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**Can**adian Adaptive Platform Trial of **Treat**ments for **COVID** in Community Settings

**Intervention Specific Sub-Protocol:** Paxlovid™ x 5 days

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**Summary**

This is a sub-protocol of the Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings (CanTreatCOVID). For more information on CanTreatCOVID, visit [www.CanTreatCOVID.org](http://www.CanTreatCOVID.org).

Participants meeting the platform inclusion and exclusion criteria will be randomized to receive one of two interventions:

1. Nirmatrelvir/ritonavir (Paxlovid™) BID x 5 days
2. Usual care (i.e., supportive care and symptom relief)

Our co-primary outcomes are time to recovery and hospitalization and/or death at 28 days, and key secondary outcomes include symptom severity, incidence of post-acute sequelae of SARS-CoV-2 (long COVID), quality of life, and cost-effectiveness of each therapeutic. CanTreatCOVID uses numerous approaches to recruit, including a multi-faceted public communication strategy and outreach through primary care, out-patient clinics, and emergency departments.

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# ABBREVIATIONS

|  |  |
| --- | --- |
| ACE2 | Angiotensin Converting Enzyme-2 |
| AE | Adverse Event |
| CanTreatCOVID | Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings |
| CKD | Chronic Kidney Disease |
| DSMC | Data Safety & Monitoring Committee |
| dNHBE | Differentiated human bronchial epithelial |
| eGFR | Estimated Glomerular Filtration Rate |
| ISSP | Intervention-Specific Sub-Protocol |
| PSSP | Province-Specific Sub-Protocol |
| RAR | Response Adaptive Randomizations |
| SAP | Statistical Analysis Plan |
| SAE | Serious Adverse Event |

# PROTOCOL STRUCURE

The CanTreatCOVID protocol structure, which includes an overarching Master Protocol and intervention-specific sub-protocols (ISSP) is different to that used for conventional trials because this trial is highly adaptive, and the description of these adaptations is better understood and specified using a sub-protocol design. While all adaptations are pre-specified and approved by research ethics prior to implementation, the use of sub-protocols is designed to allow the trial to evolve over time, for example by the introduction or removal of interventions and/or geographical regions.

The protocol structure has multiple elements. In brief, these include a Master Protocol (overview and design features of the study), a Statistical Analysis Plan (SAP; details of the current statistical analysis plan and models), and multiple ISSPs (detailing the individual interventions currently being studied in the trial).

The Master Protocol contains all information that is generic to the trial, irrespective of the provincial location in which the trial is conducted and interventions that are being tested. The Master Protocol may be amended, but it is anticipated that such amendments will be infrequent.

The Master Protocol does not contain information about the intervention(s) included in the trial because one of the trial adaptations is that interventions will change over time. Information about interventions is covered in each ISSP. These ISSPs are anticipated to change over time, with removal, addition, or revision of elements within. Each modification to a ISSP will be subject to an ethics application for approval.

The Master Protocol does not contain detailed information about statistical analyses or simulations, because the analysis model will change overtime in accordance with trial adaptations, however this information is contained in the SAP.

The Master Protocol also does not contain information that is specific to a particular province in which the trial is conducted, as the locations that participate in the trial are also anticipated to change over time. Information that is specific to each province that conducts the trial is contained within a province-specific sub-protocol (PSSP). This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each province, only that province’s PSSP, and any subsequent modifications, will be submitted for ethical review in that province.

# SUB-PROTOCOL SPECIFIC APPENDIX VERSION

The version of the Paxlovid™ x 5 days-specific sub-protocol is in this document’s footer and on the cover page.

## Version History

|  |  |
| --- | --- |
| Version 1.0 | Approved by Unity Health Toronto on: |
|  |  |

# BACKGROUND AND RATIONALE

## Sub-Protocol Definition

This is a sub-protocol within the CanTreatCOVID adaptive platform trial to test the clinical and cost-effectiveness of Paxlovid™ x 5 days versus usual care among non-hospitalized patients with mild to moderate SARS-CoV-2.

## Sub-Protocol-Specific Background

### Potential Mechanism of Action

Paxlovid™ consists of nirmatrelvir tablets and ritonavir tablets taken together. Nirmatrelvir (PF-07321332) is a protease inhibitor developed specifically for treatment of SARS-CoV-2, which works by inhibiting viral replication by inhibiting the SARS-CoV-2 main protease (3CL).1 Ritonavir inhibits metabolism of nirmatrelvir, resulting in increased plasma concentration to therapeutic levels.

### Current Evidence for Potential Benefit of Paxlovid™ in SARS-CoV-2 Infection

In Vitro Studies

*In vitro* studies demonstrated that nirmatrelvir (PF-07321332) was a potent inhibitor of the SARS-CoV-2 3CL protease inhibitor in biochemical enzymatic assays and in testing with human adenocarcinoma-derived alveolar basal epithelial (A549) cells expressing Angiotensin Converting Enzyme-2 (ACE2) and in differentiated human bronchial epithelial (dNHBE) cells.1

In Vivo Studies

Nirmatrelvir (PF-07321332) antiviral activity was evaluated in an *in vivo* mouse-adapted SARS-CoV-2 model (SARS-CoV-2 MA10). Mice treated twice daily with nirmatrelvir (PF-07321332) at both 300 mg/kg and 1000 mg/kg doses had reduced weight loss, and lung viral levels evaluated in CCID50 assays were lower compared to placebo-treated mice.1

Phase I Studies

In a phase I randomized placebo-controlled study, nirmatrelvir (PF-07321332) was given to healthy volunteers and was well tolerated.2 Nirmatrelvir (PF-07321332) exposure and half-life were increased by ritonavir and supported the selection of nirmatrelvir/ritonavir dosing for phase II/III trials at 300/100 mg BID for 5 days to achieve serum concentrations above those required for 90% inhibition of viral replication *in vitro.*2

Phase II/III Studies

The efficacy of Paxlovid™ to treat people infected with SARS-CoV-2 was assessed in the Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) study.3 This study suggested that nirmatrelvir/ritonavir may reduce the risk of hospitalization by 88%. However, this study was in unvaccinated patients and predated the most recent variants of SARS-CoV-2.3

The Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (EPIC-SR) study showed a non-significant relative risk reduction in the endpoint of hospitalization or death between the treatment and placebo arms, and a subgroup analysis of 721 vaccinated adults with at least one risk factor for progression to severe COVID-19 similarly demonstrated a non-significant relative risk reduction in hospitalization or death.4

# SUB-PROTOCOL OBJECTIVES

The objective of this sub-protocol is to determine the clinical- and cost-effectiveness of Paxlovid™ x 5 days among non-hospitalized patients with mild to moderate SARS-CoV-2 infection. It is hypothesized that the probability of occurrence of the co-primary outcomes specified in the Master Protocol will differ based on the allocation to Paxlovid™ x 5 days or usual care. The following interventions will be available:

1. Nirmatrelvir/ritonavir (Paxlovid™) x 5 days
2. Usual Care (i.e., supportive care and symptom relief)

We hypothesize that the treatment effect of Paxlovid™ x 5 days is different depending on age and vaccination strata status.

# TRIAL DESIGN

The sub-protocol will be conducted as part of the CanTreatCOVID trial. Treatment arm allocation will occur on the day of enrollment using an interactive web-based system, as described in the Master Protocol. Briefly, participants will be allocated to a trial arm using fixed, equal randomization ratios corresponding to the number of eligible arms in the trial. Participants will be stratified based on age and vaccination status and random sized permuted blocks will be used.

## Population

CanTreatCOVID enrolls non-hospitalized patients with mild to moderate SARS-CoV-2 infection.

## Eligibility Criteria

Participants are eligible for this sub-protocol if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in the CanTreatCOVID Master Protocol.

Participants otherwise eligible for CanTreatCOVID may have conditions that exclude them from the current sub-protocol. These are described below.

### Sub-Protocol Inclusion Criteria

As per the Master Protocol.

### Sub-Protocol Exclusion Criteria

Participants will be excluded from this sub-protocol if the participant:

* History of clinically significant hypersensitivity to the active substances in Paxlovid™ (nirmatrelvir /ritonavir) or to any of its excipients.
* Patients with known rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
* Patients with known current severe liver impairment (characterized by severe ascites, encephalopathy, jaundice, or prolonged INR. People with liver disease without any of these features are eligible).
* Patients with known moderate or severe renal disease (defined as CKD stage 3, 4 or 5 or current acute kidney injury or most recent eGFR in the past 6 months <60 ml/min).
* Currently taking Paxlovid™.
* Clinical requirement to continue taking a drug which is contraindicated or not recommended for administration with Paxlovid™ in the context of CanTreatCOVID (Appendix 5.4) or is taking a drug which in the opinion of the investigator would put the subject at unacceptable risk.
* Has a known or suspected pregnancy.
* Is breastfeeding.
* Is of childbearing potential and is not willing to use a highly effective contraceptive.

To confirm that the participant meets the criteria defined above, information will be elicited through a direct discussion between the participant and a medically qualified prescribing pharmacist. Those assessing eligibility will take a relevant drug history and obtain a complete medication list from the participants usual pharmacy. If after reviewing this list and discussion with the patient, the recruiting health care professional considers the potential participant eligible, the participant may then be randomised to Paxlovid™.

## Interventions

Participants will be randomly allocated to one of the following trial arms:

1. Nirmatrelvir/ritonavir (Paxlovid™) x 5 days
2. Usual Care (i.e., supportive care and symptom relief)

CanTreatCOVID is an open-label trial so participants will be aware of which trial arm they have been allocated to. If a participant is allocated to the Paxlovid™ x 5day arm, the medication will be shipped to their residence immediately after their eligibility is confirmed.

### Usual Care

Participants randomized to usual care will not receive Paxlovid™ x 5 days. After randomization, they will receive supportive care (i.e., rest and fluids) and symptom relief (e.g., short-acting bronchodilator for wheezing) from their primary care provider. Administration of any study medication to treat SARS-CoV-2 infection, up until study day 28, will be considered a protocol deviation.

### Nirmatrelvir/ritonavir (Paxlovid™) x 5 days

*Dosing and Duration of Treatment*

Paxlovid™ is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir will result in plasma levels of nirmatrelvir that will be insufficient to achieve the desired therapeutic effect.

The dosage for Paxlovid™ is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together orally twice daily for 5 days. Participants will be advised to complete the full 5-day treatment course.

The 5-day treatment course of Paxlovid™ should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset.

Adherence to trial medication will be assessed by self-report.

*Dosing Considerations*

If the participant misses a dose of Paxlovid™ within 8 hours of the time it is usually taken, the participant should take it as soon as possible and resume the normal dosing schedule. If the participant misses a dose by more than 8 hours, the participant should not take the missed dose and instead take the next dose at the regularly scheduled time. The participant should not double the dose to make up for a missed dose.

If a participant overdoses with Paxlovid™, they will be advised to get in touch with their primary care provider or local emergency department, if required.

If a patient requires hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid™, the patient should complete the full 5-day treatment course at the discretion of their healthcare provider.

Paxlovid™ can be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.

*Renal failure*

No dose adjustment is necessary for patients with mild renal impairment (eGFR ≥60 ml/min, CKD stage 1-2). Patients with moderate renal impairment (eGFR ≥30 to <60 mL/min, CKD stage 3) will not be eligible for randomization to Paxlovid™, as the dose of Paxlovid™ should be reduced to nirmatrelvir /ritonavir 150 mg/100 mg (1 tablet of each) twice daily for 5 days, and this is not feasible in this large scale trial. Patients with severe renal impairment (eGFR <30 ml/min, CKD stage 4-5) are not recommended to have Paxlovid™ and are also not eligible for randomization to the Paxlovid™ arm.

*Hepatic impairment*

No dose adjustment is required for patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment are not recommended for Paxlovid™ and are not eligible for randomization to the Paxlovid™ arm.

*Concomitant therapy with ritonavir- or cobicistat-containing regimen*

No dose adjustment is needed. The dose of Paxlovid™ is 300 mg/100 mg twice daily for 5 days. Patients diagnosed with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection who are receiving ritonavir- or cobicistat-containing regimen should continue their treatment as indicated.

*Potential serious adverse reactions due to drug-drug interactions*

Paxlovid contains ritonavir. Ritonavir is an inhibitor, inducer, and substrate of various drug- metabolizing enzymes and/or drug transporters. Most notably, as a strong inhibitor of CYP3A, it may increase concentrations of certain concomitant medications, thereby increasing the potential for significant drug toxicities. CYP3A inhibition by ritonavir typically resolves 3 to 5 days after the drug is discontinued. When ritonavir is used for a treatment duration of 5 days, its induction properties are less likely to be clinically relevant than when the drug is used chronically for HIV. See Appendices 5.3 and 5.4 for lists of contraindicated concomitant medications and concomitant medications that may be taken with caution.

Medications that induce or inhibit CYP3A may also reduce or increase Paxlovid™ levels. Induction of 3A4 may result in sub-therapeutic Paxlovid™ levels, increasing the risk of development of viral resistance.

*Hepatotoxicity*

Increased hepatic transaminases, hepatitis, and jaundice have occurred in patients receiving ritonavir. Patients with known severe liver disease will not be eligible to be randomized to Paxlovid™.

*Excipients*

PF-07321332 tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take Paxlovid™.

*Concomitant medications*

Medications that may interact with Paxlovid™, and the implications for eligibility for CanTreatCOVID, are listed in Appendix 5.4. This list is based on the summary of product characteristics (Appendix 5.1) and will be updated as new information becomes available. Clinical judgement is required to evaluate potential drug interactions. Detailed advice is also available from the Liverpool COVID-19 Drug Interactions Checker website:

<https://www.covid19-> druginteractions.org/.

Participants who are taking Paxlovid™ as part of the trial will be advised that they must check with a clinician before initiating any new medications while taking Paxlovid™ to ensure that the potential for drug-drug interaction has been considered. Participants will also be provided with a participant information sheet (Appendix 3) and wallet card (Appendix 4), which includes information on the arm that they have been randomized to and contact information in the case of an emergency.

## Concomitant Care

All treatment that is not specified by assignment within the current trial will be determined by the participants usual health care provider.

## Endpoints and Outcomes

### Primary Outcomes

As per the Master Protocol.

### Secondary Outcomes

As per the Master Protocol.

# TRIAL CONDUCT

## Sub-Protocol-Specific Data Collection

### Clinical Data Collection

An additional safety call will be made on Day 4 (Appendix 6) for participants randomized to Paxlovid arm only. The purpose of the day 4 safety call is to detect any early side-effects of Paxlovid and to enable investigators to suggest changes to participants medication including stopping where required.

## Criteria for Discontinuation

Refer to the CanTreatCOVID Master Protocol for criteria for discontinuation of participation in the trial.

## Blinding

### Blinding

Paxlovid™ x 5 days will be administered on an open-label basis.

### Unblinding

Not relevant.

# ETHICAL CONSIDERATIONS

## Risks

###  Adverse events

In the EPIC-HR trial, among 2,224 symptomatic unvaccinated adults age ≥18 years of age and at high risk of developing severe COVID-19 illness, n=1,109 received at least one dose of Paxlovid™ and n=1,115 received placebo.3 23% versus 24% experienced adverse events (AE), and 1.6% versus 6.6% experienced serious adverse events (SAEs), including COVID-19 related AEs, in the Paxlovid™ group versus placebo group, respectively.3 AEs (all grades regardless of causality) in the Paxlovid™ group (≥1%) that occurred at a greater frequency (≥5 subject difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and<1%). 2% of participants in the Paxlovid™ group and 4% in the placebo group discontinued treatment due to an AE.3

In an interim analysis of the EPIC-SR trial among standard risk patients (i.e., unvaccinated with no risk factors for severe disease or vaccinated with a risk factor for severe disease), AEs (22% versus 21%), SAEs (1.4% vs 1.9%) and discontinuation of trial drug due to AEs (2.1% vs. 1.2%) were comparable between Paxlovid™ (22%) and placebo (21%).4

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid™ to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

Adverse events will be monitored from the time of randomization to week 36. Adverse events and serious adverse events may be collected through the daily diary, communicated on study surveys or to research staff directly, or communicated through the toll-free study hotline maintained by study staff between 5 AM to 8 PM ET.

### Risk of drug interactions

CYP3A-related drug interactions listed in Appendix 5.4 could lead to clinically significant adverse reactions, including severe, life threatening, or fatal events due to increased levels of concomitant medications, or increased levels of Paxlovid™. Medications that induce CYP3A may also reduce Paxlovid™ levels, leading to sub-therapeutic Paxlovid™ levels and the risk of development of viral resistance. This may occur if Paxlovid™ is initiated in patients receiving CYP3A metabolized medications, or if CYP3A metabolized medications are initiated among patients receiving Paxlovid™.

### Risk of pregnancy in participants receiving combined oral contraceptives

Ritonavir may reduce ethinyl estradiol concentrations and reduce the efficacy of combined oral contraceptive methods. This is unlikely to impair contraceptive efficacy, particularly considering the short duration of nirmatrelvir/ritonavir treatment, though it may increase the risk of irregular bleeding. We will advise participants of childbearing potential who are using combined hormonal contraception (oral, transdermal, or intravaginal) to use an additional barrier method of contraception during treatment with Paxlovid™, and until one menstrual cycle is completed after the last dose of Paxlovid™.

### Risks in pregnancy and during breastfeeding

There is no human data on the effect of Paxlovid™ on pregnancy or in breastfeeding. The summary of product characteristics states that breastfeeding should be discontinued during treatment with Paxlovid™ and for 14 days after the last dose of Paxlovid™. Therefore, to be eligible for randomization to Paxlovid™, participants are required to use a highly effective method of contraception for the duration of the treatment and 28 days of follow-up. Pregnant and breastfeeding participants will not be eligible.

### Antiretroviral resistance

In individuals with HIV-1 viraemia (either undiagnosed or diagnosed but not controlled), the low dose ritonavir in Paxlovid™ may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors. However, due to the short duration of ritonavir exposure, and the high genetic barrier to HIV-1 drug resistance with HIV protease inhibitors, this risk is thought to be low.

## Benefits

Paxlovid™ may reduce SARS-CoV-2 viral loads and severity of disease.

In the Phase II/III EPIC-HR trial among 2246 non-hospitalized high-risk adults with laboratory confirmed SARS-CoV-2 infection and with symptom onset ≤5 days, hospital admissions and deaths were 88% lower in the Paxlovid™ group compared to placebo.3 Day 5 nasopharyngeal viral load levels were approximately 9-fold lower in the Paxlovid™ group versus placebo.3

In an interim analysis of the Phase II/III EPIC-SR trial among non-hospitalized **standard-risk** adults with laboratory confirmed SARS-CoV-2 infection and with symptom onset ≤5 days, there was no difference in self-reported alleviation of all symptoms, but hospitalizations were 70% lower in the Paxlovid group versus placebo. Viral loads were also 10-fold lower in the Paxlovid group.4

## Data Safety and Monitoring Committee

The DSMC will receive results reported as Group A (arm 1), Group B (arm 2), etc. Should there be a significant difference in outcomes or adverse events, data will be unblinded to the DSMC chair and then shared with the Steering Committee to reach a unanimous decision with respect to next steps (i.e., continue or stop the trial). Stopping rules are pre-determined and included in the SAP related to efficacy, futility, and safety, and sub-protocol stopping rules are described in section 10.1.

The DSMC should be aware that the superiority, efficacy, inferiority, futility, or equivalence of different interventions with respect to the co-primary outcomes are possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary outcomes. The DSMC should take into account the public health, as well as clinical significance, of the analyses of this sub-protocol and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

## Sub-Protocol Specific Consent Concerns

As endorsed by the World Health Organization, in the absence of evidence of effectiveness of specific treatments for SARS-CoV-2, the use of a usual care control is both appropriate and ethical.

Health care providers will be directed not to refer an individual patient for enrollment if they believe that participation in this sub-protocol is not in the best interests of the patient.

# GOVERNANCE CONCERNS

## Funding of Sub-Protocol

Funding sources for CanTreatCOVID are specified in the Master Protocol and sub-protocol cover page. This sub-protocol did not receive any additional funding.

## Funding of Sub-Protocol Interventions

Paxlovid™ will be provided by the Public Health Agency of Canada.

## Sub-Protocol-Specific Declarations of Interest

All members of the CanTreatCOVID Canadian COVID-19 Out-Patient Therapeutics Committee, which makes decisions regarding the treatments to be evaluated in this trial are collected and updated on an annual basis.

# REFERENCES

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# APPENDICES

Appendix 1 - Information sheet and consent

Appendix 2 - Initial Contact Script and Screening Form

Appendix 3 - Participant Information Sheet

Appendix 4 - Wallet Contact Card

Appendix 5 - Product Monogram

* Appendix 5.1 - Summary of Product Characteristics for Paxlovid
* Appendix 5.2 - Drugs that Require Adjustment when Co-Administered
* Appendix 5.3 - What Prescribers and Pharmacists Need to Know
* Appendix 5.4 - Paxlovid Drug-Drug Interactions

Appendix 6 - Follow-up at Day 4