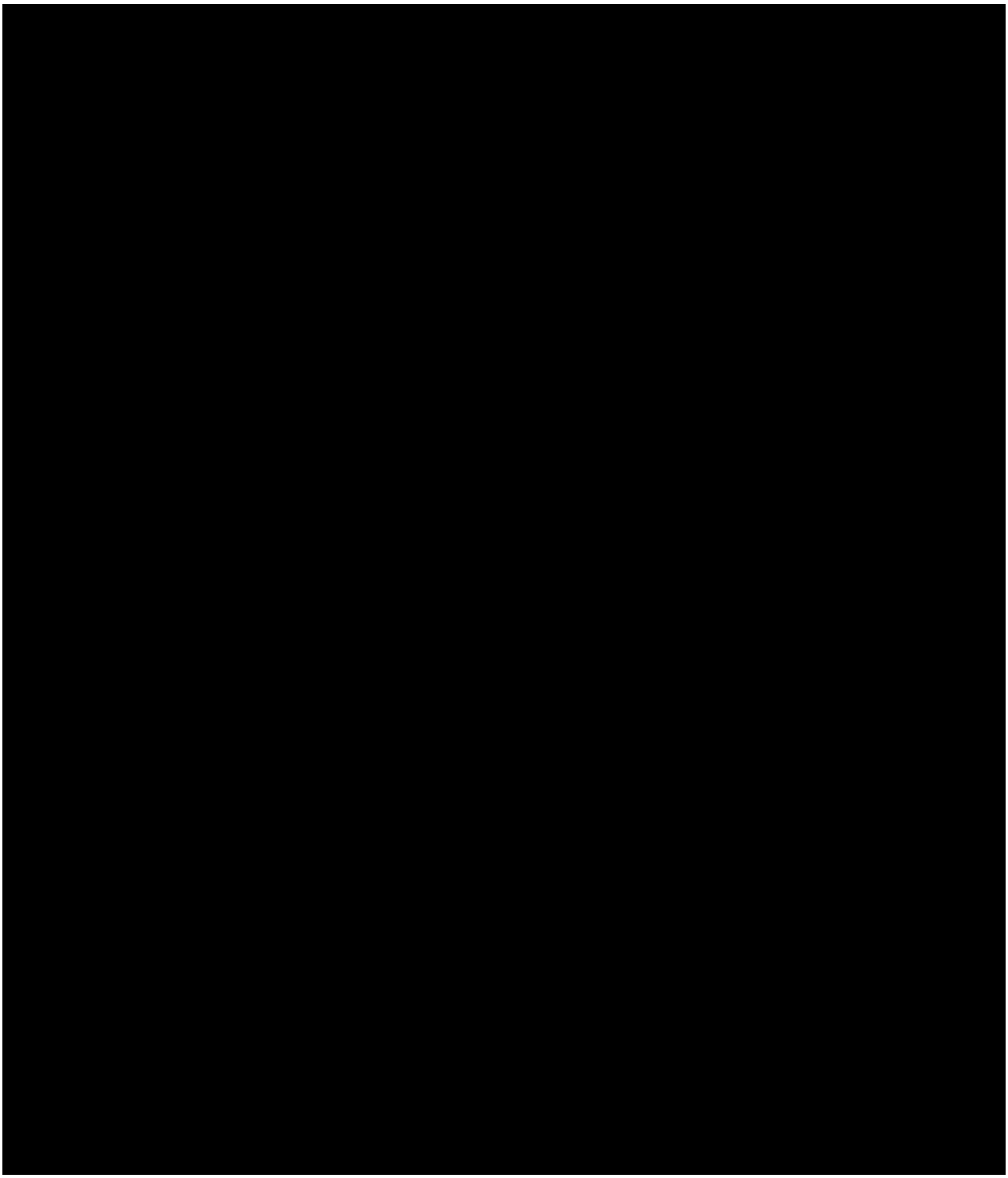
The child cohort described in section 9.2.2.2 will be used for this analysis.
The mean (SD) and median number (IQR) of COPD exacerbations, defined in section 9.3.2.2, during the baseline period preceding the date of initiation of first maintenance therapy will be reported. For the mean, plots will be generated depicting the mean and SD (as error bars) number of COPD exacerbations. Categories of number of COPD exacerbations (0, 1, 2, 3, 4, 5+) will also be reported as a percentage.

- Number of COPD Exacerbations in the Year Before Second Maintenance Therapy

The grandchild cohort described in section 9.2.2.3. will be used for this analysis.
The mean (SD) and median number (IQR) of COPD exacerbations, defined in section 9.3.2.2, during the baseline period preceding the date of initiation of second maintenance therapy will be reported. Categories of number of COPD exacerbations (0, 1, 2, 3, 4, 5+) will also be reported as a percentage.







9.8 QUALITY CONTROL

Aetion will build measures for cohort inclusion, outcomes and covariates. Some of the measure algorithms will be based on those collaboratively developed for another respiratory-related protocol with clinical input from external pulmonology expert. When available, algorithms that have been validated in administrative databases will be used. When validated algorithms are not available, coding criteria will be based on clinical input and through searches of medical claim coding systems.

All measures created, cohorts developed, statistical analyses implemented, and tables completed will undergo quality control review by at least 1 additional analyst or scientist under the supervision of the senior scientist.

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.

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].

Quality controls include checks for the validity and logical content of codes and checks for missing values and variables. In order to control for potential inconsistencies and errors, all variables will be tabulated. In addition, the distribution of each variable will be examined. Extreme observations with values larger than ± 3 standard deviations (SD) will be examined as potential outliers and consequently excluded from the dataset.

9.9 LIMITATIONS OF THE RESEARCH METHODS

MarketScan
This study will be conducted using data from insurance claims and is subject to certain limitations. One limitation is that these are based on a large, non-random convenience sample, which may contain biases or lack generalizability to other populations. Data also come mostly from large employers, and although the database also includes a large amount of data from health plans, data from medium and small firms may be underrepresented.

Additionally, the MarketScan database also poses some limitations inherent to administrative claims data. Electronic outpatient pharmacy dispensing records are considered accurate because pharmacists fill prescriptions with little room for interpretation and are reimbursed by insurers on the basis of detailed, complete, and accurate claims submitted electronically (Stergachi 1988, Levy 2003). Pharmacy dispensing information is usually seen as the gold standard of drug exposure information compared to self-reported information (West 1995) or prescribing records in outpatient medical records (West 1994). However, drugs used during hospital stays are not recorded in this data source. Finally, while the EMR system records the prescribing of medications, including over-the-counter medications, it does not verify whether patients fill the medications at the pharmacy, and up to 50% of prescriptions are never filled (Fischer 2010). Further, these prescriptions do not ensure that medications were taken as prescribed, and any medications filled over-the-counter or provided as samples by the physician will not be observed in the claims data. Finally, patients are required not to have used any maintenance medications in the year before COPD claim confirming diagnosis, but use of these medications may have occurred beyond one year.

CPRD
This study will be conducted using data from electronic medical records, which is subject to certain limitations. While the electronic medical records from CPRD strive for high quality data, this relies upon correct entry of the data by health practitioners. Therefore, it is possible that there may be missing values where data has not been recorded, or values which have been recorded incorrectly. This may affect the data we have on patient demographics and comorbidities, and the factors we are interested in investigating which may influence the choice of therapy.
Finally, prescription data is likely to be entered correctly as the electronic system requires that the data is input in order to generate a patient prescription. These prescriptions do not ensure that medications were taken as prescribed, and any medications filled over-the-counter or provided as samples by the physician will not be observed in the claims data. Finally, patients are required not to have used any maintenance medications in the year before COPD claim confirming diagnosis, but use of these medications may have occurred beyond one year.

9.10 OTHER ASPECTS

Not applicable.

9.11 SUBJECTS

9.11.1 Cases

See Section 9.2.2.

9.11.2 Controls

Not applicable.

9.12 BIAS

The population-based nature of the CPRD will avoid selection bias and ensure external validity. However, the validity of research based on any automated database depends on the quality and completeness of data recorded. The CPRD carries out a series of ongoing checks to ensure quality of the data; this comprises assessment of both patient data (age, gender, registration details and event dates) and the completeness, continuity and plausibility of electronic data recording in key areas at the practice level (for example, ensuring a minimum specified percentage of deaths have cause of death recorded, a minimum referral rate per 100 patients, and a minimum number of prescriptions per patient per month) (Herrett 2015). Prescription data in the CPRD are known to be well documented as the prescriptions are automatically recorded in the database. The therapy file is therefore considered complete, except for prescriptions issued in secondary care and for drugs that are purchased over the counter (Herrett 2015). Validity of the diagnoses has been assessed in numerous validation studies. However, because this database is limited to general practice, specialist care and hospitalization events may not be captured.
In principle, in the US when a patient goes to a pharmacy and gets a drug dispensed, the pharmacy bills the insurance carrier for the cost of that drug. Electronic outpatient pharmacy dispensing records are considered accurate because pharmacists fill prescriptions with little room for interpretation, and are reimbursed by insurers on the basis of detailed, complete, and accurate claims submitted electronically (Levy 2013, Stergachis 1988). Pharmacy dispensing information is usually seen as the gold standard of drug exposure information compared to self-reported information or prescribing records in outpatient medical records. Yet, the obvious limitation in these data is that drugs purchased out of pocket will not result in a pharmacy claim.
To minimize misclassification of the recorded patient characteristics, previously validated algorithms or code lists will be used whenever available. Code lists will be reviewed by the qualified medical reviewers prior to implementation. Basic plausibility checks will be implemented for continuous variables (e.g. BMI, patient age etc.).

10. PROTECTION OF HUMAN SUBJECTS

The final study CPRD protocol will be submitted 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 (MREC) for all observational research using CPRD data without patient involvement; however, ISAC may recommend that the MREC review the study documentation if any ethical issues arise.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE 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.
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. Specifically, as stated in section VI.C.1.2.1 of Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products, for non-interventional study designs, which are based on use of secondary data, reporting of adverse reactions is not required.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will primarily serve internal decision making for future studies on comparative effectiveness. These baseline results will be published as an abstract and/or manuscript. Conference and Journal to be decided.

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13.2 UNPUBLISHED REFERENCES

None