Retrospective Observational Database Study Protocol

Drug Substance   Symbicort

Study Code   000152

Date

A U.S. Retrospective Database Analysis Evaluating the Comparative Effectiveness of Budesonide/Formoterol (BFC) vs. Fluticasone/Salmeterol (FSC) Combination in Patients with COPD

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

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PROTOCOL SYNOPSIS

A U.S. Retrospective Database Analysis Evaluating the Comparative Effectiveness of Budesonide/Formoterol (BFC) vs. Fluticasone/Salmeterol (FSC) Combination in Patients with COPD

Principal Investigator:

Co-investigators:

Objectives: The objective of this study is to compare the real-world effectiveness of budesonide/formoterol (BFC, SYMBICORT®) vs. fluticasone/salmeterol (FSC, ADVAIR®) in COPD patients

Study design Retrospective cohort study

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

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

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

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

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

Limitations Non-randomized study which can detect associations but causation cannot be inferred. Limited generalizability to the 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
AIC	Akaike information criterion
BFC	Budesonide/formoterol fumarate dihydrate combination
CAD	Coronary artery disease
CI	Confidence Interval
COC	Continuity of care
COPD	Chronic Obstructive Pulmonary Disease
DCI	Deyo-Charlson comorbidity index
ED	Emergency department
FSC	Fluticasone propionate/salmeterol combination
GPI	Generic product identifier
GPP	Good Pharmacoepidemiology Practice
GRACE	Good Research for Comparative Effectiveness
HIRE	HealthCore Integrated Research Environment
ICD9	The International Classification of Diseases ninth revision diagnosis codes (9th revision)
ICS	Inhaled corticosteroid
ICS/LABA	Inhaled corticosteroid + Long-acting ß2-adrenergic agonist combination
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISPE	International Society for Pharmacoepidemiology
LABA	Long-acting ß2-adrenergic agonist
LAMA	Long acting muscarinic antagonists
LTRA	Leukotriene receptor antagonist
LV	Left ventricular
MPR	Medication possession ratio
OCS	Oral corticosteroids

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

1. STUDY INVESTIGATORS

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

Table 1. **Investigating team**

See addresses below

1.2 List of collaborating institutions

2. INTRODUCTION

2.1 Background

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

The Global Initiative for Chronic Obstructive Lung 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 therapies are considered a first-line option.[3]

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, the 160/4.5 strength was approved for maintenance treatment of airflow obstruction in patients with COPD in February 2009.[5] Another ICS/LABA combination medication fluticasone/salmeterol (FSC, Advair, GlaxoSmithKline, NC), administered through a dry-powder inhaler - DISKUS®, was initially approved by FDA to treat asthma patients in August 2000. In November 2003, its 250/50 strength was approved for COPD associated with chronic bronchitis. In April 2008, FDA further extended its indication, making Advair DISKUS 250/50 the first medication in the US for the maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD, including chronic bronchitis and emphysema.[6]

To date, no randomized clinical trials (RCTs) have been conducted to compare the treatment effectiveness between BFC and FSC in COPD patients. However, some comparative effectiveness data is available through observational studies. A Swedish retrospective matched cohort study (PATHOS) evaluating the real-world effectiveness of BFC versus FSC among COPD patients showed that patients receiving BFC experienced significant lower exacerbation rate (adjusted RR 0.74, 95% CI 0.69 to 0.79) compared to FSC.[7] Another retrospective matched cohort study from found that COPD patients initiating BFC had significantly lower rates of ED visits (adjusted RR 0.75; 95% CI 0.58 to 0.97) and hospitalizations (adjusted RR 0.61; 95% CI 0.47 to 0.81) for COPD compared with FSC during a 12 month follow-up.[8] A similar

observational study conducted in the US shortly after the launch of BFC found that BFC patients utilized fewer SABA and SAMA versus FSC, with no significant differences between the two groups with respect to exacerbation rates and other clinical outcomes.[9] However, due to the limitation of short follow-up period of 6 months, a more robust study with a longer follow-up time is needed to assess the treatment effectiveness in COPD patients in the US.

Moreover, increased risk of pneumonia is considered the key safety issue of the combination therapy due to the use of ICS. This risk is suggested to be different between fluticasone and budesonide, while the ICS dose relationship to the risk remains unclear.[10] The PATHOS study reported a significantly higher pneumonia rate (adjusted RR 1.73; 95% CI 1.57 to 1.90) and more hospital admissions due to pneumonia (adjusted RR 1.74; 95% CI 1.56 to 1.94) in the FSC patients.[11]

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

2.2 Scientific and Business Rationale and Significance

Aligned with AZ US Brand Strategy and Global Payer Strategy, the AZ global team would like to evaluate ICS/LABA medications for treatment of COPD in the spirit of the PATHOS study in a US cohort. Further data may help address some aspects of market competition in the near future as BREO (GlaxoSmithKline, ICS/LABA) was just approved for COPD treatment in the US in May 2013.

Comparative data is available from Canada and Sweden, suggesting effectiveness difference in favor of BFC versus FSC (i.e., exacerbations and SABA use).[7-9,11] However, US payer/providers require US data given the difference in the device as well as regional variations in healthcare delivery and population characteristics. To date, no RCTs have compared exacerbation rates between BFC and FSC in COPD patients in the US. And limited comparative data is available in the US.[9]

This study is intended to evaluate treatment effectiveness with BFC compared to FSC in COPD patients new to ICS/LABA combination therapy, which can provide input and inform design for RCTs. The primary outcome of the study is COPD exacerbation rate, which is consistent with the PATHOS study. Compared to an alternate outcome of time to first exacerbation, the exacerbation rate will use a full 12 months of follow-up, which allows to capture more exacerbation events and provide more longitudinal information than censoring patients at the first event. In addition, switching between the ICS/LABA medications is expected to be low and thus there should be minimal impact of incorrectly attributing an exacerbation to the index medication while a patient is taking a different ICS/LABA.

As pneumonia is one of the key patient safety concerns of the ICS/LABA combination therapy, comparing pneumonia rates between BFC and FSC users with COPD in the US is aligned with

the spirit of the PATHOS study. In addition, this study will validate pneumonia diagnoses by confirming the diagnosis through medical chart abstraction to support the validity of the study results.

3.   STUDY OBJECTIVES

The objective of this study is to compare the effectiveness of budesonide/formoterol (BFC, SYMBICORT®, 160/4.5 strength) and fluticasone/salmeterol (FSC, ADVAIR®, 250/50 strength) in COPD patients new to FDA approved ICS/LABA combination therapies in the US.

3.1   Primary objective

The primary objective is to compare the effectiveness of BFC vs. FSC in the reduction of COPD exacerbations (exacerbation rate) during the 12 months after initiation of BFC or FSC. A COPD exacerbation is defined as the occurrence of any of the following events:

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

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

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

3.2   Secondary objectives

3.2.1   Subgroup and sensitivity analyses for the primary outcome of COPD exacerbation

1. *Sensitivity:* To evaluate time to first event as an outcome for BFC vs. FSC patients

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

3. *Subgroup:* Perform analysis in subset of switchers and non-switchers, separately (descriptive analysis only, further statistical analysis may be conducted if needed)

4. *Subgroup:* Perform analysis in patients aged 65 and older

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

1. To compare severe exacerbation rates (i.e. hospitalizations and ED-visits).

2. To evaluate individual components of an exacerbation separately.

3.2.3 All-cause and COPD related healthcare resource utilization

1. To compare COPD respiratory medication use for BFC vs. FSC patients.

2. To compare all-cause and COPD-related healthcare resource utilization and costs for BFC vs. FSC patients.

3. To evaluate treatment patterns (including ICS/LABA switching) and adherence to index medication.

3.2.4 Baseline/Pre-index analysis

To describe patient characteristics at the time of BFC or FSC initiation, and evaluate prior exacerbation rates, healthcare utilization and cost during the 12 month pre-index period prior to and after propensity score matching.

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

3.3 Pneumonia objectives

1. To validate the claims-based ICD-9 codes used to identify a pneumonia event through the use of medical record abstraction data.

Upon the completion of the validation of pneumonia diagnosis, the following analysis will be performed if the positive predictive value (PPV) is $\geq 80\%$:

2. To compare pneumonia rates for BFC vs. FSC patients.

   a. *Sensitivity:* To compare pneumonia rates for BFC vs. FSC patients using all follow-up time (i.e., >12 months)

3. To compare pneumonia-related healthcare resource utilization and costs for BFC vs. FSC patients.

More detailed information for the pneumonia validation and analysis can be found in Sections 0 and 13.

4. STUDY PLAN AND PROCEDURES

4.1 Overall study design and flow chart

Index date: Date of BFC or FSC initiation [anytime between 3/1/2009 and 3/312012]

Observation period used to capture eligibility and outcome metrics for an individual patient [anytime between 3/1/2008-3/31/2013]: Index date-365 days (pre-index period) to Index date+365 days (post-index period)

Figure 1.   Study Time Frame Diagram

Study Intake Period

3/01/2009   3/31/2012

Index Date
(Date of first BFC or FSC fill)

12 months Pre-index   **12 months Post-index**

3/01/2008   Medical, pharmacy, and eligibility data   3/31/2013
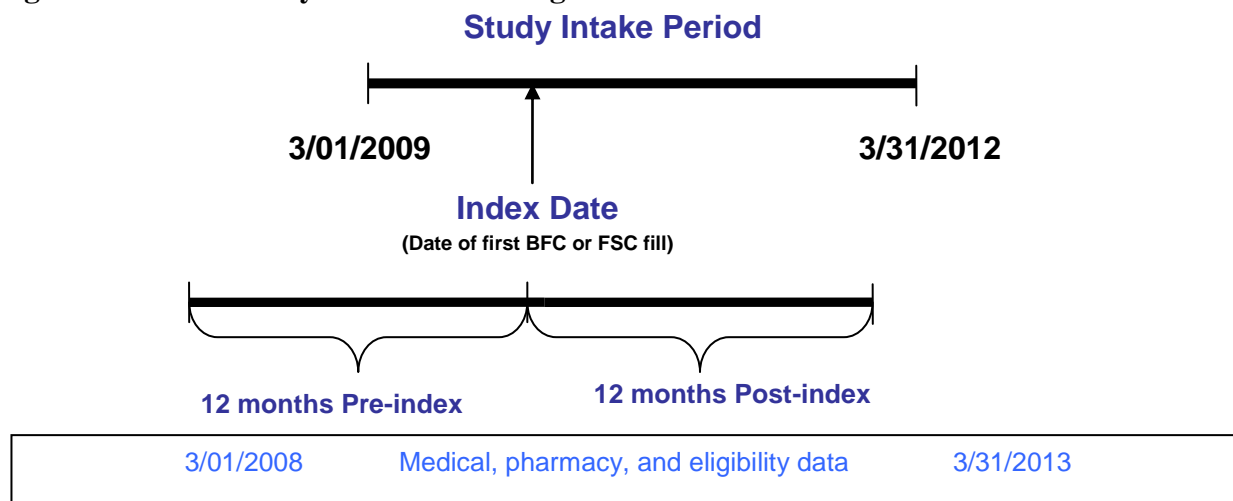
 Note: The *index date* may be at any time within the intake period. Health plan enrollment will be confirmed from each patient's index date.

Figure 2.   **Study Flow Chart**
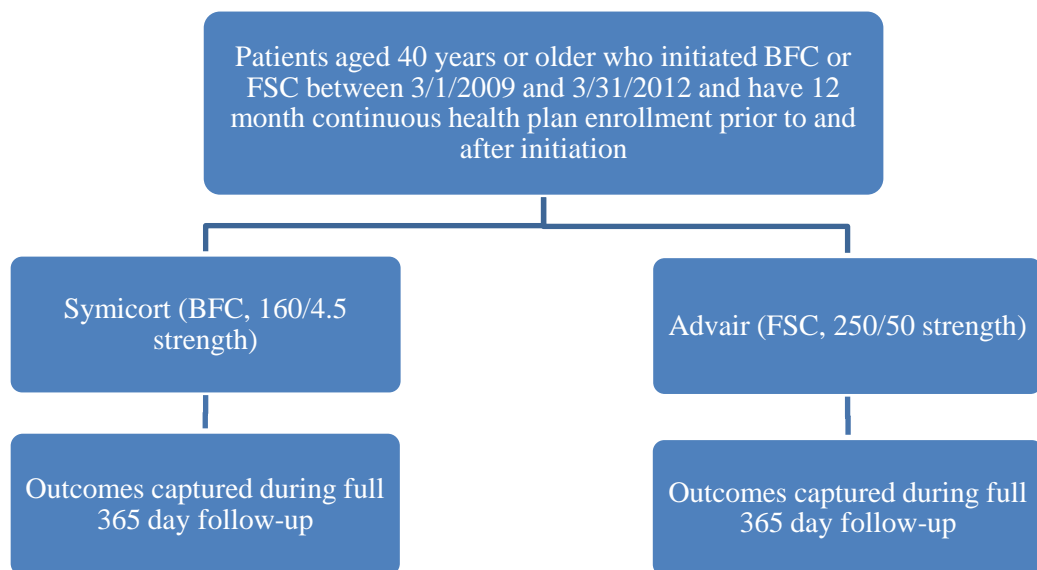
5.   STUDY DESIGN SELECTION AND RATIONALE

5.1   Rationale for study design

This is a retrospective matched cohort study utilizing administrative claims data from the HealthCore Integrated Research Environment (HIRE), which contains pharmacy and medical claims data for 32.1 million of patients. The administrative claims data will be utilized to describe COPD patients who are newly initiating BFC or FSC. A retrospective cohort study design allows us to easily capture the population of patients initiating BFC or FSC 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 ICS/LABA medications used for COPD maintenance currently available on the US market with a substantial patient population: Symbicort (BFC, 160/4.5 strength) and Advair (FSC, 250/50 strength). Dulera (MFC), a third ICS/LABA combination therapy, is not included as a comparator because it is only approved for asthma in the US.

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 3/31/2013 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 3/31/2013.

Current Data Availability:

Approximately 31.8 million lives having medical and pharmacy coverage in total database, with continuous eligibility for:

- ➢ 1 year – approximately 20.9 million

- ➢ 2 years – approximately 14.3 million

- ➢ 3 years – approximately 10.1 million

- ➢ 4 years – approximately 6.9 million

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

- ➢ 1 year – approximately 7.7 million

- ➢ 2 years – approximately 6.1 million

- ➢ 3 years – approximately 4.8 million

- ➢ 4 years – approximately 3.8 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 January 1, 2006 and extend to the most currently available data, March 31, 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.

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 (BFC or FSC), 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 BFC or FSC group. Table 1 in Appendix A presents the Generic Product Identifier (GPI) codes of interest for identifying claims for BFC and FSC prescriptions.

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

7.1   Participant eligibility

Members aged 40 years or older at the index date, with a COPD diagnosis as described above, in the HIRE from 3/1/2009 and 3/31/2012 will be eligible for this study.

7.1.1   Inclusion criteria

1. Patients must have at least one prescription fill for BFC (160/4.5 strength, per US COPD indication[5]) or FSC (250/50 strength, per US COPD indication[6]) during the intake period. Patients must be naive to ICS/LABA combination therapies in the year prior to first prescription claim.[1] The date of the first pharmacy claim (i.e. pharmacy process date) for one of the study medications during the intake period will be the *index date*. Patients using BFC or FSC will be identified via the use of Generic Product Identifier (GPI) Codes (See Appendix A for codes)

2. Patients must meet one of the following diagnosis criteria for COPD (see Appendix B for ICD-9 codes) during the 12 months prior to or on the index date:
    - At least one inpatient visit with a primary diagnosis for COPD, and/or
    - At least one ED visit with a COPD diagnosis (either primary or secondary), and/or
    - At least two other medical claims with a COPD diagnosis (either primary or

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

secondary)

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 enrollment <u>prior to and following</u> the index date, including continuous medical and pharmacy coverage

7.1.2 Exclusion criteria[2]

1. Patients with prescription claims for ICS/LABA combination (see Table 1 in Appendix A) during the 12 month pre-index period.

2. Patients with prescription claims for both BFC and FSC on the index date.

3. Patients with ≥180 days of total length of therapy for any OCS medication (see Appendix E) during the 12 month pre-index period.

4. Patients diagnosed with cancer (ICD-9 code 140.xx – 209.3x, 230.xx – 234.xx) during the 12 month pre-index period will be excluded due to their extreme costs and ability to skew the healthcare resource utilization and cost results of an entire population; and because of the inability distinguish between different stages of cancer/cancer severity to ensure comparable distribution of cancer patients between the two treatment groups. A cancer diagnosis requires at least two diagnoses for the same type of cancer (based on 3 digit ICD-9 codes) within 60 days of each other.[12]

8. EXPOSURES OF INTEREST

8.1 Drug-specific exposure/treatment

Budesonide/formoterol (BFC, Symbicort®, 160/4.5 strength) vs. Fluticasone/salmeterol (FSC, Advair®, 250/50 strength)

8.2 Treatment Compliance

Treatment compliance cannot be directly measured. The continuity of care (COC), 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 full definitions).

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

9.   PARTICIPANT FOLLOW-UP

All patients in this study will have at least 24 months of observation. Patient observation begins 12 months prior to the index date and extends through 12 months post-index. A sensitivity analysis of the primary outcome will include all follow-up data, which means observation will not end at the end of the 12 month post-index period and patients will be followed as long as possible until the end of the health plan enrollment or the end of the study period.

10.   DEFINITIONS OF OUTCOME VARIABLES

10.1   Primary outcome variables

The primary outcome of this study is to **compare the rates of COPD exacerbation** between BFC and FSC patients during the 12 month post-index follow up period.

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

The count of COPD exacerbations is the number of times that any of the three conditions defined below occur during the 12 month post-index period.

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

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

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

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

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

2. ED visits that result in a hospital stay will be counted as an inpatient hospitalization only.

3. Any OCS or antibiotic prescription fill defined above occurring within 14 days of an ED/inpatient hospitalization will be counted as the ED visit/hospitalization only, rather than a separate event.

4. If multiple OCS and/or antibiotic prescriptions are filled within 10 days of the same COPD visit, this will be considered one event.

10.2 Secondary outcome variables

10.2.1 Sensitivity and subgroup analysis for the primary outcome

The following sensitivity and subgroup analyses will be performed for the primary outcome. See Section 15.2.1 for more details on the statistical analysis of each.

Sensitivity analysis:

1. Time to first COPD exacerbation

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

   Follow up starts on the index date and continues for up to 365 days or until the first exacerbation, whichever comes first. The time to first COPD exacerbation will be calculated as the date of first COPD exacerbation minus index date.

2. On-treatment analysis

   Switching to non-index ICS/LABA medication during the post-index period may attribute an exacerbation to the index medication even though the patient was being treated with a different ICS/LABA therapy. To control for this effect, an on-treatment analysis will be conducted.

   For patients who fill a non-index ICS/LABA, follow-up will be stopped at the time of filling the non-index ICS/LABA medication (including Dulera). Patients who do not switch will be followed for the entire 12 month post-index period.

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

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

   Patients will be followed as long as possible until the end of the continuous health plan enrollment, or the end of the study period. All COPD exacerbations will be captured during the entire patient follow-up.

Subgroup analysis:

4. Switchers and non-switchers

   Switching index ICS/LABA medication[3] to other ICS/LABA medication (including Dulera) may make it difficult to attribute the outcome to the index medication. Thus, a

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[3] "switching" only refers to switching medication therapy within the ICS/LABA medication class.

descriptive analysis of the primary outcome for the BFC and FSC patients will be performed within the two following subgroups, separately:

- Switcher group includes patients who filled any other ICS/LABA medication (including Dulera, see Appendix A) at any time during the post-index period.
- Non-switcher group includes those who did not fill any other ICS/LABA medication (including Dulera) during the post-index period.

The subgroups will be analyzed descriptively only, with no formal inference. Further exploration and statistical analysis may be conducted if needed. See Section 15.2.2 for more details.

10.2.2 Rate of severe COPD exacerbation and each individual event during 12 month post-index period

1. <u>Severe exacerbation rate</u> (i.e. inpatient hospitalizations and ED-visits)

   Severe COPD exacerbation <u>ONLY</u> includes the following conditions:

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

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

2. <u>Individual components of an exacerbation separately</u>

   Individual components of exacerbation include:

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

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

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

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

1. COPD respiratory medication use (0 vs. 1+ event and total number of fills for each; see Appendix E): ICS, LAMA, LABA, roflumilast, theophylline, SABA, SAMA, SABA/SAMA combo, OCS, LTRA, omalizumab, and antibiotics use. The use of non-index ICS/LABA medications will be assessed in each cohort. Antibiotics use will be assessed overall and within 10 days of OCS Rx.

Total number of COPD medication classes filled: 0 vs. 1+, and also 0 through 12, individually.

10.2.4 COPD related healthcare utilization during 12 month post-index period

1. Presence of COPD exacerbation (0, 1, and 2+ events), overall and for each type of exacerbation, separately, during the 12 month post-index period will be evaluated for each patient. See Section 10.1 for definition of COPD exacerbation.

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

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

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

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

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

1. 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 visits (0 vs. 1+, and total number of events). An emergency department visit resulting in inpatient hospitalization will be counted as inpatient hospitalization only.

2. 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

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

1. Costs will be reported for the following resource uses: inpatient hospitalizations, ED visits, outpatient 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, skilled nursing facility) with any diagnosis for COPD. COPD prescription costs will include costs for any medications in Appendix A or Appendix E. All costs will be adjusted to year 2012 given the most accurate and updated consumer price index information provided by the Bureau of Labor Statistics for Medical Care Services (MCS).[13] The following types of costs will be captured:

- Plan paid costs

- Patient paid costs

- Total costs (plan paid + patient paid)

10.2.7 Treatment patterns and adherence

1. Continuity of care (COC): Continuity of care during the 12 month post-index period will be measured with the Bice and Boxerman index.[14] The original index allows for referral physicians and the physicians who referred them to count as one physician, however this level of granularity is not available in the HIRE and all physicians will be counted separately. Values range from 0 to 1, with 0 indicating that the patient saw a different physician at every medical visit and 1 indicating that the patient always saw the same physician. The equation for COC follows:

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

Where:

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

n_j = number of visits to provider j

s = number of providers

COC will only be determined for patients with ≥2 outpatient visits during the 12 month post-index period.

2. Proportion of days covered (PDC) will be used to measure the compliance of index medication (BFC or FSC) 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 1.0.

3. 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.

10.2.8 ICS/LABA switching

1. Switching: The number of patients who fill an ICS/LABA different from their index medication will be captured during the 12 month post-index period. The date on which patients fill an ICS/LABA different from their index medication will be the treatment switch date. (See Appendix A for codes.)

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

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

11.1 Demographic and clinical variables

11.1.1 Patient demographics

1. Age: Continuous and categorical (40-49, 50-59, 60-64, 65+)

2. Gender: Male, Female

3. Health plan type: HMO, PPO, CDHP

4. Geographic region: Northeast, Midwest, South, West

5. Index date:

    1. By year

    2. By quarter (within each year)

    3. By calendar month (regardless of year, to account for seasonality of the disease)

11.1.2 Index and Pre-index clinical characteristics

1. Comorbidities, defined by the presence of at least one ICD-9 diagnosis code in any position of a claim during the 12 month pre-index period (y/n for each, see Appendix C for codes): insomnia, allergic rhinitis, sinusitis, GERD, anxiety, major depressive

disorder, diagnosed obesity[4], 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

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

3. Prescribing physician specialty: Physician prescribing index treatment / providing care is a Pulmonologist, Internal medicine, Family medicine/general practitioner, Cardiologist, Allergist/Immunologist, Non-physician, or other specialty[5].

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

11.2 COPD related pre-index utilization and costs

11.2.1 COPD related utilization during 12 month pre-index period

The same measures captured for the post-index period will also be captured for the pre-index period. This includes: COPD respiratory medications (0 vs. 1+ for each); COPD related

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[4] 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.

[5] 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*

outpatient (0, 1, and 2+; and total number), ED (0, 1, and 2+; and total number), inpatient, (0, 1, and 2+; and total number) and ICU visits (0, 1, and 2+; and total number); lengths of stay for COPD related inpatient and ICU visits; COPD related procedures (0 vs. 1+ and total number). See sections 10.2.3 and 10.2.4 for complete definitions.

11.2.2   COPD related costs during 12 month pre-index period

Similar to the post-index costs in section 10.2.6, COPD related 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 (primary diagnosis for COPD)
- ED visits (any diagnosis for COPD)
- Outpatient visits (any diagnosis for COPD)
- Other medical costs (skilled nursing facility with any diagnosis for COPD)
- Total medical
- COPD medication prescriptions

All costs will be adjusted to year 2012 based on U.S. medical care services consumer price index (CPI) from Bureau of Labor Statistics.[13]

11.3   All cause healthcare utilization and costs

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

1. Frequency of all-cause healthcare utilization during the 12 month pre-index period will be captured similarly to the post-index utilization outlined in Section 10.2.5 for the following categories: Inpatient stay and length of stay, ICU admissions and length of stay, ED visits, and outpatient visits. Emergency department visit resulting in inpatient hospitalization will be counted as a hospitalization only.

2. 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 visits
- Other medical (skilled nursing facility)
- Total medical
- Total pharmacy

All costs will be adjusted to year 2012 based on U.S. medical care services consumer price index (CPI) from Bureau of Labor Statistics.[13]

12. VALIDATION OF PNEUMONIA DIAGNOSIS MEDICAL CHART REVIEW

12.1 Pneumonia diagnosis to be validated

The diagnosis codes used to identify pneumonia (see Appendix L), including both viral pneumonia and bacterial pneumonia, in the administrative claims database will be validated through medical chart review.

12.2 Patients included for the medical chart abstraction

A subset of study patients who have at least one medical claim with a pneumonia diagnosis during the post-index period (see Appendix L) will be identified from the administrative claims data for the inpatient and outpatient medical chart abstraction to validate the claims based identification of pneumonia patients.

12.3 Medical chart abstraction process

HealthCore will develop a chart abstraction form and provide a chart vendor with a patient sample list and the chart abstraction form. A HIPAA Waiver of Authorization will be applied for from an Institutional Review Board (IRB). Once this waiver is approved, provider offices and other health care facilities do not need to obtain patient authorization for HealthCore to access charts for research purposes.

To help ensure consistency of data collection, the chart reviewers will be trained on the study's design and presented with a standardized data collection form that will be developed by HealthCore and AstraZeneca and approved by the IRB. The chart vendor will obtain the inpatient and outpatient charts, abstract the data, and provide HealthCore with a data file of abstracted Information. As part of the training, a pilot phase will be conducted to review a sample of charts (i.e., 5-10 charts) to help ensure that the abstractors are accurately collecting the data.

All chart abstractions will be conducted by trained nurses or pharmacists and all data will be entered into a study database maintained by HealthCore with a masked identifier so that it can be matched with corresponding claims data without the use of identifiers, such as patient name or medical record number. A limited number of specifically designated protected health information (PHI) users exist at HealthCore. Those users will link the PHI with masked patient identification number, date of birth and provider information for the patients selected for inclusion in the medical/hospital chart abstraction. HealthCore will use the data entered into the secure database to complete the validation analysis.

12.4 Validation statistics

For the validation analysis, the validity of the administrative claims will be evaluated by finding out whether or not the patient has a diagnosis of pneumonia in the medical charts (yes vs. no).

The presence of diagnosis may come from either a diagnosis code for pneumonia or a written statement from the physician on the chart stating a pneumonia diagnosis.

The positive predictive value (PPV) for any diagnosis of pneumonia will be calculated using the medical chart review as the gold standard. PPV represents the proportion of pneumonia positive patients identified through the claims code algorithm that are true positives according to the medical chart. A PPV greater than or equal to 80% will considered acceptable. If the PPV falls below 80% the study will not move forward with the pneumonia analysis (Section 13).

Figure 3.   Positive predictive value calculation

	Medical Chart Review (Gold Standard)		
	Positive	Negative	
Claims code algorithm Positive	True Positive (N1)	False Positive (N2)	————

12.5   Other variables to be captured

In addition to the pneumonia diagnosis, the presence of symptoms and diagnostic tests which are typically present in a pneumonia patient will be described. The following variables have been shown to be common and/or specific to pneumonia based on medical chart reviews:[15]

Presence of symptoms and signs of pneumonia (present, absent, or unknown for each):

1. Cough
2. Fever
3. Chest pain
4. Chills
5. Dyspnea
6. Rales
7. Rhonchi
8. Wheezing
9. Decrease breath sounds
10. Temperature >100F (37.8C)

Presence of procedures/tests (present, absent, or unknown) and abnormal results (normal, abnormal, unknown) for pneumonia:

1. Respiratory rate
2. Heart rate
3. Chest X-ray
4. Chest CAT scan

5. Sputum gram stain
6. Sputum culture
7. Blood culture
8. Pleural Fluid Culture
9. Legionella Urine Antigen
10. Pneumococcal Urine Antigen

Other variables related to pneumonia:

1. Smoking status (active, former, never, unknown)
2. Smoking history – pack-year (number of pack-years, or unknown)
3. Initial antibiotic regimen (name of antibiotic)

13. DEFINITIONS OF PNEUMONIA VARIABLES

All variables defined in this section will be analyzed after the pneumonia diagnosis has been validated via medical chart review with a PPV ≥80% (see Section 0 for the details).

13.1 Pneumonia rate during the 12 month post-index period

Pneumonia rate will be calculated as the proportion of COPD patients who initiating BFC or FSC with at least one pneumonia diagnosis (see Appendix L for codes) during the 12 month post-index follow-up. The rate will be captured for the overall study population and separately for those identified via pneumonia related inpatient, ED, or outpatient visits.

13.2 Pneumonia related healthcare utilization and costs

13.2.1 Pneumonia related healthcare utilization during the 12 month post-index period

1. Pneumonia related outpatient visit (0 vs. 1+ events and total number of events): defined as any claim for an outpatient visit (anything other than an ED visit, inpatient visit, or skilled nursing facility visit) with at least one diagnosis for pneumonia.

2. Pneumonia related inpatient hospitalization visit (0 vs. 1+ events and total number of events): defined as hospitalizations with a diagnosis at any position for pneumonia.

   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.

3. Pneumonia related ED visit (0 vs. 1+ events and total number of events): defined as ED visit with a diagnosis at any position for pneumonia.

13.2.2 Pneumonia related healthcare costs during the 12 month post-index period

Costs will be reported for the following pneumonia related events: inpatient hospitalizations, ED visits, outpatient visits, and skilled nursing facility stays with any diagnosis for pneumonia. 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:

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

13.2.3 Pneumonia related healthcare utilization during the 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: pneumonia related outpatient, ED, and inpatient visits; lengths of stay for pneumonia related inpatient visits; See sections 13.2.1 for complete definitions.

13.2.4 Pneumonia related healthcare costs during the 12 month pre-index period

Similar to the post-index costs section 10.2.6, pneumonia related 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 pneumonia related utilizations:

- Inpatient hospitalizations
- ED visits
- Outpatient visits
- Skilled nursing facility
- Total medical

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]

14.   DATA MANAGEMENT

14.1   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.

14.2 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.

14.3 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.

15. STATISTICAL METHODS AND SAMPLE SIZE

15.1 Propensity score matching

The BFC and FSC cohorts are 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 measured pre-index, and create more comparable BFC and FSC cohorts.[16-18] The propensity score for each individual will be estimated as the probability of receiving BFC conditional on observed baseline characteristics. Random forests will be used to estimate the propensity scores as the probability of receiving BFC therapy.[19] The R package randomForest will be used for this estimation. The outcome variable in the model is dichotomous, indicating whether a patient received BFC (1) or FSC (0) therapy.

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

Variables that must be balanced:

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

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

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

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

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

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

9. Gender (chi-square test)

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

Additional variables to be balanced, sample size permitting:

11. Index month (chi-square test)

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

13. 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) (chi-square tests)

14. 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]) (chi-square test)

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

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

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

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

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

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

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

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

The propensity scores will be used to match a patient from the FSC cohort to a patient in the BFC 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 BFC and FSC patients. Treatment cohorts will be considered well balanced for a given variable if the difference between groups is having p>0.05. Any of the variables from #10-21 above not balanced after propensity score matching will be included as covariates in the multivariate analysis of post-index outcomes.

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

Before the matching algorithm is performed, the two cohorts will be separated into their own datasets and sorted by propensity scores obtained from the random forest 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 BFC cohort will be selected to find a matching patient in the FSC cohort. Using estimated propensity scores, the BFC cohort patient will be matched with a patient in the FSC therapy cohort who has a similar predicted probability using the Greedy nearest neighbor 1:1 matching technique (with no replacement).[18] 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 FSC 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 FSC patients (using random number generation with a specified seed of 52784), so that if two or more FSC 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 at least 1,500 per group after matching). See Section 15.3 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.

15.2 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. BFC
2. FSC

Statistical testing (two-sided) will be done for comparisons between the propensity score matched FSC and BFC cohorts with FSC 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, not adjust for multiplicity, and $p<0.05$ will be considered statistically significant. The adjustment for multiplicity is not necessary in this study because there is only one pre-defined primary outcome compared between two comparison cohorts in this study, with all secondary outcomes and sensitivity/subgroup analysis being considered as supportive results.

All possible confounders that are not balanced/significantly different ($p<0.05$) between treatment cohorts will included in the model.

Possible confounders to be included as covariates include:

- Those listed in Section 15.1, but not balanced after the propensity score matching ($p<0.05$)

- As well as other covariates (if p<0.05 between groups): DCI score, index year, prescribing physician type (other than pulmonologist listed above), health plan type, geographic region, other comorbid conditions (see Appendix H)
- Analogous pre-index variable (regardless of p-value): For each post-index outcome, the analogous pre-index variable will be controlled for (e.g., when analyzing the number of COPD related hospitalizations in the post-index, the model will control for the number of pre-index COPD related hospitalizations).

15.2.1   Statistical model for the primary outcome:

A **GLM** model using **negative binomial** and **a log link function** will be used to model the number of exacerbations. If there is any imbalance in any of the variables listed in Section 15.1, the GLM model will adjust for covariates using the covariate selection methodology explained in the previous paragraph. A 95% confidence interval will be provided with the rate ratio (relative risk) along with a corresponding p-value. A confidence interval that does not include 1.0 will be considered statistically significant ($p<0.05$), though the magnitude of the point estimate (i.e., relative risk) and width of the confidence interval will be primarily used for interpretation of results.

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

15.2.2   Statistical models to be used for secondary outcomes

Sensitivity and subgroup analyses for the primary outcome

Time to first event: Outcome will be the time to first COPD exacerbation event. Patients will be censored at the first event. A Cox proportional hazards model will be used, adjusting for covariates, to calculate the hazard ratio and its 95% confidence interval along with a corresponding p-value.

Subgroup analysis of switchers and non-switchers: A subgroup analysis, which will only involve the descriptive analysis of the primary outcome, will be performed within only those patients who do not fill any other ICS/LABA medications during the post-index period; and alternatively within patients who fill the other ICS/LABA medications during follow-up. Descriptive statistics (e.g. means and CI's) will be produced. No formal inference will be made, but further exploration of the data can be done if required. These subgroup results should be interpreted in line with the overall population result (e.g. by means of a forest plot) and with caution

Subgroup analysis of patients aged 65 years or older: A subgroup analysis will be performed for the primary outcome within patients aged 65 years or older at the index date. The analysis will be

performed in the same manner as the primary outcome (exacerbation rate analyzed via GLM with negative binomial distribution and log link)

Sensitivity analysis looking beyond 12 months: Perform primary analysis allowing for follow-up greater than 12 months. The analysis will be performed in the same manner as the primary outcome (exacerbation rate analyzed via GLM with negative binomial distribution and log link), except that the entire patient history will be used and patients will be censored at the time they are lost to follow-up instead of 12 months.

Severe COPD exacerbation and individual exacerbation outcomes

Severe exacerbation**:** Perform primary analysis with only two possible end points: 1) inpatient hospitalization with a primary diagnosis of COPD; or 2) an ED visit with a COPD diagnosis.

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

Other secondary outcomes

Models and the descriptive statistics to be reported differ by outcome type. All statistical models will adjust for covariates as described in the beginning of Section 15.2.

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

   - Logistic regression will be used for all-cause 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 all-cause 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.

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

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

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

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

- COC, MPR, PDC – differences between cohorts analyzed using Gaussian (i.e., normal) regression

15.2.3   Pre-index analyses

Bivariate analysis, unadjusted for covariates, will be performed for the following baseline variables to make sure the comparable cohorts balanced via the propensity matching technique. Point estimates, 95% confidence intervals, and p-values will be reported alongside descriptive statistics (frequency/% or mean/sd/median):

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

- All-cause, COPD related, and pneumonia 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.

15.2.4   Pneumonia analyses

After the pneumonia diagnosis is validated, pneumonia related outcomes will be analyzed as outlined below:

1. Pneumonia rate:
   a. Overall proportion: Logistic regression, adjusting for covariates, will be used to analyze the proportion of patients with at least on pneumonia diagnosis during the post-index period. Frequencies, proportions, odds ratios, 95% confidence intervals, and corresponding p-values will be reported.
   b. Time to event: Cox regression, adjusting for covariates, will be used to model the time to first pneumonia diagnosis during the 12 month post-index period. Hazard ratios, 95% confidence intervals, and corresponding p-values will be reported.
2. Pneumonia related healthcare utilization and costs: analysis will be done similarly to the analysis of all-cause and COPD related healthcare utilization and costs. Please refer to the analyses plan outlined in sections 15.2.2 and 15.2.3.

15.2.5   Other analyses

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

15.3   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 BFC vs. FSC in the reduction of COPD exacerbations in COPD patients during the 12 month before initiation of BFC vs. FSC is tested by using a negative binomial regression model with a dispersion effect of 1.2.

The expected exacerbation rate for an ICS/LABA patient is assumed to be 0.5 per person/year (based on the RAMQ-study[8]) and the expected clinically meaningful reduction for a BFC patient is 20% (which are 0.4 exacerbations per person/year). These assumptions together with an alpha level of 0.05 and a 90% power and a dispersion effect of 1.2 give a sample size of 1457 matched subjects in each cohort. We will use all matched subjects fulfilling the inclusion and exclusion criteria in the database.

Based on these calculations, this study will not be conducted if the sample size falls below 1,500 patients in each group.

16. STRENGTHS AND LIMITATIONS

Strengths

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

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

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

4. In addition to the validation of pneumonia diagnosis, 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 other validation analysis if necessary.

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

Limitations

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

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

3. Non-observed characteristics such as race and education may impact the observations

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 pharmacy medications are not present in the claims data

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

8. Obesity can only be identified through use of ICD-9 codes. Therefore results should be interpreted with caution.

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

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

11. Off-label use of the study medications is not captured and there may be ICS dose relationship to the increased risk of pneumonia.[20] Thus, the results of this study may not be generalized to overall BFC or FSC users with COPD.

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

Database study protocol template v2/7-14-2011

17. ETHICAL CONSIDERATION

See section 14.1 for data confidentiality and patient privacy protections.

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

18. ADVERSE EVENT REPORTING

Not applicable. All data is captured retrospectively.

19. 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.

20.   REFERENCES

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

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

3.   Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013 Feb;187(4):347-65.

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

5.   SYMBICORT Prescribing Information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021929s021lbl.pdf 6-20-2013.

6.   ADVAIR DISKUS Prescribing Information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021077s042lbl.pdf 6-20-2013.

7.   Larsson K, Janson C, Lisspers K, Jorgensen L, Stratelis G, Telg G, Stallberg B, Johansson G. Combination of budesonide/formoterol more effective than fluticasone/salmeterol in preventing exacerbations in chronic obstructive pulmonary disease: the PATHOS study. J Intern Med 2013 Jun;273(6):584-94.

8.   Blais L, Forget A, Ramachandran S. Relative effectiveness of budesonide/formoterol and fluticasone propionate/salmeterol in a 1-year, population-based, matched cohort study of patients with chronic obstructive pulmonary disease (COPD): Effect on COPD-related exacerbations, emergency department visits and hospitalizations, medication utilization, and treatment adherence. Clin Ther 2010 Jul;32(7):1320-8.

9.   Roberts M, Mapel D, Petersen H, Blanchette C, Ramachandran S. Comparative effectiveness of budesonide/formoterol and fluticasone/salmeterol for COPD management. J Med Econ 2011;14(6):769-76.

10. Cave CA, Hurst MM. The use of long acting b$_2$-agonists, alone or in combination with inhaled corticosteroids, in Chronic Obstructive Pulmonary Disease (COPD): A risk-benefit analysis. Pharmacology & Therapeutics 2013 Jan;130(2):114-43.

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

12. Setoguchi S, Solomon DH, Glynn RJ, Cook EF, Levin R, Schneeweiss S. Agreement of diagnosis and its date for hematologic malignancies and solid tumors between medicare claims and cancer registry data. Cancer Causes Control 2007 Jun;18(5):561-9.

13. Bureau of Labor Statistics. Series CUUR0000SAM2. http://www.bls.gov/cpi/home.htm 6-20-2013.

14. Bice TW, Boxerman SB. A quantitative measure of continuity of care. Med Care 1977 Apr;15(4):347-9.

15. Eversten J, Baumgardner DJ, Regnery A, Banerjee I. Diagnosis and management of pneumonia and bronchitis in outpatient primary care practices. Prim Care Respir J. 19, 237-241. 9-1-2010.

16. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. Am J Epidemiol 2010 Nov;172(9):1092-7.

17. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Stat Med 2008 May;27(12):2037-49.

18. Parsons, LS Reducing bias in a propensity score matched-pair sample using greedy matching techniques; In SAS SUGI 26, 2001, Paper 214-226. 6-20-2013.

19. Lee B, Lessler J, Stuart E. Improving propensity score weighting using machine learning. Stat.Med 29, 337-346. 1-1-2010.

20. Cave CA, Hurst MM. The use of long acting β_2-agonists, alone or in combination with inhaled corticosteroids, in Chronic Obstructive Pulmonary Disease (COPD): A risk-benefit analysis. Pharmacology & Therapeutics 2013 Jan;130(2):114-43.

Appendix A   ICS/LABA medications

Table 1: Study medications

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

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

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

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 muscarinic antagonists (LAMA)	
Aclidinium Bromide (Tudorza®)	4410000710
Tiotropium Bromide (Spiriva®)	4410008010
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

Drug Substance Symbicort
Study Code 000152
Date

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

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

Appendix G   Respiratory procedures

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

Appendix H   Cardiovascular conditions

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

Appendix I   Vaccination codes

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

Appendix J   Psychotropic medication codes

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

Appendix K   Cardiovascular Medications

Medication	GPI Codes	HCPCS Codes
Anti-platelet Medications		
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   Claims code algorithms to identify pneumonia patients

Pneumonia Category	ICD-9 Dx Code
Pneumonia	
Viral pneumonia	480.xx
Bacterial pneumonia	481.xx, 482.xx, 483.xx, 484.xx, 485.xx
Other/unspecified pneumonia	486.xx