Research Protocol

Title: COPD Severity and Adherence to GOLD Guidelines in the Community Pharmacy Setting

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Community Pharmacist Investigators

Each of the 35 study pharmacies will have **one** community pharmacist investigator, who will be approved by the STLCOP and added to the STLCOP investigators at a later date. **NOTE: A community pharmacy will not begin recruiting and enrolling participants until the community pharmacist investigator has been approved by the STLCOP IRB.**

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ABBREVIATIONS

COPD	Chronic obstructive pulmonary disease
HIE	Health information exchange
PFT	Pulmonary function test
CAT	COPD assessment test
mMRC	Modified Medical Research Council
CPI	Community pharmacist investigator
STLCOP	St. Louis College of Pharmacy
PDC	Proportion of days covered
MHC	Missouri Health Connection
MO-PCN	Missouri Pharmacist Care Network
NCPA	National Community Pharmacists Association
MPA	Missouri Pharmacists Association
GOLD	Global Initiative for Chronic Obstructive Lung Disease
LABA	Long-Acting Beta Agonist
SABA	Short-Acting Beta Agonist
ICS	Inhaled Corticosteroid
LAMA	Long-Acting Muscarinic Antagonist
PDE	Phosphodiesterase
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
DLCO	Diffusion capacity of carbon monoxide
SILS	Single-Item Literacy Screener
PSAO	Pharmacy Services Administration Organization

1. INTRODUCTION/BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a progressive airflow limitation marked by an inflammatory response of the airways to noxious particles or gases.[1] The incidence and prevalence in the United States varies significantly. According to the Centers for Disease Control and Prevention (CDC), the lowest prevalence in states ranges from 3.1-4.4%. The prevalence in Missouri, and several other high-prevalence states, ranges from 7.0 to 9.3%.[2] Analysis of the 2011 Behavioral Risk Factor Surveillance System (BRFSS) revealed that among BRFSS respondents in all 50 states, the District of Columbia, and Puerto Rico, 6.3% reported they'd been diagnosed with COPD.[3] The incidence and prevalence of COPD is expected to continue to rise as the population ages and people maintain exposure to cigarette smoke.[1] Although COPD was the 6th leading cause of death in 1990, it is estimated that COPD will be the third leading cause of death worldwide by 2020.[1] The economic burden to society is great. COPD costs the nation approximately $30 billion in direct care costs and $20 billion in indirect costs annually.[1]

In 2010, Missouri had one of the highest age-standardized death rates at 48-66 per 100,000 persons. COPD and its related conditions caused 528 deaths in St Louis City and County.[4] In 2009-2010, the highest rates of hospitalization due to COPD were located along a strip of adjacent ZIP codes which stretch northwest away from downtown St. Louis City. According to the CDC, approximately 8.0% (age-adjusted = 7.6%) of Missouri residents surveyed in 2011 reported being told by a health care professional that they have COPD.

In an effort to standardize care for patients with COPD, the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) introduced The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines in 2001. These guidelines are updated yearly and are evidence-based. They provide recommendations related to the diagnosis, treatment, and prevention of COPD.[1] Despite evidence-based guidelines, patients may go undiagnosed, untreated, undertreated, or even overtreated. It is estimated that only 55% of ambulatory COPD patients receive care as prescribed by guidelines.[5] Among patients surveyed in the BRFSS, those with COPD that completed an optional module, only 76.0% reported they'd been given a diagnostic breathing test, and only 55.6% were taking at least one daily medication for their breathing. Additionally, less than 50% reported seeing a physician for their breathing in the past 12 months.[3] It would be valuable to assess adherence with objective data in addition to patient reports.

Patients may not seek medical attention until the symptoms associated with COPD impact the individual's quality of life. This may take several decades of smoking or exposure to other risk factors. Therefore, patients may not present early in the disease process when airflow limitation is present with absent or minimal symptoms. Conversely, symptoms, such as chronic sputum and progressive cough may develop and precede shortness of breath, which patients may perceive to be due to long-term smoking and not an actual disease.

Patients with COPD often have poor medication adherence due to a number of factors. As the disease progresses, COPD typically requires more than one medication, which may not be delivered by similar devices. An analysis of electronic prescription and filled claims data revealed that almost 25% of first-time prescriptions were never initially obtained by the patient (i.e., primary non-adherence).[6] Also, adherence to multiple-dose inhaled regimens is historically low[7] and use of multiple delivery devices can be confusing and result in inadequate device

technique.[8] Available data on adherence comes from subjects in clinical studies and may not reflect medication-taking behavior of the typical patient.[10, 11]

Pharmacists are well positioned within the healthcare team to assist and educate patients with COPD. However, because of the lack of patient-specific health information (e.g., pulmonary function tests and exacerbation history) at the community pharmacy level, it can be very challenging for pharmacists to fully assess the appropriateness of a patient's medication regimen according to the GOLD staging criteria and risk stratification.

The progressive nature of COPD, as well as the social burden and economic impact to society, highlights the need for current information regarding community-dwelling patients with the disease. Data from Spain[12] and Japan[13] reveal under-diagnosis and suboptimal treatment of patients with COPD. Less is known about patients in the U.S., however. These patients visit community pharmacies regularly to obtain their medications. Community pharmacists have access to the patient's medication fill history, which may provide insight into patient behaviors that are not reflected in claims data alone. It would be advantageous to link medication adherence data from community pharmacy profiles with current COPD diagnosis and risk stratification to assess the appropriateness of medication use according to the GOLD guidelines.

2. OBJECTIVES

2.1. Primary

Objective 1
Determine the GOLD combined assessment (patient category A, B, C, or D), based on the following information:

- Degree of severity of airflow limitation (GOLD spirometric classifications 1 through 4), using post-bronchodilator FEV_1
- Patient symptoms and breathlessness of COPD, using the CAT or the mMRC questionnaires
- Risk of future COPD exacerbations and related hospitalizations, using the history of previous treated events in the past 12 months

2.2. Secondary

Objective 2
Determine the level of agreement between the GOLD combined assessment categories, when using the CAT versus the mMRC questionnaire, for COPD symptoms.

Objective 3
Evaluate the appropriateness of drug therapy for COPD, using GOLD guidelines, based on the combined assessment category of COPD severity.

2.3. Exploratory

Objective 4
Assess patient adherence to chronic COPD medications for the 12 months prior to study enrollment.

3. RESEARCH METHODOLOGY

3.1. STUDY DESIGN

This study will employ a cross-sectional design using validated written questionnaires. Data will be collected from study participants identified at 35 community pharmacies across the state of Missouri with an expected sample size of 875 participants (approximately 25 participants per community pharmacy). See **Appendix A** for a complete listing of pharmacies and a map of their approximate geographic location.

3.2. STUDY POPULATION

3.2.1. ELIGIBILITY CRITERIA

3.2.1.1. Inclusion Criteria

- Age 40 years and older
- Patient-reported history of COPD (ICD-9 = 491.20; ICD-10 = J44.9)
- Using at least one medication to treat COPD within past 12 months (365 days)
- English-speaking
- Willing and able to participate in a face-to-face study visit with the community pharmacist and complete the participant questionnaire

3.2.1.2. Exclusion Criteria

- Cognitive impairment that might limit their ability to participate in a face-to-face study visit and provide accurate information
- Previous participation in this study at a different pharmacy site

3.2.2. SAMPLING

Once the participant enrollment process begins, the CPIs will have up to 6 months to enroll subjects. Although the goal for each pharmacy will be to enroll 25 participants, high-performing pharmacies may be allowed to recruit more than 25 participants, if approved by the Principal Investigator. Using standardized convenience sampling methods, patients will be recruited by registered community pharmacist investigators (CPIs) in pharmacies across Missouri in the following manner.

- The investigators will obtain a waiver of consent from the STLCOP IRB for the *initial phase* of recruitment. This waiver of consent will allow the CPI to generate an initial report (and any subsequent reports of similar content, should subject recruitment slow after the initial report) used to identify potential study participants. The report will contain the following fields: patient name, current patient age (or date of birth), drug name, and fill date.

- The CPI, or another member of the pharmacy staff, will generate an electronic report from dispensing records for the past 12 months (365 days) to identify patients who had filled one or more of the following prescription medications:

Drug Class	**Medication**
Short-acting beta agonist (SABA)	**albuterol** (Proair, Ventolin) **levalbuterol** (Xopenex)
Short-acting muscarinic antagonist (SAMA)	**ipratropium** (Atrovent)
Combination SABA/SAMA	**albuterol/ipratropium** (Combivent)
Long-acting beta agonist (LABA)	**arformoterol** (Brovana) **formoterol** (Foradil) **indacaterol** (Arcapta) **olodaterol** (Striverdi) **salmeterol** (Servent)
Combination ICS/LABA	**budesonide/formoterol** (Symbicort) **fluticasone fumerate/vilanterol** (Breo) **fluticasone propionate/salmeterol** (Advair) **mometasone/formoterol** (Dulera)
Long-acting muscarinic antagonist (LAMA) or long-acting anticholinergic (LAAC)	**aclidinium** (Turorza) **glycopyrrolate** (Seebri) **tiotropium** (Spiriva) **umeclidinium** (Incruse)
Oral PDE-5 inhibitor	**roflumilast** (Daliresp)
Theophylline	**theophylline** (Various)
Combination LABA/LAMA	**glycopyrrolate/indacaterol** (Utibron) **tiotropium/olodanterol** (Stiolto) **umeclidinium/vilanterol** (Anoro)

- Next, the CPI will attempt to contact the patients from the pharmacy, either by phone or in-person, in a non-randomized fashion, to assess the patients' level of interest in participating in the project. Using a standardized script as a guide (see **Appendix B**), the community pharmacist will briefly explain the responsibilities and verbally confirm whether the patient meets the eligibility criteria to participate.
- If a patient verbally agrees to participate in the study, then the CPI will schedule a face-to-face visit at a mutually convenient time, ideally within the ensuing 30 days, to complete the study enrollment process and conduct the study visit. Before any data can be collected, all study participants must sign a written informed consent document and provide their written authorization (see **Appendix C**) for their physician to release their pulmonary function test/spirometry results to the study investigators.
- If the patient declines to participate in the study, then the CPI will thank them for their time and consideration and tell them that their lack of participation will not affect their relationship with the pharmacy in any way.
- For patients who do not participate in the study, the following reasons will be retained (**in de-identified form only**) for analysis:
  - Reason for not participating in the study
    - ✓ Patient contacted, but declined to participate in the study
    - ✓ Unable to contact patient by phone or in person OR did not attempt to contact patient
    - ✓ Patient has expired
    - ✓ Patient no longer obtains prescriptions from this pharmacy
    - ✓ Patient denies having COPD
    - ✓ Patient no longer takes any medication for COPD
    - ✓ Patient is not English-speaking
    - ✓ Patient is unable to participate (e.g., cognitive impairment)
    - ✓ Previous participant in study at a different pharmacy
    - ✓ Other
  - Patient age
    - ✓ 40-49 years
    - ✓ 50-59 years
    - ✓ 60-69 years
    - ✓ 70-79 years
    - ✓ 80-89 years
  - Number of COPD medications
  - Sex
    - ✓ Male
    - ✓ Female
  - ZIP code of PHARMACY

3.3. DATA SOURCES / DATA COLLECTION

The data sources for this study will include

Data Source	Content
Structured and Standardized Study Visits and Written (participant self-administered) Questionnaires	• Assessment of COPD symptoms, via the CAT • Assessment of breathlessness, via the mMRC • Assessment of past COPD exacerbations (number of exacerbations and hospitalizations for COPD within the past 12 months) • Demographic information • Smoking status and nicotine replacement use • Comorbidities • Health literacy screening (Single-Item Literacy Screener [SILS]) • Pulmonologist name, if applicable • Health insurance information • Source(s) of COPD medications • Participant out-of-pocket costs for medications
Pharmacy Fill Data	Information on each member's prescription fill (COPD medication, systemic antibiotic, or systemic glucocorticoid) will include: • Drug name • National Drug Code (NDC) • Fill date • Quantity dispensed • Days' supply • Copay (participant's out-of-pocket costs for the prescription) • Prescriber name • Patient name • Patient date-of-birth (DOB) • Sig (directions)
Prescriber Data	Most recent pulmonary function test/spirometry results, when available

***NOTE**: Full details of all study procedures are provided in **Appendix D**.*

3.3.1. ENDPOINTS

3.3.1.1. Primary Endpoint

Objective 1

- **GOLD Combined Assessment Category.** Data to determine this category will be obtained from 1) the participant (using two standardized questionnaires for COPD symptoms and exacerbations); 2) the medication fills (for systemic antibiotics and glucocorticoids to verify COPD exacerbations) provided by the community pharmacy; and 3) spirometry results provided by the patient's physician(s). See definitions below. The GOLD combined assessment category, using current clinical practice guidelines (2016), will be established according to the following table:

Risk GOLD classification of airflow limitation					**Risk** Exacerbation history in past 12 months
	4	**C**	**D**	≥2 or ≥1 leading to hosp.	
	3				
	2	**A**	**B**	1 (not leading to hosp)	
	1			0	
		mMRC 0-1 CAT < 10	mMRC ≥2 CAT ≥ 10		
		Symptoms (mMRC or CAT score)			

- **The GOLD classification of airflow limitation** is based on the most recent pulmonary function test/spirometry results, within the past 36 months prior to enrollment, (obtained via FAX from the prescribing physician or the pulmonologist) according to the following table:

In patients with FEV_1/FVC <0.70:		
GOLD Classification	**Severity**	**Post-Bronchodilator FEV_1**
1	Mild	<80% predicted
2	Moderate	50% to 80% predicted
3	Severe	30% to 50% predicted
4	Very Severe	<30% predicted

- **The risk of future exacerbations**, according to the GOLD guidelines, is based on previous exacerbations (within the past 12 months) and the scoring is included above in the Combined Assessment Category table. An exacerbation is defined as the use of a systemic steroid or antibiotic for a COPD exacerbation. Hospitalization is defined as a hospitalization OR emergency department visit for COPD. This information will be patient-reported on the participant questionnaire and the medication use (antibiotic or systemic steroid for COPD) will be confirmed with pharmacy fill data obtained from the community pharmacy.

- **COPD Assessment Test (CAT)**—This validated instrument, included in our participant-reported questionnaire, measures several aspects of breathing (e.g., cough, phlegm, etc.). This instrument is recommended in the GOLD guidelines to assess COPD symptoms. See **Appendix C**.

- **Modified Medical Research Council Dyspnea Scale (mMRC**)—This validated instrument is a single-item questionnaire, included in our participant-reported questionnaire, which measures shortness of breath with activity. See **Appendix D**.

3.3.1.2. Secondary Endpoint(s)

Objective 2

- **GOLD Combined Assessment Category**—This is defined above, in Objective 1.

- **COPD Assessment Test (CAT)**—This is defined above, in Objective 1. See **Appendix E.**

- **Modified Medical Research Council Dyspnea Scale (mMRC)**—This is defined above, in Objective 1. See **Appendix F**.

Objective 3

- **Appropriate Treatment.** Appropriate treatment is defined as a patient having filled (see Section 3.3) a COPD medication from a drug class (defined in Section 3.2.2), listed in the table below, and based on the Combined Assessment Patient Group (GOLD, see 3.3.1.1, Objective 1 above). We will analyze according to 1) Recommended First Choice; 2) Recommended First Choice OR Alternative Choice; and 3) Recommended First Choice OR Alternative Choice OR Other Possible Treatment.

Patient Group	Patient characteristics	Recommended first choice	Alternative choice	Other possible treatments*
A	Low risk, less symptoms GOLD grade 1-2 mMRC score0-1, CAT < 10 Exacerbation history 0-1 (not leading to hosp.)	SABA PRN **OR** SAAC PRN	LAAC **OR** LABA **OR** SABA /SAAC combo scheduled	Theophylline
B	Low risk, more symptoms GOLD grade 1-2 mMRC score >2, CAT ≥ 10 Exacerbation history: 0-1 (not leading to hosp.)	LAAC **OR** LABA	LAAC **AND** LABA	SABA AND/OR SAAC Theophylline
C	High risk, less symptoms GOLD grade 3-4 mMRC score 0-1 CAT < 10 Exacerbation history: ≥2 (or leading to hosp.)	ICS + LABA **OR** LAAC	LAAC AND LABA **Or** LAAC and roflumilast **Or** LABA and roflumilast	SABA AND/OR SAAC Theophylline

D	High risk, more symptoms GOLD grade 3-4 mMRC score ≥ 2 CAT ≥ 10 Exacerbation history:≥2 (or leading to hosp.)	ICS + LABA **AND/OR** LAAC	ICS + LABA +LAAC **OR** ICS + LABA + roflumilast **OR** LAAC + LABA **OR** LAAC & roflumilast	SABA And/or SAAC Theophylline Carbocysteine Or n-acetylcysteine

Objective 4

- **The Proportion of Days Covered (PDC)** is defined as the measurement period "covered" by prescription claims for the same medication or another in its therapeutic category (Pharmacy Quality Alliance [PQA] Measure Specifications). Data (Section 3.3) will come from the community pharmacy computer system. It is calculated by the equation:

$$\frac{\text{Total Days Drug(s) Available}}{\text{Total Days in Follow-up Period}}$$

PDC Threshold. The level of PDC above which the medication has a reasonable likelihood of achieving most of its intended therapeutic effect due to regular adherence to the regimen. In this study, the PDC threshold is defined as ≥ 0.8 (80%).

See **Appendix G** for an example of the analysis code used to calculate the PDC.

- Participant-Level Variables:

Age
Age is defined as the subject's age on the day of the study enrollment; calculated from the self-reported date-of-birth provided on the patient questionnaire.

Sex
Sex is categorized based on the subject's self-reported sex (male or female); collected on the patient questionnaire.

COPD Medications
COPD medications (individual drugs and drug classes) are listed in 3.2.2 and will be obtained from the community pharmacy records.

Health Literacy Screen
The Single-Item Literacy Screener (SILS), a validated measure, will be used to screen for possible low health literacy. Answers defining a "positive response include "Quite a Bit" OR "Extremely") and the other answers are considered "negative" responses; collected on the patient questionnaire.

mMRC
Modified Medical Research Council Dyspnea Scale (mMRC)—This is defined above, in Objective 1. See Appendix D.

CAT

COPD Assessment Test (CAT)—This is defined above, in Objective 1. See Appendix C.

Smoking/Nicotine Status
The patient's self-reported smoking status and use of nicotine replacement therapies; collected on the patient questionnaire.

Exacerbations
Exacerbations are defined above, in Objective 1; collected on the patient questionnaire.

Combined Assessment Category (GOLD)
GOLD Combined Assessment Category—This is defined above, in Objective 1.

Out-of-pocket drug spend (per month), all drugs
Out-of-pocked drug spend for all drugs is patient-reported (estimated, in dollars per month); collected on the patient questionnaire.

Out-of-pocket drug spend (per month), COPD drugs
Out-of-pocked drug spend for COPD drugs is patient-reported (estimated, in dollars per month); collected on the patient questionnaire.

Ethnicity
Patient ethnicity is self-reported; collected on the patient questionnaire.

Race
Patient race is self-reported; collected on the patient questionnaire.

- Pharmacy-Level Variables

Location
Defined by the ZIP code of the community pharmacy.

Prescription Volume
Defined by the total number of prescriptions filled by the community pharmacy per month.

3.3.1.3. Exploratory Endpoint(s)

3.4. SAMPLE SIZE / POWER CALCULATIONS

This study will involve descriptive analyses of patients with COPD. The only specific hypotheses to be tested are related to secondary outcomes. The sample size limiting outcome is the level of agreement between the GOLD combined assessment categories that are determined by the CAT and the mMRC. Based on literature, the agreement level between patients categorized using CAT or mMRC ranges between 0.51-0.94.[14-16] We used the most conservative estimate from literature for calculating sample size. To detect a significant difference at 95% confidence and 5% absolute error (precision), we will need a sample size of 384 patients. Assuming a 44% spirometry rate, we will include 875 patients in the study. We expect to have sufficient power to conduct our analysis.

3.5. HYPOTHESES

This primary outcome of this study will involve only descriptive analyses of study participants with COPD.

4. DATA ANALYSIS CONSIDERATIONS

The purpose of this section is to describe the analytic methods and procedures that are to be employed for this study. The analytic approach and methods are described for each objective and the related specific aims. All data analyses for this study will be conducted using the statistical analysis plan as a guide. All analyses of data will be conducted using SPSS (version 22.0) and SAS (version 9.4). Numbers and percentages will be provided for dichotomous and polychotomous variables. Continuous variables will be summarized by providing mean and standard deviation. Bivariate comparisons of baseline characteristics will be provided. Statistical tests of significance for differences in these distributions will be conducted. Chi-square tests (or other tests where appropriate) will be performed to evaluate the statistical significance of differences in categorical variables; T-tests (or other tests where appropriate) will be used for the means of continuous variables. The *a priori* alpha level for relevant analyses will be set at 0.05, and all statistical tests will be two-tailed, unless otherwise specified. Data will be evaluated for violations of assumptions underlying the associated statistical tests as appropriate.

4.1. Objective 1

The proportion of participants in each GOLD combined assessment category will be described

The participant demographics will be described:

- Mean age, at enrollment
- Sex, proportion male
- Mean number of COPD medications (drugs and drug categories)
- Mean number of patients with adequate health literacy screen (SILS response "Quite a Bit" or "Extremely")
- mMRC, proportion by category
- CAT, mean total score
- Smoking status, proportion currently smoking
- Nicotine status, proportion using nicotine replacement (by type)
- Comorbidities, proportion of patients, by disease/condition
- Antibiotics, proportion of patients prescribed antibiotic for COPD in past 12 months
- Steroids, proportion of patients prescribed systemic steroid for COPD in past 12 months
- Hospitalizations, proportion of patients hospitalized or ED visit for COPD in past 12 months
- PFTs/Spirometry, proportion of patients with formal PFTs or spirometry data available within past 3 years
- Health insurance status, proportion by payer type
- Non-pharmacy COPD medication sources, proportion by source
- Mean out-of-pocket drug spend (per month), all drugs
- Mean out-of-pocket drug spend (per month), COPD drugs
- Ethnicity, proportion by ethnic origin
- Race, proportion by race
- Frequency of pulmonologist, proportion
- Mean BMI

A heat map will be created, using the ZIP code of the participant's residence, to depict the geographic distribution of study participants.

4.2. Objective 2

A weighted Kappa statistic will be calculated using the two GOLD combined assessment categories determined using the CAT versus the mMRC.

4.3. Objective 3

Proportion of patients taking an appropriate (GOLD guideline recommended first-choice) COPD medication regimen (combined PDC ≥ 0.8) according to their GOLD combined assessment category

Descriptive statistics will be used for the following analyses:

- Proportion of patients receiving appropriate medication, based on their GOLD combined assessment:
    - Proportion of patients in each category categorized as "appropriate", defined as:
        - Filling one or more prescriptions recommended as first choice treatment for COPD and a combined PDC ≥ 0.8
        - Filling one or more prescriptions recommended as first choice OR an alternative choice treatment and a combined PDC ≥ 0.8
        - Filling one or more prescriptions recommended first choice OR an alternative choice OR other possible treatment and a combined PDC ≥ 0.8
    - Proportion of patients receiving one or more prescriptions in the 12-month period prior to study enrollment for a higher tier regimen for a given combined assessment (e.g., receiving a "C" regimen, but patient is categorized as "B"), in categories A, B, and C, according to their GOLD symptom and risk evaluation
    - Proportion of patients receiving one or more prescriptions in a 12-month period prior to study enrollment for a lower tier regimen for a given combined assessment (e.g., receiving a "B" regimen, but patient is categorized as "C"), in categories B, C and D, according to their GOLD symptom and risk evaluation

4.4. Objective 4 – Exploratory Analysis

- Proportion of patients categorized as "adherent" to their medications (defined as PDC $\geq$ 80%), according to the following:

Logistic regression models will be developed to identify factors associated with low PDC (less than 0.8). The models will be developed to address the study objective. The dependent variable in these models will be PDC ≤ 0.8 and the *a priori* list of hypothesized independent variables includes:

1. Drug class (categorical)
2. Device type (categorical)
3. Age (continuous)
4. Sex (categorical)
5. Number of COPD medications (continuous)
6. Health Literacy Screen [SILS] (categorical)
7. Smoking status (categorical)
8. GOLD combined assessment category (categorical)

9. Out-of-pocket monthly drug spend for all drugs (continuous)
10. Out-of-pocket monthly drug spend for COPD drugs (continuous)
11. Ethnicity (categorical)
12. Race (categorical)
13. Monthly pharmacy prescription volume (continuous)
14. Data collection month

The multivariate analysis will include the following variables selected *a priori* based on the clinical relevance hypothesized to be associated with PDC. A detailed description of these variables is provided in section 3.3.1.2.

1. Participant-level characteristics: total number of chronic medications, combined assessment GOLD category, age, sex, ZIP code of residence, race, ethnicity
2. Pharmacy-level characteristics: ZIP code of pharmacy, number of patients originally identified with COPD drug

Multicollinearity tests will be performed before variables are entered in the model. All statistical analyses will be conducted using SAS with an *a priori* significance level of alpha = 0.05.

5. LIMITATIONS

This study uses a cross-sectional study design. Because some data (e.g., pulmonary function tests/spirometry) are retrospectively done as part of usual care, they may not be available. In addition, this study collects patient-reported data via a standardized questionnaire so some data may be unreliable, due to recall bias, and other data may not be available at all. There may be sampling bias because a convenience (non-randomized) sampling method will be used. Prescriptions filled in a community pharmacy will be used to 1) recruit subjects; and 2) determine medication adherence. Some medications may not be accurately captured (e.g., medications obtained as samples or through patient-assistance programs. Finally, PFTs are retrospectively collected and are an effort-dependent test so there may be some measurement bias.

6. STUDY CONDUCT, MANAGEMENT & ETHICS

6.1. ETHICS/IRB APPROVAL

This study will be approved by the STLCOP Institutional Review Board (IRB).

6.2. INFORMED CONSENT

For the ***initial recruitment phase***, identifying potential participants in the community pharmacies, a waiver of consent will be obtained because it is not feasible to obtain written consent. A written informed consent (see **Appendix H**) ***for the data collection phase***, however, will be approved by the STLCOP IRB and signed by each study subject.

6.3. DATA PRIVACY

The research process will be conducted in strict compliance with all state, local and federal regulatory requirements. The study execution will be consistent with Good Clinical Practices, Good Epidemiological Practices, the International Convention on Harmonization, HIPAA regulations, the Department of Health and Human Services, the Office of Human Research Protection, and any applicable Internal Review Board guidelines. When applicable, the research will also be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and 56 and all applicable laws.

Initial data extracts are performed in a secure server environment that may include some Protected Health Information (PHI), such as prescription fill dates and/or plan type (Medicare or Commercial); but these will be the minimum necessary to conduct the research based on the proposed hypothesis and study objectives. All identifying member ID numbers and claim ID numbers have been either deleted or encrypted and all analyses will be carried out using only these random codes from that point forward, if applicable. The data obtained will not be used for any other purpose outside this study itself. PHI extracted for this study will not be used or disclosed to any third party (except as required by law).

Data analyses and output tables summarizing the data in a de-identified, aggregate form are generated, reviewed and interpreted by STLCOP staff. The aggregate data tables may be shared with the study sponsor as required by the study. All data provided to the study sponsor will be at an aggregate level only. The sponsor will not have access to identifiable, individual member information. Published results of this study will be at the aggregate level and will not contain PHI.

6.4. PERSONALLY IDENTIFIABLE INFORMATION (PII)

STLCOP does not share any identifiable PHI with study sponsors. When necessary, STLCOP's process for de-identifying datasets will comply with the de-identification standard in the HIPAA privacy rule, as outlined in CFR 164.514. Any use or disclosure of PHI must also comply with the minimum necessary standards presented in CFR 164.514.

6.5. ADVERSE EVENT REPORTING

Because this is an observational study, and no interventions with research participants will be made, we do not anticipate that there will be any adverse events.

6.6. DATA STORAGE/ARCHIVAL

All study-related data that are collected will be entered into REDCap (Research Electronic Data Capture) through access within the Washington University School of Medicine's Institute for Clinical Translational Sciences (ICTS). The ICTS is a CTSA (Clinical Translational Sciences Award) from the NIH. The Research Design and Biostatistics Informatics Core of the ICTS manages REDCap. St. Louis College of Pharmacy is an institutional member of the ICTS and therefore has access to their research cores and services. Several STLCOP investigators on this project are individual members of the ICTS. Washington University, belongs to a consortium of institutional partners that work to maintain a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Division of Biostatistics Informatics Core. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are securely housed in an on-site limited access data center managed by the Division of Biostatistics at Washington University. All web-based information transmission is encrypted. The data is all stored on a private, firewall protected network. All users are given individual user ids and passwords and their access is restricted on a role-specific basis. REDCap was developed specifically around HIPAA-Security guidelines and is implemented and maintained according to Washington University guidelines. REDCap currently supports > 500 academic/non-profit consortium partners on six continents and 38,800 research end-users. No Patient Identifiable Data (PID) or protected health information (PHI) will be released to GSK. In addition to protection of patient identifiable data, STLCOP will provide a study identifier to identify patients to source documents (i.e. CAT, mMRC questionnaires, etc.) in case the study documents ever need to be audited. Finally, the CPI will make a PDF file of the patient questionnaire and the informed consent document and will send that PDF file to the STLCOP investigators via MHC's CareMail. CareMail is a fully secure and electronic means for sending and receiving patient protected health information. With CareMail, clinicians can instantly send patient-related protected health information to any other provider without having to use a fax machine. Hardcopy documents will be stored securely at the community pharmacy until the end of patient enrollment; then the CPI will mail the documents to the STLCOP investigators.

7. MILESTONES

MILESTONE	GUIDANCE OR POLICY REQUIREMENT	FORECAST DATE MM-YYYY
Predicted Final Protocol Approval (FPA)		**06-2016**
Predicted GSK CSR Protocol Summary	*FPA Actual + 30 days*	**07-2016**
Predicted Statistical Analysis Plan Approved		**07-2016**
Predicted Statistical Analysis Complete (SAC Actual)		**04-2017**
Predicted Final Study Report Complete	*SAC Actual + 6 months*	**10-2017**
Predicted GSK CSR Results Summary Posting	*SAC Actual + 8 months*	**12-2017**
Predicted Manuscript Submission	*SAC Actual + 18 months*	**10-2018**

8. DISSEMINATION PLAN

The investigators anticipate that the study results will be reported, in aggregate form only—with no personally identifiable information, in one or more presentation and/or publication. The study sponsor, GSK, may also disseminate study results—with no personally identifiable information.

9. REFERENCES

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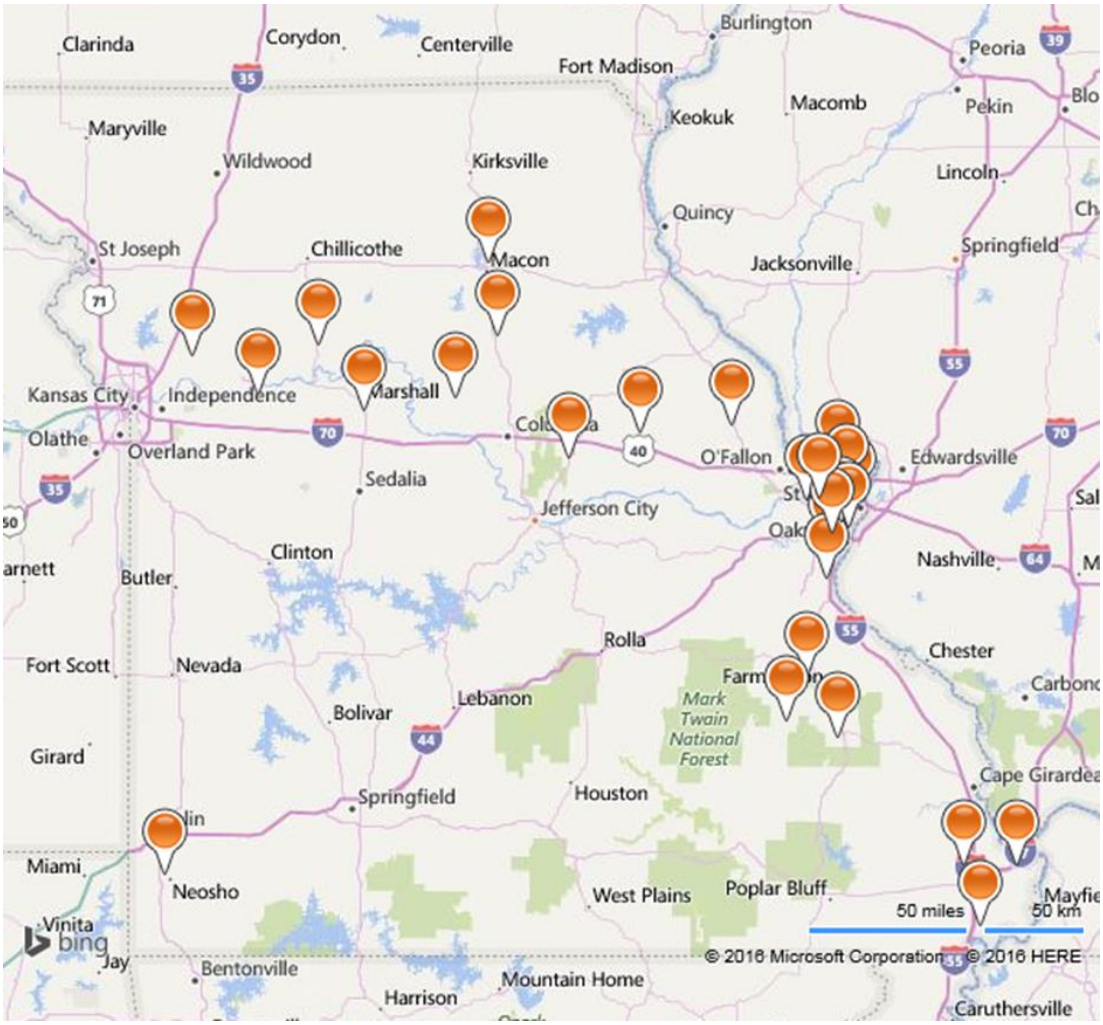
10. APPENDIX A: Participating Pharmacies



Community Pharmacy	Address		
Beverly Hills Pharmacy	7150 Natural Bridge Rd.	St. Louis	63121
Gateway Apothecary	4473 Forest Park Ave.	St. Louis	63108
Parkland Health Mart Pharmacy	617 N Cowling St, Suite G	Desloge	63601
Parkland Health Mart Pharmacy	1025 E Highway 72	Fredericktown	63645
Parkland Health Mart Pharmacy	1500 N Highway 21	Ironton	63650
Dierbergs-Southroads	12420 Tesson Ferry Road	St. Louis	63128
Dierbergs-Market Place	1730 Clarkson Road	Chesterfield	63017
Dierbergs-Heritage Place	12595 Olive Street Road	Creve Coeur	63141
Dierbergs-Florissant	222 North Highway 67	Florissant	63031
Dierbergs-Mackenzie Pointe	7233 Watson Road	St. Louis	63119
Dierbergs-Arnold Commons	860 Arnold Commons Drive	Arnold	63010
Dierbergs-Lemay Plaza	2516 Lemay Ferry Road	St. Louis	63125
Dierbergs- West Oak	11481 Olive Boulevard	Creve Coeur	63141
Medicine Shoppe #1424	10 Centerline Drive	Troy	63379

Medicine Shoppe #2028	106-A Broadway	Elsberry	63379
Medicine Shoppe #1965	106 #B Four Seasons Shopping Center	Chesterfield	63017
Medicine Shoppe #1696	635 S Sturgeon	Montgomery City	63361
Medicine Shoppe #1985	8640 Commercial Boulevard	Pevely	63070
Medicine Shoppe #128	7922 MacKenzie	Afton	63123
Mitchell's Drug Stores on the Boulevard	719 South Neosho Blvd	Neosho	64850
Mitchell's Country Care Pharmacy	1504 N Business 49	Neosho	64850
Mitchell's Downtown Drugstore	115 E Hickory St	Neosho	64850
Red Cross Pharmacy	161 S Benton	Marshall	65340
Red Cross Pharmacy	941 S Cherokee, Suite 1	Marshall	65340
Red Cross Pharmacy	1018 N Jesse James Road	Excelsior Springs	64024
Red Cross Pharmacy	1105 N. Rutherford	Macon	63552
Red Cross Pharmacy	600 Court Street	Fulton	65251
Red Cross Pharmacy	1030 Main Street	Lexington	64067
Red Cross Pharmacy	1003 N Highway 65	Carrollton	64633
Sam's Health Mart Pharmacy	300 N. Morley Street	Moberly	65270
Sam's Health Mart Pharmacy	530 E. 24 Highway	Moberly	65270
Sam's Health Mart Pharmacy	300 N. Church Street	Fayette	65248
L&S Pharmacy	406 S Main Street	Charleston	63834
Medical Arts Pharmacy (L&S)	808 E. Wakefield Ave.	Sikeston	63801
New Madrid Pharmacy (L&S)	457 Main Street	New Madrid	63869

11. APPENDIX B: Script for CPI—Initial Contact to Recruit Potential Study Participants

Script_CPI_Recruitment_Phase_1_070516

12. APPENDIX C: Authorization for Release of Medical Records (To Be Signed by Each Study Participant) to Allow Investigators to Obtain Results of Pulmonary Function Tests/Spirometry.

Authorization_Release_Medical_Record

13. APPENDIX D: Detailed Study Procedures

When the patient presents to the community pharmacy for the study visit, the CPI will escort the patient to a convenient and accessible area that is sufficient (i.e. quiet, free from distractions, confidential, and well-lit) for the informed consent, authorization, and data collection phases.

1. The CPI will provide the patient with a copy of the informed consent document. The CPI will summarize the document, in lay language that fosters patient understanding, and address any questions that the patient might ask. The CPI will encourage the patient to read the document in detail and then sign the document if the patient agrees to volunteer to participate in the study.
2. If the patient signs the document, the CPI will give the participant a copy of the signed informed consent document for their records.
3. The CPI will then give the participant the "Authorization for Release of Medical Records" document. The CPI will again summarize the document, in lay language that fosters understanding, and address any questions that the participant might ask. The CPI will encourage the participant to read the document in detail and then sign the document if the participant agrees to provide their authorization for the physician(s) to send the pulmonary function test/spirometry results to the investigators. The CPI will give the participant a copy of the signed authorization form.
4. After the participant has met all eligibility criteria and signed the informed consent document, the CPI will provide the participant with a blank copy of the written questionnaire and instruct the participant to read and complete the questionnaire in its entirety. If the participant does not have time to complete the questionnaire, the CPI is allowed to arrange another time (mutually convenient) when the CPI can administer the questionnaire by phone. This should only be a rare instance, however, and the participant must FIRST sign the informed consent and authorization for release documents in person. The CPI will be readily available to address any questions the participant might have. (Please see complete participant questionnaire embedded below)
    a. The CPI will ask the participant to read and answer Question 1 (Single Item Health Literacy Screen).
        i. If the participant answers "Extremely" or "Quite a Bit", then the participant will be allowed to complete the remainder of the questionnaire on their own.
        ii. If the participant answers "Somewhat" or "A Little Bit" or "Not at All", then the CPI must assist the participant, as needed and appropriate.
    b. The CPI will then conduct a medication history regarding the participant's use of medications to treat COPD. The CPI will have a list of COPD medications that the participant had filled in the CPI's pharmacy within the past 12 months (365 days)—this was obtained during phase 1 of the recruitment process. The CPI will reconcile the medications on the list and document the participant's current use of the medication(s) on the participant questionnaire.

Participant_Questionnaire_070516.docx

5. When the participant has completed the written questionnaire (estimated to take less than 30 minutes of time), the CPI will wrap up the study visit. Specifically, the CPI will:
    a. review the questionnaire with the participant to ensure satisfactory completion.
    b. remind the participant that their information may be shared with the prescribing physician
    c. Tell the participant that the STLCOP investigators will mail the $10 remuneration for participating in the study

6. Within 24 hours after each study visit, the CPI will create a PDF file of the completed participant questionnaire, the signed informed consent, and the authorization for records release documents. These will be sent to the STLCOP investigators via the secure email tool (CareMail) in the HIE.
7. Also within 24 hours following the study visit, the CPI will generate an electronic report in Excel format of the participant's fill data for the 12-month period preceding the participant's enrollment date. That report for each study participant will contain the following data:
    a. Prescriber name
    b. Patient name
    c. Patient DOB
    d. Drug name
    e. Drug NDC
    f. Quantity dispensed
    g. Fill date
    h. Days supply
    i. Sig (directions)
    j. Copay (out-of-pocket cost paid by participant)

8. The CPI will store all research documents in a secure manner and mail them to the STLCOP investigators after the final study visit.
9. Periodically, the STLCOP investigators will login to CareMail and check for new email messages from CPIs that contain study documents. These electronic documents will be stored, in a password-protected file on a drive dedicated to the Department of Pharmacy Practice (G:) on a secure STLCOP server. Only STLCOP investigators will have the password and access to the research documents. Note: The STLCOP IT department personnel will have administrative access to the drive and has internal policies and procedures that stipulate when they may access the drive, for maintenance and security purposes. The STLCOP investigator will also use CareMail to forward any research documents to the student investigator for data entry into REDCap (see below).
10. Periodically, the STLCOP investigators will enter the data collected into a REDCap project database that will store, in secure fashion, all research-related data. Any research documents that will be printed as a hardcopy to facilitate data entry will be destroyed by shredding immediately after use.
11. At least once during the study period, the project manager will conduct a site visit at each community pharmacy (or a representative pharmacy within a chain). The purposes of the visit(s) will be to 1) ensure adequate space is available for the study subject to provide informed consent and complete the written survey; 2) address study procedural questions from the CPI or pharmacy manager; 3) ensure adequate and secure storage of confidential study-related documents.
12. After receiving the research documents from the CPI, the STLCOP investigators will attempt to contact the prescribing physician(s) for the patient by sending a standardized FAX that requests the results of most recent pulmonary function test and/or spirometry. The content of the FAX is below:

initial physician fax
6 16 16 .docx

13. The prescribing physician(s) office will then send the requested documents to STLCOP investigators via FAX to a dedicated FAX machine located in an office of one of the STLCOP investigators. If a response from the physician office is not received within 2 weeks (14 calendar days), a second FAX request will be sent to the physician. If a response is again not received within 2 weeks (14 calendar days), then a STLCOP investigator will attempt to call the physician office to speak directly with the physician, nurse, medical assistant, or other office staff member to request the medical information. The STLCOP investigator will

then create a PDF file of any documents received and will store them, as password-protected files, on the STLCOP network drive (only accessible to STLCOP investigators) for later entry into REDCap.

14. Once all data has been entered into REDCap, a STLCOP investigator will make the following assessments and enter them into REDCap:
    a. GOLD airflow limitation classification (values range from 1 to 4, according to the 2016 GOLD guidelines) based on spirometry, if available.
    b. GOLD combined assessment (category A through D) using the various data available—i.e. based on mMRC and CAT.
15. After all relevant information is entered into REDCap, a STLCOP investigator will assess the appropriateness of therapy (see Data Analysis Considerations—Section 4) and document them in REDCap.
16. STLCOP investigators will create a de-identified dataset of the pharmacy fill data and send it to GSK for the calculation of PDC.
17. STLCOP investigators will analyze the data according to the Data Analysis Considerations—Section 4.
18. After all data are analyzed, a STLCOP investigator will notify the prescribing physician (and the pulmonologist, if applicable) the relevant findings of the study for their patient. This will be communicated via FAX in the following format:

Fax 2 summary 6 16 16 .docx

Time and Events Table

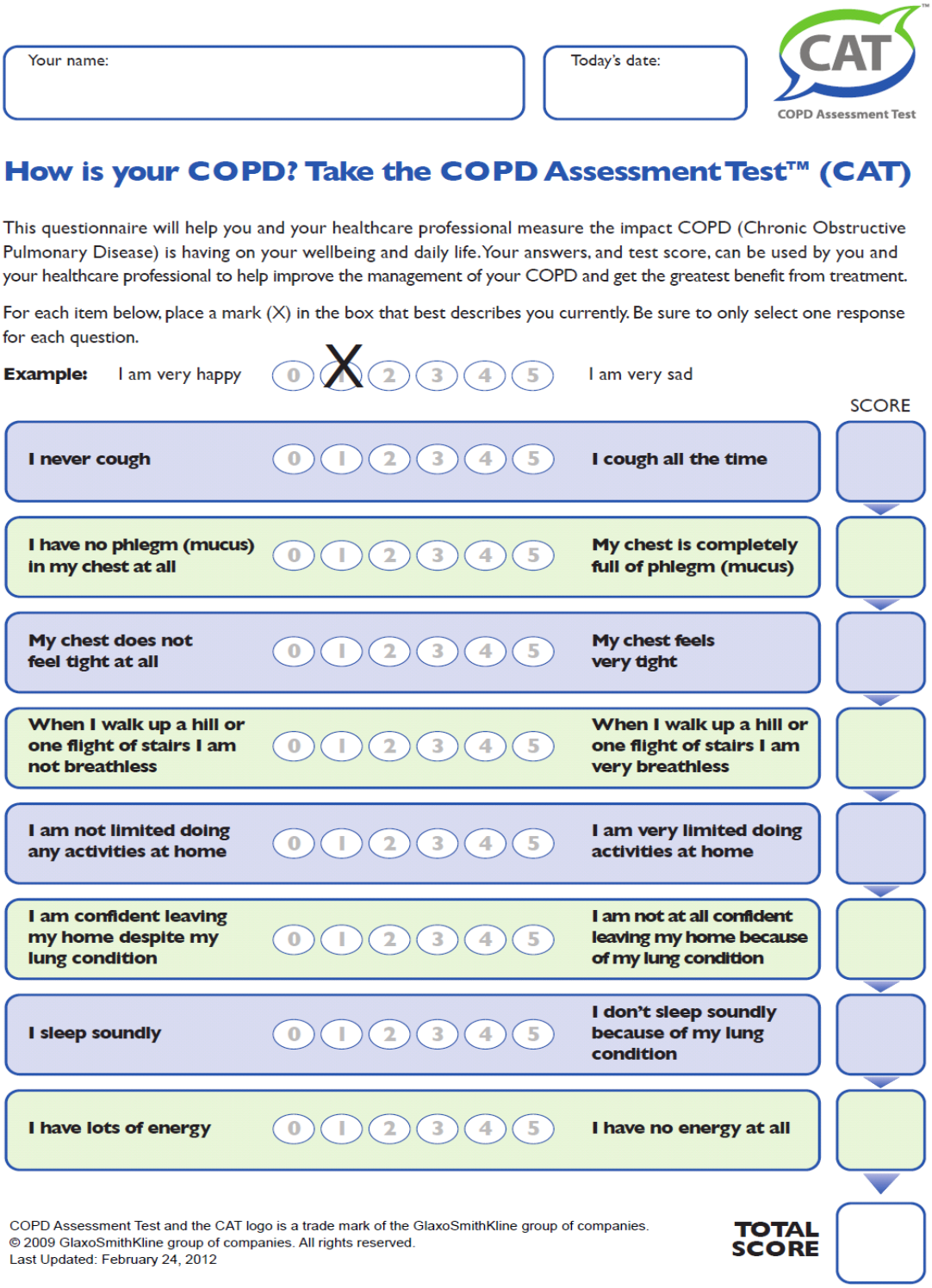
Data Collection	Enrolment	Recall PRIOR History[1] During VISIT 1	Prospectively Collected During VISIT1	Pharmacy Level Records	Physician Records
Inclusion/Exclusion Eligibility Criteria	X				
Informed Consent	X				
Authorization for release of medical records	X				
Demography			X		
CAT			X		
mMRC			X		
Smoking Status			X		
Comorbidities		X			
Health Literacy Screening [SILS]			X		
Health Insurance Information			X		
COPD Exacerbations		X			
Pharmacy Fill Data				X	
ER visits		X	X		
Hospital Admissions in past 12 Months		X	X		
FEV_1 and FVC [2]					X

1 Recall based on participant's recall of events

2 At enrolment, participants must sign a written informed consent document and provide their written authorization for their physician to release their pulmonary function test/spirometry results. Although the "most recent" results will be requested from the physician, the historical only value used for analysis will be those collected nearest to the baseline date during the past 36 months.

14. APPENDIX E: The COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is an 8-item measure designed to determine the impact of COPD on COPD patients' well-being and daily life [Jones, 2009]. The questionnaire results in four impact levels: low (score <10), medium (score of 10-20), high (>20), and very high (score of >30).



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

Last Updated: February 24, 2012

15. APPENDIX F: The Modified Medical Research Council Dyspnea Scale (mMRC)

The Modified Medical Research Council Dyspnea Scale **(**mMRC) will be used to evaluate the effect of breathlessness on COPD patient's daily activities [Bestall, 1999, Ferris, 1978]. On the basis of their difficulty with normal daily activities, such as walking or climbing stairs, patients are categorized into one of five grades: 0 (normal) to 4 (too breathless to leave the house).

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

16. APPENDIX G: Calculations for the Medication Adherence Parameter—Proportion of Days Covered (PDC).

The following calculations, and the corresponding code, will be performed for each patient. The time period will be defined as the 12-month period (when available, otherwise a minimum of 6 months data are required) preceding enrollment (start date = 365 days prior to enrollment date, and end date = enrollment date):

- PDC for Single Drug Therapy—Arrays will be created to reflect the fill dates and days-supply for each fill. The macro will adjust the patient's fill dates to account for early refills. Any medication supply that falls outside of the study period will be truncated. The PDC for a single patient for a single drug during the time period is the sum of days covered/total days in study period.

```
**********************************************************************
** Macro Parameters: ***
** input - Input Dataset name ***
** output - Output Dataset name ***
** pid - Unique patient identifier ***
** fill_dt - Prescription fill date ***
** dos - Fill days of supply ***
** start_dt - Start date of time period ***
** end_dt - End date of time period ***
**********************************************************************
%macro PDC_Single(
input=,
output=,
pid=,
fill_dt=,
dos=,
start_dt=,
end_dt=);
** Step 1: Exclude fills outside of study period **;
data &input.;
set &input.;
if &end_dt. >= &fill_dt >= &start_dt.;
run;
** Step 2: Find out the maximum number of fills a patient can have **;
** and save it into macro variable, &_mcount **;
proc sql noprint;
create table temp as
select &pid., count(*) as ct
from &input.
group by &pid.
;
select max(ct) into :_mcount from temp;
quit;
%let _mcount=&_mcount;
** Step 3: Transpose dataset **;
proc transpose data=&input. out=fill_dates(drop=_name_) prefix=fill_dt;
by &pid.;
var &fill_dt.;
run;
```

```
proc transpose data=&input. out=fill_DOS(drop=_name_) prefix=days_sply;
by &pid.;
var &dos.;
run;
data claims_refmt;
merge fill_dates fill_DOS;
by &pid.;
start_study_dt=fill_dt1;
end_study_dt=&end_dt.;
format start_study_dt end_study_dt mmddyy10.;
temp=end_study_dt - start_study_dt+1;
run;
data _null_;
set claims_refmt(keep=temp);
call symput('days',temp);
run;
** Step 4: Adjust prescription fill date for early refills **;
data pdc1(keep=&pid. adj_fill_date days_supply end_study_dt);
set claims_refmt;
array dates(*) fill_dt1 - fill_dt&_mcount.;
array dos(*) days_sply1 - days_sply&_mcount.;
adj_fill_date=dates(1);
days_supply=dos(1);
output;
do i = 2 to dim(dates) while (dates(i) ne .);
if dates(i) <dates(i-1)+dos(i-1)
then do;
dates(i) =dates(i-1)+dos(i-1);
adj_fill_date=dates(i);
days_supply=dos(i);
end;
adj_fill_date=dates(i);
days_supply=dos(i);
output;
end;
format adj_fill_date mmddyy10.;
run;
** Step 5: Truncate fills fall outside of study period **;
data pdc2;
set pdc1;
if adj_fill_date <=end_study_dt then do;
if adj_fill_date + days_supply >end_study_dt+1 then do;
days_supply=end_study_dt-adj_fill_date+1;
end;
output;
end;
run;
** Step 6: Calculate PDC at patient level **;
proc sql;
```

```
create table &output. as
select &pid.,
sum(days_supply) as dayscovered,
(calculated dayscovered)/&days. as pdc
from pdc2
group by &pid.
;
quit;
%mend PDC_Single;
** sample macro call **;
%PDC_single(
input=claims,
output=pdc,
pid=patient_id,
fill_dt=fill_date,
dos=days_supply,
start_dt='01JUL2015'd,
end_dt='30JUN2016'd);
```

- PDC for Drug Class (with similar, but modified, code as above)
- PDC for Inhalation Device Type (with similar, but modified, code as above)

17. APPENDIX H: Written Informed Consent Document

Informed_Consent_
final.6.16.16.doc