Study information

Title	Work productivity losses in the United States among high-risk patients with COVID-19 during acute and longer-term follow-up in an omicron predominant period (PULSE-US)
Protocol number	C4671066
Protocol version identifier	1.0
Date	29 August 2024
Active substance	nirmatrelvir-ritonavir ATC J05AE30
Medicinal product	Paxlovid
Research question and objectives	**Research question**: What are the indirect burden of COVID-19 and the potential benefits of nirmatrelvir-ritonavir (NMV/r) for reducing the indirect burden of disease among patients in the United States at high risk of progression to severe COVID-19 ("high-risk patients")? **Primary objectives**: • Describe demographic and clinical characteristics of adult, high-risk patients diagnosed with COVID-19, including patients who received NMV/r (treated) and those who did not receive any COVID-19 antiviral therapy (untreated) • Describe measures of workplace productivity loss, such as total days away from work and use of disability leave, as well as indirect costs associated with work loss, among high-risk treated and untreated patients, directly matched on demographic and clinical characteristics **Exploratory objective:** • Compare productivity loss and indirect cost outcomes between high-risk treated and untreated patients using multivariable models, controlling for patient characteristics
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention deficit/hyperactivity disorder
AHRQ	Agency for Healthcare Research and Quality
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control
CDHP	Consumer-driven health plan
CKD	Chronic kidney disease
COB	Coordination of benefits
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CVD	Cardiovascular disease
ECI	Elixhauser Comorbidity Index
EPO	Exclusive provider organization
ER	Emergency room
EUA	Emergency use authorization
FDA	Food and Drug Administration
GLM	Generalized linear model
HDHP	High-deductible health plan
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HMO	Health maintenance organization
HPM	Health and Productivity Management Database
ICD-10	International Classification of Diseases, 10th Revision
IRB	Institutional review board
LTD	Long-term disability
MAFLD	Metabolic dysfunction-associated fatty liver disease
NMV/r	Nirmatrelvir-ritonavir
POS	Point-of-service
PPO	Preferred provider organization
PPPM	Per-patient-per-month
QA	Quality assurance
SD	Standard deviation
SMD	Standardized mean difference
STD	Short-term disability
US	United States
WC	Worker's compensation
WPAI	Work productivity and activity impairment

3. RESPONSIBLE PARTIES**Principal Investigator(s) of the Protocol**

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3. AMENDMENTS AND UPDATES

None

4. MILESTONES

Milestone	Planned Date
MSC Study Concept Endorsement	27 March 2024
Final analysis plan	29 August 2024
MSC Protocol Endorsement	11 September 2024
Patient selection	09 October 2024 (4 weeks after analysis plan approval)
Analytic file build	20 November 2024 (6 weeks after patient selection)
Descriptive analyses	20 December 2024 (4 weeks after completion of file build)
Multivariable analyses	31 January 2025 (4 weeks after completion of descriptive analyses)
Final study report	28 February 2025 (4 weeks after completion of multivariable analyses)

5. RATIONALE AND BACKGROUND

The SARS-CoV-2 virus emerged on the world stage in late 2019, resulting in a global pandemic of what became known as coronavirus disease-2019 (COVID-19); although the pandemic phase of the virus officially ended in the United States (US) in May 2023, COVID-19 remains an endemic disease. Vaccination is the primary method of COVID-19 prevention; however, antiviral therapies are also a critical piece of COVID-19 management post-infection, especially in the face of viral mutation and decreasing vaccination rates.

In the US, nirmatrelvir-ritonavir (NMV/r; Paxlovid) is an oral antiviral used for the treatment of mild-to-moderate COVID-19 within 5 days of symptom onset in patients aged ≥12 years at high risk of progression to severe disease, including hospitalization and death.[1] NMV/r received emergency use authorization (EUA) for use among patients ≥12 years old from the US Food and Drug Administration (FDA) on December 21, 2021, and was granted full FDA approval for use among adult patients on May 25, 2023. The EPIC-HR trial demonstrated that NMV/r reduced the risk of COVID-19 related hospitalization or death from any cause by 86%, when treated within 5 days of symptom onset, compared to placebo.[2] A later study of real-world effectiveness observed a 79.6% reduction in risk of all-cause hospitalization or death within 30 days when NMV/r was dispensed within 5 days of COVID-19 symptom onset [14], thus demonstrating a continued benefit of NMV/r treatment into a period in which the omicron variant of COVID-19 has predominated (December 2021 to the present).

Economic assessments have estimated the direct burden of COVID-19 to be substantial, with COVID-19 patients incurring costs 2-to-3-fold higher than matched controls in the 6 months following infection.[3] There is also some evidence of substantial work loss due to COVID-19, including a recent study showing COVID-19 to be the second most common reason for short-term

disability (STD) between 2020 and 2022, with an average of 24 days of work lost per COVID-related STD claim among a sample including, but not limited to, high-risk patients; patients who went on long-term disability (LTD) leave due to COVID-19 lost an average of 153 days of work per claim [17]. COVID-related STD claims cost an average of approximately $3,500, while COVID-related LTD costs averaged over $19,000 per claim. However, the overall burden of disease (direct healthcare plus indirect societal burden) among a population of exclusively high-risk patients, as well as the potential impact of antivirals in modulating said burden, remains unclear. Moreover, there is a lack of contemporary estimates of disease burden that are reflective of an Omicron-predominant period among a population that is largely either vaccinated or gained natural immunity due to prior infection. Indirect associated costs and the broader impact of COVID-19 have been evaluated in a macroeconomic study; however, overall societal and cost impacts are not reflective of the Omicron period (December 2021 to present) or stratified by either high-risk status or those treated with NMV/r.[4] Work productivity and activity impairment (WPAI) were captured in EPIC-HR, and included both vaccinated and unvaccinated patients in acute COVID settings [2, 5]; however, these analyses were not able to elucidate the overall impact of antiviral therapy on work productivity loss. Similarly, recent studies examining population-level benefit and cost savings associated with Paxlovid treatment in patients with COVID-19 Omicron variant infections did not examine indirect cost savings.[6]

The current Paxlovid cost-effectiveness model only entails direct medical costs; therefore, an understanding of indirect disease burdens and potential offsets associated with Paxlovid therapy will be integral to inform and update associated indirect medical costs.[7] This study will utilize the MarketScan Commercial, Medicare, and Health and Productivity Management (HPM) Databases to investigate absence, STD, LTD, and estimated indirect costs among patients diagnosed with COVID-19 who are at high risk of progression to severe COVID-19 (“high-risk patients”) who do or do not receive treatment with Paxlovid. The MarketScan HPM Database is the gold standard choice for capturing work productivity among patients in the US due to large sample size and linkage to the claims databases. This data source has been previously leveraged by Pfizer HV&E teams supporting key brands including Ibrance and Xeljanz. [8, 9]

6. RESEARCH QUESTION AND OBJECTIVES

This study seeks to investigate the indirect burden of COVID-19 as measured by workplace productivity loss and associated costs among patients who receive NMV/r (Paxlovid) and those who do not receive any antiviral therapy during acute and longer-term follow-up among adult patients in the US with mild-to-moderate COVID-19 at high risk for progression to severe disease.[1][10]

The study will address the following primary objectives:

1. Describe demographic and clinical characteristics of adult, high-risk patients diagnosed with COVID-19, including patients who received NMV/r (treated) and those who did not receive any antiviral therapy used to treat COVID-19 (untreated).
2. Describe measures of workplace productivity loss, such as total days away from work and use of disability leave, as well as indirect costs associated with work loss, among high-risk

[1] High risk for disease progression defined as either being ≥50 years old or having a condition identified by the CDC as having evidence of high risk

treated and untreated patients, directly matched on demographic and clinical characteristics. To account for remaining imbalances between treated and untreated patients after matching, the following exploratory objective will be addressed if sample size allows:

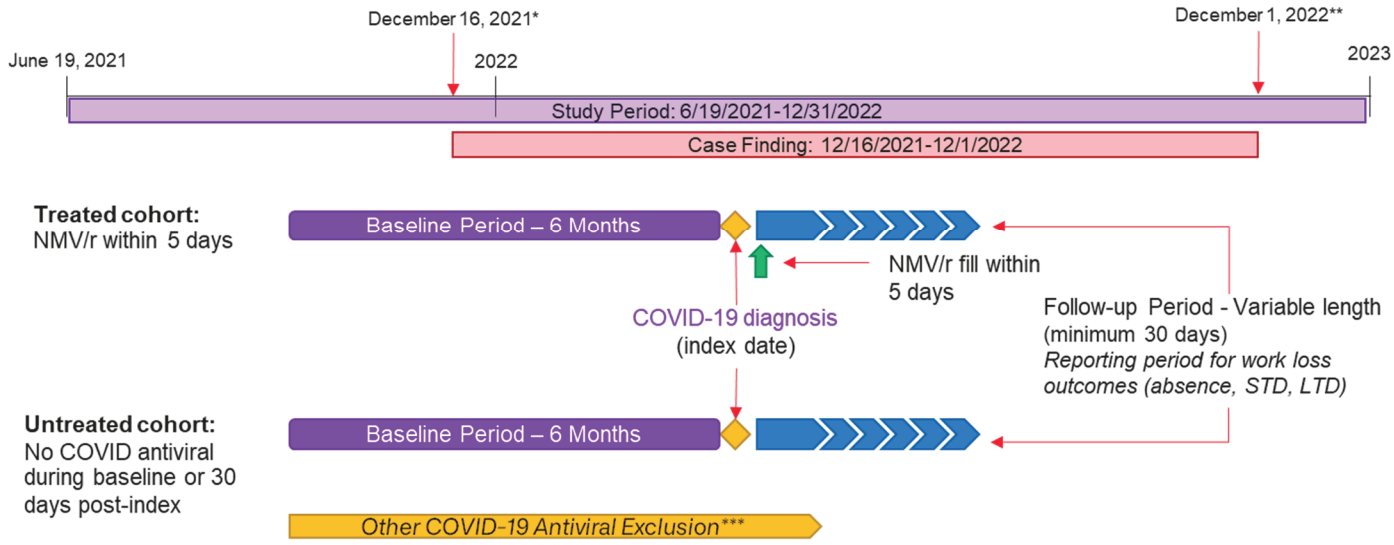
1. Compare productivity loss and indirect cost outcomes between high-risk treated and untreated patients using multivariable models to control for patient characteristics.

7. RESEARCH METHODS

7.1. Study Design

This is a retrospective cohort study of adult, high-risk patients diagnosed with COVID-19 using data from the Merative™ MarketScan® Commercial, Medicare, and Health and Productivity Management (HPM) Databases. Eligible patients will be stratified into treated and untreated cohorts, defined by receipt of NMV/r or no receipt of any antiviral therapy for COVID-19, respectively. The index date for both cohorts will be the date of the first COVID-19 diagnosis and patients will be followed over a 6-month pre-period and variable post-period. The post-period will be a minimum of 30 days to allow patients the opportunity to experience the primary study outcomes of work loss days (absence, STD, and LTD) along with associated indirect costs. Events marking the end of patients' follow-up are detailed in section 8.2.1 and include end of enrollment, end of available work loss data, death, initiation of new treatments, and a new COVID-19 diagnosis. Work loss/productivity outcomes will be reported over the variable length post-period within separate subgroups of patients with eligibility for each type of productivity loss.

Figure 1. Study Schematic



*Start of case finding is 5 days prior to the EUA for NMV/r on December 21, 2021
**End of case finding is 30 days prior to the end of study data on December 31, 2022
***Treated cohort: no non-NVV/r COVID-19 antiviral treatment baseline through 30-days post-index; Untreated cohort: no COVID-19 antiviral treatment baseline through 30-days post-index; Both cohorts will be censored at the first evidence of COVID-19 antiviral use >30-days post-index

7.2. Setting

This study will utilize the secondary, retrospective MarketScan HPM Database. Merative will create an analytic file of data from the MarketScan HPM Database for patients meeting the criteria below between June 19, 2021 and December 31, 2022.

7.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. ≥1 non-diagnostic[2] outpatient medical claim in the MarketScan Commercial or Medicare Database with the International Classification of Diseases, 10th Revision (ICD-10) diagnosis code for COVID-19 (U071) between December 16, 2021 (5 days prior to the date of emergency use authorization of NMV/r) and December 1, 2022 (30 days prior to the end of available HPM data); the date of the earliest qualifying claim is the index date.
2. Primary beneficiary on their insurance policy (i.e., eligible for inclusion in the MarketScan HPM Database)
3. ≥18 years old on the index date
4. ≥6 months of continuous enrollment with medical and pharmacy benefits in the MarketScan Commercial or Medicare Database before the index date (baseline period)
5. ≥30 days of continuous enrollment with medical and pharmacy benefits in the MarketScan Commercial or Medicare Database after and including the index date (minimum follow-up period)
    - The end of follow-up will be defined as the first of: 1) the end of continuous eligibility, 2) the end of available work loss data on December 31, 2022, 3) death,[3] 4) initiation of a non-Paxlovid COVID-19 antiviral in the treated cohort or initiation of a COVID-19 antiviral in the untreated cohort, or 5) day prior to a new diagnosis of COVID-19[4]

[2] Non-diagnostic claims are those that are not for lab tests, radiology exams, or other tests/procedures that may be used to initially establish a diagnosis. A condition may be included on a "diagnostic" claim for reimbursement purposes when the diagnosis is suspected but not yet confirmed. Requiring non-diagnostic claims ensures that only patients with a confirmed diagnosis are identified. For example, a patient tested for COVID-19 where the test result is negative may have a COVID-19 diagnosis code on the claim for the test for reimbursement purposes; this patient would not be expected to have a COVID-19 diagnosis on the office visit (or other non-diagnostic) claim(s). Patients with a COVID-19 diagnosis on a claim for a COVID-19 test will be required to also have a COVID-19 diagnosis on a separate claim that is not for a COVID-19 test (i.e., patients whose only COVID-19 diagnosis is on a claim for a COVID-19 test will not be included in the study).

[3] Death will be based on inpatient discharge status, Social Security Administration data, or employer reported death

[4] New diagnoses of COVID-19 will be defined as a COVID-19 diagnosis occurring ≥90 days following the last diagnosis on record (e.g., 90-day clean period between last COVID-19 diagnosis and start of new COVID-19 episode). Diagnoses occurring <90 days apart will be assumed to be part of the same COVID-19 episode. A new COVID-19 diagnosis may also be identified by a claim for a COVID-19 test ≥30 days post-index, followed by a non-diagnostic claim with a COVID-19 diagnosis within the next 7 days. The date of the test will be considered the date of the new COVID-19 diagnosis.

6. Either age ≥50 years at index OR ≥1 non-diagnostic medical claim with an ICD-10 diagnosis code, during the baseline period or on the index date, for one of the conditions below determined by the Centers for Disease Control and Prevention to have evidence of an association with high risk of progression to severe COVID-19: [10]
    - Cancer
    - Cerebrovascular disease
    - Chronic lung disease, including:
        - Asthma
        - Bronchiectasis
        - Chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis
        - Interstitial lung disease and pulmonary fibrosis
        - Pulmonary embolism
        - Pulmonary hypertension
    - Chronic liver disease, including:
        - Alcoholic liver disease
        - Autoimmune hepatitis
        - Cirrhosis
        - Metabolic dysfunction-associated fatty liver disease (MAFLD)
    - Cystic fibrosis
    - Dementia
    - Diabetes mellitus
    - Disabilities, including:
        - Activities of daily living impairments and dependency
        - Attention deficit/hyperactivity disorder (ADHD)
        - Cerebral palsy
        - Congenital malformations
        - Down syndrome
        - Intellectual and developmental disabilities
        - Learning disabilities
        - Spinal cord injuries
    - Heart conditions, including:
        - Aneurysm and dissection of the aorta, heart, and coronary arteries

    - Angina
    - Arrhythmias
    - Cardiac septal defect
    - Cardiomegaly
    - Cardiomyopathies
    - Congenital defects of the heart or great arteries/veins
    - Coronary artery disease/atherosclerosis and other chronic ischemia of the heart
    - Heart blocks and other conduction disorders
    - Heart failure
    - Hypertensive heart disease
    - Intracardiac thrombosis
    - Marfan syndrome
    - Myocardial degeneration
    - Myocardial infarction and other acute ischemic heart disease
    - Myocarditis
    - Non-ischemic (non-traumatic) myocardial injury
    - Pericarditis and other pericardial conditions
    - Rheumatic heart disease
    - Rupture of chordae tendineae or papillary muscle
    - Valve disorders
- Human immunodeficiency virus (HIV)
- Hypertension
- Immunocompromised state
    - Primary immunodeficiencies
    - Prolonged use of corticosteroids or other immunosuppressive medications
    - Other immunocompromised state
- Mental health conditions, including:
    - Mood disorders (e.g., depression)
    - Schizophrenia spectrum disorders
- Overweight and obesity
- Physical inactivity
- Pregnancy (current or recent)

- Primary immunodeficiencies
- Sickle cell disease or thalassemia
- Smoking (current or former)
- Solid organ or blood stem cell transplantation
- Substance use disorder
- Tuberculosis

7. Eligibility for absence, STD, or LTD during the first 30 days of the post-period
8. Treated cohort ONLY: ≥1 claim for Paxlovid within 5 days of index (index date and next 4 days)

7.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Evidence of death on the index date or the following day [15]
2. Any inpatient admission on the index date or the following day [15]
3. ≥1 inpatient claim with a COVID-19 diagnosis in any position on the claim during the 30 days before the index date
4. ≥1 non-diagnostic claim with a diagnosis code for stage 4 or stage 5 chronic kidney disease, end stage renal disease, or a procedure code for dialysis, during the baseline period or on the index date [15]
5. Any claim for one of the following medications[5] contraindicated for use with Paxlovid during the baseline period or on the index date: apalutamide, carbamazepine, phenobarbital, primidone, phenytoin, rifampin, rifapentine, lumacaftor/ivacaftor, St. John's Wort, alfuzosin, ranolazine, amiodarone, dronedarone, flecainide, propafenone, quinidine, colchicine, lurasidone, pimozide, silodosin, eplerenone, ivabradine, dihydroergotamine, ergotamine, methylergonovine, lovastatin, simvastatin, voclosporin, lomitapide, eletriptan, ubrogepant, finerenone, naloxegol, sildenafil, triazolam, oral midazolam, fibanserin, tolvaptan [1]
6. Treated cohort ONLY: No use of other (non-Paxlovid) COVID-19 antivirals baseline through 30 days post-index
7. Untreated cohort ONLY: No use of any COVID-19 antivirals baseline through 30 days post-index

[5] The MarketScan databases will only include claims for prescription medications paid at least in part by the insurance benefit; over the counter prescriptions will not be reflected in the data.

7.3. Variables

Variable	Role	Data Source(s)	Assessment Period	Operational Definition
Treated	Exposure	Outpatient pharmacy claims	Study period	Claim for Paxlovid on the index date or in the 4 days after the index date and no claims for other COVID-19 antivirals during the baseline period or within 30 days post-index
Untreated	Exposure	Outpatient pharmacy and medical claims	Study period	No claims for any COVID-19 antivirals during the baseline period or within 30 days post-index
Absence from work, presence	Outcome	HPM claims	Post-period	Presence of any absence records
Absence from work, days	Outcome	HPM claims	Post-period	Total number of days[5] of absence, among all patients with absence eligibility and among patients with ≥1 absence
Absence from work, type	Outcome	HPM claims	Post-period	Where available, absence days will be reported by absence type (e.g., sick, disability, recreational)
Absence from work, costs	Outcome	Estimated, HPM claims	Post-period	Estimated sum of wages associated with absence days; calculated as daily wage multiplied by absence days; mean (SD) and median costs to be reported among all patients with absence eligibility and among patients with ≥1 absence
STD, presence	Outcome	HPM claims	Post-period	Presence of STD claim
STD, days	Outcome	HPM claims	Post-period	Sum of STD days, among all patients with STD eligibility and among patients with ≥1 STD claim
STD, reason	Outcome	HPM claims	Post-period	Where available, reason for STD will be classified as COVID-19 related (ICD-10: U071) or non-COVID-19 related (other ICD-10 code)
STD, costs	Outcome	Estimated, HPM claims	Post-period	Estimated sum of wages associated with STD days; calculated as 70% of daily wage multiplied by STD days; mean (SD) and median costs to be reported among all patients with STD eligibility and among patients with ≥1 STD claim
LTD, presence	Outcome	HPM claims	Post-period	Presence of LTD claim
LTD, days	Outcome	HPM claims	Post-period	Sum of LTD days, among all patients with LTD eligibility and among patients with ≥1 LTD claim
LTD, reason	Outcome	HPM claims	Post-period	Where available, reason for LTD will be classified as COVID-19 related (ICD-10: U071) or non-COVID-19 related (other ICD-10 code)
LTD, costs	Outcome	Estimated, HPM claims	Post-period	Estimated sum of wages associated with STD days; calculated as 70% of daily wage multiplied by LTD days;

				mean (SD) and median costs to be reported among all patients with LTD eligibility and among patients with ≥1 LTD claim
Age	Demographic covariate	Demographics table	Index date	Age, years
Age group	Demographic covariate	Demographics table	Index date	Age at index grouped into the following categories: • 18-29 • 30-39 • 40-49 • 50-64 • 65-74 • 75+
Sex	Demographic covariate	Demographics table	Index date	Sex (male or female)
Region of residence	Demographic covariate	Demographics table	Index date	Region (Northeast, North Central, South, West, or Other/missing)
Payer type	Demographic covariate	Demographics table	Index date	Commercial, Medicare Advantage, Medicare Supplemental
Insurance plan type	Demographic covariate	Demographics table	Index date	Health plan type (comprehensive/indemnity, exclusive/preferred provider organization [EPO/PPO], point-of-service w/ or w/o capitation [POS], health maintenance organization [HMO], consumer-driven/high-deductible health plan [CDHP/HDHP], other/missing)
Industry type	Demographic covariate	Demographics table	Index date	Employer industry type (oil & gas extraction/mining, manufacturing [durable goods], manufacturing [non-durable goods], transportation/communications/utilizes, retail trade, finance/insurance/real estate, services, agricultural/forestry/fishing, construction, wholesale, other, missing)
Index quarter	Characteristic covariate	Calculated	Index date	Year and quarter (Q1, Q2, Q3, or Q4) of the index date
Duration of follow-up	Characteristic covariate	Calculated	Post-period	Number of months from (and including) the index date to the end of patients' variable-length follow-up period
Charlson Comorbidity Index (CCI) [11]	Baseline characteristic covariate	Medical claims	Pre-period	Mean, standard deviation, and median CCI score
Elixhauser Comorbidity Index (ECI) [16]	Baseline characteristic covariate	Medical claims	Pre-period	Mean, standard deviation, and median ECI score

Comorbidity groups, presence	Baseline characteristic covariate	Medical claims	Pre-period	Number and percentage of patients with ≥1 claim with a diagnosis in the following groups of conditions: • Immunocompromised status (HIV, immunocompromised state, or solid organ/stem cell transplant) • Chronic kidney disease (CKD) • Chronic liver disease • Obesity and smoking (obesity, overweight, or smoking related diagnoses)[6] • Diabetes mellitus • Cardiovascular and cerebrovascular (heart conditions, hypertension, and stroke/cerebrovascular disease) • Respiratory illnesses (lung disease or tuberculosis) • Neurodevelopmental disorders and other medically complex conditions (substance abuse disorder, mood disorders, dementia, disability, and sickle cell disease/thalassemia • Pregnancy • Cancer (active disease and history of)
Number of high-risk conditions	Baseline characteristic covariate	Outpatient pharmacy and medical claims	Pre-period	Mean, standard deviation, and median number of high-risk conditions
COVID-19 vaccination status	Baseline characteristic	Outpatient Pharmacy and Medical claims	Pre-period	Number and percentage of patients with ≥1 claim for a COVID-19 vaccination during the baseline period[7]
Prior hospitalization	Baseline characteristic covariate	Medical claims	Pre-period	Indicates patients who had one or more inpatients visits in the baseline period
Prior ER visit	Baseline characteristic covariate	Medical claims	Pre-period	Indicates patients who had one or more ER visits in the baseline period

[redacted]

[6] Patients' total hours of absence will be divided by 8 to determine the number of absence days, and so the total days of absence may not be whole numbers for some patients

[6] Lifestyle-related diagnoses (e.g., weight and health behaviors) are known to be under-reported in administrative claims

[7] MarketScan data will only identify patients who receive a COVID-19 vaccination through their insurance benefit during the pre-period. Patients who receive a vaccination through other means (e.g., mass vaccination site) or received a COVID-19 vaccination prior to the pre-period will not be reflected as vaccinated in this study.

7.4. Data Sources

Merative will use the MarketScan Commercial, Medicare, and HPM Databases for this study. These databases provide access to complete patient inpatient and outpatient medical and prescription drug claim records along with lost work productivity stemming from absence, short-term disability, or long-term disability. The HPM database is composed of the subset of the overall MarketScan Commercial and Medicare Databases where patients have eligibility for work loss reporting. During the time period of this study (June 2021 through December 2022), data for approximately 23.6 million enrollees were contained in the Commercial and Medicare Databases, with approximately 3.9 million enrollees having data in the HPM Database during that time. Descriptions of the MarketScan Commercial, Medicare, and HPM databases are below.

The **MarketScan Health and Productivity Management Database** contains workplace absence, short- and long-term disability (STD, LTD), and workers' compensation (WC) data for primary beneficiaries (i.e., employees), which can be linked to medical and pharmacy utilization data from large United States employers. Not all data contributors contribute all types of productivity data. Data through December 2022 are currently available in the HPM Database.

The **MarketScan Commercial Database** contains the inpatient, outpatient, and outpatient prescription drug experience of employees and their dependents, covered under a variety of fee-for-service and managed care health plans, including exclusive provider organizations, PPOs, POS plans, indemnity plans, and health maintenance organizations (HMOs).

The **MarketScan Medicare Database** contains the healthcare experience (both medical and pharmacy) of retirees with Medicare Advantage and Medicare Supplemental insurance plans paid for by employers. The database includes the employer-paid portion and out-of-pocket patient expenses for both Advantage and Supplemental plans, as well as the Medicare-covered portion of payment (represented as Coordination of Benefits [COB] Amount) for Supplemental plans.

The MarketScan Databases are closed system and include an eligibility file for medical and pharmacy benefits as well as each type of work loss event. Presence of these files facilitates imposition of continuous eligibility over the study period, thus researchers can interpret the lack of services or productivity losses as an absence of events, as opposed to potentially missing data. Similarly, demographics of age and sex are available for all patients in the MarketScan databases; other demographics are available for the vast majority of patients.

7.5. Study Size

There are no a priori hypotheses specified for this study, thus sample size calculations are not applicable. However, estimated counts within the MarketScan HPM databases for patients with a diagnosis of COVID-19 and workplace productivity eligibility are presented below

Table 1. Estimated Sample Size

CRITERIA	N
All patients with any enrollment in the MarketScan Commercial or Medicare Database between 12/16/2021 and 12/1/2022	21,722,414
Any enrollment in the MarketScan HPM Database between 12/16/2021 and 12/1/2022	3,643,363
Patients in the HPM Database with ≥1 non-diagnostic claim for COVID-19 between 12/16/2021 and 12/1/2022 (first claim serves as index date)	357,274
Aged ≥18 on index	357,272
Continuous eligibility with medical and pharmacy benefits for ≥6 months prior to index	297,291
Continuous eligibility with medical and pharmacy benefits for ≥30 days after and including the index date	290,371
Aged ≥50 on index or evidence of conditions associated with high-risk of COVID-19 progression in the baseline period or on the index date	192,479
No evidence of inpatient admissions on the index date or the following day	188,867
No evidence of advanced CKD (stage 4 or above) or dialysis in the baseline period or on the index date	187,876
No evidence of fills for contraindicated medications in the baseline period or on the index date	175,808
No claims for other non-Paxlovid COVID-19 antivirals in the baseline period or in the 30 days after and including the index date, and no claims for Paxlovid in the baseline period	171,143
No inpatient claims with a COVID-19 diagnosis in any position on the claim during the 30 days before the index date	170,841
TREATED - Claim for Paxlovid on the index date or in the next 4 days	28,532
Work loss eligibility* during the 30 days after and including the index date	
Absence	1,959
STD	20,083
LTD	20,404
UNTREATED - No evidence of COVID-19 antiviral treatment during the baseline period or during the 30 days after and including the index date	142,120
Work loss eligibility during the 30 days after and including the index date	
Absence	10,595
STD	101,145
LTD	106,705

*Indicates patients for whom absence, STD, and/or LTD data would be available (e.g., collected) during the 30 days after and including the index date

7.6. Study Population

The full study sample will be composed of patients who meet all inclusion and exclusion criteria above. The treated cohort will include all eligible treated patients for whom a direct match can be identified; it is assumed that untreated matches will be able to be identified for the vast majority if not all treated patients. The untreated cohort will be composed of those patients who met eligibly criteria and were successfully matched to a treated patient. Given the larger number of untreated compared to treated patients, it is expected that there will be untreated patients who are eligible for analyses but not included in the final sample due to their not being matched to a treated patient.

7.6.1. Subgroups

Given the differential availability of absence, STD, and LTD data, results will be reported in defined subgroups of patients with absence, STD, or LTD eligibility. Direct matching of the treated and untreated cohorts will occur at the subgroup (e.g., patients with absence eligibility) level. As a result, patients who are eligible for multiple subgroups (e.g., have STD and LTD eligibility) may have different matches for the different work loss type analyses. Results will not be reported for the overall eligible cohort (e.g., patients with absence, STD, or LTD eligibility).

7.7. Data Management

The Merative MarketScan Commercial, Medicare, and HPM Databases are commercially available databases; rights for the use of the data for this study were purchased by Pfizer. The raw data from the MarketScan Databases, as well as the analytic data files created for this study, will be managed by Merative using SAS software (Carey, NC).

Study data will be extracted once, as part of the analytic file build. Data will be extracted for all patients meeting eligibility criteria for the treated or untreated cohorts (e.g., adults at high risk of COVID-19 complications diagnosed with COVID-19 between December 16, 2021 and December 1, 2022. Extracted data include eligibility information, patient characteristics, healthcare resource utilization, and work productivity losses (See Section 8.3).

7.8. Missing Data

Analyses will only include patients with continuous eligibility during the study period. Continuous eligibility with medical and pharmacy benefits will be required during the pre- and post-periods, while continuous eligibility for the specific work loss type (e.g., absence in the absence sample) will be required during the post-period. The presence of continuous eligibility, either medical, pharmacy, or work loss, indicates that all data are being collected for that specific concept during the study period. As a result, the lack of services (e.g., lack of an inpatient visit) or lack of work loss events (e.g., lack of STD claims) will be interpreted as that event not having occurred, as opposed to missing data.

7.9. Data Analysis

The study sample will be composed of the eligible cohorts of treated and untreated patients who meet all study inclusion criteria. Untreated patients will be directly matched to treated patients with a ratio of up to 5:1 without replacement. Direct matching will initially be based on age (+/- 5 years)

sex, CCI category (0-1, 2, 3+), index date (+/-14 days), and the presence/absence of any hospitalization or ER visit during the baseline period. In the event of sample size issues using this matching procedure, the matching criteria may be modified or relaxed (e.g., matching on age group, allowing a +/- 30-day difference in index date, replacing CCI categories with categories for the number of high-risk conditions). Matching will be conducted within cohorts based on work loss eligibility (e.g., a treated patient with absence data will only be matched to an untreated patient with absence data) to facilitate comparison of primary outcomes across the treated and untreated cohorts; patients will not be required to have eligibility for all three types of work loss data in the post-period. Matching methods will be consistent across the work loss types. Standardized mean differences (SMD) will be reported between the treated and untreated cohorts prior to and following matching to evaluate imbalances between cohorts; SMDs >0.1 are generally considered to represent imbalances.

To address the first primary objective, demographics on the index date and clinical characteristics during the six-month baseline period will be reported among treated and untreated patients within cohorts based on work loss eligibility; these characteristics will be reported for both the unmatched and matched samples. To address the second primary objective, absence, STD, and LTD outcomes will be reported within the matched groups of treated and untreated patients with post-period eligibility for the relevant work loss type (e.g., absence results among patients with post-period absence eligibility). Indirect costs associated with each work loss type will also be estimated within the matched groups of treated and untreated patients, to address the third primary objective. Indirect costs will be reported within the subset of patients with evidence of a work loss event as well as within the overall eligible population; the latter reporting is intended to provide Pfizer with data that could be combined to estimate overall indirect costs of COVID-19. For descriptive reporting, continuous variables will be reported as mean, median, and standard deviation, while categorical variables will be reported as frequency and percent. During the variable length post-period, continuous variables will be reported in a per-patient-per-month format to address the differing durations of follow-up across patients. Outcomes will be compared between the treated and untreated cohorts using relevant statistical tests (e.g., Student's T-test, Chi-square test, Kruskal-Wallis test, etc.).

All study outcomes, including unadjusted absence days, STD days, LTD days, and associated costs will be reported over the variable length post-period within relevant subgroups of matched treated and untreated patients based on work loss productivity type eligibility. Data for absence, STD, and LTD days will be obtained directly from fields in the MarketScan HPM Database; indirect costs (in 2022 US dollars) associated with work loss will be calculated based on median daily wage in the US in 2022 (employed full time wage and salary workers), as defined by the Bureau of Labor Statistics, and number of lost productivity days; resultant STD and LTD costs will be multiplied by 0.70, since STD and LTD benefits typically pay about 70% of an employee's wages [12,13]. Indirect costs associated with each work loss type will be defined as:

- Absence: median daily wage * total absence days
- STD: (median daily wage * total absence days) * 0.7
- LTD: (median daily wage * total absence days) * 0.7

To address the exploratory objective, up to six multivariable models may be constructed to assess the relationship between NMV/r treatment and the work loss and indirect cost outcomes from the second and third primary objectives. These models will adjust for any potential remaining differences in

demographics and baseline characteristics between the treated and untreated cohorts after matching. It is intended to use generalized linear model (GLM) methods to compare work loss and indirect cost outcomes between the treated and untreated cohorts. Each outcome type (absence, STD, LTD) consists of a pair of variables i.e., a count (day) and a continuous variable (cost). Because of issues with counts and costs having values of zero, two-part models are likely to be used. The first part for both counts and costs will be a GLM model (logistic regression of binary data) comparing the probability of having zero (or non-zero) counts or costs between the treated and untreated cohorts. The second part will be a GLM regression (gamma distribution, log link) of the greater than zero counts expressed in per-patient-per-month (PPPM) form; and a GLM regression (gamma distribution, log link) for greater than zero cost. The PPPM form is preferred because of the variable length of follow-up and use of the gamma distribution and log link because of probable skewed data for both PPPM counts and costs. It is anticipated that model covariates will include demographics and baseline clinical characteristics, potentially some of the same covariates used in the match. Covariates of interest will be selected based on both remaining imbalance between cohorts following matching as well as clinical relevance. More specifics of the models, including choice in model type and covariates, will be determined in collaboration with Pfizer following assessment of the descriptive results. At this time the six models will include the following outcomes:

- Number of absence days
- Indirect costs related to absence
- Number of STD days
- Indirect costs related to STD
- Number of LTD Days
- Indirect costs related to LTD

7.10. Additional Analyses

The team may elect to conduct subset analyses to further investigate the burden of COVID-19 within select patient subgroups. At this time the team has identified the following subgroups as those of potential interest:

- Sex
- Immunocompromised status
- Age (≥50 vs. <50)
- Presence of specific conditions in the baseline period (e.g., CVD, respiratory conditions)

Decisions on whether to proceed with subgroup reporting, the specific subgroups of interest, and exact methods for reporting will be determined following review of the results of the planned analyses outlined in this document.

It is important to note that some of the above subgroups are based on variables not included as direct matching variables. Therefore, the above subgroups are unlikely to maintain balance imposed by the

direct matching of the overall eligible treated and untreated cohorts (i.e., matches will be broken). At this time, the Merative team is suggesting the following potential methods to address likely imbalances between subgroups:

- Conduct a purely descriptive analysis of subgroups derived from the directly matched treated and untreated cohorts with the caveat that groups may no longer be comparable due to 'broken matches'

- Utilize multivariate modeling to control for differences (resulting from 'broken matches') in subgroups derived from the directly matched treated and untreated cohorts

- Identify patients eligible for subgroups from either the pre-match or post-match eligible samples and conduct a second direct matching to establish the final subgroups for analyses

Scope of the subgroup analysis would be defined once the specific subgroups of interest and analytic method is defined.

Additionally, since the timing of COVID symptom onset is lacking in claims data, and because Paxlovid is intended to be prescribed within 5 days of symptom onset, a sensitivity analysis will be conducted to examine the sample size of treated patients using a 3-day time period after and including the index date to look for the first claim for Paxlovid. Depending on the difference in sample sizes between using the 3-day and 5-day windows, patient characteristics may be descriptively compared between the two samples.

7.11. Quality Control

The MarketScan database build QA process begins when the individual client databases are created and continues as the databases are combined and enhanced to form the MarketScan Research Databases.

Quality checks completed when the databases are updated include:

- **Reasonableness of data**: We ensure relationships between two or more fields are reasonable by comparing them with normative data. For example, we check to see if the age and gender distribution of our database continues to follow the distribution in AHRQ's Medical Expenditure Panel Survey.
- **Validity**: We ensure that selected fields are valid by comparing records with lists of possible valid values. Data require additional processing if invalid results are present more than one percent of the time.
- **Claims lag**: We do not release annual data files until close to 100 percent of claims have been paid. This process takes approximately six months after the close of a calendar year or a quarter and ensures that researchers have the most complete and accurate financial data. These data are used primarily for outcomes research projects, which typically require this type of financial accuracy. However, our Early View Database has a 90-day lag that includes paid amounts for 100 percent of prescription drugs, approximately 85 percent of physician office visits, and approximately 70 percent of hospital claims. These data are used when data timeliness is paramount to track product uptake, market share, etc.

Merative's specific quality assurance (QA) practices as they relate to individual studies are described below:

- **Project team buy-in to analysis plan**: The research leader and analyst are responsible for creating the analysis plan and detailed specifications for a project. The entire project team reviews these documents to make sure that all of Pfizer's needs outlined in the proposal are included in the analysis plan and specification. They also confirm that every project team member is interpreting the analysis in the same manner.
- **Documentation and diagnostics applied to computer code development**: The primary programmer is responsible for creating and documenting all project-specific SAS code, including comments as to why changes are made over the course of the project. In addition to evaluating diagnostic output independently, the programmer evaluates this output with the entire project team before results tables are generated.
- **Independent code review**: A second programmer is assigned to a project for the express purpose of performing code review. The code review programmer works with the primary programmer in order to confirm that SAS code is written with correct syntax and generates results as specified in the analysis plan. Issues identified by the code reviewer are documented and resolved.
- **Validation of study results**: The research leader and analyst are responsible for validating the results tables to confirm that results are consistent across analysis tables and that the results make sense from a "real world" perspective. If applicable, results are compared with previous trend reports to ensure consistency.
- **Peer review of final deliverables**: In addition to the research leader and analyst reviewing all final reports and manuscripts before they go to Pfizer, an internal peer reviewer is also assigned to evaluate final products. This peer reviewer is an analyst who examines the final results and reports to ensure concordance among all final documents as well as to evaluate content for consistency.
- **Overall QA process**: The research leader has ultimate responsibility for making sure that all facets of the QA process have been completed and are documented. All project-related materials are stored in a central location to maximize efficiency in case additional, follow-on analyses or project updates are required.

7.12. Limitations of the Research Methods

Limitations of this study include those associated with retrospective administrative claims analyses in general and include the potential for misclassification due to coding errors or limitations of coding taxonomy. Additionally, as the HPM database is composed of employed individuals with employer sponsored commercial or Medicare insurance whose employers contribute work loss data to the MarketScan Databases; therefore, results from this analysis may not generalize to unemployed patients or individuals with other forms of insurance (e.g., Medicaid) or those whose employers do not contribute work loss data. Results are also likely to be more reflective of outcomes among full-time employees, as many employers do not offer medical benefits to part-time employees. Although specific information around sick or vacation time benefits are not known, it is likely that the employees reflected in this analysis have some form of available benefit; as a result, individuals in

this database may be more likely to take an absence from work due to illness than a part-time hourly worker with no benefits.

Specifically for this study, the coding taxonomy around COVID-19 does not include information on severity of presentation. It's also worth noting that only medically attended cases of COVID-19 would ever generate a claim on the medical record. As a result, this analysis will be reflective of work loss associated with disease that is severe enough to spur an interaction with a healthcare provider. Towards the point of severity, patients are required to maintain eligibility for 30 days following COVID-19 diagnosis and patients with evidence of a hospitalization or death in the 2 days following index will be excluded from the study sample. Therefore, results of this analysis are likely to be reflective of patients with symptomatic, but not severe COVID-19 – consistent with the prescribing indications for Paxlovid. However, data regarding the timing of symptom onset will not be available, and therefore the receipt of Paxlovid within 5 days after and including the date of diagnosis will be used a proxy for the 5-day window after symptom onset in which Paxlovid should be prescribed. A sensitivity analysis of the number of patients included using a 3-day vs. 5-day window will be conducted, and patient characteristics may be compared between the two groups depending on the difference in the sample sizes. Additionally, though imposing any minimum amount of follow-up time introduces survival bias, the nature of the study outcomes (work productivity loss) requires that patients have enough follow-up time to have the opportunity to experience work loss; therefore, patients are required to have at least 30 days of post-index database enrollment and so results may not be generalizable to treated or untreated high-risk patients who die within 30 days of diagnosis. Given the limitations of claims data information on relevant clinical factors such as the specific COVID-19 variant, will not be available; vaccination status is also likely to be unknown or incomplete given the use of a 6-month pre-period and the prevalence non-insurance-based vaccination sites (e.g., mass vaccination sites) early in the pandemic.

The study design addresses issues around severity through the requirement for patients to be at high risk for COVID-19 progression, matching of the treated and untreated cohorts, and use of multivariable modeling to control for remaining measured differences between cohorts; however, differences between cohorts, especially those not able to be assessed via administrative claims data, may remain. Patients in the treated cohort are also required to receive Paxlovid within 5 days of the first COVID-19 diagnosis, consistent with prescribing guidelines; however, the study team will have no way of knowing when symptoms first appeared. As such, some patients in the treated cohort may be initiating Paxlovid more than five days after the start of symptoms; if anything, this point would be expected to reduce effect sizes associated with Paxlovid therapy. Similarly, a claim for Paxlovid in the MarketScan Databases indicates that a patient received the medication; it is assumed that patients took the medication as prescribed.

8. PROTECTION OF HUMAN PARTICIPANTS

8.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

8.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

8.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

All database records are de-identified and fully compliant with United States patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The databases have been evaluated and certified by an independent third party to be in compliance with the HIPAA statistical de-identification standard. The databases were certified to satisfy the conditions set forth in Sections 164.514 (a)-(b)1ii of the HIPAA privacy rule regarding the determination and documentation of statistically de-identified data.[8] Because the study proposed herein uses only de-identified patient records and does not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board (IRB) approval to conduct this study is not necessary. An IRB exemption was obtained on 17 October 2024.

8.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in CT24-WI-GL02-RF04 External Guidance Document for the Design and Conduct and Non-Interventional Studies.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

As this is an analysis of de-identified retrospective data, adverse event/adverse event reporting is not applicable. . In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the *minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.*

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will include a final report for consumption of results by the Pfizer team. External publications (e.g., abstracts, posters, manuscripts) may also be developed for dissemination of results to a broader audience.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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[8] Regulations state:
§ 164.514 Other requirements relating to uses and disclosures of protected health information.
(a) ***Standard: De-identification of protected health information.*** Health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual is not individually identifiable health information.
(b) ***Implementation specifications: Requirements for de-identification of protected health information.*** A covered entity may determine that health information is not individually identifiable health information only if:
(1) A person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable: **(i)** Applying such principles and methods, determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information; and **(ii)** Documents the methods and results of the analysis that justify such determination

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12. LIST OF TABLES

13. LIST OF FIGURES

Document Approval Record

Document Name:	C4671066_Pfizer Paxlovid HPM study protocol_Final_17OCT2024
Document Title:	C4671066_Pfizer Paxlovid HPM study protocol_Final_17OCT2024

Signed By:	Date(GMT)	Signing Capacity
PPD	21-Oct-2024 16:58:47	Manager Approval