Study Title: Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings (CanTreatCOVID)
Control #: 269011
Study Sponsor: Unity Health Toronto
Application Type: CTA-A
Subject: Summary of Changes – CanTreatCOVID Protocol(s)

Please see below a description of the proposed changes to the previously approved protocol(s) for the CanTreatCOVID study

The following is a summary of key changes to the previous version of the Master Protocol (V1.4 -28Oct2022) including the rationale for each change. Formatting changes and minor administrative changes (typos, grammatical changes, minor clarifications in wordings) are not included in this table.

1 Changes to Master Protocol [V2.0 – 16Jun2023]

Original Text	Modified Text	Rationale
5.1 STUDY DESIGN		
Outcome (primary): All cause hospitalization or death at 28 days **Outcome (secondary):** Symptom severity; incidence of post-acute sequelae of SARS-CoV-2; quality of life; costs and cost/QALY	**Outcome (primary):** COVID-related emergency department (ED) visits or hospitalization or death at 28 days **Outcome (secondary):** Time to recovery; Symptom severity; incidence of post-acute sequelae of SARS-CoV-2; quality of life; costs and cost/QALY	The Steering Committee has elected to revise the primary outcome for our study. It will now focus on COVID-related emergency department visits, hospitalizations, or death within a 28-day period. This adjustment was prompted by a significant decrease in COVID-related hospitalizations and death rates. Furthermore, the measurement of 'time to recovery' has been reclassified as a secondary outcome. The rationale for this change lies in the nature of our study. Given that this is an open-label trial and 'time to recovery' is a patient-reported metric,
5.2 ENDPOINTS AND OUTCOMES		
Primary outcome: **Hospitalization or death at 28 days** from symptoms onset, captured during participant follow up and corroborated with administrative data. Based on a robust understanding of SARS-CoV-2 infection, it is likely that severe outcomes would occur within 28 days of symptom onset[32,33], and this outcome has been used in several key studies of SARS-CoV-2 treatments in community settings.[31,34–36] Time to recovery, using the questions: "Do you feel recovered today? (i.e. symptoms associated with illness are no longer a problem), used in PRINCIPLE AND	***Primary outcome:*** COVID-related **ED visits or Hospitalization or death at 28 days** from randomization, captured during participant follow up and corroborated with administrative data. Based on a robust understanding of SARS-CoV-2 infection, it is likely that severe outcomes would occur within 28 days of symptom onset[32,33], and this outcome has been used in several key studies of SARS-CoV-2 treatments in community settings.[31,34–36 31,3637] ***Secondary outcomes:***	

PANORAMIC[31,36]; and Flu Pro Plus questions about returning to usual health and activities, which can be used to determine time to recovery.[37] ***Secondary outcomes:*** • **Symptom severity**, using the questions: "*How well are you feeling today? Please rate how you are feeling now using a scale of 1 – 4, where 1 is no symptoms, and 4 is very severe symptoms"* and by rating symptoms, if present, as *"No problem, mild problem, moderate problem, or major problem."*	• **Time to recovery**, using the questions: "Do you feel recovered today? (i.e. symptoms associated with illness are no longer a problem), used in PRINCIPLE and PANORAMIC[31,36]; and Flu Pro Plus questions about returning to usual health and activities, which can be used to determine time to recovery.[37]	there is a possibility of bias. This shift has subsequently prompted us to adjust our sample size calculation in alignment with these changes (refer to page 28).
Section 5.3 Measures to minimize bias, randomization and blinding Patients will be stratified based on age (<65 years vs. older) and vaccination status (2+ doses vs. less),[41,42] and will use random sized permuted blocks.	**Section 5.3 Measures to minimize bias, randomization and blinding** Patients will be stratified based on age (<65 years vs. older) [41,42] and will use random sized permuted blocks.	Another significant update in our Master Protocol involves a change in our randomization strategy based on recommendation from the Methods and Statistics Committee. Initially, the plan was to stratify randomization based on age and vaccination status. However, we have been stratifying our randomization based on age. The reason behind this change is to simplify the study process. As we add more stratification layers, the study design and execution become increasingly complex. This doesn't mean we're disregarding the impact of vaccination status. Should it prove influential, we can always perform subgroup analysis or adjust our primary analysis accordingly.

Section 5.4 Drug Description; Pg. 12 At this point, the study pharmacist will conduct a detailed review of the participant's medications, a process which will include obtaining a medication list from the participants usual pharmacy, if available, to confirm their eligibility to participate in the study. Medications will be recorded in a medication log (Appendix 9). Based on their review of the participants medication list, the study pharmacist will make a recommendation to the provincial principal investigator (PI) regarding the participants eligibility. If in agreement, the provincial PI will sign off on the participants eligibility. Once eligibility has been confirmed, participants will be randomized to a study arm and if applicable, a notification will be sent to a provincial study pharmacy to ship the study therapeutic to the patient. This approach has been already successfully used in a variety of Canadian outpatient trials.	**Section 5.4 Drug Description; Pg. 14** At this point, the study pharmacist will conduct a detailed review of the participant's medications, a process which will include obtaining a medication list from the participants usual pharmacy via verbal communication, if available, to confirm their eligibility to participate in the study. Medications will be recorded in a medication log (Appendix 9). In circumstances where the pharmacist requires more data to establish eligibility, they will examine the participant's medical history, medication, and lab results. They will leverage relevant electronic clinical resources, such as the Connecting Ontario portal for Ontario residents, to acquire necessary information for eligibility determination. If there is still a need for more information, the study team may contact the participant's primary care provider to acquire additional details. Following a thorough review of the participant's medications, and once their eligibility for the study is confirmed, the study pharmacist will make a recommendation to the provincial principal investigator (PI) regarding the participants eligibility. If in agreement, the provincial PI will sign off on the participants eligibility. Once eligibility has been confirmed, participants will be randomized to a study arm and if applicable, a notification will be sent to a provincial study pharmacy to ship the study therapeutic to the patient. However, the study drug may also be securely stored within the designated space of the study team and, if necessary, be distributed to the participant by a member of the research team. This approach has been already successfully used in a variety of Canadian outpatient trials.	We have revised the section on eligibility assessment (refer to page 14, 22, and Table 1). Our aim here is to provide a more transparent, detailed explanation of how we determine participant eligibility.

Table 1: Participant schedule of events Pharmacist review of medications A study pharmacist reviews participants medication list, including obtaining a medication list from the participants usual pharmacy, if available, and confirms their eligibility to participate in the study. The study pharmacist will then provide their recommendation to the PI regarding the participants eligibility for the trial.	**Table 1: Participant schedule of events** Pharmacist's assessment of eligibility A study pharmacist will perform a comprehensive review of the participant's medication list, which may involve obtaining additional data from the participant's regular pharmacy via phone. If additional information (medical history, lab data, etc.) is needed to assess eligibility, pharmacist may also use relevant digital health resources, like the Connecting Ontario portal for Ontario-based participants, to gather the necessary information. In cases where further details are required, the study team might reach out to the participant's primary care provider. The study pharmacist will then provide their recommendation to the PI regarding the participants eligibility for the trial.	
Section 5.4 (Pg 13) Once eligibility has been confirmed, participants will be randomized to a study arm and if applicable, a notification will be sent to a provincial study pharmacy to ship the study therapeutic to the patient. This approach has been already successfully used in a variety of Canadian outpatient trials.	Section 5.4 (Pg 14) Once eligibility has been confirmed, participants will be randomized to a study arm and if applicable, a notification will be sent to a provincial study pharmacy to ship the study therapeutic to the patient. However, the study drug may also be securely stored within the designated space of the study team and, if necessary, be distributed to the participant by a member of the research team. This approach has been already successfully used in a variety of Canadian outpatient trials.	Another change in our protocol involves the handling of the study drug. We now allow for secure storage in a designated area by the study team, and if required, distribution to participants by a research team member. This enhances our flexibility while ensuring drug security. We're also closely monitoring storage temperature, vital for the drug's stability and efficacy, and for compliance with regulatory guidelines.
Table 1: Participant schedule of events Medication order placed If participant randomized to a treatment arm, the distribution pharmacy receives the order and ships the study medications.	***Table 1: Participant schedule of events*** Medication order placed If participant randomized to a treatment arm, either the distribution pharmacy receives the order and ships the study drugs or they may be stored and shipped by the study team from a secure location.	

Prospective engagement through primary care practice-based research networks: Study team members include national and international experts in using primary care electronic medical data (EMR) data for trial recruitment. We will engage practices and physicians, and with their permission, will use existing primary care EMR data from these networks to identify patients who meet our eligibility criteria. This would then allow prospective communication to facilitate enrollment should they become infected as described below. This has been effective in recruitment for other trials we have led.	***Prospective engagement through primary care practice-based research networks:*** Study team members include national and international experts in using primary care electronic medical data (EMR) data for trial recruitment. We will engage practices and physicians, and with their permission, will use existing primary care EMR data from these networks to identify patients who meet our eligibility criteria. This would then allow prospective communication to facilitate enrollment should they become infected as described below. This has been effective in recruitment for other trials we have led. In clinics where physicians act as their own Health Information Custodian (HIC), we will seek permission (Appendix 4.4) to request access their patient EMR data for use in the study. In clinics where a designated (HIC) is assigned for an entire clinic, we will request permission from the Central HIC for the clinic as a whole to participate (Appendix 4.4.1). After receiving permission from the Central HIC, a two week-opt out period will commence where each individual physician is emailed with the opportunity to leave the study.	For engaging prospective participants through primary care practice-based research networks, we have outlined two distinct approaches: a. Individual Health Information Custodians (HICs): In clinics where physicians serve as their own HIC, we will request permission (refer to Appendix 4.4.1) to access their patient Electronic Medical Record (EMR) data for inclusion in the study. b. Central HICs: In clinics where a single HIC is assigned to oversee the entire clinic, we will seek approval from the Central HIC to involve the clinic in the study.

Outreach through out-patient infectious disease clinics, EDs, and pharmacies: Our team includes specialists based in numerous out-patient infectious disease clinics, emergency departments and pharmacies. We will disseminate recruitment materials (e.g., posters) broadly, and also use internal communication channels to regularly remind providers about referring patients, in particular to providers for high-risk out-patient populations such as oncology and transplant patients.	***Outreach through various out-patient setting:*** Our team includes primary care and specialist clinicians based in numerous out-patient settings, including but not limited to community primary care clinics and health centers, urgent care clinics, specialty clinics, as well as infectious disease clinics, emergency departments, and pharmacies. We will disseminate recruitment materials (e.g., posters) broadly, and also use internal communication channels to regularly remind providers about referring patients, in particular to providers for high-risk out-patient populations such as oncology and transplant patients.	We have broadened our recruitment strategies (refer to page 20-21): We have also extended our reach to include outpatient settings, broadening our engagement with a wider participant pool.
Section 8 - #5) None	Section 8 - #5) None 5) Leveraging institutional and provincial databases for participant engagement: Our interdisciplinary team is affiliated with various institutions, all of which maintain databases of participants from past studies who have consented to future contact for research purposes. This valuable resource allows us to directly connect with potential participants who have previously demonstrated a willingness to contribute to scientific research. In addition to our internal databases, we will also collaborate with provincial organizations such as the Ministry of Health. Our goal is to gain access to their database of patients who have received the COVID-19 vaccination and have given their consent to be contacted for research purposes. Of course, this strategy is contingent on receiving the necessary regulatory approvals from these organizations. We will work closely with these entities to ensure all data sharing complies with the relevant privacy and ethical guidelines. Once we have gained the necessary approvals and access to the databases, our team will reach out to potentially eligible participants via mail, SMS, or email, depending on the contact preferences they have indicated. We will provide them with information about the study (as detailed in	Furthermore, we are leveraging institutional and provincial databases for participant recruitment. This includes reaching out to individuals from past studies who have previously consented to be contacted for future research opportunities. Our efforts will not only utilize internal databases, but also extend to collaborations with provincial entities, such as the Ministry of Health.

	Appendix 4.5.2) and how to reach out if they become symptomatic.	
Section 9 – Consent and Screening If the participant agrees to participate in the trial, a signed copy of the ICF will be requested to be returned via email. If it is not possible for the participant to return a signed ICF via email, verbal consent will be sought via telephone, in the presence of a witness. The witness will also provide an attestation (Appendix 2.1) that the potential participant has provided their informed consent. A copy of the ICF will also be mailed to their address.	Section 9 – Consent and Screening If the participant agrees to participate in the trial, we offer three methods to provide their consent: 1. E-Consent Module: Participants can use the E-Consent module on the Research Electronic Data Capture (REDCap) system, hosted on the secure servers at the Applied Health Research Centre (AHRC) at St. Michael's Hospital, to provide consent. Once participants opt for this method, they will receive an email containing a link to the ICF. Upon clicking the link, participants will be directed to a secure webpage where they can review the ICF at their own pace. After reviewing the ICF, if the participant agrees to participate in the study, they can provide their consent by signing the online form. All information provided through REDCap is encrypted and securely stored, ensuring the highest degree of confidentiality and data protection. 2. Email Consent: Participants can receive the ICF and return a signed copy of the ICF via email. 3. Verbal Consent: If options 1 and 2 are not feasible, verbal consent will be sought via telephone, in the presence of a witness. The witness will also provide an attestation that the potential participant has provided their informed consent. A copy of the ICF will also be mailed to their address.	We have clarified the consent process in the Master Protocol. We offer three flexible options for providing consent: through a secure E-Consent Module hosted by REDCap, via Email Consent with a signed copy of the ICF, or by Verbal Consent over the phone in the presence of a witness (refer to page 22).
Section 8 – Recruitment # 2) – Pg 19	Section 8 – Recruitment # 2) – Pg 20	We have introduced a $40 service fee as a token of appreciation for healthcare

Family physicians and nurse practitioners will be invited to take part in the study. If family physicians and nurse practitioners agree, we will **search primary care EMR data for patients** that are 50+ years old or 18-49 years old with 1+ chronic medical condition and/or who are immunosuppressed (see inclusion criteria in Section 6.1).	Family physicians and nurse practitioners will be invited to take part in the study. If family physicians and nurse practitioners agree, we will **search primary care EMR data for patients** that are 50+ years old or 18-49 years old with 1+ chronic medical condition and/or who are immunosuppressed (see inclusion criteria in Section 6.1). In cases where we are not granted direct access to the EMR data, we acknowledge the administrative time commitment this process entails. As such, we are prepared to reimburse any staff time involved in this data access at the rate of $40/hr. This is in recognition of the valuable role the administrative staff play in this research and to minimize any potential disruption to their routine tasks.	providers who refer qualifying patients to the CanTreatCOVID study. Please see Appendix 1 at the end of this document for a more detailed explanation behind this decision
Section 8 – Recruitment # 3) – Pg 19 We will disseminate recruitment materials (e.g., posters) broadly, and also use internal communication channels to regularly remind providers about referring patients, in particular to providers for high-risk out-patient populations such as oncology and transplant patients.	Section 8 – Recruitment # 3) – Pg 21 We will disseminate recruitment materials (e.g., posters) broadly, and also use internal communication channels to regularly remind providers about referring patients, in particular to providers for high-risk out-patient populations such as oncology and transplant patients. Additionally, pharmacists and primary care providers who refer participants that are subsequently enrolled into the study will be offered a $40.00 gift card, as a token of gratitude, acknowledging the significant time and effort that goes into these referrals. This approach, as corroborated by its successful implementation in similar studies such as PANORAMIC[51], highlights the critical role of healthcare professionals in enhancing the success of research studies.	

2 Changes to Paxlovid x5 Sub-Protocol [V2.0 – 16Jun2023]

The following is a summary of key changes to the previous version of the Paxlovid x5 days Sub-Protocol (V1.1 -28Oct2022) including the rationale for each change. Formatting changes and minor administrative changes (typos, grammatical changes, minor clarifications in wordings) are not included in this table.

Updated Text	Rationale
Section 6.2.2 Sub-Protocol Exclusion Criteria • Is a recipient of a solid organ transplant and taking immunosuppressant medications	We have updated the Paxlovid sub-protocol's specific exclusion criteria based on recent adverse drug reaction reports to Health Canada. We will now exclude individuals who are solid organ transplant recipients currently taking immunosuppressant medications. We have also added a Standard of Care Information Sheet for participants randomized to the control group, that offers guidance on how to best self-manage symptoms at home.

Appendix 1- Providing compensation to health care providers for referring individuals to CanTreatCOVID

We are writing to propose an essential amendment to our current remuneration structure for healthcare providers involved in the CanTreatCOVID adaptive platform trial. As you are aware, the provincial government in Ontario has authorized the broad distribution of Paxlovid™, with community pharmacists assessing patients, prescribing, and dispensing the drug, for which they receive a total service fee of $32.25.

Community Pharmacist Activity	Service Fee
Assessing a patient with SARS-CoV-2 infection with the purview of initiating outpatient treatment with Paxlovid™	$19
Dispensing Paxlovid™	$13.25
Total	$32.25

The widespread availability of Paxlovid™ might inadvertently lead patients to perceive Paxlovid™ as the sole approved outpatient treatment for SARS-CoV-2, while in reality, the robustness of the evidence supporting its use remains uncertain. Moreover, the complex interaction between vaccination and previous infections in Ontario further complicates the situation. Misinformation through media outlets exacerbates these misconceptions. Given this, we believe that healthcare providers play a critical role in informing and educating patients about the scope and potential limitations of Paxlovid™.

CanTreatCOVID provides an alternative for healthcare providers, particularly community pharmacists, who might feel compelled to prescribe Paxlovid™ due to government announcements. A service fee for healthcare providers would compensate for detailed discussions with patients about risks, benefits, and the importance of supporting Canadian government funded research. Healthcare providers, including community pharmacists should not be worse off financially for taking the time to discuss the importance of supporting Canadian-based research.

We are proposing a $40 service fee to be compensated to health care providers who refer individuals that become participants in CanTreatCOVID. The referral process is not a simple hand-off; it involves the provider's time, effort, and professional expertise to identify suitable individuals who may be a good fit for the CanTreatCOVID study. The referral fee is, in essence, a recognition of the healthcare provider's critical role in the study. It acknowledges the resources they commit to ensure the study is a success. While the current dispensing fee for a community pharmacist is $32.5, the referral process can be more complex and time-consuming than dispensing medication. It's important to note that while this fee serves as an incentive for healthcare providers to participate, it is very unlikely to motivate physicians to refer patients solely for financial gain. Physicians uphold a code of ethics that prioritizes patient welfare above all else. It is, therefore, reasonable to assume that their referrals will be based on an individual's eligibility and potential benefit from the study, rather than the service fee. Furthermore, this amount is comparable to referral fees in other similar studies such as PANORAMIC. It is intended as fair compensation for their contribution, not to unduly influence their medical judgement or decision-making.

Furthermore, to ensure transparency and accountability in this remuneration process, we plan to document the following information:

1. Name of the referring health care provider
2. Services provided
3. Total fees for services
4. Payment schedule (default – monthly via email money transfer)
5. Duration of (term) the agreement (default – 6 months)

Your careful consideration of this proposal is vital to us. We are readily available to provide further information or clarifications to address any questions or concerns you may have regarding this proposed amendment.

Sincerely,

Andrew D. Pinto, MD CCFP FRCPC MSc
Principal Investigator