Non-Interventional Study Protocol

C4671050

A Retrospective Observational Non-Interventional Study (NIS) to assess Patient Characteristics and Healthcare Resource Use (HRU) among COVID-19 Patients Receiving Treatment with Nirmatrelvir/Ritonavir (PAXLOVID™) and a comparison to control patients who were offered PAXLOVID but refused treatment in the Kingdom of Bahrain.

Statistical Analysis Plan (SAP)

Version: 1

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AMENDMENTS FROM PREVIOUS VERSION(S)

Not Applicable

INTRODUCTION

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

In December 2019, COVID-19 was identified as a new, potentially fatal, respiratory infection caused by the novel coronavirus, SARS-CoV-2. The WHO declared COVID-19 a Public Health Emergency of International Concern[Error! Reference source not found.] *on 30 January 2020 and further characterized the disease outbreak as a pandemic on 11 March 2020.*[Error! Reference source not found.] *As of 01 January 2022, more than 289,000,000 cases have been confirmed worldwide, and at least 5,440,154 deaths have occurred.*[Error! Reference source not found.] *Despite widespread use of COVID-19 vaccine since 2020 in Bahrain, COVID-19 caused 702830 cases, 26194 hospitalizations and 1546 deaths during the period 2020-2023 in Kingdom of Bahrain.*

The clinical presentation of COVID-19 varies widely, ranging from an asymptomatic infection to critical illness characterized by respiratory failure, septic shock and other multiple organ dysfunction or failure.[Error! Reference source not found.] *Although the majority of cases are asymptomatic or mild,*[Error! Reference source not found.] *patients who are hospitalized with COVID-19 may have significant morbidity and mortality.*[Error! Reference source not found.-Error! Reference source not found.] *Between February 2020 and September 2021, the United States CDC estimated that of a total of 146.6 million infections, 85% of patients were symptomatic and only 5% required hospitalization for treatment.*[Error! Reference source not found.]

According to the NIH guidelines, management of non-hospitalized patients with acute COVID-19 should include supportive care, advise on when to contact a health care provider and seek an in-person evaluation, and COVID-19 specific therapy for patients who have a high risk of disease progression. [Error! Reference source not found.] *More specifically, non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk of clinical progression may receive (listed in order of preference) nirmatrelvir (PF-07321332)/ritonavir (Paxlovid™), sotrovimab, remdesivir, or molnupiravir.*[Error! Reference source not found.]

Kingdom of Bahrain:
Kingdom of Bahrain is one of the leading countries in COVID-19 outpatient treatment care. A unique outpatient clinic has been established in May 2021 to provide outpatient care for patients with positive Coronavirus. Treatment including monoclonal antibodies such as Bamlamivimab, Regen-Cov, Sotorovimab and Paxlovid™ are offered for all high-risk and close contact patients, such treatments are in line with the guidelines of the FDA.

The clinic has a dedicated call center providing different services to ease the patient treatment process and provides follow-up care. The overall aim of the clinic is to target mild to moderate high risk COVID-19 patients and provide outpatient treatment as early as possible to reduce disease progression, including hospitalization and death.

On 01 January 2022, the National Health Regulatory Authority (NHRA) approved the emergency use of Paxlovid™ for mild-moderate cases who are at high risk – identified as per WHO definition of high-risk group – of developing severe COVID-19. Since approval, Paxlovid™ has been established as the first line therapy along with Sotrovimab in the Kingdom of Bahrain.

*In the EPIC-HR trial, Paxlovid™ reduced the risk of hospitalization or death by 88% compared to placebo in non-hospitalized adults with laboratory-confirmed SARS-CoV-2 infection and a risk factor for progression to severe disease, when treatment was initiated within 5 days of symptom onset.***Error! Reference source not found.**,***Error! Reference source not found.** *Other efficacies reported for COVID-19 therapies, include sotrovimab (ie, 85% relative reduction reported),***Error! Reference source not found.**,***Error! Reference source not found.** *and remdesivir (ie, 87% relative reduction reported)***Error! Reference source not found.**,***Error! Reference source not found.** *and molnupiravir (ie, 30% relative reduction reported).***Error! Reference source not found.**,***Error! Reference source not found.** *Furthermore, in vitro analyses, suggested that Paxlovid™ is active against the B.1.1.529 (Omicron) variant of concern (VOC).***Error! Reference source not found.***

COVID-19 has put significant pressure on the healthcare system worldwide and caused an enormous economic burden to society. While patient characteristics, healthcare resource utilization (HRU) and healthcare costs of patients hospitalized with COVID-19 have previously been described in US studies, ***Error! Reference source not found.**-***Error! Reference source not found.** *such data are limited among non-US countries.***Error! Reference source not found.**,***Error! Reference source not found.** *Furthermore, while the majority of current research focuses on hospitalized COVID-19 patients, little is known about COVID-19 patients identified in an outpatient setting.*

The availability of antiviral treatments in the outpatient setting, such as Paxlovid™, have potential to complement vaccination strategies during the COVID-19 pandemic and further reduce the burden on healthcare system capacity in the short- and long-term. There is a need to identify patients in the real-world setting globally, who are diagnosed with COVID-19 and may be at an increased risk of healthcare resource utilization, as prior literature suggests these patients are most likely to benefit from outpatient therapies. With the authorization (ie, EUA) of Paxlovid™, there is also a growing need to complement clinical trial findings and address data gaps by generating real-world evidence that may help inform healthcare decision-making globally during this early EUA utilization phase.

This study aims to describe the characteristics, outcomes and treatment patterns of COVID-19 patients, who are receiving Paxlovid™ in Bahrain according to the local drug label.

1.1 STUDY DESIGN

This study is a retrospective cohort study examining COVID-19 patients who were treated with Paxlovid. It will also include a control group of COVID-19 patients who were offered, but refused, Paxlovid. It will involve a secondary data analysis of patient data from the ISeha electronic medical records.

Study population

Patients will be eligible for inclusion in the study if they were diagnosed with COVID-19 between February and November 2022, were treated in an outpatient setting in the Kingdom of Bahrain, and were offered Paxlovid. Paxlovid was offered to patients in the Kingdom of Bahrain if they were at high risk of complications from COVID-19 due to age ≥ 50 years, BMI ≥ 35, or a medical history of chronic kidney disease (eGFR ≥30 ml/min), diabetes mellitus, primary or secondary immunosuppressive disease or receiving immunosuppressive treatment, cardiovascular disease or hypertension, chronic lung diseases, sickle cell disease, neurodevelopmental disorders, or having a medical-related technological dependence. There are no exclusion criteria.

EHRs from approximately 3000 COVID-19 patients who were treated with Paxlovid, all of whom gave verbal consent for treatment that was recorded in the medical record, will be included in the study. These patients were treated between February and November 2022, and consist of approximately 53% of the total eligible patient population from the timeframe. A comparison group of patients will also be included. This group will consist of approximately 1000 patients with COVID-19 that were offered Paxlovid therapy but who refused treatment, over this same time period.

Data source

This study will involve a secondary data analysis of COVID-19 patients' data from the ISeha Electronic health records. The following data will be used: patient demographic characteristics, clinical characteristics, and COVID-19 disease outcomes. The ISeha EHR data will be anonymized. Demographic and clinical data from eligible patients were recorded in ISeha electronic health records by medics on the ward. Patient-reported symptom outcomes in the five-days following Paxlovid prescription were determined by a follow-up telephone call.

1.2 STUDY OBJECTIVES

The overall aim of this study is to examine the baseline demographic, clinical, and outcome characteristics of COVID-19 patients who received Paxlovid.

The objectives are

(i) to describe the demographic, clinical, and outcome characteristics of COVID-19 patients who received Paxlovid and COVID-19 patients who were offered, but refused Paxlovid

(ii) to examine differences in the demographic characteristics (e.g., age, sex, nationality, type of outpatient encounter, vaccination status) between COVID-19 patients who received Paxlovid and COVID-19 patients who refused Paxlovid,

(iii) to examine differences in the clinical characteristics (e.g., comorbidities, symptoms, duration of symptoms) between COVID-19 patients who received Paxlovid and COVID-19 patients who refused Paxlovid over a five-day follow-up,

(iv) to examine differences in outcomes (e.g., hospitalisations, time spent in an intensive care unit, time spent with invasive mechanical ventilation, supplemental oxygen usage, re-admission to hospital, deaths) between COVID-19 patients who received Paxlovid and COVID-19 patients who refused Paxlovid over a five-day follow-up.

(v) To examine differences in the proportion of COVID-19 patients who meet the most up-to-date WHO recommendations for the use of therapeutics in the treatment of COVID-19 (ie, version 14, published 10Nov2023) in comparison to Kingdom of Bahrain national recommendations.

HYPOTHESES AND DECISION RULES

Not applicable

1.3 STATISTICAL HYPOTHESES

Not applicable

1.4 STATISTICAL DECISION RULES

Not applicable

ANALYSIS SETS/POPULATIONS

1.5 FULL ANALYSIS SET

The full analysis set will consist of approximately 8263 adult COVID-19 patients with pre-existing comorbidities who attended outpatient clinics in the Kingdom of Bahrain. It includes approximately 3000 patients who received Paxlovid and approximately 1000 COVID-19 patients who were offered Paxlovid therapy but who refused treatment.

1.6 SAFETY ANALYSIS SET

Not applicable

1.7 OTHER ANALYSIS SET

Not applicable

1.8 SUBGROUPS

Not applicable

ENDPOINTS AND COVARIATES

Patients were treated according to clinical practice. Therefore, the decision of what measures to record was not pre-specified in the protocol. Variables from EHRs that align with the data required by the protcol will be used.

The following variables will be extracted from EHRs, if available:

Table 1: *Patient Demographic Variables*

Variable	Operational definition
Group	Received Paxlovid or did not receive Paxlovid
Age	Age will be defined as of the date of COVID-19 diagnosis using a PCR test and will be used to assign patients to age groups: 18-29, 30-49, 50-64, 65-74, ≥75 years and unknown/missing age
Sex	Female, male and unknown/missing sex patients
Nationality	Nationality of the patient (Bahrain, other Middle East and North Africa, India, Pakistan, South East Asia, Caucasian)
Enrollment Date Place of Service (POS)	Type of outpatient encounter during the enrollment date (e.g., office visit, emergency room (ER), outpatient hospital, other, etc.)
Enrollment Date	Date (defined as MM/YYYY) of the enrollment date specified
Specialty of Provider at enrollment Date	Provider specialties present during the enrollment date. Patients with no provider specialty recorded will be included in an “Unknown/missing specialty” category
COVID-19 Symptom Onset Date	Date of symptom onset prior to presentation to healthcare facility

Time to COVID-19 Symptom Resolution	Time from onset of COVID-19 symptoms to resolution of symptoms
Date of COVID-19 Vaccination	Date of each COVID-19 vaccination received. Note: patient-specific vaccination history may require more than 6-months pre-index time period.
Date of Paxlovid prescription written and/or fill history (e.g., prescription claim)	Date of Paxlovid prescription written or fill history. Note: if both dates are available within the database, use the most recent date provided.

Table 2: *Clinical Characteristic Variables*

Variable	**Operational definition**
Comorbidities	Asthma, emphysema, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, obesity, cerebrovascular disease, neurological disease, chronic kidney disease, chronic liver disease, malignancy, etc.
Risk Factors for Severe COVID-19	• Age ≥50 years • Obesity (BMI ≥ 35) • Chronic kidney disease (eGFR ≥30 ml/min) • Diabetes Mellitus • Primary and Secondary Immunosuppressive disease or immunosuppressive treatment • Cardiovascular disease (including congenital heart disease) or hypertension • Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension) • Sickle cell disease • Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies) • Having a medical-related technological dependence(for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])

Patient-reported COVID-19 symptoms	List of COVID-19 symptoms to be added by study team (US, CDC definition). 1- Stuffy or runny nose 2- Sore throat 3- Shortness of Breath 4- Cough 5- Low energy/Tiredness/fatigue 6- Muscle ache/body aches 7- Headache 8- Chills or shivering 9- Feeling hot/feverish 10- Nausea or vomiting 11- Diarrhea 12- Loss of sense of smell 13- Loss of sense of taste
Death	Died on or after the enrollment date in the follow up period
Inpatient Death	Died during a hospitalization in the follow-up period

Table 4: *COVID-19 disease outcome variables*

Variable	Operational definition
Hospitalizations	Number of all-cause and COVID-related hospitalizations (excluding within 24 hours of Paxlovid initiation) during the baseline and follow-up period per patient
Number of Hospitalizations per Patient	The number of hospitalizations per patient in the baseline and follow-up periods for all-cause and COVID-related hospitalizations (excluding within 24 hours of Paxlovid initiation)
Number of Hospitalizations per Patient among Patients with Readmissions	The number of all-cause and COVID-related hospitalizations (excluding within 24 hours of Paxlovid initiation) per patient in the baseline and follow-up periods will be described among patients with readmissions during the same period. The cause for readmission will be reported when available.
Time to First Outpatient Encounter	Time from COVID-19 diagnosis to the earliest outpatient encounter to occur after diagnosis during the baseline period.

Hospital Length of Stay	The total length of stay (LOS) recorded for all hospitalizations during the baseline period and follow-up period in days (excluding within 24 hours of Paxlovid initiation)
ICU/Non-ICU LOS	The total number of days in the intensive care unit (ICU) and the number of days that were not spent in the ICU (non-ICU) recorded for all hospitalizations during the baseline period and follow-up period in days (excluding within 24 hours of Paxlovid initiation)
IMV/No IMV LOS	The total number of days with and without invasive mechanical ventilation (IMV) recorded for all hospitalizations during the baseline period and follow-up period in days (excluding within 24 hours of Paxlovid initiation)
ICU Admission	ICU admission during COVID-related hospitalizations in the baseline and follow-up periods (excluding within 24 hours of Paxlovid initiation)
IMV Usage	IMV (i.e., intubation and mechanical ventilation) usage, including extracorporeal membrane oxygenation (ECMO), during COVID-related hospitalizations in the baseline and follow-up periods (excluding within 24 hours of Paxlovid initiation)
Supplemental Oxygen Usage	supplemental oxygen usage during COVID-related hospitalizations in the baseline and follow-up periods (excluding within 24 hours of Paxlovid initiation)
Non-invasive Ventilation Usage	Non-invasive ventilation usage during COVID-related hospitalizations in the baseline and follow-up periods (excluding within 24 hours of Paxlovid initiation)
High-flow Nasal Cannula Usage	High-flow nasal cannula usage during COVID-related hospitalizations in the baseline and follow-up periods (excluding within 24 hours of Paxlovid initiation)
Hospital Discharge Status	Patient discharge status for COVID-related hospitalizations during the baseline and follow-up periods (excluding within 24 hours of Paxlovid initiation)

Time from COVID-19 Test to Paxlovid Treatment	Time from the earliest COVID-19 test in the baseline period to the earliest date of Paxlovid prescription written date AND dispense date.
COVID-19 Lab Tests with Positive Result	COVID-19 lab test with a positive result during the baseline and follow-up periods.
COVID-19 Lab Test with Variant Type	When available, COVID-19 variant of concern (VOC) during the baseline period.
Treatment drugs being receiving at the index date	-Use Positive test as the INDEX Date and record use of any medicine listed in the potential DDI/Contraindications section of the EUA/:Label
Monoclonal Antibody Usage	Monoclonal antibody usage during the baseline and follow-up periods. Monoclonal antibody usage will include tocilizumab and bamlanivimab/etesevimab. (Yes/No)
Antiviral Usage	Antiviral therapy usage during the baseline and follow-up periods. Antiviral therapy usage will include remdesivir, nirmatrelvir/ritonavir (paxlovid) and molnupravir. (Yes/No)
Steroid therapy	Steroid therapy during admission (Yes/No)

WHO guidelines on COVID-19 therapeutics include the following groups

- **High risk**: people who are immunosuppressed; estimated hospitalization rate of 6%.
- **Moderate risk**: >65 years of age, conditions like obesity, diabetes and/or chronic conditions including chronic obstructive pulmonary disease, kidney or liver disease, cancer, with disabilities, and with comorbidities of chronic disease; estimated hospitalization rate of 3%.
- **Low risk**: those who are not in the high or moderate risk categories; low risk of hospitalization (0.5%) – most people are low risk.

Using these criteria, we will look at frequency and percentage of COVID-19 patients who will fall in those criteria to understand strongly recommended or conditionally recommended use of Paxlovid™ in comparison to the country of issue recommendations.

1.9 SAFETY ENDPOINTS

Not applicable.

1.10 OTHER ENDPOINTS

Not applicable.

1.11 COVARIATES

Not applicable.

HANDLING OF MISSING VALUES

Missing data patterns, including the amount of missing data for each variable and individual and possible reasons for missing data, will be explored. As this is a descriptive study, missing data will not be imputed. The number and percentage of patients with missing data will be reported for each variable.

STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

1.12 STATISTICAL METHODS

Descriptive statistics will be presented separately for the demographic, clinical, and outcome characteristics of COVID-19 patients taking Paxlovid, and for COVID-19 patients who were offered Paxlovid therapy but who refused treatment. Inferential statistics will be used to assess any differences in demographic characteristics, clinical characteristics, and disease outcomes between patients who received Paxlovid and patients who refused Paxlovid.

1.13 STATISTICAL ANALYSES

Descriptive statistics
Categorical variables will be presented in terms of raw numbers (n) and percentages (%). Continuous variables will be presented as means and standard deviations or as medians and interquartile ranges, depending on the level of skewness and kurtosis of the data.

Inferential statistics
Between-group differences in categorical variables will be examined using proportions tests, Chi-square tests of independence or Fisher exact tests as approriate. Differences in continuous variables will be examined using independent t-tests.

Differences in proportions or means (as appropriate) and 95% confidence intervals between COVID-19 patients taking Paxlovid, and COVID-19 patients who were offered Paxlovid therapy but who refused treatment will be reported. Additionally, Cramer's V or Cohen's d will be reported.

Cramer's V is a measure of association that quantifies the strength and direction of the relationship between the two categorical variables being compared. Cramer's V ranges from 0 to 1, where 0 indicates no association between the variables, and 1 represents a perfect association. The magnitude of Cramer's V will be interpreted as follows:

Cramer's V	**Effect Size**
0.1	Weak
0.3	Medium
0.6	Large

Cohen's d quantifies the standardized difference between the means of the two groups, and is calculated by taking the difference between the means of the two groups and dividing it by the pooled standard deviation. The magnitude of Cohen's d will be interpreted as follows:

Cohen's d	**Effect Size**
0.2	Small
0.5	Medium
0.8	Large

An a priori alpha level of 0.05 has been selected for all tests. As this work is exploratory no adjustment for multiple comparisons will be made.

Selection of the control groups will consider the following characteristics based on the availability of data using propensity-score matched:

- age,
- sex,
- COVID vaccination status,
- high-risk status for severe COVID-19 outcomes (WHO definition),
- assessment of healthcare seeking behavior in 365 days prior to COVID infection (such as flu or streptococcus pneumoniae vaccine, has primary healthcare provider, number of primary care/hospital visits),
- socioeconomic factors (such as household income, employment status),
- geographic location of residence,
- comorbidities.

[redacted]

1.13.1 Safety Analyses

Not applicable.

1.13.2 Analyses of Endpoints

Not applicable.

7.2.3 Summary of Analyses

Descriptive statistics will be presented for all variables. Inferential statistics will be used to examine difference in demographic, clinical, and outcome characteristics between COVID-19 patients who received Paxlovid and those who were offered, but refused, Paxlovid.

LIST OF TABLES AND TABLE SHELLS

Table 3: Descriptive statistics for baseline variables

	Group		P-value	Effect size
Variables	**Paxlovid**	**Control**		
Age, % (n)				
18-29				
30-49				
50-64				
65-74				
≥75 years				
Gender, % (n)				
Male				
Female				
Nationality, % (n)				
Bahrain				
Other Middle East and North Africa				
India				
Pakistan				
South East Asia				
Caucasian				

Enrollment Date Place of Service (POS), % (n)				
Office visit				
Emergency room				
Outpatient hospital				
Other				
Specialty of Provider at enrollment Date				
Interns				
Residents				
Family Phyiscans				
Specialist				
Consultants				
Number of days from COVID-19 symptom onset to resolution, mean (SD)				
Number of days from vaccination to contracting COVID-19, mean (SD)				
Number of days from contracting COVID-19 to being prescribed Paxlovid, mean (SD)				
Number of days from COVID-19 test to Paxlovid treatment, mean (SD)				
COVID-19 Lab Tests with Positive Result, % (n)				
COVID-19 Lab Test with Variant Type, % (n)				

Table 6: Descriptive statistics for clinical characteristics

Variables	Group		P-value	Effect size
	Paxlovid	**Control**		
Patient-reported Covid-19 symptoms, % (n)				
Stuffy or runny nose				
Sore throat				
Shortness of Breath				
Cough				
Low energy/Tiredness/fatigue				
Muscle ache/body aches				
Headache				
Chills or shivering				
Feeling hot/feverish				
Nausea or vomiting				
Diarrhea				
Loss of sense of smell				
Loss of sense of taste				
Comorbidities (ICD-10)				
Vaccination Status, % (n)				
Completely				

Partially				
Unvaccinated				
Risk factors for severe Covid-19, % (n)				
Age ≥50 years				
Obesity (BMI ≥ 35)				
Chronic kidney disease (eGFR ≥30 ml/min)				
Diabetes Mellitus				
Primary and Secondary Immunosuppressive disease or immunosuppressive treatment				
Cardiovascular disease (including congenital heart disease) or hypertension				
Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)				
Sickle cell disease				
Neurodevelopmental disorders				
Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])				
Death, % (n)				
Inpatient death, % (n)				

Table 7: Descriptive statistics for outcome variables

Outcome Variables	Group		P-value	Effect size
	Paxlovid	**Control**		
Hospitalizations, % (n)				
Number of hospitalizations per patient, mean (SD)				
Number of hospitalizations per patient among patients with readmissions, % (n)				
Time to first outpatient encounter, mean (SD)				
ICU Admission, % (n)				
Hospital Length of Stay, mean (SD)				
ICU/Non-ICU LOS, mean (SD)				
IMV/No IMV LOS, mean (SD)				
Treatment				
IMV Usage, % (n)				
Supplemental Oxygen Usage, % (n)				
Non-invasive Ventilation Usage, % (n)				
High-flow Nasal Cannula Usage, % (n)				
Hospital Discharge Status				
Went home, % (n)				
Transfer to skilled nursing facility, % (n)				

Transfer to other healthcare facility, % (n)				
Transfer to other long-term care facility, % (n)				
Transfer to hospice, % (n)				
Death, % (n)				
Medication Usage, % (n)				
Antibiotic, % (n)				
Antiviral (incl. Paxlovid, COVID-19 monoclonal antibodies), % (n)				
Antithrombotic, % (n)				
Anti-inflammatory (incl. steroids), % (n)				

Table 8: Comparison of WHO[4] and Bahrain national recommendation for Paxlovid Treatment in COVID-19 patients

Outcome Variables	**WHO recommendation for Paxlovid treatment**		**Bahrain national recommendation for Paxlovid treatment**
	Stongly recommended	**Conditionally recommended**	**Strongly recommended**
All COVID patients			
Paxlovid group			
Control group			

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