Retrospective Observational Database Study Protocol

Drug Substance Symbicort

Study Code

Date

Adherence and COPD Exacerbation Rates in Patients Initiating ICS/LABA Therapy

Name and address of requesting AZ department: Global Health Economics and Outcomes Research 1800 Concord Pike Wilmington, DE

Therapeutic area: Respiratory Therapeutic Area

Names of Requestor:

Sponsor: AstraZeneca LP, US Symbicort Brand Team; Wilmington, DE

Name and address of RWE Engagement Lead:

Name and address of RWE Design and Analytics Core members:

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	**Date of Amendment**		

Administrative Change No.	**Date of Administrative Change**		

PROTOCOL SYNOPSIS

Adherence and COPD Exacerbation Rates in Patients Initiating ICS/LABA Therapy

Principal Investigator:

Co-investigators:

Objectives: The objective of this study is to assess COPD exacerbation rates, healthcare utilization, COPD related medication use – including SABA, SAMA, and SABA/SAMA use, and costs among COPD patients initiating ICS/LABA therapy, comparing those who are adherent to therapy with those who are non-adherent.

Study design Retrospective cohort study

Databases to be used Administrative claims data from the HealthCore Integrated Research Environment (HIRE)

Target subject population COPD patients newly initiating ICS/LABA combination therapies

Exposures of Interest BFC and FSC in COPD patients new to ICS/LABA combination therapies

Outcomes of Interest COPD exacerbation rate during 12 month post-index period

Statistical methods Matched cohorts via propensity scores; A GLM model using negative binomial and a log link function for primary outcome; Cox proportional hazards model for analysis of time to first event; Poisson, negative binomial, logistic, normal, and gamma regression for secondary outcomes

Limitations Non-randomized study which can detect associations but causation cannot be inferred. Limited generalizability to US commercial health plan enrollees.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	Adverse event
AIC	Akaike information criterion
BFC	Budesonide/formoterol fumarate dihydrate combination
CAD	Coronary artery disease
CI	Confidence Interval
COC	Continuity of care
COPD	Chronic Obstructive Pulmonary Disease
DCI	Deyo-Charlson comorbidity index
ED	Emergency department
FSC	Fluticasone propionate/salmeterol combination
GPI	Generic product identifier
GPP	Good Pharmacoepidemiology Practice
GRACE	Good Research for Comparative Effectiveness
HIRE	HealthCore Integrated Research Environment
ICD9	The International Classification of Diseases ninth revision diagnosis codes (9^{th} revision)
ICS	Inhaled corticosteroid
ICS/LABA	Inhaled corticosteroid + Long-acting ß2-adrenergic agonist combination
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISPE	International Society for Pharmacoepidemiology
LABA	Long-acting ß2-adrenergic agonist
LAMA	Long acting muscarinic antagonists
LTRA	Leukotriene receptor antagonist
LV	Left ventricular
MPR	Medication possession ratio
OCS	Oral corticosteroids
OR	Odds ratio

Abbreviation or special term	Explanation
PDC	Proportion of days covered
pMDI	Pressurized meter dose inhaler
PPV	Positive predictive value
RCT	Randomized clinical trial
SABA	Short-acting ß2-adrenergic agonist
SAMA	Short acting muscarinic antagonist
SABA/SAMA	Short-acting ß2-adrenergic agonist + Short acting muscarinic antagonist combination therapy
SAE	Serious adverse event
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

1. STUDY INVESTIGATORS

1.1 Investigator name, title, degree, address, and affiliation

Table 1. Investigating team

See addresses below

1.2 List of collaborating institutions

2. INTRODUCTION

2.1 Background

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by deterioration in lung function due to airway obstruction and inflammation and includes two main chronic lower respiratory disease conditions – emphysema and chronic bronchitis.(1) More than 12 million Americans are currently diagnosed with COPD.(1;2)As the third leading cause of death in the U.S. estimated cost of COPD in 2010 was approximately $49.9 billion, including $29.5 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs and $12.4 billion in indirect mortality costs.(1)

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (www.goldcopd.org) guidelines cite the prevention and treatment of exacerbations as one of the primary goals of COPD management, due to the tremendous negative impact they have on patients and the healthcare system.(3;4) Current COPD treatment guidelines (GOLD 2015) suggest the initiation of controller medications based on history of exacerbations and symptoms. For patients with a history of COPD exacerbations, ICS/LABA combination therapies are considered a first-line option.(5) To date, FDA approved ICS/LABA combination medications for COPD maintenance therapy include budesonide/formoterol (BFC, Symbicort 160/4.5 µg strength, AstraZeneca LP, Wilmington),(6) fluticasone/salmeterol (FSC, Advair, 250/50 µg strength, GlaxoSmithKline),(7) and fluticasone furoate/vilanterol (Breo, 100/25 µg strength, GlaxoSmithKline).(8)

The clinical efficacy and safety of ICS/LABA combination therapy has been repeatedly reported by randomized clinical trials (RCTs).(9;10) However, clinical trial results are based on patient populations with high adherence to the assigned treatment, which is not always the case in a real world setting. Restrepo and colleagues suggested that only an average of 40%-60% of patients with COPD adhere to the prescribed medication.(11) To date, there are a few retrospective observational studies evaluating the real-world effectiveness and safety outcomes of ICS/LABA combination therapy in COPD population; however, none compared the outcomes between adherent patients and non-adherent patients.(12-15)

This study will utilize a large administrative claims data from the HealthCore Integrated Research Environment (HIRE) to evaluate treatment effectiveness of ICS/LABA combination therapy by adherence status in COPD patients new to ICS/LABA combination therapies in a real world setting.

2.2 Scientific and Business Rationale and Significance

Patient adherence plays an important role in patients receiving the maximum benefit of their medication, and low rates of medication adherence is a major and growing concern in COPD care.(16;17) In clinical trials patient adherence is higher than what is found in the real world,(17) and results of those trials may not reflect the benefit of the medication when used in a real world

setting due to the differing rates of adherence. Thus, it is important to understand the association between disease control and medication adherence in a real world setting, since it is unable to be studied in clinical trials where all patients have high rates of adherence.

Adherence to medication may be both a cause of disease control (e.g., high adherence leads to higher control), but also may be the consequence of disease severity (e.g., those with severe disease and thus more likely to be symptomatic may take their medication more often than those with mild disease who are less symptomatic). These two scenarios would lead to opposite conclusions about the association between adherence and disease control; that is, in the first scenario high adherence is associated with higher control, while in the second scenario (mild disease with fewer symptoms and a perceived lower need to take medication regularly) low adherence is associated with higher control where the finding is confounded by disease severity. Because of these conflicting scenarios it is important to study the role of adherence within different patient subgroups.

This study aims to analyze the association between adherence and COPD exacerbations, and whether this relationship differs by the number of prior exacerbations or presence of comorbidities that may confound or modify this association.

3. STUDY OBJECTIVES

The objective of this study is to assess effectiveness of ICS/LABA combination therapies among COPD patients new to the ICS/LABA combination therapies in the US, comparing those who are adherent to the index medication and those who are non-adherent.

***Note**: ICS/LABA combination therapies only refer to Symbicort (BFC, 160/4.5 μg strength) and Advair (FSC, 250/50 μg strength) which are currently approved in the US for COPD maintenance therapy. Dulera (MFC), a third ICS/LABA combination therapy, is not included because it is only approved for the treatment of asthma in the US. Breo, the latest ICS/LABA to be approved for the treatment of COPD, is not included due to it unavailability during the study intake period (launched in the US at the end of October 2013).*

3.1 Primary objective

The primary objective is to compare the effectiveness of ICS/LABA combination therapy in the reduction of COPD exacerbations (exacerbation rate) during the 12 months after initiation of BFC or FSC between those who are adherent to the index medication and those who are non-adherent. Adherence will be measured using the proportion of days covered (PDC) with the index medication, and is defined in detail in Section 8. A COPD exacerbation is defined as the occurrence of any of the following events:

1) COPD related inpatient hospitalization (inpatient hospitalization with a primary diagnosis for COPD); or

2) COPD related emergency department (ED) visit (an ED visit with a diagnosis in any position for COPD); or

3) An outpatient visit with a diagnosis for COPD and a pharmacy claim for either OCS and/or antibiotics on the same day as or within 10 days after the visit.

3.2 Secondary objectives

More detailed definitions of secondary outcomes can be found in Section 10.2.

3.2.1 Sensitivity analyses of primary outcome

1. *Sensitivity:* Analysis of primary objective (exacerbation rate) using all follow-up (i.e., patients may be followed beyond 12 months)

2. *Sensitivity:* Analysis of primary objective (exacerbation rate) only including severe COPD exacerbation events (COPD-related inpatient hospitalization or emergency department visit)

3. *Sensitivity:* Analysis of primary objective (exacerbation rate) with follow-up starting at day 31 after treatment initiation

3.2.2 Additional secondary objectives related to the primary outcome during the 12 month post-index period

1. To evaluate time to first event as an outcome

2. To evaluate individual components of an exacerbation separately.

3.2.3 COPD related healthcare resource utilization

1. To assess COPD respiratory medication use, specifically SABA, SAMA, and SABA/SAMA combination, as well as others.

2. To assess COPD-related healthcare resource utilization and costs.

3. To evaluate post-index treatments.

3.2.4 All-cause related healthcare resource utilization

1. To assess healthcare resource utilization and costs for any reason.

3.2.5 Baseline/Pre-index analysis

To describe patient characteristics at the time of ICS/LABA combination therapy initiation, and evaluate prior exacerbation rates, COPD-related healthcare utilization and costs, and all-cause healthcare utilization and costs during the 12 month pre-index period.

3.2.6 Subgroup analysis

To examine the primary outcome described above between adherent and non-adherent cohorts within the following six subgroups.

Subgroup 1: Patients with comorbid asthma

Subgroup 2: Patients with frequent exacerbations: those with a history of 2 or more COPD exacerbations during the pre-index period

Subgroup 3: Patients with 1 or more exacerbations during the pre-index period

Subgroup 4: Patients with no exacerbations during the pre-index period

Subgroup 5: Patients with cardiovascular comorbidities

Subgroup 6: Patients with a Deyo-Charlson Comorbidity Index score at or above the 75th percentile.

Subgroup 7: Patients with add-on LAMA therapy (triple therapy) during the follow-up period

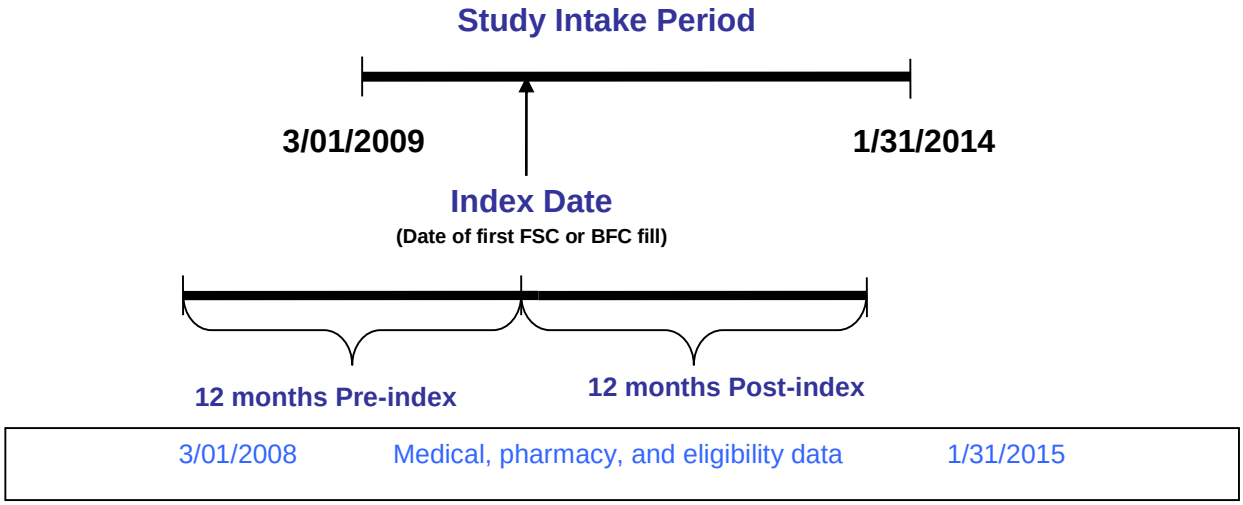
4. STUDY PLAN AND PROCEDURES

4.1 Overall study design and flow chart

Index date: Date of FSC or BFC initiation [anytime between 3/1/2009 and 1/31/2014]

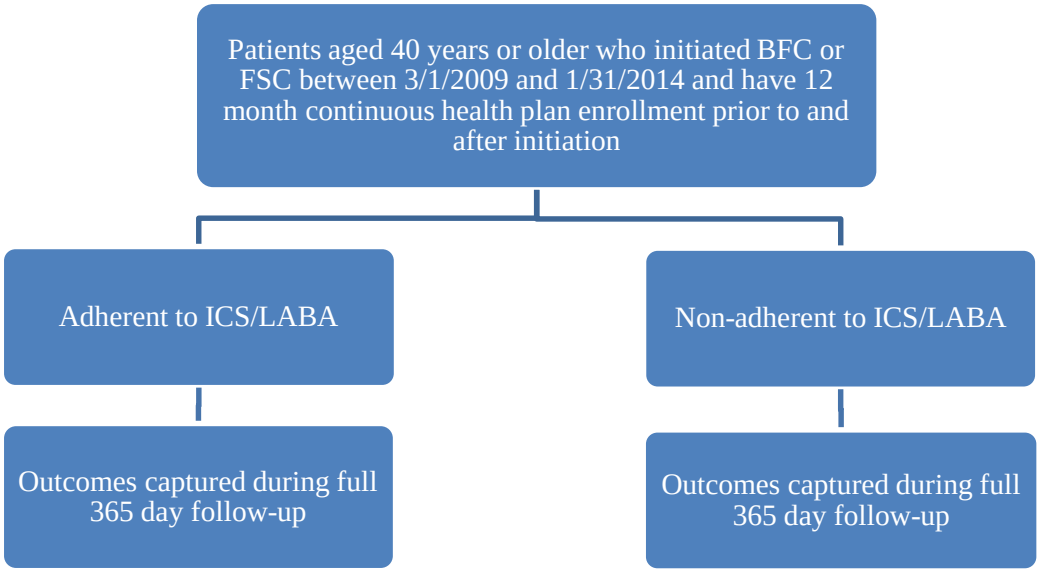
Observation period used to capture eligibility and outcome metrics for an individual patient [anytime between 3/1/2008-1/31/2015]: Index date-365 days (pre-index period) to Index date+365 days (post-index period)

Figure 1. Study Time Frame Diagram



Note: The *index date* may be at any time within the intake period. Health plan enrollment will be confirmed from each patient's index date.

Figure 2. Study Flow Chart



5. STUDY DESIGN SELECTION AND RATIONALE

5.1 Rationale for study design

This is a retrospective matched cohort study utilizing administrative claims data from the HealthCore Integrated Research Environment (HIRE), which contains pharmacy and medical claims data for 37.3 million patients. The administrative claims data will be utilized to describe

COPD patients who are adherent to the newly initiated ICS/LABA combination therapies and those who are non-adherent. A retrospective cohort study design allows us to easily capture the patient population over a large time period. It also allows the ability to look both backwards and forwards in time to describe the pre-index characteristics of the patient population and capture post-index outcomes.

5.2 Rationale for selection of comparators

The comparators are COPD patients initiating ICS/LABA combination therapy who are adherent to the index medication and those who are nonadherent. Comparison groups were chosen to analyze the association between medication adherence on COPD exacerbations and other secondary outcomes such as rescue medication use. The definition of adherence can be found in Section 8.2.

6. DATABASE(S) TO BE USED

Administrative claims data in the HIRE with a service date during the time period from 3/1/2008 through 1/31/2015 will be used for this research study.

The HealthCore Integrated Research Environment (HIRE) contains a broad, clinically rich and geographically diverse spectrum of longitudinal claims data from health plans in the Northeast, Midwest, South, and West of the United States. The database represents claims information from the largest commercially insured population in the United States and includes the lines of business such as health maintenance, point of service, preferred provider organizations, and indemnity plans.

The following provides information on dates of data availability and approximate counts of lives in the database with medical and pharmacy eligibility through 1/31/2015.

Current Data Availability:

Approximately 37.4 million lives having medical and pharmacy coverage in total database, with continuous eligibility for:

- 1 year – approximately 24.8 million
- 2 years – approximately 17.2 million
- 3 years – approximately 12.4 million
- 4 years – approximately 8.9 million

Approximately 10.1 million lives **currently active** with medical and pharmacy coverage in available health plans, with continuous eligibility from most recent date looking back for:

- 1 year – approximately 7.3 million

- 2 years – approximately 5.3 million
- 3 years – approximately 4.3 million
- 4 years – approximately 3.6 million

The full HIRE database dates back to 1/1/2006 and the majority of data can be accessed from that time period through the most recent monthly update, which usually lags by approximately 3-4 months from the present. The data collected for this study date from 3/1/2008 and extend to the most currently available data, 1/31/2015.

HealthCore accesses the data in a manner that complies with federal and state laws and regulations, including those related to privacy and security of individually identifiable health information.

Some of the claims data to which HealthCore has access may include supplemental claims for patients who have traditional state/federally sponsored Medicare/Medicaid, with commercial, supplemental coverage through a health plan. HealthCore does not have the federal Medicare/Medicaid claim information stored in its database.

7. SELECTION OF POPULATION TO BE STUDIED

The study intake period was chosen to coincide with the FDA approval of Symbicort (BFC) to treat COPD on February 27, 2009.

Patients will be assigned to one of two groups based on treatment adherence to their initial prescription fill (BFC or FSC), referred to as their index medication. Patients filling prescriptions for more than one type of index medication on the index date will be excluded from this study; Table 1 in Appendix A presents the Generic Product Identifier (GPI) codes of interest for identifying claims for BFC and FSC prescriptions.

Patients will be considered as having COPD based on having at least one inpatient hospitalization (primary COPD diagnosis) or ED visit (any COPD diagnosis), or two or more other medical claims with a diagnosis of COPD prior to or on the index date (see Appendix B for ICD-9 diagnosis codes for COPD).

7.1 Participant eligibility

Members aged 40 years or older at the index date, with a COPD diagnosis as described above, in the HIRE from 3/1/2009 and 1/31/2014 (intake period) will be eligible for this study.

7.1.1 Inclusion criteria

1. Patients must have at least one prescription fill for BFC (160/4.5 μg strength, per US COPD indication (6)) or FSC (250/50 μg strength, per US COPD indication (7)) during

the intake period. Patients must be naive to ICS/LABA combination therapies in the year prior to first prescription claim[i].

2. The date of the first pharmacy claim (i.e. pharmacy process date) for one of the study medications during the intake period will be the ***index date***. Patients using BFC or FSC will be identified via the use of Generic Product Identifier (GPI) Codes (See Appendix A for codes)
3. Patients must be 40 years or older at the time of index date
4. Patients must meet one of the following diagnosis criteria for COPD (see Appendix B for ICD-9 codes) during the 12 months prior to or on the index date:
   - At least one inpatient visit with a primary diagnosis for COPD, and/or
   - At least one ED visit with a COPD diagnosis (any position), and/or
   - At least two other medical claims with a COPD diagnosis (any position)
5. Patients must have ≥1 prescription for SABA, SAMA, and/or SAMA/SABA during the 12 month pre-index period
6. Patients must have at least 12 months of continuous health plan enrollment <u>prior to and following</u> the index date, including continuous medical and pharmacy coverage

7.1.2 Exclusion criteria[ii]

1. Patients with prescription claims for ICS/LABA combination (see Table 1 in Appendix A) during the 12 month pre-index period.
2. Patients with prescription claims for both BFC and FSC on the index date.
3. Patients with ≥180 days of total length of therapy for any OCS medication (see Appendix E) during the 12 month pre-index period.
4. Patients diagnosed with cancer (ICD-9 code 140.xx – 209.3x, 230.xx – 234.xx) during the 12 month pre-index period will be excluded due to their extreme costs and ability to skew the healthcare resource utilization and cost results of an entire population; and because of the inability to distinguish between different stages of cancer/cancer severity to ensure comparable distribution of cancer patients between the two treatment groups. A cancer diagnosis requires at least two diagnoses for the same type of cancer (based on 3 digit ICD-9 codes) within 60 days of each other.(18)

[i] Naive patients are defined as having no claims for any ICS/LABA therapy (Symbicort, Advair, Dulera, or Breo) in the 12 months prior to index date (See Tables 1 and 2 in Appendix A for list of all codes)

[ii] Exclusion based on chronic antibiotic use was considered, but ultimately decided against based on a very low proportion of patients with chronic use and to maintain generalizability of the study (~2% of BFC patients had ≥40 days of continuous antibiotic use pre-index)

8. EXPOSURES OF INTEREST

8.1 Drug-specific exposure/treatment

Patients initiating budesonide/formoterol (BFC, Symbicort®, 160/4.5 μg strength) and fluticasone/salmeterol (FSC, Advair®, 250/50 μg strength) will be included in this study, however, the effects of these individual drugs is not of interest of the study and patients of both drugs will be combined into a single group. Treatment adherence is the main exposure of interest for this study

8.2 Treatment adherence

Measures of adherence will be based on a proportion of days covered (PDC) of ≥0.80 and three different cutoffs of non-adherence will be defined. The three comparisons are:

- PDC ≥ 0.80 (adherent) will be compared with PDC ≥ 0.50 to <0.80 (non-adherent)
- PDC ≥ 0.80 (adherent) will be compared with PDC ≥ 0.30 to <0.50 to (non-adherent)
- PDC ≥ 0.80 (adherent) will be compared with PDC <0.30 (non-adherent)

PDC is based on the index medication and is calculated by:

1. Calculating the total days supply of the index medication as the sum of days supply of each index medication fill from index date until the end of the observation period*. If days supply of a fill goes beyond the end of the observation period then only the days up to this point will be counted (i.e., days supply was capped at the end of the post-index period).
2. Calculating PDC as the total days supply calculated in step 1 divided by the total length of follow-up, in days.
3. Capping PDC at 1.00. i.e. if calculation comes out to >1.00 then PDC = 1.00.

*The observation period for the primary analysis is up to 365 days (index date to index date + 365); if a patient switches ICS/LABA therapy prior to the one year of follow-up, the observation period for PDC calculations will end at the time of the switch. For the sensitivity analysis that follows patients beyond 365 days the observation period will be until the end of their follow-up (defined in Section 10.2.1).

9. PARTICIPANT FOLLOW-UP

Patient observation begins 12 months prior to the index date and extends up to 12 months post-index.

For all outcomes (including sensitivity analyses) patients will be censored (and follow-up will end) if they fill an ICS/LABA medication different than their index drug (i.e., switching

ICS/LABA therapy). Censoring will occur on the date of filling the non-index ICS/LABA. See the complete definition of ICS/LABA switching in Section 10.2.3 and the definition of the switch date which will be used as the censoring date. Follow-up will stop on the date of being censored and thus all outcomes will be reported as "per patient year".

A sensitivity analysis of the primary outcome will include all follow-up data, which means observation will not end at the end of the 12 month post-index period and patients will be followed as long as possible until the end of the health plan enrollment, the end of the study period, or until switching ICS/LABA medication.

10. DEFINITIONS OF OUTCOME VARIABLES

10.1 Primary outcome variables

The primary outcome of this study is to compare the rates of COPD exacerbation between patients who were adherent to the index ICS/LABA medication and those not adherent during the follow up period.

The rate of COPD exacerbations will be calculated as the number of COPD exacerbations per patient year of follow-up, i.e.:

$$\text{Rate of COPD exacerbation} = \frac{\sum(\text{COPD exacerbations during follow up})}{\sum(\text{person years of follow up})}$$

The count of COPD exacerbations is the number of times that any of the three conditions defined below occur during the post-index period.

1. COPD related inpatient hospitalization (inpatient hospitalization with a primary diagnosis for COPD)

2. COPD related emergency department (ED) visit (an ED visit with a diagnosis in any position for COPD)

3. An outpatient visit with a diagnosis for COPD and a pharmacy claim for OCS and/or antibiotics on the same day as or within 10 days after the visit.

The time of an exacerbation is the earliest date of evidence for that exacerbation (e.g., admission to COPD-related hospitalization, or date of the COPD outpatient visit where OCS/antibiotic treatment follows), not the end of treatment for the exacerbation (e.g., not the discharge from hospitalization, or the fill date or end of OCS treatment).

Patients may have multiple exacerbations during the follow-up. However, the following rules will apply to avoid double-counting:

1. Exacerbations occurring within 14 days of each other will be calculated as one event.

2. ED visits that result in a hospital stay will be counted as an inpatient hospitalization only.
3. Any OCS or antibiotic prescription fill defined above occurring within 14 days of an ED/inpatient hospitalization will be counted as the ED visit/hospitalization only, rather than a separate event.
4. If multiple OCS and/or antibiotic prescriptions are filled within 10 days of the same COPD visit, this will be considered one event.

10.2 Secondary outcome variables

Note: Like the primary outcome, secondary outcomes in all the following sections of 10.2 will end follow-up at the time of switching ICS/LABA therapy or at 12 months following the index date, whichever comes first.

10.2.1 Sensitivity analysis for the primary outcome

The following sensitivity analyses will be performed for the primary outcome. See Section 13.2.1 for more details on the statistical analysis of each.

1. Using all follow-up (i.e., ≥12 months)

   To take advantage of longer follow-up times, and thus to capture more exacerbations, an analysis will be conducted using time beyond the initial 12 month post-index period.

   All patients will be followed for a minimum of either 12 months or until they switch ICS/LABA therapy (as defined in the primary outcome) and follow-up may continue beyond 12 months, ending at the earliest time of the following: discontinuation of their index treatment, switching ICS/LABA therapy, the end of continuous health plan enrollment, or the end of the study period. The treatment discontinuation date will be calculated as the last observed fill date for their index therapy plus days supply. If a patient discontinues treatment prior to 12 months of follow-up, the observation will continue until (and end on) 12 months following the index date or the time of switching prior to 12 months (i.e., consistent with the primary analysis).

   PDC and all COPD exacerbations will be captured during this time. The exacerbation rate will then be calculated as the number of COPD exacerbations during follow-up divided by total follow-up time (in years).

2. Severe exacerbation rate (i.e. inpatient hospitalizations and ED-visits)

   Severe COPD exacerbation ONLY includes the following conditions:

   i. COPD related inpatient hospitalization (inpatient hospitalization with a primary diagnosis for COPD), and/or

ii. COPD related emergency department (ED) visit (an ED visit with a diagnosis in any position for COPD).

3. Starting follow-up on day 31

According to the BFC and FSC labels it may take 1-2 weeks or longer to achieve maximum benefit of the medication(6;7) and previous studies have allowed for a 30 day window between treatment initiation and capturing outcomes.(19) To ensure patients are allowed adequate exposure to the study medication before attributable outcomes are assessed a second follow-up period will be considered for analyzing the primary outcome. For this sensitivity analysis follow-up starts 30 days after the index date (where index date is considered day 1) and continues until 365 days post-index date.

10.2.2 Secondary objectives related to the primary outcome during the post-index period

1. Time to first COPD exacerbation

In addition to the primary outcome of COPD exacerbation rate, time to the first COPD exacerbation will be evaluated to mitigate the effect of switching or discontinuation of the index ICS/LABA medication due to treatment failure.

Follow up starts on the index date and continued for up to 365 days or until the first exacerbation, whichever comes first. The time to first COPD exacerbation will be calculated as the date of first COPD exacerbation minus index date for patients with an event. Patients without COPD exacerbations will be censored at the end of the observation period.

2. Individual components of an exacerbation separately

Individual components of exacerbation will be analyzed separately:

i. COPD related inpatient hospitalization (inpatient hospitalization with a primary diagnosis for COPD)

ii. COPD related emergency department (ED) visit (an ED visit with a diagnosis in any position for COPD)

iii. An outpatient visit with a diagnosis for COPD plus a pharmacy claim for OCS and/or antibiotics on the same day as or within 10 days after that visit

10.2.3 COPD respiratory medication use during post-index period

1. **SABA, SAMA, and SABA/SAMA combination use:** 0 vs. 1+ fill and total number of fills for each class will be assessed. In addition to overall use of each, the use of nebulized and non-nebulized forms of each medication class will be analyzed. See Appendix E for codes.

2. **Other COPD respiratory medication use** (0 vs. 1+ fill and total number of fills for each class; see Appendix E): ICS, LAMA, LABA, LABA/LAMA combination, roflumilast, theophylline, OCS, LTRA, omalizumab, and antibiotics use. Antibiotics use will be assessed overall and within 10 days of an OCS prescription. In addition to overall use of LABA, the use of nebulized and non-nebulized forms of LABA will be analyzed.

   Total number of COPD medication classes filled (including all classes in bullets 1 and 2 above): 0 vs. 1+, and also 0 through 12, individually.

3. **Add-on LAMA/triple therapy**

   Patients who are adding on LAMA to ICS/LABA combination therapy, resulting in triple therapy, will be identified. The average time to the first LAMA fill will be captured.

   An add-on of LAMA requires a fill of any LAMA medication occurring at the same time or after one fill of the index medication and prior to the next fill of the index medication. That is, the following pattern must occur at any time during the post-index period:

   ….index ICS/LABA → LAMA → index ICS/LABA…

   The date of the first fill of LAMA that satisfies the requirements of an add-on therapy (i.e., the instance of LAMA in the diagram above) will be considered the LAMA add-on date.

4. **ICS/LABA Switching**

   Note: the definition of ICS/LABA switching is used for censoring of patients in the primary and secondary analyses of COPD exacerbations.

   The number of patients who fill an ICS/LABA different from their index medication will be captured during the post-index period.

   A treatment switch will be defined as:

   - For those who indexed with BFC: a fill of FSC, Dulera or Breo
   - For those who indexed with FSC: a fill of BFC, Dulera or Breo

The date on which patients fill an ICS/LABA different from their index medication will be the treatment switch date. (See Appendix A for codes.)

Time to treatment switch: Defined as the time from index date to treatment switch date (defined above); calculated as treatment switch date minus index date.

10.2.4 COPD related healthcare utilization during the post-index period

1. Presence of COPD exacerbation (0, 1, and 2+ events), overall and for each type of exacerbation, separately, during the post-index period will be evaluated for each patient. See Section 10.1 for definition of COPD exacerbation.

2. COPD related outpatient visit (0, 1, 2+ events and total number of events): defined as any claim for an outpatient visit (anything other than an ED visit, inpatient visit, or skilled nursing facility visit) with at least one diagnosis for COPD. This will not be considered an exacerbation (unless followed by an OCS and/or antibiotic prescription) as it could be a routine check-up.

3. COPD related inpatient hospitalization length of stay: For hospitalizations with a primary diagnosis for COPD, the length of stay of all hospitalizations during the post-index period is defined as the number of nights from admission to discharge. Same date admission and discharge will be counted as one.

4. COPD related ICU admission and length of stay: defined as an ICU admission (see Appendix F for codes) occurring during a COPD related inpatient hospitalization. Number of events (as well as 0, 1, and 2+ events) will be captured along with length of stay of all ICU admissions during the post-index period. ICU length of stay is defined as the number of nights from the first claim for an ICU stay to the last claim for an ICU stay during the same hospitalization. Same date admission and discharge will be counted as one.

5. COPD procedures (0 vs. 1+ claim and total number of claims for each): Chest X-ray, chest CT scan, pulmonary function tests, oximetry, 6 minute walk, pulmonary rehab, home oxygen use. (See 0 for codes).

10.2.5 All-cause healthcare utilization during the post-index period

The presence of each type of visit (inpatient hospitalization, ICU admissions, ED visit, outpatient/office visit, and skilled nursing facility) and the number of visits of each, for any reason or diagnosis, will be captured. The length of stay for inpatient hospitalizations and ICU stays will also be captured.

10.2.6 COPD related healthcare costs during the post-index period

Costs will be reported for the following resource uses: inpatient hospitalizations, ED visits, outpatient visits, skilled nursing facility, total medical, and prescriptions. COPD related events include inpatient hospitalizations with a primary diagnosis of COPD, and all other types of medical services (ED, outpatient, skilled nursing facility) with any diagnosis for COPD. COPD prescription costs will include costs for any medications in Appendix A or Appendix E. All costs will be adjusted to year 2014 given the most accurate and updated consumer price index information provided by the Bureau of Labor Statistics for Medical Care Services (MCS).(20) The following types of costs will be captured:

- Plan paid costs
- Patient paid costs
- Total costs (plan paid + patient paid)

10.2.7 All-cause healthcare costs during post-index period

Costs will be reported for the following resource uses: inpatient hospitalizations, ED visits, outpatient visits, skilled nursing facility, total medical, and prescriptions. All costs will be adjusted to year 2014 given the most accurate and updated consumer price index information provided by the Bureau of Labor Statistics for Medical Care Services (MCS).(20) The following types of costs will be captured:

- Plan paid costs
- Patient paid costs
- Total costs (plan paid + patient paid)

10.2.8 Continuity of care

Continuity of care (COC) during the 12 month post-index period will be measured with the Bice and Boxerman index.(21) The original index allows for referral physicians and the physicians who referred them to count as one physician, however this level of granularity is not available in the HIRE and all physicians will be counted separately. Values range from 0 to 1, with 0 indicating that the patient saw a different physician at every medical visit and 1 indicating that the patient always saw the same physician. The equation for COC follows:

$$COC = \frac{\sum_{j=1}^{s} n_j^2 - n}{n(n-1)}$$

Where:

n = total number of outpatient visits during the 12 month post-index period

n_j = number of visits to provider j

s = number of providers

COC will only be determined for patients with ≥2 outpatient visits during the post-index period.

11. DEFINITIONS OF DEMOGRAPHIC, BASELINE, AND OTHER CLINICAL VARIABLES

11.1 Demographic and clinical variables

11.1.1 Patient demographics

1. Age: Continuous and categorical (40-49, 50-59, 60-69, 70-79, 80+)
2. Gender: Male, Female
3. Health plan type: HMO, PPO, CDHP
4. Geographic region: Northeast, Midwest, South, West
5. Index date:
    1. By year
    2. By quarter (within each year)
    3. By calendar month (regardless of year, to account for seasonality of the disease)

11.1.2 Index and Pre-index clinical characteristics

1. Comorbidities, defined by the presence of at least one ICD-9 diagnosis code in any position of a claim during the 12 month pre-index period (y/n for each, see Appendix C for codes): insomnia, allergic rhinitis, sinusitis, GERD, anxiety, major depressive disorder, diagnosed obesity[iii], asthma, and sleep apnea, bronchiectasis, cystic fibrosis, coal worker pneumoconiosis, asbestosis, pneumoconiosis due to other silica, pneumoconiosis due to inorganic dust, pneumoconiosis due to inhalation of other dust,

[iii] Because the claims do not have height or weight data, BMI cannot be calculated directly. Instead obesity will be captured via ICD-9 codes and not as body mass index (BMI) alone. As the code is only likely to be used in the events where an intervention is provided, obesity is likely to be underestimated.

pneumoconiosis unspecified, respiratory conditions due to chemical fumes and vapors or other unspecified external agents, post-inflammatory pulmonary fibrosis, other alveolar and parietoalveolar pneumonopathy, lung involvement in conditions classified elsewhere, other diseases of lung, extrinsic allergic alveolitis, tuberculosis, lipoid pneumonia, detergent asthma, hypertension, osteoporosis, diabetes mellitus, dyslipidemia, hyperglycemia, congestive heart failure, pulmonary hypertension, peripheral vascular disease / atherosclerosis, myocardial infarction, unstable angina, other coronary artery disease, stroke / TIA / cerebrovascular disease, chronic hypercapnic respiratory insufficiency, depression, CAD, left ventricular failure

2. Deyo-Charlson Comorbidity Index (DCI): score between 0 and 33, as well as categorically (0, 1-2, 3-4, 5+) during 12 month pre-index period. See Appendix D for full explanation of DCI calculation.

3. Prescribing physician specialty: Physician prescribing index treatment / providing care is a Pulmonologist, Internal medicine, Family medicine/general practitioner, Cardiologist, Allergist/Immunologist, Non-physician, or other specialty[iv].

   Type of prescriber of index medication will be assigned using information from pharmacy and medical claims using the classifications listed above. Prescriber information is available through pharmacy claims in HIRE. In case of missing prescribing physician information, the medical claims will be utilized to assign a physician. Medical claims data will be assessed one month prior to index date for a COPD related visit. If there is more than one COPD related visit within one month, the order in which specialties are listed above will be used as a hierarchical order for assignment.

11.2 COPD related pre-index utilization and costs

11.2.1 COPD related utilization during 12 month pre-index period

The same measures captured for the post-index period will also be captured for the pre-index period. This includes: COPD respiratory medications (0 vs. 1+ for each); COPD related outpatient (0, 1, and 2+; and total number), ED (0, 1, and 2+; and total number), inpatient, (0, 1, and 2+; and total number) and ICU visits (0, 1, and 2+; and total number); lengths of stay for COPD related inpatient and ICU visits; COPD related procedures (0 vs. 1+ and total number). See sections 10.2.3 and 10.2.4 for complete definitions.

[iv] Other specialties include*: Anesthesiologist/pain management, dermatology, emergency medicine, endocrinology/metabolism, gastroenterology, geriatrics, hematology, infectious disease, nephrology, neurology, nuclear medicine, obstetrics/gynecology, oncology, ophthalmology, otolaryngology, physical medicine/rehab, podiatry, psychiatry, radiology, rheumatology, surgery, urology*

11.2.2 COPD related and all-cause costs during 12 month pre-index period

Similar to the post-index costs in section 10.2.5, COPD related and all-cause costs will be captured for the 12 month pre-index period. All costs will be adjusted to year 2014 based on U.S. medical care services consumer price index (CPI) from Bureau of Labor Statistics.(20) Plan paid costs, patient paid costs, and total costs (plan paid + patient paid) will be reported for the following places of service:

- Inpatient hospitalizations
- ED visits
- Outpatient visits
- Skilled nursing facility
- Medication prescriptions

12. DATA MANAGEMENT

12.1 Confidentiality of study data

Safeguards to Patient Confidentiality

HealthCore is committed to conducting health outcomes research in compliance with state and federal laws and regulations related to the privacy and security of individually identifiable health information, such as the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule). This compliance is achieved with contractual, structural and procedural protections.

Contractual Protections

In all cases, HealthCore will either have standing agreements in place with health plans and other covered entities that maintain or create patient data or will enter into agreements with the covered entities for the duration of the research study.

In order to carry out research with this patient level information, HealthCore will, in those cases where study design allows for patient authorization, obtain patient authorization for use of their personal health information in the research study. If the study design is not amenable to obtaining patient authorization, HealthCore will submit the proposed research to an Institutional Review Board (IRB) for a waiver of patient authorization approval. Individually identifiable patient information will not be accessed by HealthCore until the IRB has approved the research and waived the need for patient authorization.

For study designs that do not require direct patient identification (applicable to this study), Limited Data Sets as defined by the Privacy Rule will be used. To the extent applicable, a Data Use Agreement will be implemented with the covered entity that is disclosing the patient data.

HealthCore contracts with its vendors and sub-agents obligating them to adhere to appropriate privacy and security conduct.

Structural Protections

HealthCore's computer networks have been designed to separate patient identified data from de-identified or masked data. Network security, firewalls, and password permissions control which HealthCore personnel have access to patient identifiers. Unless the study protocol calls for patient authorization or a waiver of authorization as granted by an IRB, no research analyst will have access to patient identifiers within HealthCore's computer systems. All research analysis databases have been de-identified.

HealthCore's data coordination center (DCC) is also physically secured by a controlled access facility, with only authorized personnel having access to network servers, tape libraries and other media that contains patient identifiers.

Procedures and Policies

Research analysis files used by HealthCore do not contain patient identifiers unless necessary to perform such research; if such is the case, access will be made after receipt of the patient's authorization or IRB waiver of such authorization has been granted. It is also HealthCore policy to provide for secure storage of study materials, including data, reports, and other files after the study is completed, with a destroy date assigned based on study requirements.

HealthCore reviews data requirements for each study to assure that only the minimum of patient information is obtained to answer the research question(s). For those studies where direct patient identifiers are needed for additional data collection such as medical chart abstracts, access to information will be limited to the greatest possible extent within the research team. Both structural and contractual safeguards reinforce policies to minimize the risk of breaching patient privacy. The structural safeguards include a clearly defined data flow process. This process minimizes the risk of individual identifiers being improperly used or disclosed. The contractual safeguards include contractual binding to confidentiality of individuals involved in the research.

12.2 Data storage and retention

HealthCore maintains a close working relationship with each health plan that provides access to claims data. In this way, HealthCore gains knowledge and documentation on the variety of databases that a health plan generates in the process of adjudicating health claims. By maintaining this working relationship, HealthCore is assured of being informed of changes and updates to data files as they occur.

HealthCore receives a full cut of data from most of its health plans, rather than project specific data extracts. This is more efficient, giving HealthCore control over the early definition of data extracts. Initial data files received from health plans go through the same subsequent analysis and refinement once the data is within the HealthCore Data Center.

The first consideration when working with administrative claims data is to ascertain the portion of a health plan's population for which data are available. For example, a plan may have traditional fee-based benefit plans as well as preferred provider (PPO)/ prospective payment system (PPS) or health maintenance organization (HMO) products. Each health plan product line will have differing levels of benefits and access. Generally, HealthCore looks for those product lines where coverage is available for both medical and pharmacy services. In those cases where HealthCore receives a full cut of data, HealthCore obtains from the health plan the methods, coding and values that will define the health plan lines of business and products that should be included in the analytic file.

12.3 Quality control and management procedures

Once the line of business and products are defined and selected, HealthCore reviews the data for having the appropriate claim lines. Denied claims or rejected claims are deleted from the analytic file. This helps assure that the analytic file only reflects the true direct medical costs related to the delivery of health care. Duplicate claims or unqualified services are also not included. This review also includes the roll-up or aggregation of adjusted claims. As a claim line goes through an adjustment process, claim systems generally will generate duplicate claim lines that allow the health plan to track the various steps of reprocessing. As health outcomes researchers, HealthCore wants only the final adjudication and payment to be reflected in the analytic file.

The final step after selecting the appropriate lines of business/products, and helping to ensure the appropriate claim lines are captured, is to review the values within individual data elements for accuracy and consistency. This is done at the individual file level such as pharmacy, hospital, medical, and eligibility as well as checking for consistency across these various file types. For example, dates of service are examined to help ensure that each claim line has valid values for dates. Frequency distributions on values for a particular data element are run to check for normalcy and outlier values. When skewed data or outliers are found, they are handled per the requirements of the data analysis protocols and plan. After all files are examined for valid values, HealthCore then reviews and converts data fields if necessary so that all files have consistent formats for common data elements. Particular care is taken with any fields, like dates, subscriber and patient ID's and other fields that are analyzed across integrated data files.

For individual study database and analytic datasets, the HealthCore Data Center incorporates standard definitions, and processing so that each health outcomes researcher has standardized data to work with. Processes to integrate data across types of claims and across health plans are

done in a predefined manner. Definitions of derived data are provided and pre-coded for the researcher.

13. STATISTICAL METHODS AND SAMPLE SIZE

13.1 Propensity score matching

The adherent and non-adherent cohorts are not randomly assigned, which may lead to comparisons between cohorts being confounded by selection bias. To reduce the selection bias, propensity score matching will be used to adjust for measured confounders during pre-index, and create more comparable adherent and non-adherent cohorts.(22-24) The propensity score for each individual will be estimated as the probability of being adherent to the index ICS/LABA combination therapy conditional on observed baseline characteristics. Logistic regression will be used to calculate the scores. The outcome variable in the model is dichotomous, indicating whether a patient was adherent to the index ICS/LABA combination therapy (1) or non-adherent (0).

The goal of the matching algorithm is to have similar distribution of patients in each cohort for the variables listed below. To assess that the groups have similar distributions for each of the variables below, unadjusted bivariate tests (test noted in parentheses after each variable) will be conducted where a p-value >0.05 will be considered well balanced between groups:

Variables that must be balanced:

1. Number of COPD related inpatient hospitalizations during pre-index period, hospitalizations with a primary diagnosis of COPD (mean) (GLM w/ negative binomial distribution and log link)

2. Number of COPD related ED visits during pre-index period, ED visits with any diagnosis of COPD (mean) (GLM w/ negative binomial distribution and log link)

3. Number of OCS fills during pre-index period (mean) (GLM w/ negative binomial distribution and log link)

4. Number of fills for antibiotics during pre-index period (mean) (GLM w/ negative binomial distribution and log link)

5. Number of SABA fills during pre-index period (mean) (GLM w/ negative binomial distribution and log link)

6. Number of SAMA fills during pre-index period (mean) (GLM w/ negative binomial distribution and log link)

7. Number of SABA/SAMA fixed dose combination fills during pre-index period (mean) (GLM w/ negative binomial distribution and log link)

8. Number of LABA fills during pre-index period (mean) (GLM w/ negative binomial distribution and log link)

9. Number of LAMA fills during pre-index period (mean) (GLM w/ negative binomial distribution and log link)

10. Age at index, years (mean) (t-test)

11. Gender (chi-square test)

12. Asthma, ≥1 diagnosis during pre-index period (yes vs. no) (chi-square test)

Additional variables to be balanced, sample size permitting:

13. Index month (chi-square test)

14. Index medication prescribed by a pulmonologist (y/n) (chi-square test)

15. Pre-index hospital admissions (cardiovascular [any inpatient hospitalization with a procedure or diagnosis code in 0], pneumonia [see Appendix C for codes] and asthma-related [see Appendix C for codes]; 0 vs. 1+ for each) (chi-square tests)

16. Long-term use of oxygen therapy (0 vs. 1+), Patients are considered to have long term oxygen therapy of they have consecutive medical claims (subsequent claim is within 30 days of previous claim) with any CPT/HCPCS codes for oxygen use for ≥ 3 months. [See 0)] (chi-square test)

17. Comorbid conditions: pneumonia, pulmonary hypertension, chronic respiratory failure, anxiety, depression and/or use of psychotropic drugs [see Appendix J for medication codes], coronary artery disease, left ventricular failure, diabetes, heart failure, hypertension, stroke [see Appendix C for diagnosis codes] (y/n for each) (chi-square tests)

18. Influenza vaccination (y/n) [Appendix I] (chi-square test)

19. Pneumococcal vaccination (y/n) [Appendix I] (chi-square test)

20. Total inpatient hospitalization length of stay > 5 days during the pre-index period (y/n) (chi-square test)

21. Pre-index use of COPD medications (ICS, LAMA, LABA, roflumilast, Theophylline, SABA, SAMA, LTRA, and omalizumab, 0, 1, 2+) [Appendix E, Table 1] (chi-square test)

22. Any pre-index OCS use (0, 1, 2+) [Appendix E, Table 1] (chi-square test)

23. Any pre-index antibiotic use (0, 1, 2+) [See Appendix E, Table 2] (chi-square test)

24. Cardiovascular medications (0, 1, 2+) [See Appendix K] (chi-square test)

The propensity scores will be used to match a patient from the non-adherent cohort to a patient in the adherent cohort using a Greedy nearest neighbor 1-to-1 matching technique without replacement. The analysis of COPD exacerbations and all other outcomes will be performed on the matched sample of adherent and non-adherent patients. Treatment cohorts will be considered well balanced for a given variable if the difference between groups is having $p>0.05$. Any of the variables from #13-24 above not balanced after propensity score matching will be included as covariates in the multivariate analysis of post-index outcomes.

The success of the propensity score model will be judged by whether balance was achieved between two cohorts on the covariates listed above, regardless of what variables are included in the final propensity model.

Before the matching algorithm is performed, the two cohorts will be separated into their own datasets and sorted by propensity scores obtained from the logistic model (low to high). This is done so that matching can be replicated in the future as long as the data is sorted the same way prior to initiating the algorithm. The patient with the lowest propensity score in the adherent cohort will be selected to find a matching patient in the non-adherent cohort. Using estimated propensity scores, the adherent cohort patient will be matched with a patient in the non-adherent cohort who has a similar predicted probability using the Greedy nearest neighbor 1:1 matching technique (with no replacement).(24) First, the algorithm will run to find matches with differences in propensity scores of less than 10^{-7}, and then it will run for the remaining subjects to find matches with differences less than 10^{-6}. This pattern will continue up to 10^{-1}, after which no further matches will be made. After the first adherent patient is either matched or not matched with a patient from the non-adherent cohort, the adherent patient with the next lowest propensity score will be selected to find a match, and so on. Random numbers will be assigned to all non-adherent patients (using random number generation with a specified seed of 52784), so that if two or more non-adherent patients have the same propensity score and are considered the best match for an adherent patient, the patient with the numerically lowest random number will be chosen as the match.

The model which provides balance between groups while providing the largest sample size will be chosen as the final model (i.e., minimal loss in sample due to unmatched patients; sample size

must be at least 1,500 per group after matching). See Section 13.3 for details of the sample size calculation.

After the best fitting propensity score model is determined, and the matched sample selected based on the propensity scores, the distribution of propensity scores in the treatment groups will be examined, and the subpopulation of unmatched patients will be described. Demographic and baseline characteristics will be summarized by treatment cohort for the unmatched patients.

13.2 Statistical evaluation – general aspects

Descriptive statistics will be presented and statistical analysis will be performed. Each table will contain the variables of interest reported by study cohorts. All results will be presented for the overall population and for each group:

1. Adherent
2. Non-adherent

Note: This study will adopt three different definitions of adherence based on PDC value. Therefore, the entire analysis will be replicated three times, once for each adherence definition.

Statistical testing (two-sided) will be done for comparisons between the propensity score matched non-adherent and adherent cohorts with non-adherent cohort as the reference group. For all variables, 95% confidence intervals will be presented. The magnitude of point estimates and the width of confidence intervals will be used primarily to interpret results. We will be reporting nominal p-values, will not adjust for multiplicity, and $p<0.05$ will be considered statistically significant.

Covariates in the multivariate models will include:

- Post-index follow-up time, to adjust for differences in length of observation
- All pre-index and index variables defined previously that are not balanced/significantly different ($p<0.05$) between treatment cohorts
- Analogous pre-index variable (regardless of p-value): For each post-index outcome, the analogous pre-index variable will be controlled for (e.g., when analyzing the number of COPD related hospitalizations in the post-index, the model will control for the number of pre-index COPD related hospitalizations).

13.2.1 Statistical model for the primary outcome:

A GLM model using negative binomial and a log link function will be used to model the number of exacerbations. If there is any imbalance in any of the variables listed in Section 13.1, the GLM model will adjust for covariates using the covariate selection methodology explained in the previous paragraph. A 95% confidence interval will be provided with the rate ratio (relative risk)

along with a corresponding p-value. A confidence interval that does not include 1.0 will be considered statistically significant ($p<0.05$), though the magnitude of the point estimate (i.e., relative risk) and width of the confidence interval will be primarily used for interpretation of results.

Exacerbation rates will also be graphically represented via bar/column graphs to visually represent the differences between groups. The distribution of exacerbations within each cohort will also be examined via bar charts (i.e., showing the number of patients with 0, 1, 2, 3, etc. exacerbations).

13.2.2 Statistical models to be used for secondary outcomes

Sensitivity analyses for the primary outcome

1. Using all follow-up (i.e., ≥12 months)

   The analysis will be performed in the same manner as the primary outcome (exacerbation rate analyzed via GLM with negative binomial distribution and log link), except that the entire patient history will be used and patients will be censored at the time they discontinue or switch therapy, are lost to follow-up, or the end of the study period.

2. Severe exacerbation rate (i.e. inpatient hospitalizations and ED-visits)

   The analysis will be performed in the same manner as the primary outcome (exacerbation rate analyzed via GLM with negative binomial distribution and log link) for severe COPD exacerbation events, which only include the following 2 end points: 1) inpatient hospitalization with a primary diagnosis of COPD; or 2) an ED visit with a COPD diagnosis.

3. Starting follow-up on day 31

   The analysis will be performed in the same manner as the primary outcome (exacerbation rate analyzed via GLM with negative binomial distribution and log link), except that observation period for COPD exacerbation events will start from day 31 following the treatment imitation.

Additional secondary objectives related to the primary outcome

1. Individual exacerbation outcomes:

   The same analysis for the primary outcome (exacerbation rate analyzed via GLM with negative binomial distribution and log link) will be performed to examine each of the following COPD exacerbation events, separately: 1) inpatient hospitalization with a primary diagnosis of COPD, 2) ED visit with a diagnosis at any position for COPD, and 3) a fill for OCS and/or antibiotics on the same day as or within 10 days after an outpatient visit with a diagnosis for COPD.

2. Time to first event

Outcome is the time to first COPD exacerbation event. Patients will be followed until their first event, switching ICS/LABA therapy (censored) or the end of the observation period (censored), whichever came first. A Cox proportional hazards model will be used, adjusting for covariates, to calculate the hazard ratio and its 95% confidence interval along with a corresponding p-value. Kaplan-Meier curves will be produced.

Other secondary outcomes

Models and the descriptive statistics to be reported differ by outcome type. All statistical models will adjust for covariates as described in the beginning of Section 13.2.

1. Categorical and dichotomous data: n(%), odds ratio, 95% CI, differences between cohorts analyzed using logistic regression or ordinal logistic regression

    - Logistic regression will be used for medication use (0 vs. 1+ fill for each medication/medication class of interest). Models for the post-index medication use of interest (e.g., 0 vs. 1 post-index outpatient visit) will control for the analogous pre-index variable (e.g., 0 vs. 1 pre-index medication use) as a covariate.

    - Ordinal logistic regression will be applied for COPD related healthcare resource use (0, 1, and 2+). Models for the post-index COPD related healthcare resource use of interest will control for the analogous pre-index variable as a covariate.

2. Continuous and count data: mean, median, SD, 95% CI, 75^{th}/95^{th} percentiles (for costs)

    - Healthcare cost variables during post-index period – differences in costs between cohorts will be analyzed using gamma regression with log-link function. To account for baseline differences in pre-index costs post-index cost models will control for the analogous pre-index cost (log-transformed to normalize) as a covariate.

    - Number of visits (outpatient, ER, inpatient), medication fills, and length of stays – differences between cohorts analyzed using negative binomial regression with log-link function (determined after performing goodness of fit tests). Models for the post-index resource use of interest (e.g., number of post-index COPD related outpatient visit) will control for the analogous pre-index variable (e.g., number of pre-index COPD related outpatient visit) as a covariate.

    - Continuity of care– differences between cohorts analyzed using Gaussian (i.e., normal) regression

13.2.3 Pre-index analyses

Bivariate analysis, unadjusted for covariates, will be performed for the following baseline variables to make sure the comparable cohorts balanced via the propensity matching technique.

Point estimates, 95% confidence intervals, and p-values will be reported alongside descriptive statistics (frequency/% or mean/sd/median):

- Patient baseline demographics and characteristics: age, gender, health plan type, index year, geographic region, prescribing physician type, and comorbid conditions. Chi-square analysis will be used for categorical/dichotomous variables. T-test will be used for age as a continuous variable.

- COPD related and all-cause healthcare utilization/cost variables during the 12 month pre-index period. The negative binomial and gamma regression models described for the post-index health care resource utilization and cost models above will also be used for the pre-index variables.

13.2.4 Subgroup analysis

The analysis of comparing the primary outcome described above between adherent and non-adherent patients will be duplicated within the following six subgroups for each adherence definition. Descriptive analysis of baseline demographics (age, gender, health plan type, and geographic region) and comorbid conditions will be reported.

***Note**: when creating subgroups matching/covariate balance attained via propensity score matching may be lost.*

1. Subgroup 1: Patients with comorbid asthma
2. Subgroup 2: Patients with frequent exacerbations: those with a history of 2 or more exacerbations during the pre-index period
3. Subgroup 3: Patients with 1 or more exacerbations during the pre-index period
4. Subgroup 4: Patients with no exacerbations during the pre-index period
5. Subgroup 5: Patients with cardiovascular comorbidities
6. Subgroup 6: Patients with a Deyo-Charlson Comorbidity Index score $\geq$ the 75th percentile
7. Subgroup 7: Patients with add-on LAMA therapy (triple therapy) during the follow-up period

13.3 Sample size

This retrospective observational study will include all patients meeting inclusion/exclusion criteria. After matching is successfully completed to balance all pre-specified covariates, the matched patients will constitute the analytic population.

Based on prior research the number of eligible patients is expected to be approximately 17,000. Of those, 1900 are expected to be considered adherent based on a PDC ≥0.80. Most of the adherent patients are expected to be matched to each of the three definitions of non-adherence, due to the adherent sample size being smaller than any of the non-adherent definitions.

Subgroup analysis sample sizes are estimated based on prior research and are as follows:

Group	**N per comparison group (adherent and non-adherent)**
Total sample	1800
Subgroup 1: Prior asthma diagnosis	642
Subgroup 2: 2+ prior exacerbations	540
Subgroup 3: 1+ prior exacerbations	1098
Subgroup 4: No prior exacerbation	702
Subgroup 5: Cardiovascular comorbidities	1260
Subgroup 6: DCI ≥75th percentile	450
Subgroup 7: Triple therapy	450

14. STRENGTHS AND LIMITATIONS

Strengths

1. Using claims data from a commercially insured population across the nation allows access to a large number of patients with geographic diversity.

2. The retrospective nature allows looking both backwards and forwards from a given point in time (the index date) without having to actively follow patients over time as would be done in a prospective study.

3. Inpatient hospitalization claims in the HIRE distinguish between the primary diagnosis and all other diagnoses. This makes it possible to identify hospitalizations that were primarily due to COPD.

4. At least 12 months continuous follow-up in this retrospective study enables researchers to determine treatment adherence for the medication of interest.

5. Data can be generalized to the commercially insured US population.

Limitations

1. Administrative claims data from commercially insured population cannot be generalized to the general US population of COPD patients, particularly the 65+ Medicare population is under represented in the commercially insured population and Medicaid patients are not included.

2. The administrative claims data are primarily collected for billing and reimbursement purpose, and in general are subject to potential coding errors and inconsistencies and may be affected by the absence of clinical data.

3. Clinical measures of COPD disease severity, such as spirometry results, are not available in the claims data.

4. Using claims data from a commercially insured population may over-diagnose some conditions and under-diagnose others. COPD related utilization is based on having a claim for COPD, which can either overestimate or underestimate actual utilization for COPD for any given patient or population.

5. Prescription claim date is the date a medication is filled, not necessarily the date a patient begins treatment, though this date is assumed to be the beginning of the treatment. Furthermore, the study does not have data to indicate how patients took their medication.

6. Inpatient administered pharmacy medications are not present in the claims data

7. It is not possible to determine the primary reason for outpatient visits including ED visits via claims data. Although a COPD diagnosis code is present, these visits may be due to routine follow-up or non-COPD related reasons, and not necessarily due to a COPD exacerbation.

8. Mortality will not be assessed because, as per inclusion criteria, every patient in the study must be continuously enrolled for the entire 12-month follow-up period. However, the lack of cause of death is a limitation of the long follow-up sensitivity analysis.

9. Exacerbation rates could be underestimated as we are not capturing events through prescription dispensing via telephone (in the absence of an office visit)

10. The statistical models are not adjusting for multiplicity. The rate of false positives may be inflated and thus the conclusion for the effectiveness in the secondary outcomes as well as subgroup/sensitivity analyses may be unsustainable.

15. ETHICAL CONSIDERATION

See section 12.1 for data confidentiality and patient privacy protections.

The study will adhere to AstraZeneca's Standard Operating Procedures for Non-Interventional Studies.

16. ADVERSE EVENT REPORTING

Not applicable. All data is captured retrospectively.

17. CHANGES TO THE PROTOCOL

Study procedures will not be changed without the mutual agreement of the Study Investigators and AstraZeneca.

Any amendments, new versions, or administrative changes must be approved by the study investigators and AstraZeneca.

18. REFERENCES

Reference List

(1) American Lung Association. COPD fact sheet. 2011. http://www.lung.org/lung-disease/copd/resources/facts-figures/COPD-Fact-Sheet.html . 2013. 6-20-2013.
Ref Type: Electronic Citation

(2) What is COPD? National Heart Lung and Blood Institute; U.S.Department of Health & Human Services. http://www.nhlbi.nih.gov/health/health-topics/topics/copd/ . 2013. 6-20-2013.
Ref Type: Electronic Citation

(3) Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. MMWR Surveill Summ 2002; 51(6):1-16.

(4) Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187(4):347-365.

(5) Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD, 2015. Accessed at: http://www.goldcopd.org . 2015. 2-18-2015.
Ref Type: Electronic Citation

(6) SYMBICORT Prescribing Information, AstraZeneca. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021929s021lbl.pdf . 2010. 6-20-2013.
Ref Type: Electronic Citation

(7) ADVAIR DISKUS Prescribing Information, GlaxoSmithKline. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021077s042lbl.pdf . 2010. 6-20-2013.
Ref Type: Electronic Citation

(8) BREO Prescribing Information, GlaxoSmithKline. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204275s000lbl.pdf . 2013.
Ref Type: Electronic Citation

(9) Dong YH, Lin HH, Shau WY, Wu YC, Chang CH, Lai MS. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. Thorax 2013; 68(1):48-56.

(10) Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. Cochrane Database Syst Rev 2014; 3:CD010844.

(11) Restrepo RD, Alvarez MT, Wittnebel LD, Sorenson H, Wettstein R, Vines DL et al. Medication adherence issues in patients treated for COPD. Int J Chron Obstruct Pulmon Dis 2008; 3(3):371-384.

(12) Blais L, Forget A, Ramachandran S. Relative effectiveness of budesonide/formoterol and fluticasone propionate/salmeterol in a 1-year, population-based, matched cohort study of patients with chronic obstructive pulmonary disease (COPD): Effect on COPD-related exacerbations, emergency department visits and hospitalizations, medication utilization, and treatment adherence. Clin Ther 2010; 32(7):1320-1328.

(13) Janson C, Larsson K, Lisspers KH, Stallberg B, Stratelis G, Goike H et al. Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting beta2 agonist: observational matched cohort study (PATHOS). BMJ 2013; 346:f3306.

(14) Larsson K, Janson C, Lisspers K, Jorgensen L, Stratelis G, Telg G et al. Combination of budesonide/formoterol more effective than fluticasone/salmeterol in preventing exacerbations in chronic obstructive pulmonary disease: the PATHOS study. J Intern Med 2013; 273(6):584-594.

(15) Roberts M, Mapel D, Petersen H, Blanchette C, Ramachandran S. Comparative effectiveness of budesonide/formoterol and fluticasone/salmeterol for COPD management. J Med Econ 2011; 14(6):769-776.

(16) Bourbeau J, Bartlett SJ. Patient adherence in COPD. Thorax 2008; 63(9):831-838.

(17) Sanduzzi A, Balbo P, Candoli P, Catapano GA, Contini P, Mattei A et al. COPD: adherence to therapy. Multidiscip Respir Med 2014; 9(1):60.

(18) Setoguchi S, Solomon DH, Glynn RJ, Cook EF, Levin R, Schneeweiss S. Agreement of diagnosis and its date for hematologic malignancies and solid tumors between medicare claims and cancer registry data. Cancer Causes Control 2007; 18(5):561-569.

(19) Dalal AA, Roberts MH, Petersen HV, Blanchette CM, Mapel DW. Comparative cost-effectiveness of a fluticasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2011; 6:13-22.

(20) Bureau of Labor Statistics. Series CUUR0000SAM2. http://www.bls.gov/cpi/home.htm . 2013. 6-20-2013.
Ref Type: Electronic Citation

(21) Bice TW, Boxerman SB. A quantitative measure of continuity of care. Med Care 1977; 15(4):347-349.

(22) Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Stat Med 2008; 27(12):2037-2049.

(23) Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. Am J Epidemiol 2010; 172(9):1092-1097.

(24) Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques; In SAS SUGI 26, 2001, Paper 214-226. http://www2.sas.com/proceedings/sugi26/p214-26.pdf [SUGI 26], 214-226. 2001. SAS. 6-20-2013.

Ref Type: Electronic Citation

Appendix A ICS/LABA medications

Table 1: Study medications

Name of Medication	GPI
Budesonide+formoterol (BFC, Symbicort®) – 160/4.5 strength	44209902413240
Fluticasone+salmeterol (FSC, Advair®) – 250/50 strength	44209902708030

Table 2: Other ICS/LABA medication (used for clean period identification and post-index switching)

Name of Medication	GPI
Other ICS/LABA therapy	
Budesonide+formoterol (BFC, Symbicort®), other strength	44209902413220
Fluticasone+salmeterol (FSC, Advair®), other strength/form	442099027032, 44209902708020, 44209902708040
Mometasone furoate+ formoterol (MFC, Dulera®)	4420990290
Fluticasone furoate + vilanterol (Breo Ellipta®)	4420990275

Appendix B COPD Patient Identification Codes

Disease Diagnosis	ICD-9 dx code
COPD	491.xx, 492.xx, 496.xx

Appendix C Comorbidities

Comorbidity	ICD-9 Dx Code
Insomnia	327.0x, 307.41, 307.42, 780.51, 780.52
Allergic rhinitis	477.xx
Sinusitis	461.xx, 473.xx
GERD	530.81
Anxiety	300.0x
Major depressive disorder	296.2x, 296.3x
Other depression	300.4x, 311.xx, 309.0x, 309.1x, 296.90
Obesity[1]	278.00, 278.01, V85.3x,V85.4x, 278.02 V85.2x
Asthma	493.xx
Sleep apnea	327.2x, 780.51, 780.53, 780.57
Pneumonia	480.xx-486.xx, 997.31
Bronchiectasis	494.xx
Cystic fibrosis	277.0x
Coal worker pneumoconiosis	500.xx
Asbestosis	501.xx
Pneumoconiosis due to other silica	502.xx
Pneumoconiosis due to inorganic dust	503.xx
Pneumoconiosis due to inhalation of other dust	504.xx
Pneumoconiosis unspecified	505.xx
Respiratory conditions due to chemical fumes and vapors or other unspecified external agents	506.xx, 508.xx
Post-inflammatory pulmonary fibrosis	515.xx
Other alveolar and parietoalveolar pneumonopathy	516.xx
Lung involvement in conditions classified elsewhere	517.xx
Other diseases of lung	518.xx
Chronic respiratory failure	518.83, 518.84
Extrinsic allergic alveolitis	495.xx
Tuberculosis	010.xx - 018.xx
Lipoid pneumonia	507.1x
Detergent asthma	507.8x
Osteoporosis	733.0x
Diabetes mellitus	250.xx
Dyslipidemia	272.xx

Hyperglycemia	790.29
Hypertension	401.xx-405.xx
Pulmonary hypertension	416.0x, 416.8x
Congestive heart failure	402.x1, 404.x1, 404.x3, 428.xx
Left ventricular heart failure	428.1x
Pulmonary hypertension	416.0x, 416.8x
Peripheral vascular disease / atherosclerosis	440.xx, 443.9x
Coronary artery disease	410.xx-414.xx, 429.2x
Myocardial infarction	410.xx, 412.xx
Unstable Angina	411.1x
Other coronary artery disease	411.0x, 411.8x, 413.xx, 414.xx, 429.2x
Stroke	430.xx, 431.xx, 433.x1, 434.x1
TIA and other cerebrovascular disease [does not include stroke]	432.xx, 433.x0, 434.x0, 435.xx, 436.xx, 437.xx, 438.xx, V12.54

1: Obesity includes diagnoses for Overweight, Obesity, and Morbid Obesity

Appendix D Deyo-Charlson Comorbidity Index Calculation

The table below outlines the Deyo-Charlson comorbidity index. To quantify comorbidity, the Deyo-Charlson comorbidity score is computed by adding the weights that are assigned to the specific diagnoses. A score of 1 is attributed to myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, and diabetes mild to moderate. The following diseases are scored as 2: hemiplegia or paraplegia, moderate or severe renal disease, diabetes and complications and malignancy including leukemia and lymphoma. Moderate or severe liver disease is scored 3. Finally, a score of 6 is assigned to metastatic solid tumor and AIDS.

Each diagnosis is only counted once (e.g. if a patient has ICD-9 code 410.xx and 412.xx, they will receive a score of 1 for MI, not 2). The minimum possible score is 0 and the maximum possible score is 33.

Comorbidity	ICD-9 Codes	Deyo-Charlson Weight
Myocardial Infarction	410.xx, 412.xx	1
Congestive Heart Failure	428.xx	
Peripheral Vascular Disease	441.x, 443.9x, 785.4x, V43.4x, 38.48(P)	
Cerebrovascular Disease	430.xx-437.xx, 438.xx	
Dementia	290.xx	
Chronic Obstructive Pulmonary Disease	490.xx-496.xx, 500.xx-505.xx, 506.4x	
Rheumatologic Disease	710.0x-710.1x, 710.4x, 714.0x-714.2x, 714.81, 725.xx	
Peptic Ulcer Disease	531.4x-531.7x, 532.4x-532.7x, 533.4x-533.7x, 534.4x-534.7x, 531.0x-531.3x, 532.0x-532.3x, 533.0x-533.3x, 534.0x-534.3x, 531.9x, 532.9x, 533.9x, 534.9x	
Mild Liver Disease	571.2x, 571.4x, 571.5x, 571.6x	
Diabetes mild to moderate	250.0x-250.3x, 250.7x	
Hemiplegia or Paraplegia	342.xx, 344.1x	2
Moderate or Severe Renal Disease	582.xx, 583.0x-583.7x, 585.xx, 586.xx, 588.xx	
Diabetes + Complications	250.4x-250.6x	
Malignancy	140.xx-172.xx, 174.xx-195.xx, 200.xx-208.xx	
Moderate to Severe Liver Disease	572.2x-572.8x, 456.0x-456.2x	3
Metastatic Solid Tumor	196.xx-199.xx	6
AIDS	042.xx-044.xx	

Adapted from W. D'Hoore[21], ME Charlson[22], RA Deyo[23]

Appendix E COPD medication codes

Table 1: Respiratory Medications

COPD Med	GPI code
Inhaled corticosteroids (ICS)	
All ICS	**4440**
Beclomethasone	44400010
Budesonide	44400015
Ciclesonide	44400017
Dexamethasone	44400020
Flunisolide	44400030
Fluticasone (propionate (Flovent) and furoate (Arnuity Ellipta))	44400033
Mometasone	44400036
Triamcinolone	44400040
Long acting muscarinic antagonists (LAMA)	
Aclidinium Bromide (Tudorza®)	44100007
Tiotropium Bromide (Spiriva®)	44100080
Umeclidinium Bromide (Incruse Ellipta®)	44100090
Long acting beta-2 adrenergic agonist (LABA)	
Inhaled LABAs	
Salmeterol	44201058 (all non-nebulized)
Formoterol	44201027 Nebulized: 44201027102520 Non-nebulized: 44201027100120
Clenbuterol	44201022 (all non-nebulized)
Indacaterol	44201042 (all non-nebulized)
Arformoterol	44201012 (all ARE nebulized)
Olodaterol	44201052 (all non-nebulized)
Oral LABAs (all are non-nebulized)	
Vospire	44201010107410 44201010107420
Volmax	44201010100480 44201010107470 44201010107480
Proventil CR	44201010100410
LAMA/LABA combination	
Umeclidinium-Vilanterol (Anoro Ellipta®)	4420990295

PDE4 inhibitor	
Roflumilast	44450065000320
Methylxanthine	
Theophylline	4430004000, 4430004001, 4499100240, 4499100242, 4499100250, 4499300322, 4499320440, 4499900305
Short acting beta-2 adrenergic agonist (SABA)	
Albuterol	44201010 (Exclude controlled release formulations 442010101004, 442010101074 these are in LABA) Nebulized: 44201010102100, 442010101025 Non-nebulized: all others
Bitolterol	44201020 Nebulized: 44201020102520 Non-nebulized: 44201020103405
Levalbuterol	44201045 Nebulized: 442010451025 Non-nebulized: 44201045503220
Metaproterenol	44201050 Nebulized: 442010502025 Non-nebulized: all others
Pirbuterol	44201055 (all forms are NON-nebulized)
Terbutaline	44201060 (all forms are NON-nebulized)
Short acting muscarinic antagonists (SAMA)	
Ipratropium	44100030 Nebulized: 441000301020 Non-nebulized: all others
SABA/SAMA combination	
Albuterol/ipratropium (nebulizer)	442099020120
Albuterol/ipratropium (inhalation) [includes Combivent and Combivent Respimat]	442099020132, 442099020134
Oral corticosteroids (OCS)	
Prednisone	22100045000305, 22100045000310, 22100045000315, 22100045000320, 22100045000325, 22100045000330, 22100045000335, 22100045001205, 22100045001310, 22100045002005, 22100045002010, 22100045002015, 22100045006405, 22100045006410

Prednisolone	22100040000305, 22100040001203, 22100040001205, 22100040006420, 22100040200910, 22100040202020, 22100040202040, 22100040202060, 22100040207215, 22100040207220, 22100040207240
Methylprednisolone	22100030000305, 22100030000310, 22100030000315, 22100030000320, 22100030000325, 22100030000330, 22100030006405, 22100030006410
Hydrocortisone	22100025000303, 22100025000305, 22100025000310, 22100025201810
Dexamethasone	22100020000310, 22100020000315, 22100020000320, 22100020000325, 22100020000330, 22100020000335, 22100020000340, 22100020000345, 22100020001005, 22100020001320, 22100020002005, 22100020002010, 22100020006400, 22100020006420
Betamethasone	22100010000305, 22100010002010
Cortisone Acetate	22100015100303, 22100015100305, 22100015100310
Triamcinolone	22100050000305, 22100050000310, 22100050000315, 22100050000320, 22100050006405, 22100050201203, 22100050201205
Leukotriene receptor antagonist (LTRA)	
All LTRAs	**4450**
Zileuton	44504085
Montelukast	44505050
Zafirlukast	44505080
Monoclonal antibody	
Omalizumab (Xolair)	44603060

Table 2: Antibiotics

Antibiotics	GPI code (first 2 digits)
Penicillins	01
Cephalosporins	02

Macrolides	03
Tetracyclines	04
Fluoroquinolones	05
Aminoglycosides	07
Sulfonamides	08
Other anti-infectives	1600 - 1629, 1699

Appendix F ICU Codes

Intensive Care (ICU)	**Revenue Code**
General classification	200
Surgical	201
Medical	202
Pediatric	203
Psychiatric	204
Burn care	207
Trauma	208
Coronary Care (CCU) **Considered part of ICU**	**Revenue Code**
General classification	210
Myocardial infarction	211
Pulmonary care	212
Heart transplant	213
Intermediate CCU	214
Other coronary care	219

Appendix G Respiratory procedures

Procedure	ICD-9 procedure	CPT code	HCPCS code
X-ray of chest	87.39, 87.44, 87.49	71010-71035	
CT of chest	87.41, 87.42	71250-71275	
Pulmonary function tests (e.g., spirometry)		94010-94799	
Pulse or ear oximetry		94760-94762	
Pulmonary stress testing (e.g., 6-minute walk test)		94620	
Pulmonary rehabilitation session		G0424, S9473	
In-home oxygen use		E0424, E0430-E0444	
Mechanical ventilation		94002, 94003	
Oxygen use	V46.2	4030F	E0424-E0444, E1390-E1392, K0738, S8120, S8121
Long term oxygen therapy	Patients are considered to have long term oxygen therapy of they have consecutive medical claims (subsequent claim is within 30 days of previous claim) with any CPT/HCPCS codes for oxygen use for ≥ 3 months.		

Appendix H Cardiovascular conditions

Established CVD Events	ICD-9-CM Codes	ICD-9 proc (in the list)	CPT (in the list)	HCPCS
Myocardial infarction	410.xx, 412.xx			
Stroke	430.xx, 431.xx, 433.x1, 434.xx (excl. 434.x0)			
TIA and other cerebrovascular disease (including prior disease) [does not include stroke]	432.xx, 433.x0, 434.x0, 435.xx, 437.xx, 438.xx, V12.54			
Unstable angina	411.1x			
Angina pectoris	413.xx			
Congestive heart failure	402.x1, 404.x1, 404.x3, 428.xx			
Peripheral vascular disease	440.xx, 443.9x	38.13, 38.18, 39.25, 39.26, 39.29, 39.50, 39.90	34101 - 34111, 34201 - 34203, 35311 - 35381, 35454 - 35456, 35459, 35470, 35473 - 35474, 35482 - 35485, 35492 - 35495, 35533, 35541 - 35571, 35641, 35646, 35654, 75962 - 75964, 75992 - 75993, 93668	
Other coronary heart disease	411.xx (excl. 411.1x), 414.xx, 441.xx,	36.01 - 36.09, 36.1, 36.2, 38.12,	33510 - 33516, 33517 - 33545, 33572, 35301, 35390, 92975, 92980 - 92981, 92982 - 92984, 92995 - 92996	
Revascularization (Percutaneous coronary intervention, PCI)				
Primary coronary angioplasty without stent		00.66, 36.09	92982, 92984, 92995, 92996	
Drug eluting stent (DES)		36.07		C1874, C1875
Bare metal stent (BMS)		36.06		C1876, C1877
Stent (unspecified type)*			92980, 92981	G0290, G0291
CABG		36.1x – 36.2x	33510-33516, 33517-33523, 33530, 33533-33536	S2205-S2209

Appendix I Vaccination codes

Vaccination	CPT code	GPI codes
Influenza vaccination	90470, 90653-90664, 90666-90668 HCPCS: G9142, G9141, Q2034-Q2039	17100020
Pneumococcal vaccination	90669, 90670, 90732	17200065

Appendix J Psychotropic medication codes

Drug class	GPI codes	CPT codes
Anti-anxiety	57	
Antidepressants	58	
Antipsychotic/Antimanic agents	59	J2794, J2358, J3486, J0400, J2426
Sedative/hypnotics	60	
Stimulants, Misc. ADHD	61	
Anticonvulsants	72	

Appendix K Cardiovascular Medications

Medication	GPI Codes	HCPCS Codes
Anti-platelet Medications GP IIb/IIIa inhibitors	8515 (excl. 85156010)	
Clopidogrel	85158020	
Ticlopidine	85150050, 85158080	
Cilostazol	85155516	
Dipyridamole	85150030, 85159902	J1245
Prasugrel	85158060	
Ticagrelor	85158470	
Vorapaxar	85155780	
Combo of Dipyridamole + Aspirin	85159902	
Abciximab	85153010	J0130
Eptifibatide	85153030	J1327
Tirofiban	85153060	J3246
Vitamin K anti-coagulants	8320	
Dicumarol	83200010	
Warfarin	83200030	
Heparins and heparin-like medications	8310	
Unfractionated heparin (Heparin)	83100020	J1642, J1644
Low molecular weight heparin (Enoxaparin, Tinzaparin, Dalteparin, Certoparin)	83101020, 83101080, 83101010, 83100030	J1650, J1655, J1645
Fondaparinux	83103030	J1652
Direct Factor Xa Inhibitors	8337	
Rivaroxaban	83370060	
Apixaban	83370010	
Fibrinolytic Drugs	8560	
Thrombolytics/Thrombin inhibitors (Streptokinase,Urokinase, Alteplase,Anistreplase,Reteplase,Tenecteplase, etc)	85600010, 85600020, 85601010, 85601020, 85601070, 85601075	J2995, J3364, J3365, J2997, J0350, J2993, J3101
Direct thrombin inhibitors	8333 (excl. 83334030)	
Argatroban, Lepirudin	83337015, 83334050	C9121,J1945
Bivalirudin	83334020	J0583
Dabigatran	83337030	
Anti-Dyslipidemic Medications		
Bile Acid Sequestrants	3910	
Fibric Acid Derivatives	3920	
Intestinal Cholesterol Absorption Inhibitors	3930	

Statins	3940	
Nicotinic Acid Derivatives	3945	
Other lipid lowering	3950,3999	
Anti-Hypertensive Medications		
ACEI	3610	
ARB	3615	
Direct Renin Inhibitors	3617	
Beta Blockers	3310	
Thiazide diuretics	3760	
Loop diuretic	3720	
Potassium Sparing Diuretics	3750	
Calcium channel blockers	3400	
Other anti-hypertensives	3620,3625,3630,3640,3660	
Combination Drugs	3699	