Observational and Non-Interventional Study (ONIS) using Existing Data Protocol

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Brief lay title:	Oxygen Therapy Use in Patients with Fibrotic ILD
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Research question and objectives:	The purpose of this study is to examine oxygen therapy utilization and assess the impact of oxygen therapy on clinical and economic outcomes of ILD patients. There are three aims for this project: ***Aim 1:*** *To describe initiation and use of oxygen therapy among patients with fibrotic ILD. The specific objectives for Aim 1 are to:* • Examine the incidence and prevalence of oxygen therapy among patients with fibrotic ILD • Assess the time to first oxygen therapy among fibrotic ILD patients naive to oxygen therapy, and examine factors/variables associated with oxygen therapy initiation ***Aim 2:*** *To assess the impact of oxygen therapy on clinical outcomes among patients with fibrotic ILD. The specific objective for Aim 2 is to:* • Evaluate the impact of oxygen therapy initiation on clinical outcomes, including disease progression and mortality, among fibrotic ILD patients ***Further Aim:*** *To assess the impact of oxygen therapy on economic outcomes among patients with fibrotic ILD. The specific objective for this aim is to:* • Evaluate the impact of oxygen therapy initiation on health care resource utilization (HCRU) and healthcare costs among fibrotic ILD patients
Country(-ies) of study:	United States
Author:	[redacted]
Marketing authorisation holder(s):	
In case of PASS, add: **MAH contact person:**	N/A
In case of PASS, add: **<EU-QPPV:>**	N/A
In case of PASS, add: **<Signature of EU-QPPV:>**	N/A

Date:	July 7th, 2023

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1. LIST OF ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPI	Consumer Price Index
CPT	Current Procedural Terminology
CT	Computed Tomography
DLCO	Diffusing Capacity for Carbon Monoxide
EHR	Electronic Health Record
ER	Emergency Department
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GLM	Generalized Linear Models
HCPCS	Healthcare Common Procedure Coding System
HCRU	Health Care Resource Utilization
HIPAA	Health Information Portability and Accountability Act of 1996
HP	Hypersensitivity Pneumonitis
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IIP	Idiopathic Interstitial Pneumonia
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IPTW	Inverse Probability of Treatment Weighting
KM	Kaplan-Meier
LTOT	Long-Term Oxygen Therapy
MAH	Marketing Authorization Holder
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
PFT	Pulmonary Function Test
PS	Propensity Score
PSM	Propensity Score Matching
SD	Standard Deviation
SpO2	Oxygen Saturation

2. RESPONSIBLE PARTIES

2.1.1 ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: NA			
Name of active ingredient: NA			
Protocol date: *07 JUL 2023*	**Study number:**	**Version/Revision:**	**Version/Revision date:**
Title of study:	Oxygen Therapy Use in Patients with Fibrotic ILD		
Rationale and background:	Interstitial lung disease (ILD) is a broad term that describes more than 200 diverse lung disorders, including idiopathic pulmonary fibrosis (IPF), autoimmune ILD, Nonspecific Interstitial Pneumonia (NSIP), hypersensitivity pneumonitis (HP), and sarcoidosis. Typical symptoms of ILD include cough and dyspnea, as well as decreased lung capacity, which leads to exercise intolerance and hypoxemia. The major goal of therapy in ILD patients is to slow disease progression as well as to improve the associated dyspnea, exercise capacity, and health-related quality of life. Approved treatment options for fibrosing ILD comprise antifibrotic treatments including nintedanib and pirfenidone, which slow the rate of decline in forced vital capacity (FVC). Other commonly prescribed treatment options are corticosteroids, immunosuppressants, opioids, and lung transplantation. Despite advances in pharmacotherapy, many patients continue to have disease progression. Supplemental oxygen (O2) is commonly prescribed in clinical practice for patients with fibrotic ILD to reduce breathlessness and increase physical capacity; however, robust evidence to support its long-term use is lacking. Recommendations for long-term oxygen therapy (LTOT) for resting hypoxemia in ILD are largely extrapolated from trials conducted in chronic obstructive pulmonary disease (COPD), where a survival benefit is well established. The American Association for Respiratory Care guideline recommends the use of oxygen therapy to maintain the oxygen saturation (SpO2) range of 94–98% for most hospitalized patients. Despite its frequent use, there is a paucity of studies evaluating the incidence, prevalence, and impact of LTOT on outcomes such as disease progression or mortality in ILD. This study will help fill in the gaps in increasing the understanding of the use of oxygen therapy among fibrosing ILD patients and assess whether the use of oxygen leads to better or worse outcomes.		

Research question and objectives:	The purpose of this study is to examine oxygen therapy utilization and assess its impact on clinical and economic outcomes of ILD patients. There are three aims for this project: ***Aim 1:*** *To describe initiation and use of oxygen therapy among patients with fibrotic ILD. The specific objectives for Aim 1 are to:* • Examine the incidence and prevalence of oxygen therapy among patients with fibrotic ILD • Assess the time to first oxygen therapy among fibrotic ILD patients naive to oxygen therapy, and examine factors/variables associated with oxygen therapy initiation ***Aim 2:*** *To assess the impact of oxygen therapy on clinical outcomes among patients with fibrotic ILD. The specific objective for Aim 2 is to:* • Evaluate the impact of oxygen therapy initiation on clinical outcomes, including disease progression and mortality, among fibrotic ILD patients [redacted]

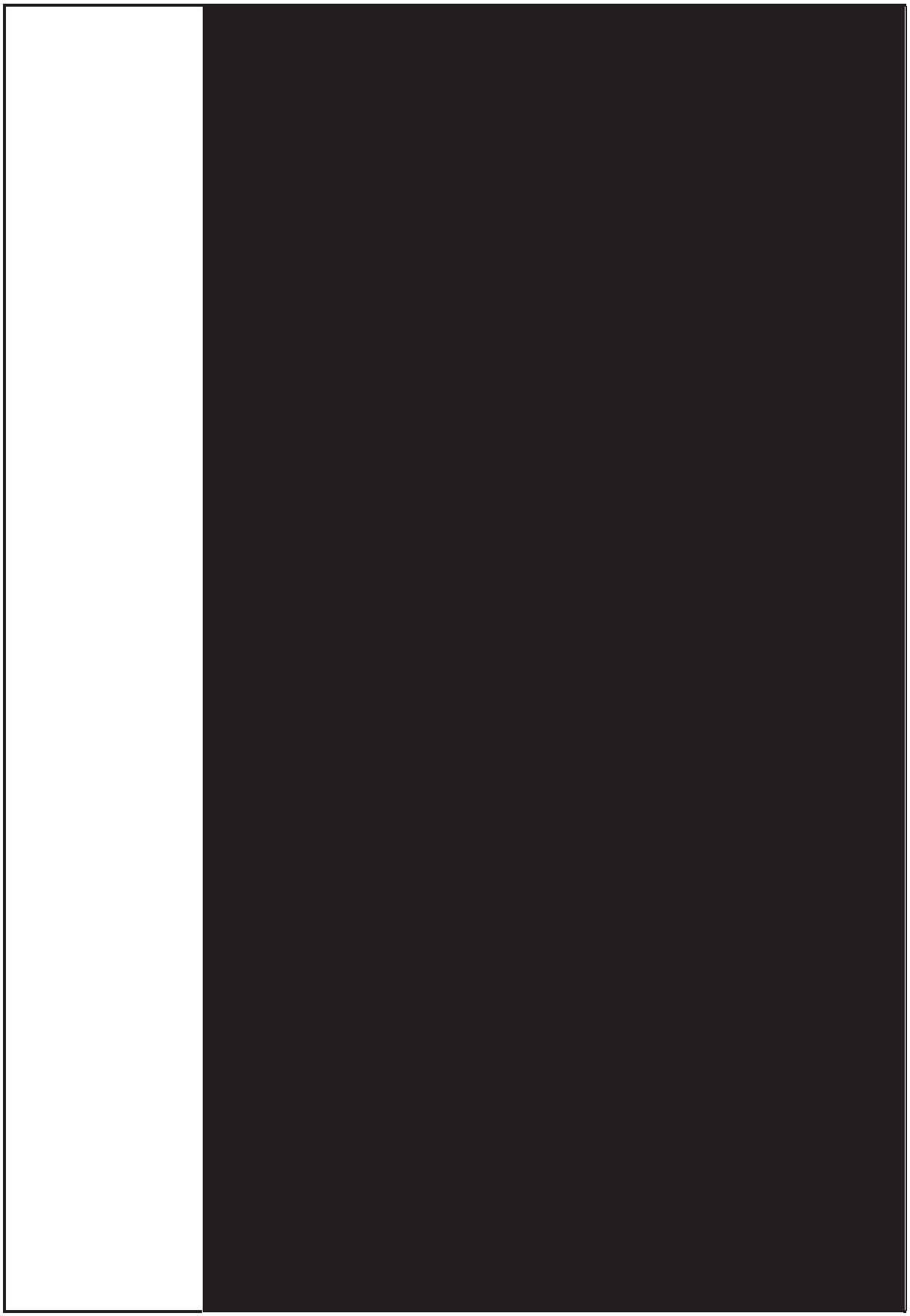
Study design:	This is a non-interventional study of patients enrolled in a commercial, Medicaid, or Medicare plan, using existing administrative claims and electronic health record (EHR) data in Optum's Market Clarity Integrated Claims + Clinical database for the period of 01 October 2015 through 30 June 2022 (study period). The study period may be extended though latest data available at the time of study implementation to increase study sample. Patients aged ≥18 years with newly diagnosed fibrosing ILD will be identified from 01 October 2016 through 30 June 2022 (patient identification period). Patients will be required to have 12 months of baseline continuous enrollment prior to fibrosing ILD diagnosis for collecting patient demographics and clinical characteristics. The pre-ILD baseline period will also be used to describe baseline prevalence of oxygen therapy use. To describe the initiation and use of oxygen therapy after first fibrosing ILD diagnosis (Aim 1), patients will be followed for a variable period from the fibrosing ILD diagnosis date until the earlier of disenrollment from the health plan, end of study period, or death. Oxygen therapy use will be described, and results will be stratified by underlying cause of fibrosis (e.g., IPF vs. non-IPF ILD). Factors associated with initiation of oxygen therapy will be assessed using multivariable methods. To assess the impact of oxygen therapy use on outcomes (Aim 2 [redacted]), patients with fibrosing ILD who initiated oxygen therapy will be propensity score matched to those who did not yet initiate oxygen therapy. The index date will be defined as the date of oxygen therapy initiation for oxygen therapy cohort, or a date that is eligible for index and is similar to the matched case's index date for no oxygen therapy cohort. Disease progression, acute exacerbations, [redacted].

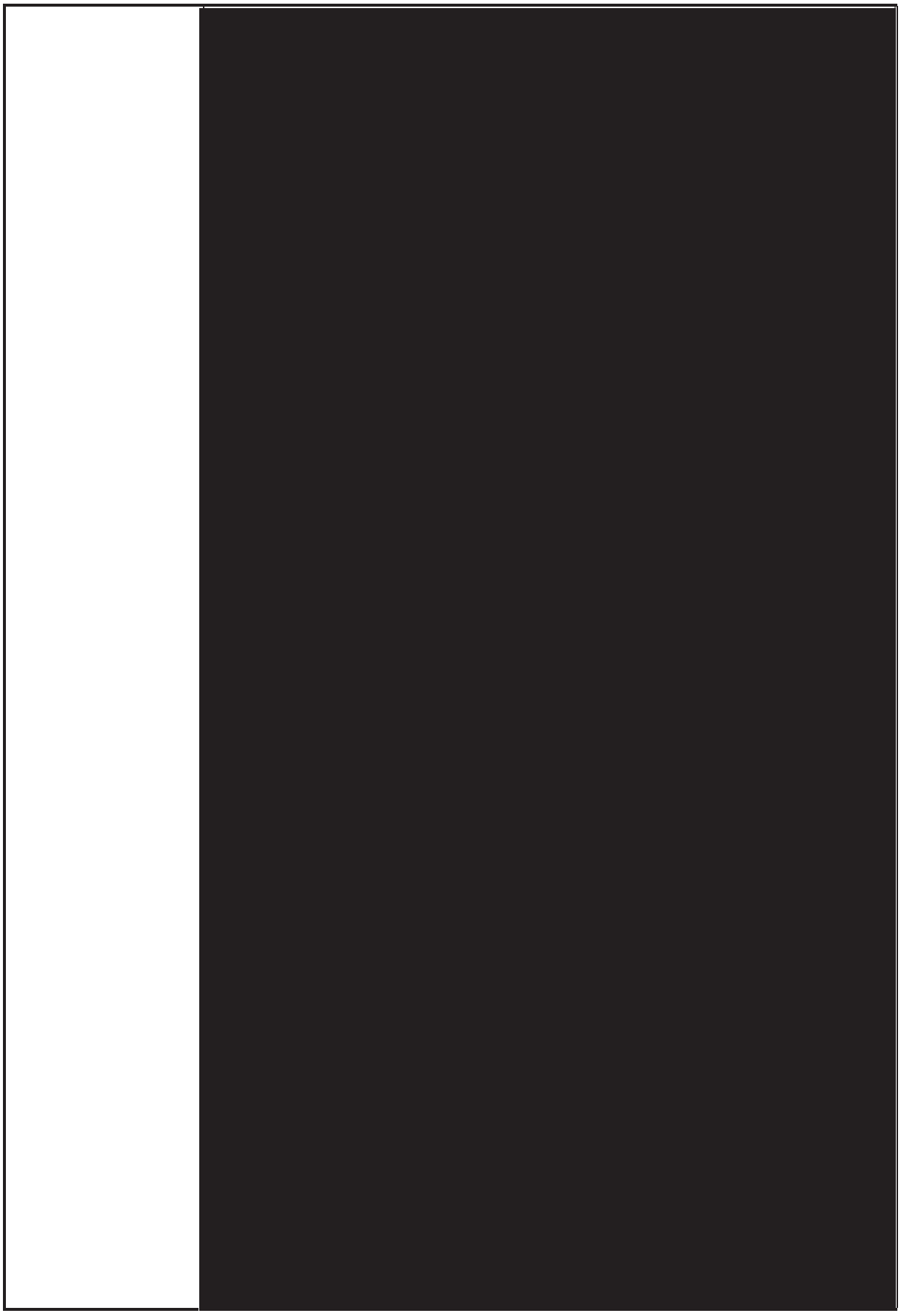
Population:	This study will include patients newly diagnosed with fibrosing ILD between 01 October 2016 through 30 June 2022. **Study Population: Aim 1** The analysis for Aim 1 will include patients newly diagnosed with fibrosing ILD during the patient identification period. Patients must meet the following selection criteria to be included in the study: <u>*Inclusion Criteria*</u> • ≥2 fibrosing ILD diagnoses in any position on different dates of service, within 365 days of each other, and in the same continuous enrollment period during the patient identification period. The ***fibrosing ILD diagnosis date*** will be defined as the date of the first fibrosing ILD diagnosis. The two fibrosing ILD diagnosis codes can be one of the following combinations: o 2 fibrosis codes o 1 fibrosis code & 1 ILD code that requires fibrosis code • ≥18 years of age as of the fibrosing ILD diagnosis date • Continuous enrollment with medical and pharmacy coverage for 12 months prior to the fibrosing ILD diagnosis date (***pre-ILD baseline period***) <u>*Exclusion Criteria*</u> • Fibrosing ILD diagnosis in the 12-month pre-ILD baseline period • Unknown gender, geographic region, or insurance type **Cohort Assignment** Patients meeting initial selection criteria for Aim 1 will be assigned to cohorts based on known cause of fibrosis: • **IPF**— ≥2 medical claims with diagnosis for IPF in any position during the study period • **Non-IPF ILD**— < 2 medical claims with diagnosis for IPF during the study period **Study Population: Aim 2** [redacted] The analysis for Aim 2 and Further Aim will include patients identified for Aim 1 who meet the following additional selection criteria. Final oxygen therapy cohorts will be determined during the propensity score matching (PSM) procedure. • **Oxygen therapy cohort** o ILD patients with ≥1 medical claim for oxygen therapy after fibrosing ILD diagnosis. The ***index date*** will be defined as the first date of a claim for oxygen therapy. • **No oxygen therapy cohort** o Matched to a patient in the oxygen therapy cohort. The ***index date*** will be assigned as a date that is eligible to set an index

	date (i.e., similar to the matched oxygen therapy patient in time from the fibrosing ILD diagnosis date to the index date, and during the same continuous enrollment period as the fibrosing ILD diagnosis date). NOTE: Following review of results from Aim 1, the study team will determine whether continuous enrollment criteria for Aim 2 and Further Aim requires revision.

Variables:	**Aim 1** Outcomes: time to initiation of oxygen therapy; time to sustained oxygen therapy use; sustained oxygen therapy use within the first 12 months of follow-up Baseline covariates: demographic characteristics (age, sex, race/ethnicity, geographic region, insurance type, index year), clinical characteristics (underlying ILD type; respiratory diseases; other clinical characteristics; Quan-Charlson comorbidity score; Agency for Health Research and Quality [AHRQ] comorbid conditions; smoking; pulmonary rehabilitation) healthcare utilization characteristics (provider specialty; medication use; all-cause HCRU; all-cause health care costs) Stratification: IPF vs non-IPF ILD **Aim 2** [redacted] Exposure: oxygen therapy vs no oxygen therapy Primary Outcomes: Time to disease progression; time to all-cause mortality; time to hypoxemia, time to acute exacerbations, counts of acute exacerbations [redacted] Baseline covariates: demographic characteristics (index year, age, sex, race/ethnicity, geographic region, insurance type), clinical characteristics (underlying ILD type; respiratory diseases; other clinical characteristics; Quan-Charlson comorbidity score; AHRQ comorbid conditions; smoking; pulmonary rehabilitation) healthcare utilization characteristics (provider specialty; medication use; all-cause HCRU; all-cause health care costs)
Data sources:	Optum's Market Clarity Integrated Claims + Clinical database Research Database, a fully de-identified and HIPAA compliant database in which clinical data are combined with adjudicated medical and pharmacy claims from both Optum-affiliated and non-affiliated payers. The Market Clarity dataset links EHR data with historical, linked administrative claims data, pharmacy claims, physician claims, facility claims (with clinical information), medications prescribed and administered, diagnoses, procedures, and information derived from clinical notes using NLP. For this study, the subset of individuals with health plan enrollment data available will be used. Insurance coverage will include commercial, Medicaid, and Medicare.
Study size:	Using data from Optum's Market Clarity Integrated Claims + Clinical database from 01 Jan 2016 - 31 May 2022, 1,179,017 patients with fibrosing-ILD were identified. Among them, 34,299 adult patients had at least one claim for oxygen therapy with 6 months of continuous enrollment in claims and 6 months of continuous activity in EHR. These counts are for informational purposes only and may not reflect the final sample size. Application of other inclusion and exclusion criteria required for this study or other factors may reduce the sample size.

Data analysis:	**Aim 1 Analysis** *Descriptive Analysis* All variables will be analyzed descriptively, and results will be stratified by cohort (IPF vs non-IPF ILD). Numbers and percentages will be provided for categorical variables. Means, medians, and standard deviations, will be provided for continuous variables. Appropriate statistical comparisons will be conducted based on the distribution of the measure. *Kaplan-Meier Analysis* Kaplan–Meier (KM) analysis will be used to evaluate time to oxygen therapy initiation from the fibrosing ILD diagnosis date among patients without baseline oxygen therapy use. When KM analysis is conducted, results will include censored-adjusted percentage of patients who have the event of interest at pre-specified time periods of interest (e.g., 6 month, 9 months, 12 months). In addition, the median (and 25th and 75th percentile) time to event and the 95% confidence interval (CI) around the median (and 25th and 75th percentile) will be reported. Censoring will occur at the first of the following: disenrollment from the health plan, end of the study period, or death. Graphs of the cumulative incidence functions (i.e., 1-S(t) where S(t) is the survival function) will be presented along with the cumulative percentage of patients with oxygen therapy initiation following the fibrosing ILD diagnosis date. Methods may account for competing events (e.g., death as competing event for oxygen therapy initiation). *Multivariable Analysis* Cox proportional hazards regression will be used to identify factors associated with initiation of oxygen therapy. Covariates included in the adjusted model will be determined based on statistical significance and clinical rationale. Baseline covariates may include: • Demographic characteristics: index year, age group, gender, race/ethnicity, insurance type, geographic region • Baseline clinical characteristics: all-cause HCRU, all-cause health care costs, medication use, respiratory disease, Quan-Charlson comorbidity score, AHRQ comorbid conditions, smoking, provider specialty, pulmonary rehabilitation Following standard procedures, regression diagnostics will be performed for each model to assess goodness of fit and violations of model assumptions (e.g. multicollinearity, non-proportionality). Violations of the model assumptions will be documented, and appropriate corrections will be made to the analysis. Hazard ratios and associated 95% CIs and p-values will be reported for all covariates in the model. [redacted]





Milestones:	Start of data extract: AUG 2023 End of data analysis: DEC 2023 Final report of study results: FEB 2024

3. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1				
2				

4. MILESTONES

Milestone	Planned Date
Start of data extract	AUG 2023
End of data analysis	DEC 2023
Final report of study results	FEB 2024

5. RATIONALE AND BACKGROUND

Interstitial lung disease (ILD) is a broad term that describes more than 200 diverse lung disorders, including idiopathic pulmonary fibrosis (IPF), autoimmune ILD, hypersensitivity pneumonitis (HP), and sarcoidosis.[1] Typical symptoms of ILD include cough and dyspnea, as well as decreased lung capacity[2], which leads to exercise intolerance and hypoxemia.

The major goal of therapy in ILD patients is to slow disease progression as well as improve the associated dyspnea, exercise capacity, and health-related quality of life.[3] Approved treatment options for fibrosing ILD comprise antifibrotic treatments including nintedanib and pirfenidone, which slow the rate of decline in forced vital capacity (FVC). Other commonly prescribed treatment options are corticosteroids, immunosuppressants, opioids, and lung transplantation.[4] Despite advances in pharmacotherapy, many patients continue with disease progression. Oxygen therapy is commonly administered to reduce breathlessness and increase physical capacity by improving gas exchange.[5]

Supplemental oxygen (O2) is commonly prescribed in clinical practice for patients with fibrotic ILD; however, robust evidence to support its long-term use is lacking. Recommendations for long-term oxygen therapy (LTOT) for resting hypoxemia in ILD are largely extrapolated from trials conducted in chronic obstructive pulmonary disease (COPD), where a survival benefit is well established.[6,7] The American Association for Respiratory Care guideline recommends the use of oxygen therapy to maintain the oxygen saturation (SpO2) range of 94–98% for most hospitalized patients.[8] Despite its frequent use, there is a paucity of studies evaluating the incidence, prevalence, and impact of LTOT on outcomes such as disease progression or mortality in ILD. This study will help fill in the gaps in increasing the understanding of the use of oxygen therapy among fibrosing ILD patients and assess whether the use of oxygen leads to better or worse outcomes.

6. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to examine oxygen therapy utilization and assess its impact on clinical and economic outcomes of ILD patients. There are three aims for this project:

Aim 1*: To describe initiation and use of oxygen therapy among patients with fibrotic ILD. The specific objectives for Aim 1 are to:*

- Examine the incidence and prevalence of oxygen therapy among patients with fibrotic ILD
- Assess the time to first oxygen therapy among fibrotic ILD patients naïve to oxygen therapy, and examine factors/variables associated with oxygen therapy initiation

Aim 2*: To assess the impact of oxygen therapy on clinical outcomes among patients with fibrotic ILD. The specific objective for Aim 2 is to:*

- Evaluate the impact of oxygen therapy initiation on clinical outcomes, including disease progression and mortality, among fibrotic ILD patients

[redacted]

7. RESEARCH METHODS

7.1 STUDY DESIGN

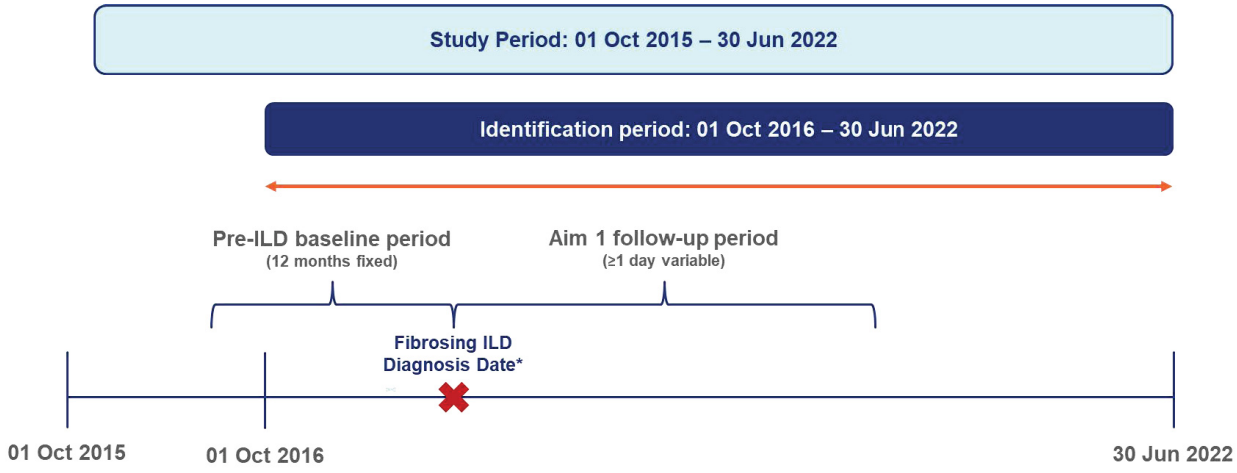
This is a non-interventional study of patients enrolled in a commercial, Medicaid, or Medicare plan, using existing administrative claims and EHR data in Optum's Market Clarity Integrated Claims + Clinical database for the period of 01 October 2015 through 30 June 2022 (study period). The study period may be extended through latest data available at the time of study implementation to increase study sample.

To describe the initiation and use of oxygen therapy after first fibrosing ILD diagnosis (**Aim 1**), patients aged ≥18 years with newly diagnosed fibrosing ILD will be identified from 01 October 2016 through 30 June 2022 (patient identification period). A schematic of the observation and identification periods is presented in Figure 1. Patients will be required to have 12 months of baseline continuous enrollment prior to fibrosing ILD diagnosis for collecting patient demographics and clinical characteristics. The pre-ILD baseline period will also be used to describe baseline prevalence of oxygen therapy use. Patients will be followed for a variable period from the fibrosing ILD diagnosis date (Section 7.2.2) until the earlier of disenrollment from the health plan, end of study period, or death. Oxygen therapy use will be described, and results will be stratified by underlying cause of fibrosis (e.g., IPF vs non-IPF ILD). Factors associated with initiation of oxygen therapy will be assessed using multivariable methods.

To assess the impact of oxygen therapy use on outcomes (**Aim 2 and Further Aim**), patients with fibrosing ILD who initiated oxygen therapy will be propensity score matched to those who did not yet initiate oxygen therapy. A schematic of the observation and identification periods is presented in Figure 2. The index date will be defined as the date of oxygen therapy initiation for oxygen therapy cohort, or a date that is eligible for index and is similar to the

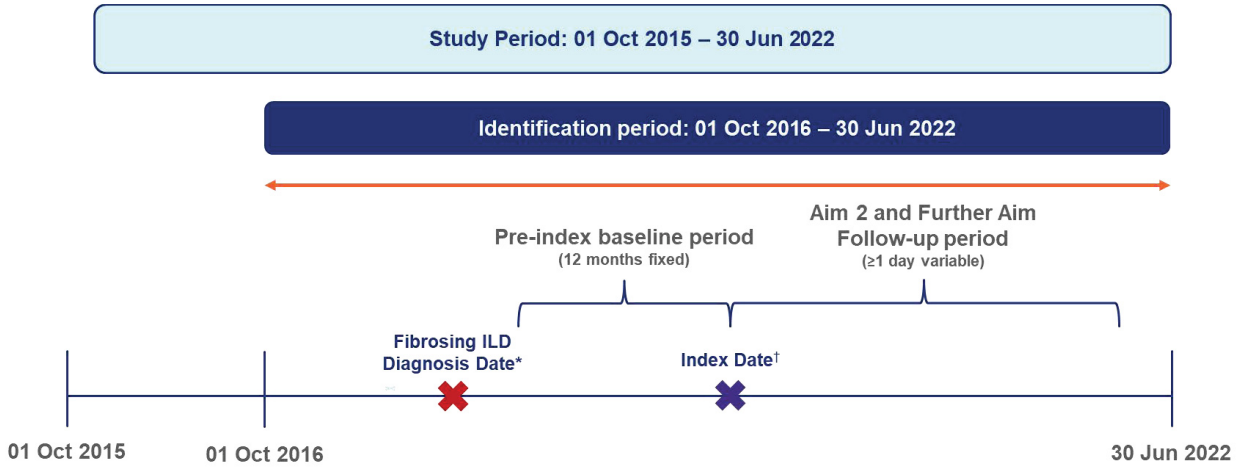
matched case's index date for no oxygen therapy cohort. Disease progression, acute exacerbations, health care resource utilization (HCRU), and health care costs in the Aim 2 follow-up period will be described and compared between matched cohorts. Outcomes will be modelled using multivariable methods.

Figure 1. Observation and Identification Periods: Aim 1



*The ILD diagnosis date will be defined as the first date of a claim with diagnosis for fibrosing ILD during the identification period.
Patients will be followed from the fibrosing ILD diagnosis date until the earlier of disenrollment from the health plan, death, or end of the study period.
Figure is not to scale and is for illustrative purposes only.

Figure 2. Observation and Identification Periods: Aim 2 [redacted]



*The fibrosing ILD diagnosis date will be before the index date and may be before or during the pre-index baselire period.
†The index date will be defined as the first date of a claim with oxygen therapy (oxygen therapy cohort), or a date that is eligible for index and is similar to the matched case's index date (no oxygen therapy cohort).
Patients will be followed from the index date until the earlier of disenrollment from the health plan, death, or end of the study period.
Figure is not to scale and is for illustrative purposes only.

7.2 SETTING

7.2.1 Secondary data source selection

The study will use administrative claims and EHR data from Optum's Market Clarity Integrated Claims + Clinical database.

7.2.2 Study population: Aim 1

The analysis for Aim 1 will include patients newly diagnosed with fibrosing ILD during the patient identification period. Patients must meet the following selection criteria to be included in the study:

Inclusion Criteria

- ≥2 fibrosing ILD diagnoses in any position on different dates of service, within 365 days of each other, and in the same continuous enrollment period during the patient identification period. The ***fibrosing ILD diagnosis date*** will be defined as the date of the first fibrosing ILD diagnosis. The two fibrosing ILD diagnosis codes can be one of the following combinations:
  - 2 fibrosis codes
  - 1 fibrosis code & 1 ILD code that requires fibrosis code
- ≥18 years of age as of the fibrosing ILD diagnosis date
- Continuous enrollment with medical and pharmacy coverage for 12 months prior to the fibrosing ILD diagnosis date (***pre-ILD baseline period***)

Exclusion Criteria

- Fibrosing ILD diagnosis in the 12-month pre-ILD baseline period
- Unknown gender or geographic region

Cohort Assignment

Patients meeting initial selection criteria for Aim 1 will be assigned to cohorts based on known cause of fibrosis:

- **IPF**— ≥2 medical claims with diagnosis for IPF in any position during the study period
- **Non-IPF ILD**— < 2 medical claims with diagnosis for IPF during the study period

7.2.3 Study population: Aim 2 [redacted]

The analysis for Aim 2 and Further Aim will include patients identified for Aim 1 in Section 7.2.2 who meet the following additional selection criteria. Final oxygen therapy cohorts will be determined during the propensity score matching (PSM) procedure outlined in Section 7.6.2.2.

- **Oxygen therapy cohort**
  - ILD patients with ≥1 medical claim for oxygen therapy after fibrosing ILD diagnosis. The ***index date*** will be defined as the first date of a claim for oxygen therapy.

- **No oxygen therapy cohort**
    - Matched to a patient in the oxygen therapy cohort. The ***index date*** will be assigned as a date that is eligible to set an index date (i.e., similar to the matched oxygen therapy patient in time from the fibrosing ILD diagnosis date to the index date, and during the same continuous enrollment period as the fibrosing ILD diagnosis date).

NOTE: Following review of results from Aim 1, the study team will determine whether criteria for Aim 2 and Further Aim require revision.

7.3 VARIABLES

Variables related to the study period will be defined as follows:

Aim 1

- **Fibrosing ILD diagnosis date**—The first ILD diagnosis date for patients with ≥2 fibrosing ILD diagnoses on different dates and within 365 days. The fibrosing ILD diagnosis date is the first day of follow-up observation time for Aim 1.
- **Pre-ILD baseline period**—The 12-month period prior to the fibrosing ILD diagnosis date.
- **Aim 1 follow-up period**—The variable period starting on the fibrosing ILD diagnosis date and continuing until the earliest of the following: disenrollment from the health plan, death, or end of the study period. The Aim 1 follow-up period will be used to assess Aim 1 outcomes.
    - **All-cause mortality**—Death will be used as a censoring event and is further defined in Section 7.3.3.1.

Aim 2 [redacted]

- **Index date**—For the oxygen therapy cohort, the first date following the fibrosing ILD diagnosis date with a claim with diagnosis for oxygen therapy; for the no oxygen therapy cohort, a date within the same continuous enrollment period as the fibrosing ILD diagnosis date that is similar to the matched oxygen therapy patient in time from fibrosing ILD to index date. The index date is the first day of follow-up observation time for Aim 2 and Further Aim.
- **Pre-index baseline period**—The 12-month period prior to the index date.
- **Aim 2 follow-up period**—The variable period starting on the index date until the earliest of the following: disenrollment from the health plan, death, or the end of the study period. Matched pairs will be given the same duration of follow-up. The Aim 2 follow-up period will be used to assess Aim 2 and Further Aim outcomes.
    - All-cause mortality—Death will be used as a censoring event and is further defined in Section 7.3.3.1.

An overview of the analytic study variables and the study periods for which each analytic variable will be reported is provided in Table 1. Additional variable information is provided in Sections 7.3.1 to 7.3.4.

Table 1. Analytic Variables by Data Source and Time Period

Characteristic	Data source		Aim 1 time period		Aim 2 time period	
	Claims*	EHR	Pre-ILD baseline	Follow-up	Pre-index baseline	Follow-up
Aim 1 outcomes						
Oxygen therapy (time to initiation, sustained oxygen therapy use)	X		X	X		
Aim 2 outcomes						
Disease progression	X	X				X
All-cause mortality	X					X
Hypoxemia	X	X	X		X	X
Acute exacerbations	X	X				X
[redacted]						
[redacted]	[redacted]					[redacted]
[redacted]	[redacted]				[redacted]	[redacted]
Patient characteristics†						
Index year	X		X		X	
Age/age groups	X		X		X	
Race/ethnicity	X		X		X	
Sex	X		X		X	
Insurance type	X		X		X	
Geographic region	X		X		X	
Clinical characteristics						
Underlying ILD type‡	X		X		X	
Respiratory diseases	X		X		X	
Smoking	X		X		X	
Quan-Charlson comorbidity score	X		X		X	
AHRQ comorbid conditions	X		X		X	
Smoking	X		X		X	
Pulmonary rehabilitation	X		X		X	
Healthcare utilization characteristics						
Provider specialty	X		X		X	
Medication use	X		X		X	
All-cause HCRU and costs	X		X		X	

*As available among the subset of patients with information from both EHR and claims

†Measured as of the index date, or first available claim after the index date with value values for each of the characteristics
‡Measured using claims from the entire study period

7.3.1 Aim 1 Outcomes

7.3.1.1 Primary Outcomes

- **Oxygen Therapy**—Evidence of oxygen use will be captured in the pre-ILD baseline and Aim 1 follow-up periods based on the presence of ≥ 1 diagnosis (ICD-10-CM), procedure (HCPCS, CPT), or revenue code for oxygen therapy. Among patients with oxygen therapy in follow-up, the following aspects of oxygen therapy will be described:
    - **Time to oxygen therapy initiation**—The time in days from the fibrosing ILD diagnosis date to oxygen therapy initiation, among patients without evidence of oxygen therapy in the pre-ILD baseline period.
    - **Sustained oxygen therapy use**—Using claims, sustained oxygen therapy use will be defined among patients with at least 12 months of follow-up after the index date (oxygen initiation date), as a binary variable for the presence of ≥ 11 claims for oxygen therapy in a 12-month period. The following aspects of sustained oxygen therapy will be described:
        - **Time to sustained oxygen therapy use**—The time in days between the index date and the earliest date that defined the sustained oxygen therapy use.
        - **Sustained oxygen therapy use within the first 12 months of follow-up**—The number of patients with the evidence of sustained oxygen therapy use during the first 12 months of follow-up.
        - **Note:** As a sensitivity analysis, sustained oxygen therapy use will also be defined as ≥ 6 claims for oxygen therapy in a 12-month period and, based on the distribution of the count of claims among the population, as the 75th percentile of claims in a 12-month period.

7.3.2 Aim 2 Exposures

The exposure of interest is oxygen therapy versus no oxygen therapy among patients with fibrosing ILD and is defined based on evidence of oxygen therapy following ILD diagnosis, as described in Section 7.2.3.

7.3.3 Aim 2 Outcomes

7.3.3.1 Primary Outcomes

All primary outcomes will be measured in the Aim 2 and Further Aim follow-up period, unless specified otherwise.

- **Time to disease progression**—Pulmonary function test (PFT) results will be captured as available in the database in the pre-ILD baseline, pre-index baseline, and Aim 2 follow-up periods among the subset of patients who have EHR data during the same

time of ILD diagnosis and oxygen therapy. All valid result values will be captured. Values closest to the fibrosing ILD diagnosis date will be reported for the pre-ILD baseline period; values closest to the index date will be reported for the pre-index baseline period; the latest values prior to the end of follow-up will be reported for the Aim 2 follow-up period. PFT tests may potentially include forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, lung volumes, and diffusing capacity for carbon monoxide (DLCO), as available.

Among patients or matched pairs with FVC results in the pre-index and follow-up periods, disease progression will be defined as a 10% relative change between the pre-index value and the follow-up value. Time to disease progression will be reported. Additionally, time in days from pre-index FVC result to the index date and from index date to follow-up FVC result will be reported.

- **Time to all-cause mortality**—We will assign the date of death as the 15th day in the month of death. Time to all-cause mortality will be calculated as time between index date and mortality date.

7.3.3.2 Secondary Outcomes

- **Hypoxemia**—Sample size permitting, hypoxemia (i.e., oxygen saturation [SpO_2] <90%) will be captured as available in the database using specific ICD-10-CM codes or EHR data among the subset of patients with both claims and EHR in the Market Clarity database. Time to hypoxemia will be reported as time between index date and first evidence of hypoxemia.
- **Respiratory deterioration/Acute exacerbations**—An acute exacerbation of fibrosing ILD has been defined clinically as an unexplained worsening or development of dyspnea within 30 days in combination with a high-resolution CT indicating interstitial pneumonia, and excluding pulmonary infection, left heart failure, pulmonary embolism or other identifiable causes of acute lung injury.[9] Based on these clinical criteria, acute exacerbations will be defined as follows:
  - ≥1 claim with procedure code for CT scan, and
  - Evidence of dyspnea, as defined by ICD-10-CM codes or EHR data in the integrated database, within 30 days prior to date of CT scan, and
  - No claims with diagnosis for pulmonary infection, left heart failure, pulmonary embolism, or other identifiable causes of acute lung injury within 30 days prior to date of CT scan.

  The time to first exacerbation and population annualized counts of exacerbations (sum of all exacerbations for all individuals / sum of follow-up time [person years] for all individuals) will be described. Exacerbations occurring within 14 days of each other will be considered a single exacerbation episode. The start date of the exacerbation episode will be the service date of the first event (i.e., dyspnea or CT scan). The end date of the exacerbation episode will be defined as the last observed exacerbation event date (or discharge date if event occurs during an inpatient stay) + 14 days. Exacerbation episodes that include an inpatient stay will also be reported separately as exacerbations involving a hospitalization.

7.3.5 Baseline Covariates (Aim 1, Aim 2, and Further Aim)

Clinical characteristics will be measured during the pre-ILD baseline and pre-index baseline periods unless otherwise specified.

7.3.5.1 Demographic Characteristics

- **Index year**—The year of the patient's fibrosing ILD diagnosis date or index date will be identified.
- **Age**—Age will be defined as of the index year.
- **Age groups**—Patients will be assigned to one of the following age groups: 18–44, 45–64, and 65+.
- **Sex**—Sex will be captured from enrollment data; patients with undefined gender will be removed from the study sample
- **Race/ethnicity**—Patients will be classified as Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, Other/Unknown. This variable depends on the

availability of data within the sociodemographic data and will be missing for some patients.

- **Insurance type**—Payer type will be defined as commercial, Medicare, Medicaid.
- **Geographic region**—The U.S. region in which the patient is enrolled in a health plan will be described. States will be categorized into geographic regions in accordance with the U.S. Census Bureau's region designations. The five health plan regions are presented in Table 2.

Table 2. Health Plan Regions

Region	State
Northeast	CT, MA, ME, NH, RI, VT, NJ, NY, PA
Midwest	IL, IN, MI, OH, WI, IA, KS, MN, MO, ND, NE, SD
South	DC, DE, FL, GA, MD, NC, SC, VA, WV, AL, KY, MS, TN, AR, LA, OK, TX
West	AZ, CO, ID, MT, NM, NV, UT, WY, AK, CA, HI, OR, WA
Other	Armed Forces, American Samoa, Federated State of Micronesia, Guam, Marshall Islands, Commonwealth of the Northern Mariana Islands, Puerto Rico, Palau, Virgin Islands

7.3.5.2 Clinical Characteristics

- **Underlying ILD type**—Patients will be classified into the following underlying ILD types based on claims from the entire study period: autoimmune ILD, HP, sarcoidosis, unclassified ILD/IIP, and multiple. The underlying ILD type will be defined based on the presence of ≥1 specific ICD-10-CM diagnosis code for autoimmune ILD, HP, and sarcoidosis. Patients without any underlying ILD diagnosis will be classified into the unclassified ILD/IIP type. Patients with diagnoses for >1 underlying ILD types will be classified as multiple.
- **Respiratory diseases**—Separate indicator variables will be created for the presence of ≥1 diagnosis code in any position on a medical claim. The following conditions will be included: pulmonary hypertension, acute respiratory failure, asthma, COPD, pneumonia, lung transplantation, upper respiratory tract infection, lower respiratory tract infection, lung cancer, and cystic fibrosis.
- **Other clinical characteristics** – Similar to respiratory disease, a separate indicator variables will be created for the presence of ⩾1 diagnosis code in any position on a medical claim. The following conditions will be included: gastroesophageal reflux disease (GERD), heart failure, and obstructive sleep apnea.
- **Quan-Charlson comorbidity score**—A comorbidity score will be calculated based on the presence of diagnosis codes on medical claims.[10, 11] The Quan-Charlson comorbidity score will also be categorized into the following groups: zero, one to two, three to four, and five or more.
- **Comorbid conditions**—General comorbid conditions will be defined using the Clinical Classifications Software managed by the Agency for Healthcare Research and Quality (AHRQ).[12] This measure generates indicator variables for specific disease

conditions based on ICD-9-CM and ICD-10-CM diagnoses. The top 20 comorbid conditions will be presented.

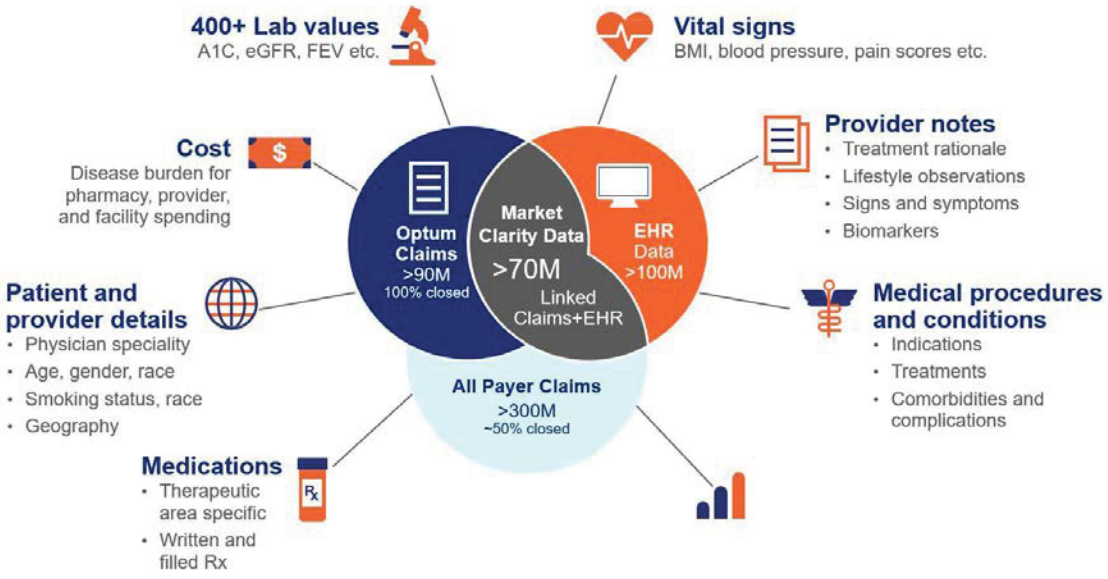
- **Smoking**—An indicator variable will be created to identify patients with evidence of current or prior tobacco use based on diagnosis codes or pharmacy fills for smoking cessation treatments (bupropion, varenicline tartrate, or nicotine [inhalation, gum, lozenge, transdermal]).
- **Pulmonary rehabilitation**—Indicator and count variables will be created for the presence of procedure codes for pulmonary rehabilitation.

7.3.5.3 Healthcare Utilization Characteristics

- **Provider specialty**—A count of unique days with a non-inpatient claim for treatment by provider specialty category (primary care physician [including general/family practice, internal medicine], pulmonology and rheumatology) will be reported.
- **Medication use**—ILD medication use will be captured at the class level, including administrations and prescription fills. The number of prescriptions fills within each class will also be calculated. Treatment categories will include corticosteroids (methylprednisone, prednisone, prednisolone), biologics, (abatacept, denosumab, etanercept, tocilizumab, infliximab, rituximab), calcineurin inhibitors (cyclosporine, tacrolimus), and other immunosuppressants (mycophenolate mofetil, hydroxychloroquine, leflunomide, methotrexate, sulfasalazine, chloroquine phosphate).
- **All-cause HCRU**—HCRU will be calculated for ambulatory visits (physician office and hospital outpatient), emergency department (ER) visits, inpatient admissions, and pharmacy fills.
- **All-cause health care costs**—Health care costs will be presented as standardized costs. Total costs will be calculated and presented in categories of pharmacy costs and medical costs (outpatient, inpatient, professional services). Costs will be adjusted using the annual medical care component of the Consumer Price Index (CPI) to reflect inflation between the date of the claim and the most recent year for which the annual CPI is available.

7.4 DATA SOURCES

Figure 3. Optum Data Ecosystem



Optum's Clinical EHR Database aggregates extensive clinical encounter data from a network of 140,000+ providers at more than 700 hospitals and 7,000+ clinics. The Clinical EHR Database currently has more than 104 million unique patients across the United States, with an average of 45 months of observed data per patient.

The Clinical EHR Database is robust, longitudinally linked, compliant with the Health Information Portability and Accountability Act of 1996 (HIPAA), and statistically de-identified. Data elements include demographics; medications prescribed and administered; immunizations; allergies; lab results (including microbiology); vital signs and other observable measurements; clinical and inpatient stay administrative data; and coded diagnoses and procedures.

Optum's Clinical EHR Database can deliver a longitudinal record that covers a comprehensive spectrum of patient health, medical information, and treatment decisions.

Optum Market Clarity dataset

The Optum Market Clarity dataset includes de-identified, deterministically linked claims data integrated with Optum's Clinical EHR data. It is fully HIPAA-compliant and statistician-certified. Clinical data are combined with adjudicated medical and pharmacy claims from both Optum-affiliated and non-affiliated payers. The Market Clarity dataset links EHR data with historical, linked administrative claim data, pharmacy claims, physician claims, facility claims (with clinical information), medications prescribed and administered, diagnoses, procedures, and information derived from clinical notes using NLP. For this study, the subset of individuals with health plan enrollment data available will be used. Insurance coverage will include commercial, Medicaid, and Medicare.

Figure 4. Market Clarity Data

7.5 STUDY SIZE

Using data for Market Clarity integrated claims and clinical EHR data from 01 Jan 2016 - 31 May 2022, 1,179,017 patients with fibrosing-ILD were identified. Among them, 34,299 adult patients had at least one claim for oxygen therapy with 6 months of continuous enrollment in claims and 6 months of continuous activity in EHR.

These counts are for informational purposes only and may not reflect the final sample size. Application of other inclusion and exclusion criteria required for this study or other factors may reduce the sample size.

Table 3. Feasibility Counts from Market Clarity

Criteria	N
Commercial and Medicare Advantage health plan members with ≥1 medical claim or EHR diagnosis for fibrosing interstitial lung disease (ILD) during 01 JAN 2016 and 31 MAY 2022 (study period). First diagnosis is index date.	1,179,017
Patients with at least one evidence for oxygen therapy anytime during the post-index period (12 months)	214,725
Patients aged >=18 years as of the index date	212,466
Patients with at least 6 months of pre-index continuous enrollment and EHR clinical activity	80,151
Patients with at least 6 months of post-index continuous enrollment and EHR clinical activity	34,299

7.6 DATA ANALYSIS

All analysis will be conducted using SAS statistical software (version 9.4 or higher, [redacted]) and Microsoft Excel.

7.6.1 Aim 1 Analysis

7.6.1.1 Descriptive Analysis

All variables will be analyzed descriptively, and results will be stratified by cohort (IPF vs non-IPF ILD). Numbers and percentages will be provided for categorical variables. Means, medians, and standard deviations, will be provided for continuous variables. Appropriate statistical comparisons will be conducted based on the distribution of the measure.

7.6.1.2 Kaplan-Meier Analysis

Kaplan–Meier (KM) analysis will be used to evaluate time to oxygen therapy initiation from the fibrosing ILD diagnosis date among patients without baseline oxygen therapy use. When KM analysis is conducted, results will include censored-adjusted percentage of patients who have the event of interest at pre-specified time periods of interest (e.g., 6 month, 9 months, 12 months). In addition, the median (and 25th and 75th percentile) time to event and the 95% confidence interval (CI) around the median (and 25th and 75th percentile) will be reported. Censoring will occur at the first of the following: disenrollment from the health plan, end of the study period, or death.

Graphs of the cumulative incidence functions (i.e., 1-S(t) where S(t) is the survival function) will be presented along with the cumulative percentage of patients with oxygen therapy initiation following the fibrosing ILD diagnosis date. Methods may account for competing events (e.g., death as competing event for oxygen therapy initiation).

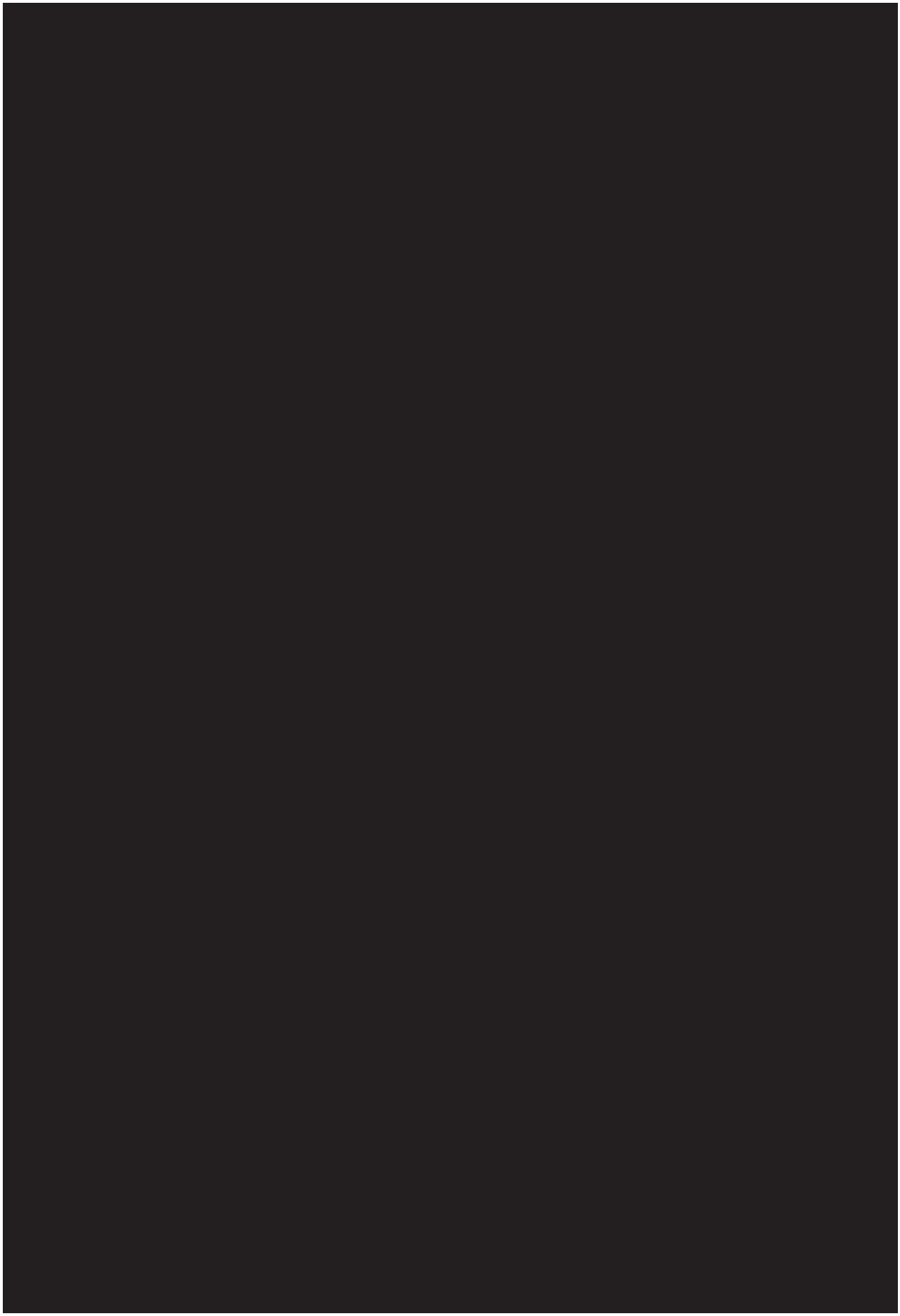
7.6.1.3 Multivariable Analysis

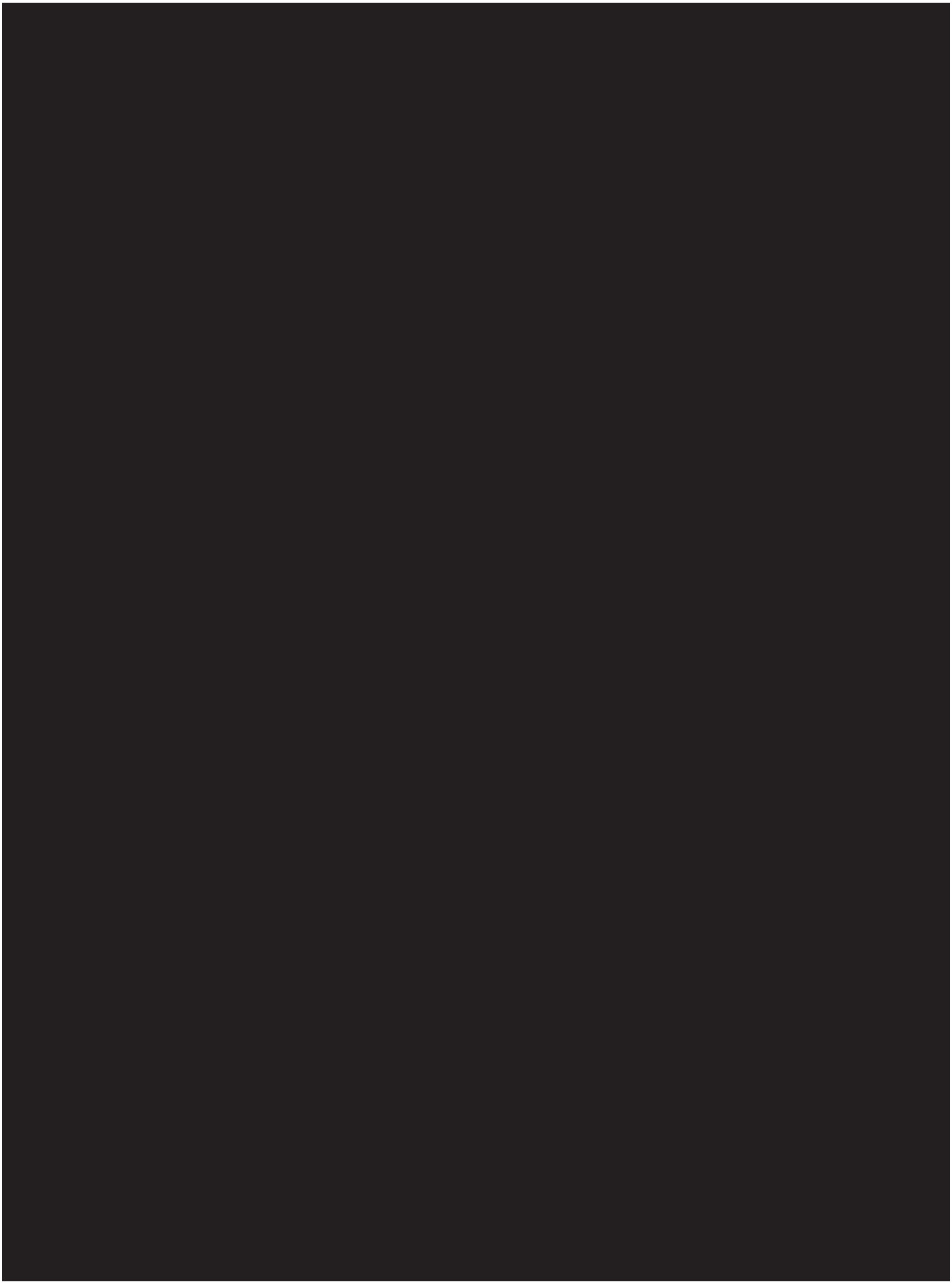
Cox proportional hazards regression will be used to identify factors associated with initiation of oxygen therapy. Covariates included in the adjusted model will be determined based on statistical significance and clinical rationale. Baseline covariates may include:

- Demographic characteristics: index year, age group, gender, race/ethnicity, insurance type, geographic region
- Baseline clinical characteristics: all-cause HCRU, all-cause health care costs, medication use, respiratory disease, Quan-Charlson comorbidity score, AHRQ comorbid conditions, smoking, provider specialty, pulmonary rehabilitation

Following standard procedures, regression diagnostics will be performed for each model to assess goodness of fit and violations of model assumptions (e.g. multicollinearity, non-proportionality). Violations of the model assumptions will be documented, and appropriate corrections will be made to the analysis.

Hazard ratios and associated 95% CIs and p-values will be reported for all covariates in the model.





7.7 QUALITY CONTROL/DATA QUALITY

Optum's research approach centers on judicious scientific rigor and accuracy. In particular, Optum focuses on quality results at each step of the process.

- Optum develops study approaches of sound scientific design that meet clinically stringent review. Researchers develop detailed protocols that include definitions, codes, analyses, and table shells. The coding strategy is then reviewed by a clinical team member for validity and relevance. The protocol further provides Optum and BI an opportunity to solidify research questions and address any potential gaps in information.
- Code lists are developed by clinical coding experts and reviewed by Optum research teams during protocol development and review. Optum does not warrant that code lists accurately reflect how the codes are used in clinical practice and does not consider proposed code lists final until the client has carefully checked and approved them for use. It is the client's responsibility to check code lists carefully before approving the final protocol. Additional timeline and effort for code list exploration during dataset construction can be incorporated into projects for an additional fee. Changes to the project code lists following protocol approval will result in additional timeline and fees.
- A study is only as good as the data set created for analysis. Therefore, Optum incorporates meticulous quality assurance checks during data set construction to generate the most accurate data set. Our analysts perform record-level verification of data elements, double-program certain portions of the data set, program data edit checks, visually review raw claims data against the constructed data elements and review the analysis to assess the validity of results.
- Analysis is performed by a statistician or senior analyst under the supervision of the project director. The project director reviews output for consistency with the analysis plan and for quality and accuracy. Results are then reviewed with BIPI.
- The final deliverables receive internal review by a clinical consultant and/or by another senior researcher for quality and completeness.
- In addition to our meticulous internal quality processes, Optum has specific internal standard operating procedures (SOPs) for retrospective research that are monitored

continuously by the organization. Copies of SOPs can be viewed upon request, which include:

- Study Reports for HEOR Studies
- Statistical Analysis Plan (SAP) Development for HEOR Studies
- Costing for HEOR Studies
- HEOR Analytic Data Creation and Validation for Outcomes Studies
- Protocol Development for HEOR Studies
- Secure Delivery of Protected Health Information (PHI) and/or Personally Identifiable Information (PII) to External Parties by HEOR
- Data Collection Tool Development for HEOR Studies - US

7.8 LIMITATIONS OF THE RESEARCH METHODS

This study should be considered in the context of its limitations. First, identification of patients with newly diagnosed fibrosing ILD will rely on application of a claims-based algorithm. Presence of a diagnosis code does not necessarily indicate presence of disease; however, to limit misidentification of ILD patients, a confirmatory diagnosis will be required. Further, patients without ILD diagnosis in the 12-month baseline will be considered newly diagnosed. However, it is possible that patients with prevalent ILD who have not sought frequent care for their condition may be misclassified as newly diagnosed ILD patients.

Second, this study will utilize both claims and EHR data available in Optum's Market Clarity Integrated Claims + Clinical database to capture ILD symptoms, pulmonary function testing results, and hypoxemia. EHR data will be available for only a subset of the identified population; for remaining patients, these values will rely on information available in claims. Further, the analysis will rely on the availability of valid values (e.g., laboratory results) in the EHR data.

Third, all ILD patients included in this study were enrolled in a health plan (i.e., commercial, Medicare, or Medicaid) during the study period; thus, findings from this study may not be applicable to uninsured populations and patients with health plans not represented in the database.

Fourth, this study will minimize bias by utilizing propensity score matching on baseline variables (oxygen therapy versus no oxygen therapy cohorts) to examine outcomes of interest. Employing matching will enable a comparison of outcomes among patients who were similar on pre-ILD baseline characteristics. However, residual and/or unobserved confounding cannot be ruled out.

Finally, because medical and pharmaceutical claims are collected for the purpose of payment, there are inherent limitations to the use of claims databases for research. Coding errors may result in inaccurate or incomplete data, leading to potential misclassification of variables of interest and bias in research findings. A claim for a filled prescription is not an indication the medication was consumed or taken as prescribed. Also, physician-provided samples, samples taken as part of a clinical trial or over-the-counter medications will not be observed in claims data. Despite these limitations, claims data remain a robust and valuable source for the real-world examination of healthcare outcomes.

8. PROTECTION OF HUMAN SUBJECTS

This is a retrospective database study, and the data extracts will be fully de-identified and HIPAA compliant. No BIPI or Optum personnel will have the ability to link data to an identifiable individual. Data extraction will follow Optum policies and procedures for safety and security. Optum is responsible for all data extraction, analyses and storage. No raw claims data will be distributed to BIPI; only aggregated data will be shared with BIPI. Informed consent is not necessary due to the retrospective and non-invasive nature of the study.

8.1 STATEMENT OF CONFIDENTIALITY

No patient's identity or medical records will be disclosed for the purposes of this study except in compliance with applicable law.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

AE collection not required for this study which is based on secondary use of data. The study does not include chart abstraction. There is no review of individual records to collect safety data to address the study objective.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

One or more abstracts/posters may be developed and submitted to relevant scientific conference(s) and one or more manuscripts will be developed (upon request) and submitted to relevant peer-reviewed medical journals mutually agreed by all study authors.

Both Optum and BIPI teams will convene a meeting to discuss the study results and develop a plan to disseminate the study findings through conference abstracts/posters presentations and journal manuscripts. All dissemination activities are optional and will be activated after data analyses.

Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed.

11. REFERENCES

[1] Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2013;188:733–48.

[2] Podolanczuk AJ, Wong AW, Saito S, Lasky JA, Ryerson CJ, Eickelberg O. Update in interstitial lung disease 2020. *Am J Respir Crit Care*. 2021;203(11):1343–52.

[3] Raghu G, Richeldi L. Current approaches to the management of idiopathic pulmonary fibrosis. *Respir Med*. 2017;129:24–30.

[4] Glass DS, Grossfeld D, Renna HA, Agarwala P, Spiegler P, DeLeon J, Reiss AB. Idiopathic pulmonary fibrosis: Current and future treatment. *Clin Respir J*. 2022 Feb;16(2):84-96.

[5] Khor YH, Goh NS, McDonald CF, Holland AE. Oxygen therapy for interstitial lung disease: physicians' perceptions and experiences. *Ann Am Thorac Soc*. 2017 Dec;14(12):1772-78.

[6] Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980 Sep;93(3):391-8.

[7] Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981 Mar 28;1(8222):681-6.

[8] Piraino T, Madden M, Roberts KJ, Lamberti J, Ginier E, Strickland SL. AARC Clinical Practice Guideline: Management of Adult Patients with Oxygen in the Acute Care Setting. *Respir Care*. 2022 Jan 1;67(1):115-28.

[9] Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, Lasky JA, Loyd JE, et al. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2007 Oct 1;176(7):636-43.

[10] Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-82.

[11] Bayliss EA, Ellis JL, Shoup JA, Zeng C, McQuillan DB, Steiner JF. Association of patient-centered outcomes with patient-reported and ICD-9-based morbidity measures. *Ann Fam Med*. 2012;10(2):126-33.

[12] Clinical Classification Software (CCS) for ICD-9-CM. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp (discharges prior to 10/1/2015).

[13] Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41–55.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	None	N/A	N/A

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ANNEX 3. TABLE SHELLS

Table shells

ANNEX 4. CODE LISTS

Code lists

RX code lists

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

Study Title: Assessment of the Oxygen Use and Future Outcomes Associated with Oxygen Use in Patient with Fibrotic Interstitial Lung Disease

Study Number: 1159-0541

Protocol Version: v.6

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.
Note: Please insert respective signatories with regard to the Associated Document BI-VQD-27112_90-118_AD-27, Overview of Required Reviewers and Approvers for Observational and Non-Interventional Studies (ONIS) Documents.

Position: ONIS [redacted] Name/Date: [redacted] / 29 June 2023 Signature: _____

Position: ONIS [redacted] Name/Date: [redacted] 29 June 2023 Signature: _____

Position: ONIS [redacted] Name/Date [redacted] / Date Signature: _____
Line [redacted]

Position: _____ Name/Date: _____ Signature: _____

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