Utilization of Single and Multiple Inhaler Triple Therapy Among Patients with COPD in the Sentinel Distributed Database

Sentinel Study Protocol

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Administrative Information

History of Modifications

Version	Date	Modification	Author
1.0	06/17/2024	Original version	Sentinel Operations Center

List of Abbreviations

Abbreviation	Definition
CM	Clinical Modification
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CPT	Current Procedural Terminology
DP	Data Partner
FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
HCPCS	Healthcare Common Procedure Coding System
ICD	International Classification of Diseases
ICS	Inhaled Corticosteroid
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Muscarinic Antagonist
LOINC	Logical Observation Identifiers Names and Codes
MIDT	Multiple Inhaler Dual Therapy
MITT	Multiple Inhaler Triple Therapy
NDC	National Drug Code
PCS	Procedure Coding System
SIDT	Single Inhaler Dual Therapy
SIMT	Single Inhaler Monotherapy
SITT	Single Inhaler Triple Therapy
US	United States

Introduction

Background

Chronic obstructive pulmonary disease (COPD) is a common lower respiratory disease characterized by cough, difficulty breathing, and progressive and irreversible airflow limitation. As of 2020, 6.0% of Americans aged 45-64 years report COPD, increasing to 10.8% of those aged 65 years and older.[1] Many patients with COPD require access to frequent health care resources, including chronic maintenance pharmacological treatment and hospitalizations to manage acute exacerbations. Unfortunately, the progressive nature of COPD and its high prevalence have led to its consistent ranking in the top causes of death in the United States (U.S.). In 2021, over 140,000 Americans died due to chronic lower respiratory diseases, making it the sixth leading cause of death in the U.S., down slightly from its position as the fourth leading cause of death prior to the COVID-19 pandemic.[2,3]

Since treatment is not curative, maintenance therapy is aimed at improving symptoms, decreasing exacerbations, and improving quality of life.[4] Maintenance pharmacotherapy recommendations are based on a patient's symptoms and history of exacerbations, comprising primarily inhaled therapies, but also include oral therapies in certain populations (e.g., azithromycin (off-label) and roflumilast (labeled)). Inhaled therapies include long-acting beta-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and inhaled corticosteroids (ICS). Patients may begin needing only one agent but – with increased severity and symptoms – may progress to inhaled triple therapy with a LABA, LAMA, and ICS.

While multiple inhaler triple therapy (MITT) has been available in different forms since the approval of the first LAMA in 2004, single inhaler triple therapy (SITT) is a comparatively new addition with two fixed dose combination (FDC) LABA+LAMA+ICS inhalers approved since 2017. On September 18, 2017, the U.S. Food and Drug Administration (FDA) approved a once-daily, triple therapy LABA+LAMA+ICS inhaler, under the brand name Trelegy Ellipta, for the maintenance treatment of patients with COPD. Trelegy Ellipta is a combination of fluticasone furoate, umeclidinium, and vilanterol, (ICS+LAMA+LABA, respectively) delivered as a dry powder inhaler. On July 24, 2020, the FDA approved an additional once-daily triple therapy inhaler for the maintenance treatment of patients with COPD, under the brand name Breztri Aerosphere. Breztri Aerosphere combines formoterol fumarate, glycopyrrolate, and budesonide[5], (LABA+LAMA+ICS, respectively) delivered as a metered dose inhaler. In contrast, MITT use is more heterogeneous and may consist of three separate single therapy inhalers for LABA, LAMA, and ICS products, or two separate inhalers containing a permutation of these products (e.g., a dual therapy FDC inhaler containing ICS+LABA products in addition to a single therapy inhaler containing a LAMA product).

Little is known on the utilization of SITT and MITT for triple therapy. A comprehensive study leveraging real-world data may provide important information on the utilization of SITT and MITT to inform future studies. The Sentinel Distributed Database offers a large, well-curated data source for this exploration.

Objective

The objective is to describe the utilization patterns of single and multiple inhaler triple therapy among a population of triple therapy-naïve patients with COPD who had evidence of exacerbations despite dual inhaler therapy maintenance treatment in the Sentinel Distributed Database.

Methods

Design and Data Sources

Leveraging the Sentinel System infrastructure, we will conduct a retrospective observational cohort study[6] with Data Partners (DPs) providing administrative claims data for members with fee-for-service Medicare, Medicaid/CHIP[7,8] and three large national health insurance providers.

After transforming their data into the Sentinel Common Data Model version 8 or later[9] (and rigorous evaluation for quality and consistency by the Sentinel Operations Center[10]), all DPs hold their data in a standardized format such that diagnoses, procedures, and laboratory results are coded using International Classification of Diseases, Ninth and Tenth Revisions (ICD-9-CM, ICD-9-PCS, ICD-10-CM) and Logical Observation Identifiers Names and Codes (LOINC). Data on outpatient pharmacy dispensings (National Drug Codes [NDC], days, and amount supplied) and administrations (Current Procedural Terminology [CPT] and Healthcare Common Procedure Coding System [HCPCS]) are also included. After receiving and locally executing a standardized analytical program containing cohort identification and analytical parameters developed by the Sentinel Operations Center using the Sentinel Routine Querying System,[11] each contributing DP will return summary output to the Sentinel Operations Center for analysis and aggregation, consistent with privacy-preserving distributed research methods.[12] Summary output is generated from administrative data on the insured population, including member demographics, health plan enrollment, and billable clinical encounters.

Data will be analyzed using SAS 9.4.[13] Analytic and reporting programs will leverage the latest available version of Sentinel's routine querying tools, including the Cohort Identification and Descriptive Analysis module of the Query Request Package[11] as well as the Query Request Package Reporting Tool,[14] supplemented with additional custom programming to meet the study objectives.

Study Population

Our study population will include patients aged at least 40 years with uncontrolled COPD (defined below) despite evidence of chronic maintenance inhaled dual therapy (treatment with an ICS along with a LABA, or treatment with a LABA along with a LAMA) in the 365 days prior to initiation of inhaled triple therapy (concurrent treatment with ICS, LABA, and LAMA agents).

Cohort Creation

The exposures of interest in this study will be SITT and MITT. SITT is available in the Trelegy Ellipta (inhalation powder containing 100/62.5/25 mcg or 200/62.5/25 mcg of fluticasone furoate, umeclidinium bromide, and vilanterol trifenatate) or Breztri Aerosphere (metered dose aerosol containing 160/9/4.8 mcg of budesonide, glycopyrrolate, and formoterol fumarate) devices. MITT can be administered in two (LABA+LAMA and ICS, or LABA+ICS and LAMA) or three (LABA and LAMA and ICS) separate inhalers, available in several devices.

Both SITT and MITT are inhaled therapy episodes, which will be constructed from administrative dispensing data of a single or multiple inhalers in four steps. In the first step, we will bridge together dispensings for inhalers with the same component(s) (LABA, LAMA, LAMA,

LABA+LAMA, LABA+ICS, or LABA+LAMA+ICS) allowing a 30-day gap between dispensings and adjust dispensing dates to account for early or late refills (stockpiling). For example, inhalers with both a LABA and a LAMA component in a single inhaler (i.e., LABA+LAMA) would be stockpiled together regardless of specific LABA and/or LAMA drug(s) were included in the inhalers, but an inhaler containing only a LABA component would not be stockpiled with an inhaler containing only a LAMA component.

We will then assess overlap between bridged episodes and de-duplicate these episodes by component before bridging any overlapped episodes-with a 30-day gap allowance. Final therapy episodes may be single inhaler monotherapy (SIMT; a single component of LABA, LAMA, or ICS), single or multiple inhaler dual therapy (SIDT or MIDT; two components), or single or multiple inhaler triple therapy (SITT or MITT; all three components), and if there is overlap between these then the therapy with more components will take precedence.

To enter into the study, patients must index as a SITT or MITT new user between October 1, 2017 and one year prior to the end of complete data (expected to be December 31, 2021 for the Medicaid data and between April and September 2023 at the time of study execution) (Figure 1). Cohort entry (index) will occur once per patient, on the first date of all three components of inhaled therapy overlap after meeting all inclusion and exclusion criteria. The third component of inhaled triple therapy may be a LAMA agent when stepping up from ICS+LABA dual therapy or an ICS agent when stepping up from LABA+LAMA dual therapy.

Inclusion Criteria

Patients must be aged at least 40 years on the index date to be included in this study. Additionally, to be eligible for inclusion, patients must meet the following criteria (evaluated in the 365 days prior to the index date, which is referred to as the baseline period):

- Continuous enrollment in a health plan with medical and drug coverage (gaps in coverage of up to 45 days will be allowed to account for administrative processes); and
- Evidence of any COPD; and
- Evidence of chronic maintenance dual inhaled therapy; and
- Evidence of uncontrolled COPD.

COPD will be defined as the presence of at least one diagnosis in any care setting during the baseline period. Chronic maintenance dual inhaled therapy will be defined as evidence of overlapping dispensing episodes of both ICS and LABA or both LABA and LAMA agents for at least 180 of 365 days prior to index (whether dispensed as monotherapy inhalers or fixed dose combination products and whether consecutive or non-consecutive use), as well as evidence of overlapping dispensing episodes of both ICS and LABA or with both LABA and LAMA in the 60 days prior to index. Uncontrolled COPD will be defined as the presence of least one moderate or severe COPD exacerbation during the baseline period while treated with dual inhaled therapy.

Exclusion Criteria

Patients will be excluded if there is evidence of inhaled triple therapy during the baseline period, defined as at least 45 of the 365 pre-index days covered by concurrent treatment with overlapping

dispensing episodes of all three components of ICS, LAMA, and LABA. In addition, patients will be excluded from the cohort due to dispensing episodes of all three components of ICS, LAMA, and LABA as concurrent treatment of any duration in the 60 days prior to index.

Patients will also be excluded if they have evidence of any of the following over the baseline period or on the index date:

- Asthma; or
- Alpha-1-antitrypsin deficiency; or
- Sarcoidosis; or
- Cystic fibrosis; or
- Bronchiectasis; or
- Interstitial lung disease; or
- Pneumoconiosis or miscellaneous other lung diseases; or
- Treatment with chronic maintenance azithromycin or roflumilast use.

Chronic maintenance azithromycin use will be defined as evidence of a dispensing for azithromycin with days of supply greater than or equal to 14 days in the baseline period or on the index date. Roflumilast use will be defined as a dispensing for roflumilast in the baseline period or on the index date.

Furthermore, patients will be excluded if they have evidence of any of the following on the index date:

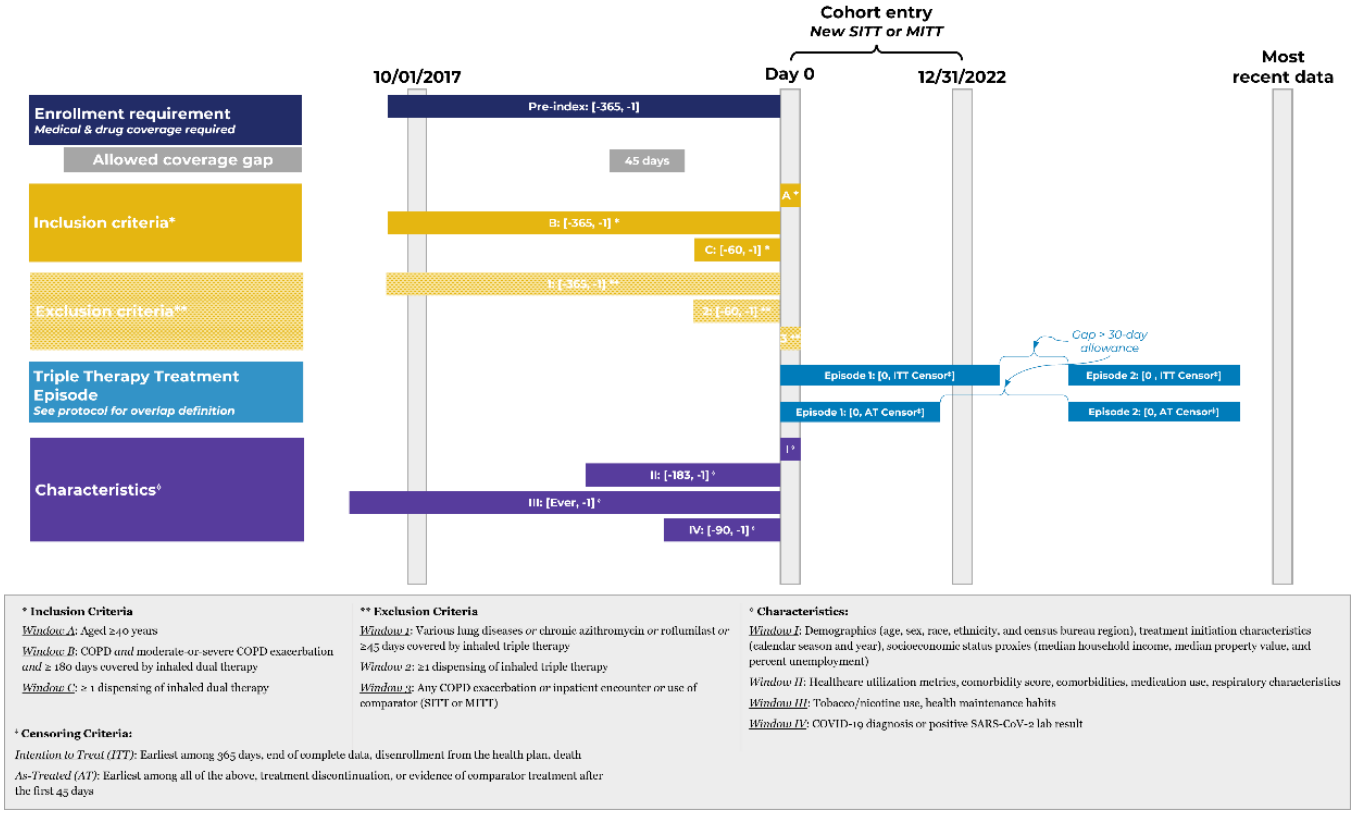
- Moderate or severe COPD exacerbation episode; or
- Inpatient encounter.

To qualify as an exclusion criterion, the events above only need to overlap the index date (i.e., they are not required to start or end on the index date). For definitions of these outcomes, see the "Characteristics of Interest" section below.

Subgroups

Subgroups of interest include age group (40-64, 65-74, and 75+ years), sex (female and male), evidence of chronic bronchitis, and evidence of emphysema in the baseline period.

Figure 1. Illustration of Study Design



Baseline characteristics of Interest

Non-Respiratory Characteristics

Information regarding demographic and clinical characteristics of our study population will be ascertained on or prior to cohort entry.

On the index date, we will ascertain:

- *Demographics*, including age, sex, race, ethnicity, and census bureau region; and
- *Treatment initiation characteristics*, including calendar season and calendar year of treatment initiation; and
- *Socioeconomic status proxies*, including median household income, median property value, and percent unemployment derived from the 2022 American Community Survey[15].

Of note, the census bureau region and proxies for socioeconomic status will be identified based on ZIP code, which is not a time-varying characteristic in the Sentinel Common Data Model. Data Partners are instructed to populate ZIP code based upon the most recent primary address. Thus, while ZIP code is ascertained on the index date, the date associated with the most recent primary residence may be different than the index date.

During the baseline period, we will identify each of the following, defined as the presence of at least one billable code unless otherwise noted:

- *Comorbidities*, including anxiety, atrial fibrillation, atrial or ventricular arrhythmias (excluding atrial fibrillation), cachexia, other cancer (non-lung), cardiovascular disease, chronic bronchitis, chronic kidney disease, cirrhosis, congestive heart failure, major depressive disorder, diabetes, emphysematous phenotype, gastroesophageal reflux disease, hypertension, lung cancer, obesity, obstructive sleep apnea, osteoporosis, pulmonary hypertension, the Combined Comorbidity Index,[16] and total number as well as evidence of at least 2 chronic conditions in said index; and
- *Medication use*, including total number of non-chronic respiratory antibiotics and total number of oral or injectable corticosteroids, and evidence of at least 5 unique generic names concurrently, and evidence of any: , amiodarone, angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, anticonvulsants, antidepressants, antiparkinsonian agents, antipsychotics, benzodiazepines, beta blockers or calcium channel blockers, COVID-19 vaccinations, dementia treatments, digoxin, diuretics, influenza vaccinations, insulins, non-benzodiazepine anxiolytics or hypnotics, non-insulin antidiabetic medications, opioids, proton pump inhibitors, and therapeutic anticoagulants ; and
- *Metrics measuring intensity of health service utilization*, including number of unique drugs and drug classes dispensed, and number of ambulatory, inpatient, and institutional stay encounters.

Finally, we will detect:

- *Health behaviors* ever prior to the index date, including tobacco smoking; and
- *Health maintenance habits* (including pneumococcal vaccination, screening for breast, cervical, colon, and prostate cancers); and
- *Evidence of recent COVID*-19 or positive SARS-COV-2 laboratory result in the 90 days prior to the index date.

Tobacco smoking will be identified by use of smoking cessation therapies or diagnosis/procedure codes indicating tobacco use or nicotine dependence in all available records prior to the index date. The algorithm to define smoking will include validated codes[17] in addition to those identified by the workgroup. Cancer screenings will be identified in the same time period by the presence of codes indicating performance of a mammogram (breast); pap smear (cervical); flexible sigmoidoscopy, colonoscopy, or CT virtual colonoscopy (colon); and prostate exam, digital rectal examination, prostate-specific antigen test (prostate). Evidence of recent COVID-19 will be defined as a COVID-19 diagnosis code or positive SARS-CoV-2 laboratory result in the 90 days prior to index.

Baseline Respiratory Characteristics

In addition to the characteristics above, we will also identify several disease characteristics related to the indication for treatment, namely respiratory symptoms and conditions related to COPD. We will identify each of the following during the pre-exposure baseline period, defined as the presence of at least one billable code unless otherwise noted:

- Number of days with at least one pulmonary function (spirometry) test,
- Use of oxygen therapy,

- Evidence of pneumonia,
- Evidence of pulmonary embolism,
- Evidence of pulmonary rehabilitation,
- Evidence of acute respiratory failure with intubation and mechanical ventilation, and
- Number of moderate-or-severe and severe COPD exacerbation episodes.

To identify exacerbation-related characteristics, we will first identify individual exacerbation events, then apply certain bridging criteria to construct exacerbation episodes composed of related exacerbation events.

COPD Exacerbation Events Prior to Cohort Entry

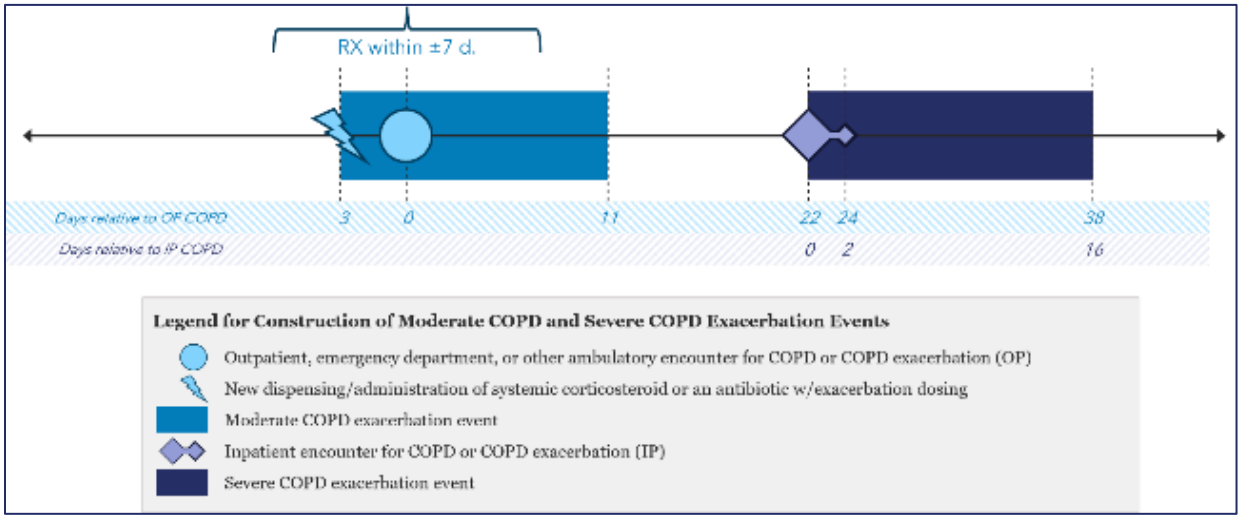
Identification of a single moderate COPD exacerbation event will rely on evidence of an outpatient encounter for COPD or COPD exacerbation, along with a pharmacy dispensing or administration of an antibiotic and/or a systemic corticosteroid within a specified timeframe. Similarly, identifying a severe COPD exacerbation will rely on evidence of an inpatient encounter for COPD or a COPD exacerbation.

Specifically, moderate COPD exacerbations will be defined as the presence of a COPD diagnosis in an outpatient, emergency department (without subsequent hospital admission), or other ambulatory care setting within seven days of which there is evidence of a new systemic corticosteroid and/or an antibiotic with exacerbation dosing. The start date of the moderate exacerbation event will be set to the earlier of the COPD encounter or the medication dispensing/administration date. The end date of the moderate exacerbation event will be set to 14 days after. Medication-related criteria will be defined as follows:

- *New systemic corticosteroid*: a dispensing of an oral corticosteroid with at least three days of supply or an administration of a corticosteroid injection without either use in the prior 14 days
- *Non-azithromycin antibiotic*: a dispensing for an antibiotic with at least three but less than 15 days of supply where the antibiotic is not azithromycin
- *Azithromycin*: a dispensing for azithromycin with at least three but less than 14 days of supply

Severe COPD exacerbation events will be identified using inpatient discharge diagnoses, where the admission date is designated as the event start date. The end date of severe COPD exacerbation events will be set to the discharge date plus 14 days. Qualifying discharge diagnoses include COPD when it is in the principal position, COPD exacerbation in any position, or acute respiratory failure together with COPD. See Figure 2 for a visualization of COPD exacerbation event construction.

Figure 2. Construction of COPD Exacerbation Events



COPD Exacerbation Episodes Prior to Cohort Entry

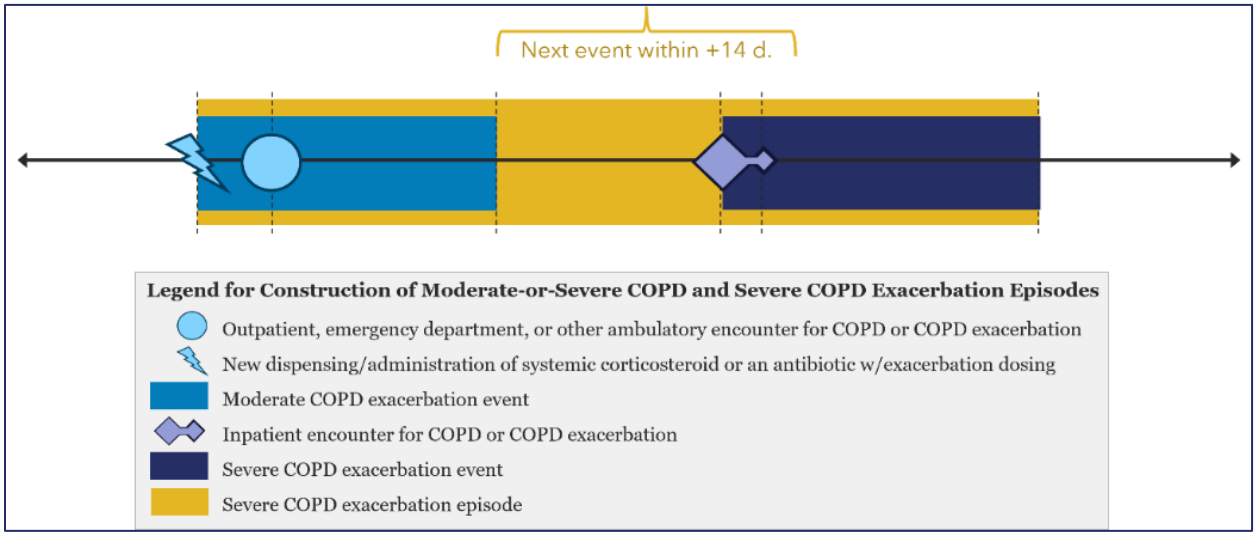
After identifying individual moderate exacerbation events and severe exacerbation events, we will construct COPD exacerbation episodes to ensure the entire exacerbation duration is captured.

Exacerbation events occurring within 14 days from the end of another exacerbation event will be bridged to the first such that an exacerbation episode may contain multiple exacerbation events. The start date of the exacerbation episode will be set to the start date of the first event in that episode. The end date of the exacerbation episode will be set to the end date of the final event in that episode.

We will explore both "moderate-or-severe" as well as "severe" exacerbation episodes as characteristics. When an exacerbation episode contains any severe events, it will be classified as a severe COPD exacerbation episode. Otherwise, episodes will be classified as moderate-or-severe exacerbation episodes.

This methodology was developed in a previous protocol;[18] a summary schematic is provided in Figure 3.

Figure 3. Construction of COPD Exacerbation Episodes Prior to Cohort Entry



Follow-Up

As noted above, the study population will consist of cohorts of new SITT and MITT users, with one index date per patient. Patients will be followed starting the day of index and will continue to be followed until the first occurrence of:

- Treatment discontinuation, or
- Treatment crossover (SITT to MITT or vice-versa), or
- Query end date (at least one year prior to end of complete data for all DPs), or
- Disenrollment from the health plan, or
- Death.

Treatment episodes will be constructed by bridging together dispensings with gaps less than or equal to 30 days based on trends observed in the preliminary utilization assessment. Once episodes are created, an additional 30 days will be added to the end of the treatment episode before it is considered discontinued. Treatment crossover is defined as any evidence of MITT among SITT users or SITT among MITT users during the at-risk period after the first 45 days of treatment. These decisions were made based on utilization trends we observed in the preliminary utilization assessment indicating likely "overflow" of prior therapy in the early days of beginning a new therapy. Switching from one LABA agent to another, one LAMA agent to another, or one ICS agent to another will not be considered a treatment crossover for the purposes of this project.

Utilization Assessment

Population Description

We will describe the SITT and MITT cohort creation in a stepwise fashion, reporting the number of members and treatment episodes remaining and excluded at attrition each step. In addition to the baseline characteristics described above, we will also provide figures visualizing the number of members in each cohort entering the study each month.

First Treatment Episodes

In addition to cohort attrition we will report several metrics related to utilization using categories (with number and percent in each category) and continuous descriptive statistics (including minimum, maximum, mean, standard deviation, median, and quartiles):

1. Length of individual dispensings (days supply per dispensing);
2. Time on inhaled triple therapy (duration of each patient's first treatment episode); and
3. Time off inhaled triple therapy (duration of each patient's first gap in therapy).

When describing time on treatment, the time bridged between treatment episodes separated by less than the allowable gap (30 days) will be included and classified as treated time. Correspondingly, since bridged gaps are considered time on treatment, time off treatment will not begin until a gap greater than the allowance occurs.

To further describe end of utilization for SITT and MITT users, we will report the number of patients whose first treatment episodes were censored for each applicable reason and a summary of treatment episode duration for episodes ending due to each criteria described in the "

Follow-Up" section above.

Second and Subsequent Treatment Episodes

As noted above, each new SITT and MITT user indexes only once, and we describe their first treatment episode using several utilization metrics. However, to provide a more complete picture, we will also describe any subsequent treatment episodes the patient experiences during follow-up after their first episode ends or is censored. Thus, for second and subsequent episodes, we will report the time on and off inhaled triple therapy. Finally, we will report a summary of all treatment for each patient, including both first and subsequent episodes.

Distributed Data Network Considerations

There are several considerations unique to the Sentinel System as a distributed data network that are relevant to this project.

Sentinel Data Partners and Operations Center Workflow

As described above, this project will leverage the Sentinel System infrastructure, including by partnering with five health insurance Data Partners that will run analyses at their own sites and

generate summary data for the Sentinel Operations Center. Three of the five Data Partners are large national insurers; the remaining are Medicare and Medicaid (provided through CMS).

As is standard within Sentinel infrastructure, the Sentinel Operations Center will translate cohort identification strategies and utilization assessments into a standardized analytic program that it will distribute to each of the DPs. Each DP will then execute said program locally, using quality-reviewed data formatted into the Sentinel Common Data Model. Once results are generated, DPs will return aggregated data (without patient identifiers) to the Sentinel Operations Center.

Once at the Sentinel Operations Center, data review will take place and reports will be generated using a standardized program.

Data Availability

The data generated from this study will not be publicly available. Sentinel uses a distributed approach in which Data Partners maintain physical and operational control of their own electronic health data after transforming it into a common data model. Sentinel does not save, maintain, or post individual level datasets to preserve patient privacy.[12]

Furthermore, two DPs (Medicare and Medicaid) participating in this project contribute data from CMS. Sentinel adheres to the CMS cell size suppression policy for all aggregated reports containing Medicare and/or Medicaid data. The policy stipulates that "no cell (e.g., admissions, discharges, patients, services, etc.) containing a value of 1 to 10 can be reported directly. A value of zero does not violate the minimum cell size policy. In addition, no cell can be reported that allows a value of 1 to 10 to be derived from other reported cells or information".[19] The Sentinel Operations Center may consider combining output categories to reduce small cell counts where applicable and meaningful.

The Sentinel Initiative is deemed a public health surveillance activity conducted under the authority of the US Food and Drug Administration and, accordingly, is not subject to Institutional Review Board oversight.

Sample Analytic Output

Sample analytic output, including table and figure shells, are presented below. These samples are for representative purposes only; analytic output will be refined over the course of study execution.

Table 1. Characteristics of SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017, to December 31, 2022.

Table 1. Characteristics of SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017 to December

	SITT New Users		MITT New Users	
Patient Characteristics	**Number/Mean**	**Percent/ Standard Deviation[1]**	**Number/Mean**	**Percent/ Standard Deviation[1]**
Unique patients	XX,XXX	N/A	XX,XXX	N/A
Demographic Characteristics				
Age (years)	X.X	X.X	X.X	X.X
Age				
40-64 years	XX,XXX	XX.X%	XX,XXX	XX.X%
65-74 years	XX,XXX	XX.X%	XX,XXX	XX.X%
≥ 75 years	XX,XXX	XX.X%	XX,XXX	XX.X%
Sex				
Female	XX,XXX	XX.X%	XX,XXX	XX.X%
Male	XX,XXX	XX.X%	XX,XXX	XX.X%
Other	XX,XXX	XX.X%	XX,XXX	XX.X%
Race[2]				
American Indian or Alaska Native	XX,XXX	XX.X%	XX,XXX	XX.X%
Asian	XX,XXX	XX.X%	XX,XXX	XX.X%
Black or African American	XX,XXX	XX.X%	XX,XXX	XX.X%
Multi-racial	XX,XXX	XX.X%	XX,XXX	XX.X%
Native Hawaiian or Other Pacific Islander	XX,XXX	XX.X%	XX,XXX	XX.X%
Unknown	XX,XXX	XX.X%	XX,XXX	XX.X%
White	XX,XXX	XX.X%	XX,XXX	XX.X%
Hispanic origin				
Yes	XX,XXX	XX.X%	XX,XXX	XX.X%
No	XX,XXX	XX.X%	XX,XXX	XX.X%
Unknown	XX,XXX	XX.X%	XX,XXX	XX.X%
Year				
2017	XX,XXX	XX.X%	XX,XXX	XX.X%
2018	XX,XXX	XX.X%	XX,XXX	XX.X%
2019	XX,XXX	XX.X%	XX,XXX	XX.X%
2020	XX,XXX	XX.X%	XX,XXX	XX.X%
2021	XX,XXX	XX.X%	XX,XXX	XX.X%
Season				
Spring	XX,XXX	XX.X%	XX,XXX	XX.X%
Summer	XX,XXX	XX.X%	XX,XXX	XX.X%
Fall	XX,XXX	XX.X%	XX,XXX	XX.X%
Winter	XX,XXX	XX.X%	XX,XXX	XX.X%
Census Bureau Region				
Northeast	XX,XXX	XX.X%	XX,XXX	XX.X%
Midwest	XX,XXX	XX.X%	XX,XXX	XX.X%
South	XX,XXX	XX.X%	XX,XXX	XX.X%
West	XX,XXX	XX.X%	XX,XXX	XX.X%
US Territories or Unknown	XX,XXX	XX.X%	XX,XXX	XX.X%

Table 2a. Categorical Summary of Days Supplied per Dispensing for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017, to December 31, 2022.

Table 2a. Categorical Summary of Days Supplied per Dispensing for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017 to December 31, 2022

		Number of Dispensings by Days Supplied											
		0-14 Days		15-30 Days		31-60 Days		61-90 Days		91-180 Days		181+ Days	
	Total Number of Dispensings	Number of Dispensings	Percent of Total Dispensings	Number of Dispensings	Percent of Total Dispensings	Number of Dispensings	Percent of Total Dispensings	Number of Dispensings	Percent of Total Dispensings	Number of Dispensings	Percent of Total Dispensings	Number of Dispensings	Percent of Total Dispensings
SITT New Users	XX,XXX	XX,XXX	XX.X%	XX,XXX	XX.X%	XX,XXX	XX.X%	XX,XXX	XX.X%	XX,XXX	XX.X%	XX,XXX	XX.X%
MITT New Users	XX,XXX	XX,XXX	XX.X%	XX,XXX	XX.X%	XX,XXX	XX.X%	XX,XXX	XX.X%	XX,XXX	XX.X%	XX,XXX	XX.X%

Table 2b. Continuous Summary of Days Supplied per Dispensing for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017, to December 31, 2022

Table 2b. Continuous Summary of Days Supplied per Dispensing for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017 to December 31, 2022

		Distribution of Days Supplied by Dispensing						
	Total Number of Dispensings	Minimum	Q1	Median	Q3	Maximum	Mean	Standard Deviation
SITT New Users	XX,XXX	XX	XX	XX	XX	XX	XX.X	XX.X
MITT New Users	XX,XXX	XX	XX	XX	XX	XX	XX.X	XX.X

The following tables appear visually similar to Tables 2a-2b but present different utilization metrics:

Table 3a. Categorical Summary of Patients' Cumulative Treatment Episode Durations for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017, to December 31, 2022.

Table 3b. Continuous Summary of Patients' Cumulative Treatment Episode Durations for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017, to December 31, 2022.

Tables 4a-b and 5a-b duplicate Tables 3a-b, but present Treatment Episode Durations for the (4) First, and (5) Second and Subsequent Treatment Episodes.

Table 6. Continuous Summary of All Treatment Episode Gaps for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017, to December 31, 2022.

Tables 7-8 duplicate Table 6, but present Distribution of Gap Durations for the (4) First, and (5) Second and Subsequent Treatment Episode Gaps.

Table 9. Summary of Reasons First Treatment Episodes Ended for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017, to December 31,2022

Table 9. Summary of Reasons First Treatment Episodes Ended for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017 to December 31,2022[1]

		Censoring Reason									
		End of Exposure Episode[2]		Occurrence of User-Defined		Disenrollment[4]		End of Data[5]		End of Study Period[6]	
	Total Number of Patients	Number of Patients	Percent of Total Patients	Number of Patients	Percent of Total Patients	Number of Patients	Percent of Total Patients	Number of Patients	Percent of Total Patients	Number of Patients	Percent of Total Patients
SITT New Users	XX,XXX	X,XXX	XX.X%	X,XXX	XX.X%	X,XXX	XX.X%	X,XXX	XX.X%	X,XXX	XX.X%
MITT New Users	XX,XXX	X,XXX	XX.X%	X,XXX	XX.X%	X,XXX	XX.X%	X,XXX	XX.X%	X,XXX	XX.X%

[1]A patient's episode may be censored due to more than one reason if they occur on the same date. Therefore, the sum of the reasons for censoring may be greater than the total number of patients.

[2]Represents episodes censored due to end of the exposure episode. In as-treated analyses, exposure episodes are defined using days supplied as recorded in outpatient pharmacy dispensing records, and episodes end after days supplied are exhausted or a pre-determined maximum episode duration is met. In point exposure analyses, exposure episodes end when a pre-determined maximum episode duration is met.

[3]Represents episodes censored due to occurrence of additional user-defined criteria using drug, procedure, diagnosis, and/or laboratory codes.

[4]Represents episodes censored due to disenrollment from health plan. Data Partners often artificially assign a "disenrollment" date equal to data end date for members still enrolled on that date. Therefore, a patient may have dual reasons for censoring as "disenrollment" and "end of data" on the same day - this can be interpreted as right-censoring in most cases.

[5]Represents episodes censored due to Data Partner data end date. This end date represents the last day of the most recent year-month in which all of a Data Partner's data tables in the Sentinel Common Data Model have at least 80% of the record count relative to the prior month.

[6]Represents episodes censored due to user-specified study end date.

The following tables appear visually similar to Table 2a, but present episode duration for subsets of patients censored for different reasons:

Table 10. Summary of Episode Duration for First Treatment Episodes Ended due to End of Exposure Episode for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017 to December 31, 2022.

Tables 11-14 duplicate Table 10, but present number of patients censored by episode length for episodes ending due to (11) occurrence of user-defined censoring criteria, (12) disenrollment, (13) end of data, and (14) end of study period.

The following table appears visually similar to Table 9, but presents reasons for censoring among all episodes (instead of restricted to each patient's first episode):

Table 15. Summary of Reasons All Treatment Episodes Ended for SITT and MITT New Users in the Sentinel Distributed Database from October 1, 2017, to December 31, 2022.

Table 16a. Total Code Counts for SITT New Users in the Sentinel Distributed Database from October 1, 2017 to December 31, 2022

Table 16a. Total Code Counts for SITT New Users in the Sentinel Distributed Database from October 1, 2017 to December 31, 2022

Code	Code Description	Code Category	Code Type	Overall Counts
XXXXXXXX	XXXXXXXXXXX	RX	N/A	XX,XXX
XXXXXXXX	XXXXXXXXXXX	RX	N/A	XX,XXX

Table 16b duplicates Table 16a, but presents code counts for MITT New Users.

Table 17. Summary of Patient-Level Cohort Attrition in the Sentinel Distributed Database from October 1, 2017, to December 31, 2022

Table 17. Summary of Patient-Level Cohort Attrition in the Sentinel Distributed Database from October 1, 2017 to December 31, 2022

	SITT New Users		MITT New Users	
	Remaining	Excluded	Remaining	Excluded
Members meeting enrollment and demographic requirements				
Enrolled at any point during the query period	XX,XXX	N/A	XX,XXX	N/A
Had required coverage type (medical and/or drug coverage)	XX,XXX	X,XXX	XX,XXX	X,XXX
Enrolled during specified age range	XX,XXX	X,XXX	XX,XXX	X,XXX
Had requestable medical charts	XX,XXX	X,XXX	XX,XXX	X,XXX
Met demographic requirements (sex, race, and Hispanic origin)	XX,XXX	X,XXX	XX,XXX	X,XXX
Members with a valid index event				
Had any cohort-defining claim during the query period	XX,XXX	X,XXX	XX,XXX	X,XXX
Claim recorded during specified age range	XX,XXX	X,XXX	XX,XXX	X,XXX
Episode defining index claim recorded during the query period	XX,XXX	X,XXX	XX,XXX	X,XXX
Members with required pre-index history				
Had sufficient pre-index continuous enrollment	XX,XXX	X,XXX	XX,XXX	X,XXX

Figure 1a. Patient Entry into Study by Month for SITT New Users in the Fee-for-Service Medicare Sentinel Data from October 1, 2017, to December 31, 2022

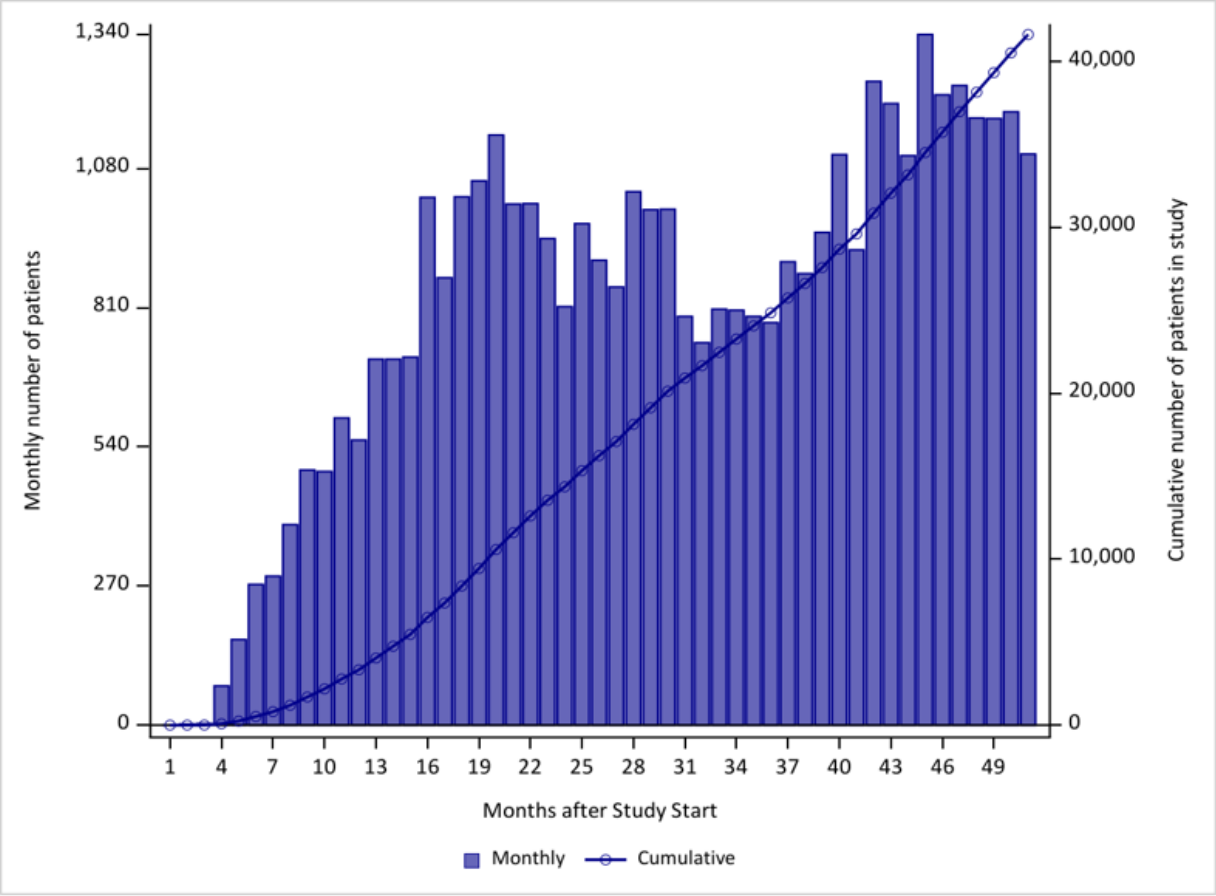


Figure 1b duplicates Figure 1a, but for MITT New Users.

Figure 2a. Reasons for End of First Treatment Episode Among SITT New Users in the Sentinel Distributed Database from October 1, 2017, to December 31, 2022

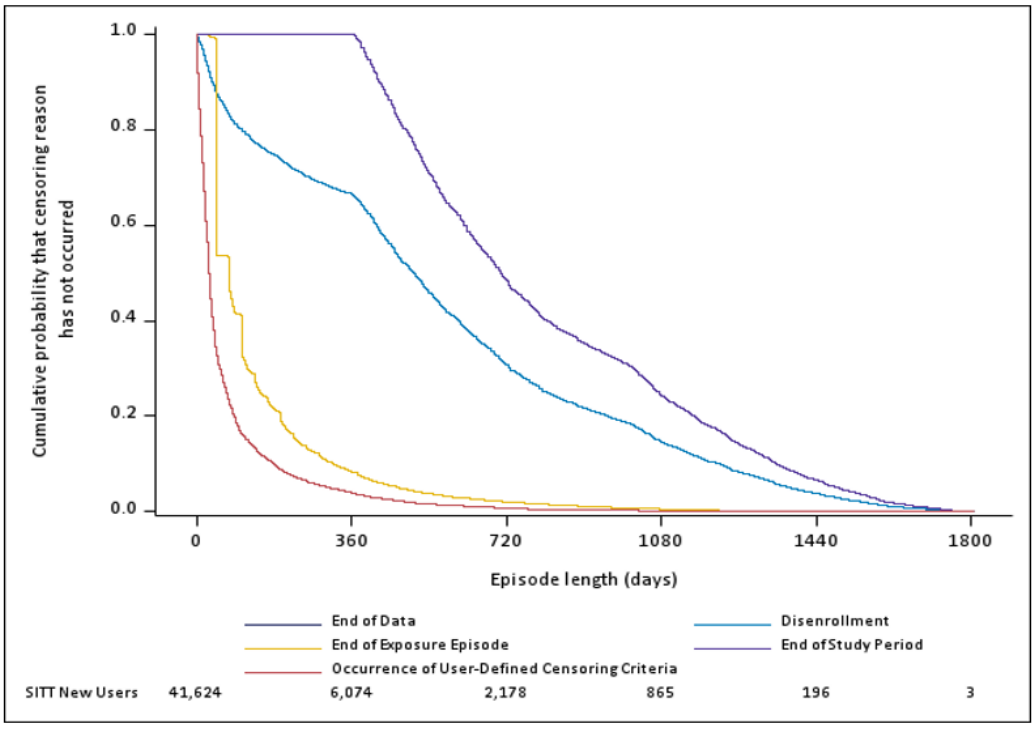


Figure 2b duplicates Figure 2a, but for MITT New Users.

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