Retrospective Observational Database Study Protocol

Drug Substance	Symbicort
Study Code	000202
Date	

A U.S. Retrospective Database Analysis Evaluating the Comparative Effectiveness of Budesonide/Formoterol (BFC) and Tiotropium Bromide among COPD Patients

Name and address of requesting AZ department:

Therapeutic area: Respiratory Therapeutic Area
Names of Requestor:

Sponsor: AstraZeneca

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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**		

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PROTOCOL SYNOPSIS

A U.S. Retrospective Database Analysis Evaluating the Comparative Effectiveness of Budesonide/Formoterol (BFC) and Tiotropium Bromide among COPD Patients

Principal Investigator:

Co-investigators:

Objectives: The objective of this study is to compare the effectiveness of budesonide/formoterol (BFC, SYMBICORT®) vs. tiotropium bromide (SPIRIVA®) in COPD patients new to ICS/LABA combination and LAMA therapies

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 and LAMA therapies

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

Outcomes of Interest Time to first COPD exacerbation during 12 month post-index period

Statistical methods Matched cohorts via propensity scores, regression models (log-rank test/Cox regression for primary outcome, Cox regression, negative binomial, logistic, normal, gamma regression for secondary outcomes) for statistical testing

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

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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
BFC	Budesonide/formoterol fumarate dihydrate combination
CAD	Coronary artery disease
CCU	Coronary Care Unit
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
ICU	Intensive Care Unit
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
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

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 Disorder (GOLD) (www.goldcopd.org) guidelines site 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 2013) suggest the initiation of controller medications based on history of exacerbations and symptoms. For patients with a history of COPD exacerbations, ICS/LABA combination and/or LAMA therapies are considered first-line options.[5]

The ICS/LABA combination medication budesonide/formoterol (BFC, Symbicort, AstraZeneca LP, Wilmington, DE), a pressurized meter dose inhaler (pMDI), was approved for use in the US for the treatment of asthma in June 2007 and, more recently, for maintenance treatment of airflow obstruction in patients with COPD in February 2009.[6] Spiriva HandiHaler (tiotropium bromide inhalation powder) is a long acting inhaled anti-cholinergic and is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema; and is also indicated to reduce exacerbations in COPD patients. Spiriva gained US approval for COPD treatment in January 2004.[7]

Competitive market insight suggests that combination therapy with long-acting bronchodilators (LAMA/LABA) may impact the treatment algorithm for first-line COPD therapy in the near future. No clinical studies have been conducted in the US to compare BFC and tiotropium. A Canadian retrospective matched cohort study evaluating the real-world effectiveness of SYMBICORT TURBUHALER versus SPIRIVA HANDIHALER among COPD patients showed patients receiving Symbicort experienced fewer COPD related hospitalizations compared to Spiriva.[8] However, real-world effectiveness of BFC compared to tiotropium in terms of impact on healthcare resources utilization and costs has not been previously studied in COPD patients in the U.S.

This study is intended to evaluate treatment effectiveness with BFC compared to tiotropium in patients new to ICS/LABA combination and LAMA therapies. In claims database studies, reasons for treatment initiation are generally unobservable. Patients' clinical characteristic, including disease severity may influence choice of therapy. In order to ensure that patients who initiated BFC and tiotropium were comparable in their probability of receiving treatment

and their probability to benefit from treatment, a patient profile study was conducted in COPD patients (See Appendix L). According to this study although many characteristics were similar between the BFC and tiotropium cohorts, there were some key differences between patients that need to be used as matching criteria for the comparative effectiveness study.

2.2 Scientific and Business Rationale and Significance

Based on recent payer insight (AZ Project Engineer 2011), there is a need for real-world effectiveness data in COPD treatment and demonstration that improvements in lung function translate to other endpoints (i.e., reduction in exacerbations, hospitalizations, etc.). Furthermore, competitive market insight suggests that combination therapy with long-acting bronchodilators (LAMA/LABA) may impact the treatment algorithm for initial choice of COPD therapy in the near future. To date no comparative effectiveness COPD studies have been done for BFC vs. tiotropium in the US; however, one study have been done in Canada.[6]

In a Canadian retrospective matched cohort study,[8] the real-world effectiveness of SYMBICORT TURBUHALER versus SPIRIVA HANDIHALER was assessed in patients with COPD. Primary outcomes including COPD exacerbation rate, ED visits and hospitalizations for COPD, OCS prescriptions and ambulatory medical visits were compared. After adjustment for all known confounding variables, patients treated with SYMBICORT TURBUHALER were found to be significantly less likely to have a hospitalization for COPD (RR=0.65; 95% CI: 0.44-0.97) and used less daily doses of SABA (mean difference =-0.48 daily dose; 95% CI: -0.67, -0.28) than those treated with tiotropium bromide although overall exacerbation rates were comparable between the two treatment cohorts.

3. STUDY OBJECTIVES

The objective of this study is to compare the effectiveness of Symbicort and Spiriva in COPD patients new to ICS/LABA combination and LAMA therapies in the U.S.

3.1 Primary objective

The primary objective is to compare the effectiveness of Symbicort and Spiriva in the time to first COPD exacerbation during the 12 months after initiation of Symbicort or Spiriva in patients who are at risk for a COPD exacerbation. See Section 10.1 for the complete definition of COPD exacerbation.

At risk patients will be identified based on having any of the following during the 12 month pre-index period: an inpatient hospitalization with a primary diagnosis for COPD; and/or an ED visit with any diagnosis for COPD; and/or having a prescription fill for OCS within 10 days after an outpatient visit for COPD.

3.2 Secondary objectives

1. To compare COPD exacerbation rates during the 12 month post-index period between patients initiating Symbicort vs. Spiriva. Comparison of COPD exacerbation rates will be analyzed overall and by event type (i.e., COPD inpatient hospitalization, COPD ED visit, and COPD outpatient visit with OCS or antibiotic use); see Section 10.1 for the complete definition of COPD exacerbation.
2. To compare all-cause and COPD related healthcare resource utilization and costs, medication use, and drug treatment adherence (PDC and MPR) during the 12 month post-index period between Symbicort and Spiriva. This will be done by evaluating each of the following:
    1) COPD respiratory medication use (ICS, LABA , SABA, LAMA, SAMA, SABA/SAMA combination, LTRA, roflumilast, theophylline, OCS, antibiotics; for patients indexed on Spiriva, use of other LAMA and ICS/LABA medications will be assessed; for patients indexed on Symbicort, use of LAMA and other ICS/LABA medications will be assessed)
    2) All-cause and COPD related healthcare resource utilization: office/outpatient visits, inpatient visits length of stay, ICU admission and length of stay
    3) All-cause and COPD related healthcare costs (plan paid, patient paid, and plan + patient paid): Costs of all COPD related medication (#1 above) and COPD related outpatient/office, ED, and inpatient visits (#2)
    4) Treatment patterns and adherence, and treatment modification
3. To estimate the difference in patient baseline demographics and characteristics (age, gender, health plan type, index year, geographic region, prescribing physician type, and comorbid conditions) at the time of Symbicort or Spiriva initiation; and to estimate the difference in all-cause and COPD related healthcare utilization/cost variables during the 12 month pre-index period.

Detailed definitions of secondary outcomes can be found in section ‘10.2’.

3.3 Exploratory analysis

Time to treatment modification (triple therapy): time to initiation of ICS/LABA in patients on Spiriva and time to initiation of LAMA for patients on Symbicort will be analyzed. Because the number of patients on triple therapy is expected to be very small, this analysis will be purely exploratory.

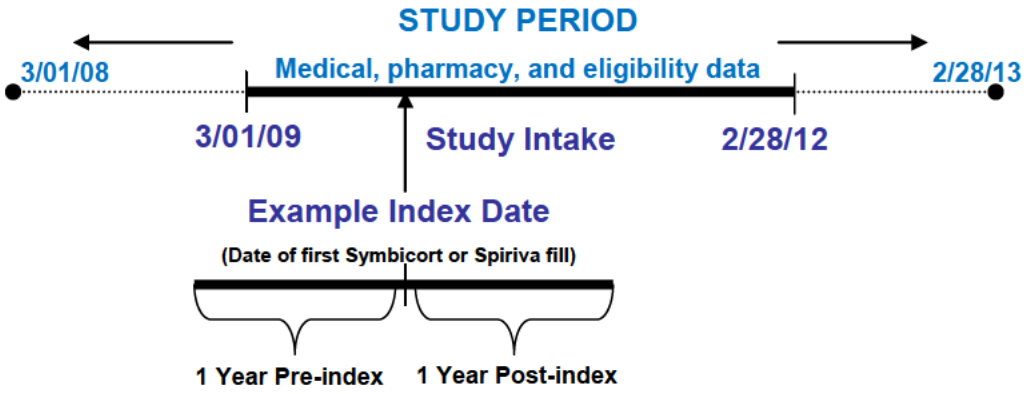
4. STUDY PLAN AND PROCEDURES

4.1 Overall study design and flow chart

Index date: Date of Symbicort or Spiriva initiation [anytime between 3/1/2009 and 2/28/2012]

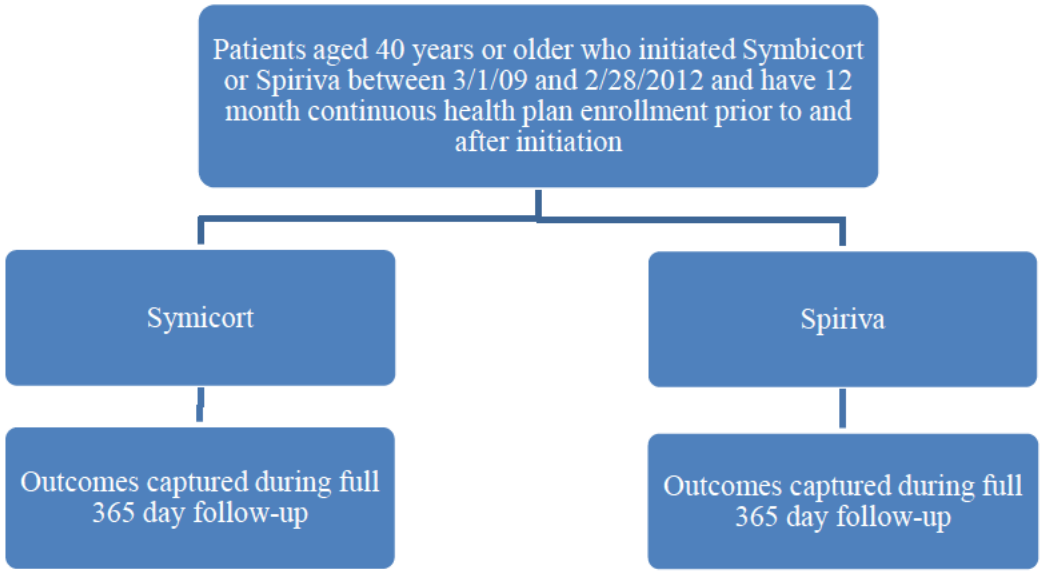
Observation period used to capture eligibility and outcome metrics for an individual patient: Index date-365 days (pre-index period) to Index date+365 days (post-index period) [anytime between 3/1/2008-2/28/2013]

Figure 1. Study Time Frame Diagram



Note: The *index date* may be at any time within the intake period. Health plan enrolment 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 study will be a retrospective cohort study utilizing administrative claims data from the HealthCore Integrated Research Environment (HIRE). The administrative claims data will be utilized to describe COPD patients who are newly initiating Symbicort and Spiriva. A retrospective cohort study design allows us to easily capture the population of patients initiating Symbicort or Spiriva 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 two COPD medications currently available on the market with a substantial patient population: Symbicort and Spiriva.

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 2/28/2013 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 2/28/2013.

Current Data Availability:

Approximately 32.1 million lives having medical and pharmacy coverage in total database, with continuous eligibility for:

- 1 year – approximately 21.1 million
- 2 years – approximately 14.4 million
- 3 years – approximately 10.2 million
- 4 years – approximately 7.0 million

Approximately 10.2 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 7.8 million

- 2 years – approximately 6.1 million
- 3 years – approximately 4.9 million
- 4 years – approximately 3.9 million

The full HIRE database dates back to January 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 1/1/2006 and extend to the most currently available data, 2/28/2013.

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.

Mortality data will be obtained from Social Security Death Index and matched with HIRE to determine death dates.

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 their initial prescription fill (Symbicort or Spiriva), referred to as their index medication. Patients filling prescriptions for more than one index medication will be excluded from this study as it is not possible to assign them to an individual group; i.e., it would not be possible to attribute treatment effectiveness to either Symbicort or Spiriva group. Table 1 in Appendix A presents the Generic Product Identifier (GPI) codes of interest for identifying claims for Symbicort and Spiriva prescriptions.

Patients will be considered as having COPD based on having at least one medical claim with a diagnosis of COPD (for ICD-9 diagnosis codes for COPD, see ‘Appendix B’).

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 2/28/2012 will be eligible for this study.

7.1.1 Inclusion criteria

1. Patients must have at least one prescription fill for Symbicort (160/4.5 MCG/ACT dose, per US COPD indication[6]) or Spiriva during the intake period. Patients must be

naive to ICS/LABA combination or LAMA therapies in the year prior to first prescription claim.[†] 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 Symbicort or Spiriva will be identified via the use of Generic Product Identifier (GPI) Codes (See Appendix A for codes)

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

2. Patients must meet one of the following diagnosis criteria for COPD (See Appendix B for ICD-9 codes) during the 12 month pre-index period:
    - At least one inpatient claim with any diagnosis code for COPD, and/or
    - At least one ED claim with a COPD diagnosis, and/or
    - At least one other medical claim with a COPD diagnosis
3. Patients must be 40 years or older at the time of index date
4. Patients must have at least 12 months of continuous health plan enrolment prior to and after index date , including continuous medical and pharmacy coverage
5. Patients must be considered as at risk population for COPD exacerbations (defined in Section 3.1). Based on the following during the 12 month pre-index period:
    - At least one inpatient hospitalization with a primary diagnosis for COPD, and/or
    - At least one ED visit with a COPD diagnosis, and/or
    - At least one prescription fill for OCS within 10 days after a COPD outpatient visit

7.1.2 Exclusion criteria

1. Patients with prescription claims for ICS/LABA combination or LAMA therapy during 12 months pre-index period. (See Tables 1 and 2 in Appendix A)
2. Patients with prescription claims for both Symbicort and Spiriva on the index date.
3. Patients with ≥180 days supply of OCS medication during the 12 month pre-index period. (See ‘ COPD medication codes’)
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 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 code) within 60 days of each other.[9]

8. EXPOSURES OF INTEREST

8.1 Drug-specific exposure/treatment

Budesonide/formoterol (BFC, Symbicort®) **vs.** Tiotropium bromide (Spiriva®)

8.2 Treatment Compliance

Treatment compliance cannot be directly measured. The proportion of days covered (PDC) and medication possession ratio (MPR) of the index treatment during the 12 month post-index period will be reported as a descriptive result (See Section 10.2 for a full definition).

9. PARTICIPANT FOLLOW-UP

All patients in this study will have 24 months of observation. Patient observation begins 12 months prior to the index date and extends through 12 months post-index.

10. DEFINITIONS OF OUTCOME VARIABLES

10.1 Primary outcome variables

The primary outcome of this study for an individual patient is the time to first COPD exacerbation during the 12 month post-index follow up period. Follow up starts on the index date and continues for 365 days. The time to first COPD exacerbation will be calculated as the date of first COPD exacerbation minus index date. A COPD exacerbation is defined as any of the following:

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

ED visits that result in a hospital stay will be counted as an inpatient hospitalization only. OCS or antibiotic use and an ED or inpatient visit must occur more than 14 days apart to be considered separate events; i.e., any OCS or antibiotic prescription fill occurring within 14 days of an ED/inpatient hospitalization will be counted as the hospitalization only and not a separate event. Multiple OCS and/or antibiotic fills within 10 days of the same outpatient visit will only be counted as one event.

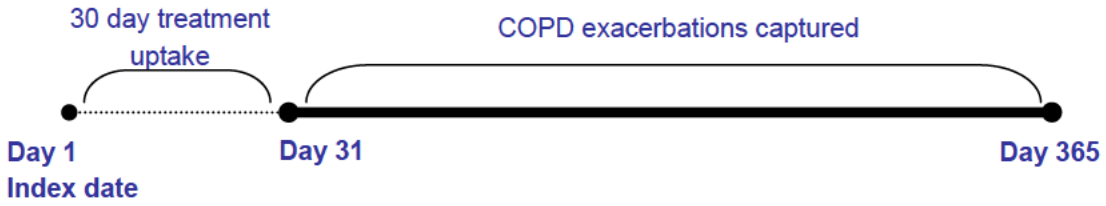
10.1.1 Subgroup and Sensitivity analysis of the primary outcome

A detailed analysis plan for each of the following subgroup and sensitivity analyses, along with sensitivity analysis based on different statistical models, can be found in Section 13.2.1.

Sensitivity Analysis 1, On-treatment analysis**:** Time to first COPD exacerbation will also be examined using on-treatment analysis, where Symbicort patients are censored if they fill a LAMA, and Spiriva patients are censored if they fill an ICS/LABA.

Sensitivity Analysis 2, Starting follow-up on Day 31: 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 of time to first COPD exacerbation. For the sensitivity analysis follow-up starts 31 days post-index date and continue until 365 days post-index date (see Figure 3).

Figure 3. Time Period for Sensitivity Analysis 2



Subgroup Analysis 1, Treatment modifiers: The primary outcome will be performed within patients having a treatment modification and within patients not having a treatment modification, separately.

Subgroup Analysis 2, Patients 65 years of age and older: A subgroup analysis will be performed within patients aged 65 years and older at the index date.

10.2 Secondary outcome variables

10.2.1 COPD exacerbation rate during 12 month post-index period

The rate of COPD exacerbation during 12 month post-index period will be evaluated during the post-index period. The rate of COPD exacerbations will be defined as the total number of COPD exacerbations during the post-index period for all patients in each treatment cohort divided by the total number of person years. The count of COPD exacerbations is the number of times any of the three conditions defined in Section 10.1 occur during the 12 month post-index period.

The exacerbation rate will be analyzed for the overall population and separately for each of the three components of exacerbation described in Section 10.1.

10.2.2 COPD respiratory medication use during 12 month post-index period

- COPD respiratory medication use (0 vs. 1+ event and total number of fills for each; see ‘ COPD medication codes): ICS, LABA, SABA, LAMA, SAMA, SABA/SAMA combination, LTRA, roflumilast, theophylline, OCS, antibiotics; for patients indexed

on Spiriva, use of other LAMA and ICS/LABA medications will be assessed; for patients indexed on Symbicort, use of LAMA and other ICS/LABA medications will be assessed. . (See Appendix E)

- Total number of COPD medication classes filled: 0 vs. 1+, and also 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13

10.2.3 COPD related utilization during 12 month post-index period

[Note COPD related inpatient hospitalizations and ED visits are captured as part of the primary outcome]

- COPD related outpatient/office visit (0, 1, 2+ events and total number of events): defined as any claim for an outpatient or office 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 as it could be a routine check-up.
- COPD related inpatient hospitalization length of stay: defined as 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.

  Presence of any COPD related inpatient hospitalizations and number of visits will be reported as part of the primary outcome (Section 10.1).
- 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 vs. 1+ event) 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.
- 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 (Appendix G for codes).

10.2.4 All-cause utilization during 12 month post-index period

- Frequency of all-cause resource use during the 12-month post-index period will be captured similarly to the COPD related healthcare resource utilization outlined in the sections above for the following categories: Inpatient hospitalizations (0 vs. 1+ and total number of events) and length of stay (calculated as number of nights, same day admission/discharge counted as one), ICU admissions (0 vs. 1+ and total number of events) and length of stay, ED visits (0 vs. 1+ and total number of events), and outpatient/office visits (0,1,2+ and total number of events). Emergency department visit resulting in inpatient hospitalization will be counted as inpatient hospitalization only.

- The number of different prescription medication classes (based on unique 4 digit GPI codes) filled during the 12 month post-index period will be determined

10.2.5 All-cause and COPD related healthcare costs during 12 months post-index period

- Costs will be reported for the following resource uses: inpatient hospitalizations, ED visits, outpatient/office visits, skilled nursing facility, total medical, and prescriptions. Costs will be reported for all-cause as well as COPD related. COPD related events include inpatient hospitalizations with a primary diagnosis of COPD, and all other types of medical services (ED, outpatient/office, skilled nursing facility) with any diagnosis for COPD. COPD prescription costs will be calculated for any medications in Appendix E. All cost will be adjusted to year 2012 given the most accurate and updated consumer price index information provided by the Bureau of Labor Statistics for Medical Care Services (MCS).[10] The following types of costs will be captured:

  1. Plan paid costs
  2. Patient paid costs
  3. Total costs (plan paid + patient paid)

10.2.6 Treatment patterns and adherence

- Continuity of care (COC): Continuity of care during the 12 month post-index period will be measured with the Bice and Boxerman index.[11] 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 and office 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 12 month post-index period.

- Proportion of days covered (PDC) will be used to measure the compliance of index medication (Symbicort or Spiriva) during the 12 month post-index period. PDC will be calculated as follows:

PDC: the ratio of the number of days covered by the index medication prescription

filled during the 12 month post-index period divided by the number of days of follow-up (which will be 365 for this study). Days that are covered by the index medication include the date that this medication is filled plus the days supply of that prescription minus one (e.g., a fill on 1/1/10 will cover days 1/1/10-1/30/10). Only days' supply that fall within the 12-month post-index period will be included in the numerator, i.e. if the days' supply of the last prescription fill goes beyond index date + 365 only the days up to index date + 365 will be counted. If one day is covered by multiple fills of index medication, it will only be counted once; thus the largest possible number of days covered is 365. PDC values range from 0.01-1.00 with higher values suggesting higher compliance. PDC will be reported both continuously and discretely: 0.01-.20, .21-.40, .41-.60, .61-.80, and .81+. It is possible that PDC calculations can be greater than 1 (i.e. patient has total days' supply greater than the days of follow-up) due to early refills and vacation supplies. However, a PDC of > 1 does not accurately reflect medication utilization and would artificially inflate medication compliance. Thus PDC for individuals will be capped at 1.

- Medication Possession Ratio (MPR) will be used to measure compliance of index medication during the 12 month post-index period. MPR will be calculated as follows:

  MPR: Medication Possession Ratio (MPR) is the ratio of the sum of days supply for all prescription fills for the index medication divided by the sum of days on therapy for the index medication.

  For each medication, days on therapy (the denominator) is calculated as the number of days between index date and last observed fill date + day supply of the last fill.

  Days supply of all prescription fills for the index medication during the post-index period will be summed together. Only days' supply that fall within the 12-month post-index period and/or prior to switching will be included in the numerator, i.e. if the days' supply of the last prescription fill goes beyond index date + 365, only the days up to index date + 365 be counted.

  MPR ranges from 0 to 1 with higher values suggesting higher compliance, where 1 is for patients who received continuous drug therapy supply. MPR will be reported both continuously and discretely: 0.00-.20, .21-.40, .41-.60, .61-.80, and .81+. It is possible that MPR calculations can be greater than 1.0 (i.e. patient has total days' supply greater than the days of continuous therapy) due to early refills and vacation supplies. However, an MPR of > 1.0 does not accurately reflect medication utilization and would artificially inflate medication compliance. Thus MPR for individuals will be capped at 1.0.

10.2.7 Treatment modification

Treatment modification (triple therapy): The number of patients who fill an ICS/LABA or LAMA different from their index medication (i.e., Spiriva patients who fill any ICS/LABA or any other LAMA; Symbicort patients filling a LAMA, or another ICS/LABA) will be captured overall and by type of medication switching to (i.e., Spiriva to ICS/LABA, Spiriva to other LAMA, Symbicort to LAMA, Symbicort to other ICS/LABA) during the 12 month post-

index period. The date on which patients fill an ICS/LABA or LAMA different from their index medication will be the treatment modification date. See Appendix A for codes.

10.3 Exploratory analysis

Time to treatment modification (triple therapy): time to initiation of ICS/LABA in patients on Spiriva and time to initiation of LAMA for patients on Symbicort will be analyzed. Defined as the time from index date to treatment modification date (defined above); calculated as treatment modification date minus index date. Because the number of patients on triple therapy is expected to be very small, this analysis will be purely exploratory.

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

11.1 Demographic and clinical variables

11.1.1 Patient demographics

- Age: Continuous and categorical (40-49, 50-59, 60-64, 65+)
- Gender: Male, Female
- Health plan type: HMO, PPO, CDHP, Other commercial
- Geographic region: Northeast, Midwest, South, West
- Index date: By year, by quarter (within each year), and calendar month (regardless of year)

11.1.2 Index and Pre-index clinical characteristics

- 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*, 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, 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

*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.

- 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.
- 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*

  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 but this data field is not populated well for all of the plans. 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 following hierarchical order to assign the prescribing ph**y**sician will be used: Pulmonologist, Internist, Family medicine/general practitioner, Cardiologist, Allergist/Immunologist, non-physician, or other*.

  "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 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; COPD related outpatient/office, ED, inpatient, and ICU visits; lengths of stay for COPD related inpatient and ICU visits; COPD related procedures. See sections 10.2.1 through 10.2.3 for complete definitions.

11.2.2 COPD related costs during 12 month pre-index period

Similar to the post-index costs section 10.2.5, COPD related pre-index costs will be captured for the 12 month pre-index period.

Plan paid costs, patient paid costs, and total costs (plan paid + patient paid) will be reported for the following COPD related utilizations:

- Inpatient hospitalizations
- ED visits

- Outpatient/office visits
- Total medical
- COPD medication prescriptions

All cost will be adjusted to year 2012 based on U.S. medical care services consumer price index (CPI) from Bureau of Labor Statistics.[11]

11.3 All cause healthcare utilization and costs

11.3.1 All-cause healthcare utilization during 12 month pre-index period

- Frequency of utilization during the 12 month pre-index period will be captured similarly to the post-index all-cause healthcare utilization outlined in Section 10.2.4 for the following utilization categories: Inpatient stay and length of stay, ICU admissions and length of stay, ED visits, and outpatient/office visits. Emergency department visit resulting in inpatient hospitalization will be counted as a hospitalization only.
- The number of different prescription medication classes (based on unique 4 digit GPI codes) filled during the 12 month pre- and post-index periods will be determined

11.3.2 All-cause healthcare costs during 12 month pre-index period

Plan paid costs, patient paid costs, and total costs (plan paid + patient paid) will be reported for the following utilizations during the 12 month pre-index period:

- Inpatient hospitalizations
- ED visits
- Outpatient/office visits
- Total medical
- Total pharmacy

All cost will be adjusted to year 2012 based on U.S. medical care services consumer price index (CPI) from Bureau of Labor Statistics.[11]

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 Symbicort and Spiriva cohorts were not randomly assigned to the treatment groups, 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, and create more comparable Symbicort and Spiriva cohorts.[12,13,14] The propensity score for each individual will be estimated as the probability of receiving Symbicort 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 received Symbicort (1) or Spiriva (0) therapy.

The goal of the matching algorithm is to have similar distribution of patients in each cohort for the following variables. 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:

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 and/or SABA/SAMA fixed dose combination fills during pre-index period (mean) (GLM w/ negative binomial distribution and log link)
6. Number of LABA fills during pre-index period (mean) (GLM w/ negative binomial distribution and log link)
7. Age at index, years (mean) (t-test)
8. Gender (chi-square test)
9. Asthma, ≥1 diagnosis during pre-index period (yes vs. no) (chi-square test)

Other **pre-index** variables to be considered for inclusion in the propensity score model, but not required to have balance between groups (i.e., p-value may be <0.05), are below. Any of the variables below not balanced after propensity score matching will be considered as covariates in the analysis of post-index outcomes.

- Index month
- Index medication prescribed by a pulmonologist (y/n)
- Continuity of care (COC)
- Pre-index hospital admissions (cardiovascular [any inpatient hospitalization with a procedure or diagnosis code in Appendix H], pneumonia [see Appendix C for codes] and asthma-related [see Appendix C for codes]; 0 vs. 1+ for each)
- 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 Appendix G)]
- 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)
- Influenza vaccination (y/n) [Appendix I]
- Pneumococcal vaccination (y/n) [Appendix I]
- Total inpatient hospitalization length of stay > 5 days (y/n)
- Pre-index use of COPD medications (ICS, SABA, theophylline, roflumilast, LABA, LTRA, 0, 1, 2+) [Appendix E, Table 1]
- Any pre-index OCS use (0, 1, 2+) [Appendix E, Table 1]
- Any pre-index antibiotic use (0, 1, 2+) [See Appendix E, Table 2]
- Cardiovascular medications (0, 1, 2+) [See Appendix K]
- Pre-index statin use (0, 1+) [See Appendix K]

The propensity scores will be used to match a patient from the Spiriva cohort to a patient in the Symbicort 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 Symbicort and Spiriva patients.

Treatment cohorts will be considered well balanced for a given variable if the p-value for the difference between groups is $p \geq 0.05$. Confidence intervals will also be calculated.

Although the interest is in balancing the cohorts with respect to the variables listed above, other variables may be used in developing the propensity score model. Such variables from the 12 month pre-index period include, but are not limited to, Deyo-Charlson comorbidity score, health plan type, year of index treatment, other comorbid conditions, and pre-index inpatient hospitalization length of stay. Interaction terms such as age * gender, age * comorbid conditions, etc. will also be entered. Although there is no consensus in the literature about how to choose the covariates to include in the score calculation (widely used method is to include all observable variables to start with and then eliminate using either backward or forward elimination or trial and error to achieve the final model), there is a general agreement that the success of the propensity score model is judged by whether the balance was achieved between two cohorts regardless of final selection method of variables. We will start with the most comprehensive model and gradually eliminate the variables to achieve a final propensity score model that provides us the best balance of the selected variables between two cohorts,

Before the matching algorithm is performed, the two cohorts were separated into their own datasets and sorted by propensity scores obtained in 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 Symbicort cohort will be selected to find a matching patient in the Spiriva cohort. Using estimated propensity scores, the Symbicort cohort patient will be matched with a patient in the Spiriva therapy cohort who has a similar predicted probability using the Greedy nearest neighbor 1:1 matching technique (with no replacement).[14] 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 BFC patient is either matched or not matched with a patient from the Spiriva cohort, the BFC patient with the next lowest propensity score will be selected to find a match, and so on. Random numbers will be assigned to all Spiriva patients (using random number generation with a specified seed of 52784), so that if two or more Spiriva patients have the same propensity score and are considered the best match for a BFC 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 1,111 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 index therapy. All results will be presented for the overall population and for each group:

1. Symbicort
2. Spiriva

Statistical testing (two-sided) will be done for comparisons between the propensity score matched Spiriva and Symbicort cohorts with Spiriva 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.
Any confounders that aren't balanced with $p<0.05$ will be adjusted for in statistical models.

Possible confounders to be included as covariates include:

- Those listed in Section 13.1: Index month, Index medication prescribed by a pulmonologist (y/n), Continuity of care (COC), Pre-index hospital admissions (cardiovascular, pneumonia and asthma-related; 0 vs. 1+ for each), Long-term use of oxygen therapy (0 vs. 1+), Comorbid conditions (pneumonia, pulmonary hypertension, chronic respiratory failure, anxiety, depression and/or use of psychotropic drugs, CAD, left ventricular failure, right heart strain on ECG, diabetes, heart failure, hypertension, stroke) (y/n for each), Influenza vaccination (y/n), Pneumococcal vaccination (y/n), Total inpatient hospitalization, length of stay > 5 days (y/n), Pre-index use of COPD medications (ICS, SABA, theophylline, roflumilast, LABA, LTRA, 0, 1, 2+), Any OCS use (0, 1, 2+), Any antibiotic use (0, 1, 2+), Cardiovascular medications (0, 1, 2+)
- As well as other possible covariates: DCI score, index year, prescribing physician type (other than pulmonologist listed above), health plan type, geographic region, other comorbid conditions

Variables that are significantly different ($p<0.05$) between treatment cohorts will be considered for inclusion. Covariates will be chosen for inclusion using forward selection. First, the candidate covariate with the lowest p-value from the bivariate association test comparing Symbicort to Spiriva will be added to the model. If the Akaike Information Criterion (AIC) of the model with the covariate is significantly lower (based on Chi-square

with 1 degree of freedom) than the AIC of the model without the covariate, then the covariate is kept in the model and the process is repeated for the candidate covariate with the next lowest p-value. The process ends when all candidates are added to the model or the addition of any of the remaining covariates does not significantly reduce the AIC.

13.2.1 Statistical model for the primary outcome:

A **log-rank test** will be used to model the time to first COPD exacerbation **if there are no imbalances between treatment cohorts** for **any** of the variables listed in Section 13.1. **If there is any imbalance** in those variables a **Cox proportional hazards model** will be used instead, adjusting for covariates. Hazard ratio will be calculated and a 95% confidence interval along with a corresponding p-value will be presented. 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., hazard ratio) and width of the confidence interval will be primarily used for interpretation of results.

Intent-to-treat (ITT) analysis: ITT analysis will be used for the primary objective. Patients will be followed for the full 12 month post-index period, and will be censored at the time of the first COPD exacerbation. All patients will be analyzed based on their index medication cohort, regardless of any treatment changes during the post-index period.

Sensitivity and subgroup analyses for the primary outcome

On-treatment analysis**:** Time to first COPD exacerbation will also be examined using on-treatment analysis. If a patient switches or adds-on an ICS/LABA or LAMA different from the index medication (i.e., Spiriva patients who fill any ICS/LABA or other LAMA therapies; Symbicort patients filling other ICS/LABA or any LAMA therapies) **prior to** a COPD exacerbation during the 12 month post-index period, they will be censored on the date of the switch. Any exacerbations occurring after this point will not be observed/analyzed. If an exacerbation occurs on the same date as a switch/add-on, the exacerbation will be counted. Log-rank test or Cox regression will be used as described for the primary analysis.

Time to event using Cox proportional hazards model: A Cox regression model, adjusting for covariates, will be used to examine the time to first COPD exacerbation. The analysis will be performed as an ITT analysis, as used in the primary analysis. Covariates may include, but are not limited to: age, gender, healthplan type, geographic region, prior exacerbations, prior COPD medication use, prior health care resource utilization, and comorbid conditions.

Starting follow-up on Day 31: To ensure patients are allowed adequate exposure to the study medication before attributable outcomes are assessed, the primary outcome of time to first COPD exacerbation for Symbicort vs. Spiriva will also be analyzed using the follow-up

period from 31 days post-index date through 12 months post-index. A log-rank test or Cox regression model will be used on an ITT population as described for the primary analysis.

Treatment modifiers: The primary outcome will be performed within patients having a treatment modification and within patients not having a treatment modification, separately, during the post-index period (treatment modification defined as Spiriva patients who fill any ICS/LABA or other LAMA therapies; Symbicort patients filling other ICS/LABA or any LAMA therapies)

Patients 65 years of age and older: A subgroup analysis will be performed within patients aged 65 years and older at the index date. All outcomes planned in Section 10, including the primary and secondary outcomes, will be carried out within this subgroup.

13.2.2 Statistical models to be used for 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
    - Healthcare resource use (0 vs. 1+ event), medication use (0 vs. 1+ fill for each medication/medication class of interest). Models for the post-index resource/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 outpatient visit) as a covariate.
2. Continuous and count data: mean, median, SD, 95% CI, 75^{th}/95^{th} percentiles (for costs)
    a. Exacerbation rate – A negative binomial model with a log link will be used to model the number of exacerbations during the post-index period; overall and separately for each event type of exacerbation. Performed both as an ITT and on-treatment analysis.
    b. 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.
    c. 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 outpatient visit) will control for the analogous pre-index variable (e.g., number of pre-index outpatient visit) as a covariate.

d. MPR, PDC – differences between cohorts analyzed using normal regression analysis

13.2.3 Statistical models to be used for exploratory analysis

Time to treatment modification (triple therapy) using Cox proportional hazards model: A Cox regression model, adjusting for covariates, will be used to examine the time to filling an ICS/LABA within Spiriva patients and time to filling a LAMA within Symbicort patients. The analysis will be performed as an ITT analysis, as used in the primary analysis. Covariates may include, but are not limited to: age, gender, healthplan type, geographic region, prior exacerbations, prior COPD medication use, prior health care resource utilization, and comorbid conditions.

Mean time to treatment modification (triple therapy) will also be analyzed within the subset of patients who have a treatment modification. Difference in mean time will be analyzed via a negative binomial model with a log-link.

13.2.4 Pre-index analyses

Unadjusted analysis will be performed for the following variables. 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.
- All-cause and COPD related healthcare utilization/cost variables during 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.

13.2.5 Other analyses

Descriptive analysis of patients, by treatment groups, who have a treatment modification during the post-index period: descriptive statistics (frequency/%, mean/sd/median) of demographics, comorbidities, and clinical characteristics will be presented.

13.3 Sample size

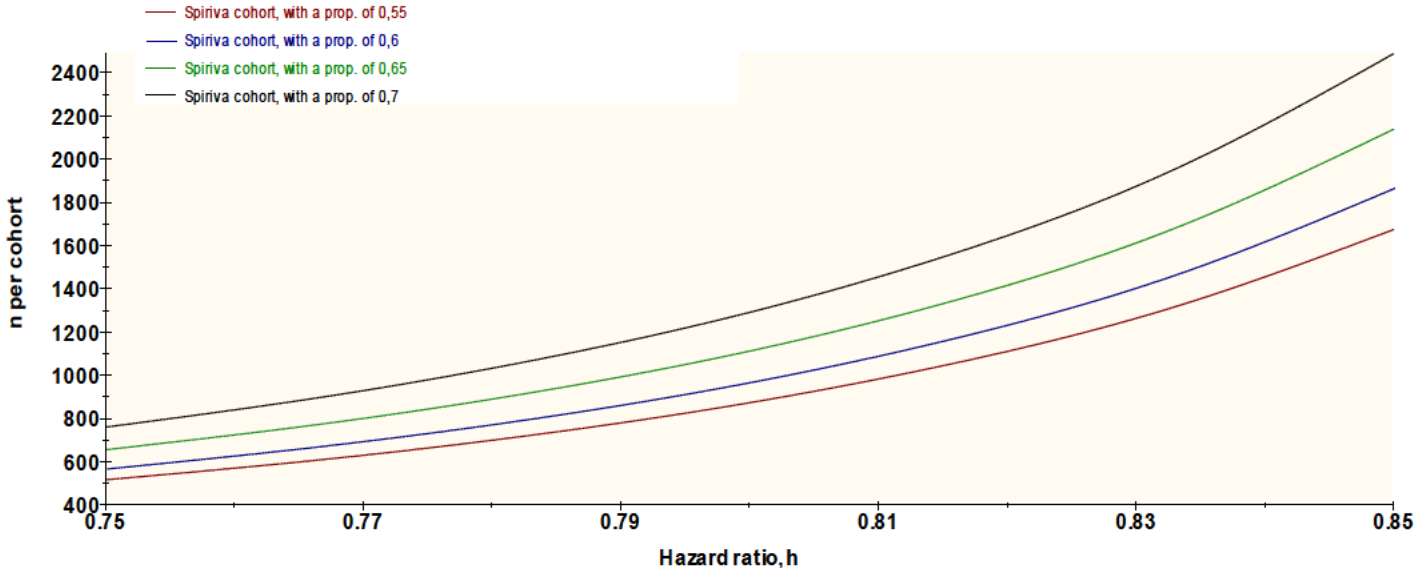
Retrospective observational studies essentially include all patients meeting inclusion/exclusion criteria. After matching based on the propensity scores is done to control for confounding, the matched patients will be included in the outcome analysis. The effectiveness of budesonide/formoterol (BFC, SYMBICORT®) vs. tiotropium bromide (SPRIVA®) in time to first COPD exacerbations will be analyzed within patients having an inpatient hospitalization (with a primary diagnosis for COPD); and/or ED visit (with any diagnosis for COPD); and/or having a prescription fill for OCS within 10 days after an outpatient visit for COPD during the 12 months before initiation of Symbicort or Spiriva. The outcome will be analyzed via log-rank test (or Cox regression).

The proportion for the Spiriva cohort not experiencing an exacerbation (the "survival" proportion) is approximately 60-65% after one year in two published studies (one randomized study[17] and one claim based register study[18]). Conservatively, we assume that the proportion not experiencing an exacerbation in our study will be 65% after one year. A log-rank test for equality of "survival" curves, with a two-sided 5 % significance level and a sample size of 1,111 patients in each cohort, with a total number of events of 844, will have 90 % power to detect a difference between a Spiriva cohort proportion after one year of 0.650 and a Symbicort cohort proportion after one year of 0.584 (a constant hazard ratio of 0.80); this assumes no dropouts before one year.

Feasibility counts applying all inclusion/exclusion criteria showed 1,298 BFC patients and 2,506 Spiriva patients eligible for study inclusion prior to matching. This leaves just less than 200 BFC patients which can be lost due to not finding a Spiriva match to meet the minimum sample size of 1,111 patients per group.

Figure 4. Sample Size Calculation

Log-rank test of survival in Sprivia vs Symbicort cohorts followed for fixed time, constant hazard ratio



The figure illustrates different sample sizes for different hazard ratio between Spiriva vs Symbicort, for four different proportions of the Spiriva cohort not experiencing an exacerbation after one year, using a log-rank test with a 5% level of significance and a power of 90%. The proportions are 55 %, 60%, 65 % and 70% respectively.

14. STRENGTH S AND LIMITATIONS

Strengths

1. Using claims data from a commercially insured population across the nation allows access to a large number of patients with a diverse background.
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. It is possible to select a subset of the population (as a study amendment or as a separate study) for whom we can abstract medical charts to perform any validation analysis if necessary.
5. Data can be generalized to the commercially insured US population.

Limitations

1. Medicare and Medicaid patients are not included in this analysis.
2. This is a retrospective observational study. General limitations for database retrospective studies apply to this one.
3. Administrative claims data in general are subject to potential coding errors and inconsistencies and may be affected by the absence of clinical 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.
6. Inpatient administered drugs 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. Obesity can only be identified through use of ICD-9 codes. Therefore results should be interpreted with caution.

9. 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

10. The causal effect of time to first exacerbation between Symbicort and Spiriva is not analyzed but the average gain from Symbicort for those who were actually treated with Symbicort compared with similar patients on Spiriva.

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.

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19. APPENDICES

Appendix A ICS/LABA and LAMA medications

Table 1: Study medications

Name of Medication	GPI
LAMA therapy	
Tiotropium (Spiriva)	44100080100120
ICS/LABA combination therapy	
Budesonide+formeterol (BFC, Symbicort®) – 160/4.5 MCG/ACT dose	44209902413240

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

Name of Medication	GPI
Other ICS/LABA therapy	
Fluticasone+salmeterol (FSC, Advair®)	4420990270
Mometasone furoate+ formoterol (MFC, Dulera®)	4420990290
Budesonide+formeterol (BFC, Symbicort®) – 80/4.5 MCG/ACT dose	44209902413220
Other LAMA therapy	
Aclidinium Bromide (Tudorza®)	4410000710

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 (excluding COPD dx codes: 493.0x, 493.1x, 493.9x), 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	44400033
Mometasone	44400036
Triamcinolone	44400040
Long acting beta-2 adrenergic agonist (LABA)	
Inhaled LABAs	
Salmeterol	44201058
Formoterol	44201027
Clenbuterol	44201022
Indacaterol	44201042
Arformoterol	44201012
Oral LABAs	
Vospire	44201010107410 44201010107420
Volmax	44201010100480 44201010107470 44201010107480
Proventil CR	44201010100410
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)

Bitolterol	44201020
Levalbuterol	44201045
Metaproterenol	44201050
Pirbuterol	44201055
Terbutaline	44201060
Short acting muscarinic antagonists (SAMA)	
Ipratropium	44100030
SABA/SAMA combination	
Albuterol/ipratropium (nebulizer)	442099020120
Albuterol/ipratropium (inhalation)	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)	44603060002120

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

Service	Revenue Code
Intensive Care (ICU)	
General classification	200
Surgical	201
Medical	202
Pediatric	203
Psychiatric	204
Burn care	207
Trauma	208
Coronary Care (CCU) also considered part of ICU	
General classification	210
Myocardial Infarction	211
Pulmonary care	212
Heart transplant	213

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 if 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		
Clopidogrel	85158020	
Ticlopidine	85158080	
Cilostazol	85155516	
Dipyridamole	85150030	J1245
Prasugrel	85158060	
Ticagrelor	85158470	
Combo of Dipyridamole + Aspirin	85159902	
GP IIb/IIIa inhibitors		
Abciximab	85153010	J0130
Eptifibatide	85153030	J1327
Tirofiban	85153060	J3246
Vitamin K anti-coagulants		
Dicumarol	83200010	
Warfarin	83200030	
Heparins		
Unfractionated heparin (Heparin)	83100020	J1642, J1644
Low molecular weight heparin (Enoxaparin, Tinzaparin, Dalteparin)	83101020, 83101080, 83101010	J1650, J1655, J1645
Direct Factor Xa Inhibitors		
Rivaroxaban	83370060	
Pentasaccharide		
Fondaparinux	83103030	J1652
Fibrinolytic Drugs		
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		
Argatroban, Lepirudin	83337015, 83334050	C9121,J1945
Bivalirudin	83334020	J0583
Dabigatran (Pradaxa)	8333703020	
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	

Appendix L AstraZeneca COPD Patient Profiling Study Results

Table 1: Patient Demographics at index date

	Group 1: Symbicort w/out previous Spiriva or ICS/LABA		Group 3: Spiriva w/out previous Spiriva or ICS/LABA		Group 1 vs. Group 3			
					Estimate[1]	95% CI[1]		P-value[1]
	N/Mean	%/SD	N/Mean	%/SD		Lower	Upper	
Number of patients	6,940		10,831					
Age (n, % for each category)								
40 to 49 years	820	11.8%	761	7.0%	1.77	1.60	1.97	<.0001
50 to 59 years	1,828	26.3%	2,436	22.5%	1.23	1.15	1.32	<.0001
60 to 64 years	1,078	15.5%	1,681	15.5%	1.00	0.92	1.09	0.9816
65+ years	3,214	46.3%	5,953	55.0%	0.71	0.67	0.75	<.0001
Mean +/-SD, median	64.27	12.12	66.93	11.82	-2.67	-3.03	-2.30	<.0001
Gender (n, %)								
Male	3,178	45.8%	5,349	49.4%	0.87	0.82	0.92	<.0001
Female	3,762	54.2%	5,482	50.6%	1.16	1.09	1.23	<.0001
HealthplanType (n, %)								
HMO	1,321	19.0%	2,416	22.3%	0.82	0.76	0.88	<.0001
PPO	4,128	59.5%	6,577	60.7%	0.95	0.89	1.01	0.0987
CDHP	198	2.9%	246	2.3%	1.26	1.05	1.53	0.0153
Other commercial	1,293	18.6%	1,592	14.7%	1.33	1.23	1.44	<.0001
Geographic Region (n, %)								
Northeast	1,227	17.7%	2,360	21.8%	0.77	0.71	0.83	<.0001
Midwest	2,766	39.9%	4,051	37.4%	1.11	1.04	1.18	0.0010
South	1,979	28.5%	2,895	26.7%	1.09	1.02	1.17	0.0092
West	968	13.9%	1,525	14.1%	0.99	0.91	1.08	0.8050

*Odds ratio is for cateogrical variables and difference in means is for continuous variables.
Statistical comparisons are comparing Symbicort to Spiriva (reference group).

Table 2: Comorbid conditions during 12 month pre-index period

	Group 1: Symbicort w/out previous Spiriva or ICS/LABA		Group 3: Spiriva w/out previous Spiriva or ICS/LABA		Group 1 vs. Group 3			
					Estimate[1]	95% CI[1]		P-value[1]
	N/Mean	%/SD	N/Mean	%/SD		Lower	Upper	
Number of patients	6,940		10,831					
DCI Mean +/-SD , median	1.90	2.00	1.93	2.12	-0.03	-0.09	0.03	0.2909

Additional comorbidities not in DCI (n, % for each comorbidity)								
Insomnia	161	2.3%	217	2.0%	1.16	0.95	1.43	0.1538
Allergic rhinitis	558	8.0%	446	4.1%	2.04	1.79	2.32	<.0001
Sinusitis	720	10.4%	711	6.6%	1.65	1.48	1.84	<.0001
GERD	888	12.8%	1,220	11.3%	1.16	1.05	1.27	0.0021
Anxiety	536	7.7%	716	6.6%	1.18	1.05	1.33	0.0047
Major depressive disorder	272	3.9%	364	3.4%	1.17	1.00	1.38	0.0505
Morbid obesity[2]	439	6.3%	498	4.6%	1.40	1.23	1.60	<.0001
Asthma	1,716	24.7%	1,377	12.7%	2.26	2.09	2.44	<.0001
Sleep apnea	781	11.3%	1,087	10.0%	1.14	1.03	1.25	0.0098
Bronchiectasis	86	1.2%	132	1.2%	1.02	0.77	1.34	0.9037
Post-inflammatory pulmonary fibrosis	165	2.4%	288	2.7%	0.89	0.73	1.08	0.2454
Other diseases of lung	1,187	17.1%	2,086	19.3%	0.87	0.80	0.94	0.0003
Hypertension	4,092	59.0%	6,552	60.5%	0.94	0.88	1.00	0.0423
Osteoporosis	322	4.6%	614	5.7%	0.81	0.71	0.93	0.0027
Diabetes mellitus	1,630	23.5%	2,404	22.2%	1.08	1.00	1.16	0.0449
Dyslipidemia	3,049	43.9%	4,801	44.3%	0.98	0.93	1.05	0.6070
Hyperglycemia	131	1.9%	199	1.8%	1.03	0.82	1.28	0.8086
Congestive heart failure	917	13.2%	1,755	16.2%	0.79	0.72	0.86	<.0001
Pulmonary hypertension	141	2.0%	297	2.7%	0.74	0.60	0.90	0.0029
Peripheral vascular disease / atherosclerosis	518	7.5%	1,056	9.8%	0.75	0.67	0.83	<.0001
Myocardial infarction	299	4.3%	645	6.0%	0.71	0.62	0.82	<.0001
Unstable Angina	126	1.8%	276	2.6%	0.71	0.57	0.88	0.0014
Other coronary artery disease	1,557	22.4%	3,038	28.1%	0.74	0.69	0.80	<.0001
Stroke, TIA or cerebrovascular disease	477	6.9%	971	9.0%	0.75	0.67	0.84	<.0001

*Odds ratio is for cateogrical variables and difference in means is for continuous variables. Statistical comparisons are comparing Symbicort to Spiriva (reference group).

Table 3: Summary of patients by Physician Specialty Associated with Prescribing Index Medication - All Specialties

	Group 1: Symbicort w/out previous Spiriva or ICS/LABA		Group 3: Spiriva w/out previous Spiriva or ICS/LABA			Group 1 vs. Group 3			
					P-value[1]	Odds ratio[1]	95% CI[1]		P-value[1]
	N	%	N	%			Lower	Upper	

Number of patients	6,940		10,831						
Prescriber specialty									
Allergist/Immunologist	170	2.5%	106	1.0%	0.0172	2.54	1.99	3.24	<.0001
Pulmonologist	1604	23.1%	2,882	26.6%	0.0017	0.83	0.77	0.89	<.0001
Cardiologist	127	1.8%	239	2.2%	.	0.83	0.67	1.03	0.0846
Internal medicine	1802	26.0%	2,939	27.1%	0.7270	0.94	0.88	1.01	0.0854
Family/general practitioner	1867	26.9%	2,916	26.9%	0.1258	1.00	0.93	1.07	0.9758
Non-physician	295	4.3%	461	4.3%	1.0000	1.00	0.86	1.16	0.9857
Other specialty[2]	131	1.9%	191	1.8%	0.1301	1.07	0.86	1.34	0.5449
Unknown[3]	944	13.6%	1,097	10.1%	0.0173	1.40	1.27	1.53	<.0001

*Statistical comparisons are comparing Symbicort to Spiriva (reference group).

**: Other specialties include anesthesiology/pain management, cardiology, dermatology, emergency medicine, endocrinology/metabolism, gastroenterology, geriatrics, hematology, infectious disease, nephrology, neurology, nuclear medicine, ob/gyn, oncology, ophthalmology, otolaryngology, physical medicine/rehab, podiatry, psychiatry, radiology, rheumatology, surgery, urology

***: Physician specialty was not specified in pharmacy claim for index medication and there is no COPD related medical claim within 1 month of the index date

Table 4: COPD controller use during 12 month pre-index period

	Group 1: Symbicort w/out previous Spiriva or ICS/LABA		Group 3: Spiriva w/out previous Spiriva or ICS/LABA		Group 1 vs. Group 3			
					Estimate[2]	95% CI[2]		P-value[2]
	N/Mean	%/SD	N/Mean	%/SD		Lower	Upper	
Number of patients	6,940		10,831					
Nebulizer treatment (n, %)	1,140	16.43%	1,189	10.98 %	1.59	1.46	1.74	<.0001
Mean number of prescription fills	0.53	1.90	0.39	1.77	0.31	0.19	0.43	<.0001
COPD respiratory medications (number of patients with at least one fill)								
ICS monotherapy use (n, %)	771	11.11%	957	8.84%	1.29	1.17	1.43	<.0001
LABA monotherapy use (n, %)	187	2.69%	244	2.25%	1.20	0.99	1.46	0.0618
ICS/LABA combination use (n, %)	0	0%	0	0%	.	.	.	.
Tiotropium (n, %)	0	0%	0	0%	.	.	.	.
LTRA monotherapy use (n, %)	802	11.56%	648	5.98%	2.05	1.84	2.29	<.0001
Theophylline use (n, %)	145	2.09%	181	1.67%	1.26	1.01	1.57	0.0427
Roflumilast (n, %)	1	0.01%	0	0%	.	.	.	.
SABA (n, %)	3,044	43.86%	3,764	34.75 %	1.47	1.38	1.56	<.0001
SAMA (n, %)	282	4.06%	407	3.76%	1.09	0.93	1.27	0.3031
SABA/SAMA combination use (n, %)	1,147	16.53%	1,367	12.62 %	1.37	1.26	1.49	<.0001
OCS monotherapy use (n, %)	3,178	45.79%	3,744	34.57 %	1.60	1.50	1.70	<.0001
COPD respiratory medications (number of fills for each)								
ICS monotherapy use (mean, sd,)	0.37	1.45	0.29	1.32	0.07	0.02	0.13	0.0028
LABA monotherapy use (mean, sd,)	0.13	0.99	0.11	0.93	0.02	-0.01	0.07	0.2496
ICS/LABA combination use (mean, sd,)	0.00	n/a	0.00	n/a	.	.	.	.
Tiotropium (mean, sd)	0.00	n/a	0.00	n/a	0.00	0.00	0.00	
LTRA monotherapy use (mean, sd,)	0.58	2.07	0.29	1.48	0.29	0.20	0.40	<.0001
Theophylline use (mean, sd,)	0.13	1.07	0.09	0.87	0.04	0.00	0.09	0.0931
Roflumilast (mean, sd)	0.00	0.01	0.00	n/a	.	.	.	.
SABA (mean, sd)	1.48	2.98	1.04	2.50	0.45	0.36	0.54	<.0001
SAMA (mean, sd)	0.13	0.96	0.12	0.95	0.02	-0.01	0.05	0.2978
SABA/SAMA combination use (mean, sd,)	0.70	2.43	0.45	1.88	0.24	0.16	0.33	<.0001
OCS monotherapy use (mean, sd,)	1.17	2.13	0.82	1.83	0.34	0.28	0.41	<.0001
Duration of OCS therapy	17.72	52.13	13.61	48.52	4.10	2.49	5.88	<.0001

Table 5: COPD severity indicators during 12 month pre-index period

	Group 1: Symbicort w/out previous Spiriva or ICS/LABA		Group 3: Spiriva w/out previous Spiriva or ICS/LABA		Group 1 vs. Group 3			
					Estimate[1]	95% CI[1]		P-value[1]
	N/Mean	%/SD	N/Mean	%/SD		Lower	Upper	
Number of patients	6,940		10,831					
COPD procedures (Number of patients with ≥1 event)								
Chest X-ray, (n, %)	4,992	71.9%	7,978	73.7%	0.92	0.86	0.98	0.0114
Chest CT scan, (n, %)	1,889	27.2%	3,195	29.5%	0.89	0.84	0.96	0.0010
Pulmonary function tests, (n, %)	3,879	55.9%	6,006	55.5%	1.02	0.96	1.08	0.5634
Oximetry, (n, %)	928	13.4%	1,286	11.9%	1.15	1.05	1.25	0.0032
6 minute walk, (n, %)	175	2.5%	383	3.5%	0.71	0.59	0.85	0.0002
Pulmonary rehab, (n, %)	6	0.1%	28	0.3%	0.33	0.14	0.81	0.0104
Home oxygen use, (n, %)	614	8.9%	1,087	10.0%	0.87	0.78	0.97	0.0086
COPD related inpatient hospitalizations								
Number of patients with ≥1 event (n, %)	491	7.1%	763	7.0%	1.01	0.89	1.13	0.9386
Number of events (mean,sd,)[2]	1.16	0.53	1.16	0.55	0.00	-0.11	0.11	0.9509
Length of Stay (LOS, nights) per patient (mean,sd,)[2, def1]	4.77	6.67	6.02	9.53	-1.26	-1.74	-0.72	0.0000
COPD related ICU stays								
Number of patients with ≥1 event (n, %)	26	0.4%	49	0.5%	0.83	0.51	1.33	0.4353
Number of events (mean,sd,)[2]	1.04	0.20	1.04	0.20	0.00	-0.39	0.61	0.9924
Length of Stay (LOS, nights) per patient (mean,sd)[2, def1]	0.00	0.00	1.80	8.43	-1.26	-1.78	-0.67	0.0001
COPD Related ED visits								
Number of patients with ≥1 event (n, %)	535	7.7%	929	8.6%	0.89	0.80	1.00	0.0400
Number of events (mean,sd,)[2]	1.26	0.82	1.30	0.92	-0.04	-0.15	0.08	0.5366
COPD Related outpatient/office visits								
Number of patients with ≥1 event (n, %)	4,747	68.4%	8,056	74.4%	0.75	0.70	0.80	<.0001
Number of events (mean,sd,)[2]	5.95	8.60	6.17	9.40	-0.22	-0.44	0.01	0.0638
Outpatient visits with a OCS/antibiotic fill within 10 days of the visit date								
Number of patients with ≥1 event (n, %)	3,051	44.0%	3,579	33.0%	1.59	1.49	1.69	<.0001
Number of events (mean,sd,)[2]	7.93	10.33	7.70	10.33	0.23	-0.12	0.60	0.1979
Ventilation use during inpatient hospitalization								
Number of patients with ≥1 utilization (n, %)	21	0.3%	16	0.2%	2.05	1.07	3.93	0.0271
Number of events (mean,sd,)[2]	1.00	0.00	1.00	0.00	0.00	-0.48	0.92	1.0000

Oxygen use during inpatient hospitalization/ED								
Number of patients with ≥1 utilization (n, %)	265	3.8%	489	4.5%	0.84	0.72	0.98	0.0246
Number of events (mean,sd,)[2]	1.13	0.38	1.15	0.55	-0.02	-0.15	0.14	0.8331

1: Odds ratio from Chi-square test is used for cateogrical variables, mean difference from negative binomial models for count variables (number of events and length of stay). Statistical comparisons are comparing Symbicort to Spiriva (reference group)

2: Including only patients with at least one event

def1: Length of stay defined as the number of nights from admission to discharge. Non-overnight stays will be counted as length of zero
def2: Length of stay defined as the number of days from admission to discharge. Same date admission and discharge will be counted as one