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Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings (CanTreatCOVID): protocol for a randomised controlled adaptive platform trial of treatments for acute SARS-CoV-2 infection in community settings

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ABSTRACT

Introduction SARS-CoV-2 is now endemic and expected to remain a health threat, with new variants continuing to emerge and the potential for vaccines to become less effective. While effective vaccines and natural immunity have significantly reduced hospitalisations and the need for critical care, outpatient treatment options remain limited, and real-world evidence on their clinical and cost-effectiveness is lacking. In this paper, we present the design of the Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings (CanTreatCOVID). By evaluating multiple treatment options in a pragmatic adaptive platform trial, this study will generate high-quality, generalisable evidence to inform clinical guidelines and healthcare decision-making.

Methods and analysis CanTreatCOVID is an open-label, individually randomised, multicentre, national adaptive platform trial designed to evaluate the clinical and cost-

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings (CanTreatCOVID) community-focused design allows enrolment without in-person visits.
⇒ The adaptive platform trial structure provides flexibility to add promising therapies and remove ineffective ones, which is critical in a rapidly changing pandemic environment.
⇒ CanTreatCOVID gathers real-world data on outpatient COVID-19 care.
⇒ The open-label design avoids logistical challenges associated with placebo controls in large-scale trials, though it may introduce bias related to subjective outcomes.
⇒ The reliance on self-reported adherence to study medications could lead to variability.

effectiveness of therapeutics for non-hospitalised SARS-CoV-2 patients across Canada. Eligible participants must present with symptomatic SARS-CoV-2 infection, confirmed by PCR or rapid antigen testing (RAT), within 5 days of symptom onset. The trial targets two groups that are expected to be at higher risk of more severe disease: (1) individuals aged 50 years and older and (2) those aged 18–49 years with one or more comorbidities. CanTreatCOVID uses numerous approaches to recruit participants to the study, including a multifaceted public communication strategy and outreach through primary care, outpatient clinics and emergency departments. Participants are randomised to receive either usual care, including supportive and symptom-based management, or an investigational therapeutic selected by the Canadian COVID-19 Outpatient Therapeutics Committee. The first therapeutic arm evaluates nirmatrelvir/ritonavir (Paxlovid), administered two times per day for 5 days. The second therapeutic arm investigates a combination antioxidant therapy (selenium 300 µg, zinc 40 mg, lycopene 45 mg and vitamin C 1.5 g), administered for 10 days. The primary outcome is all-cause hospitalisation or death within 28 days of randomisation.

Ethics and dissemination The CanTreatCOVID master protocol and subprotocols have been approved by Health Canada and local research ethics boards in the participating provinces across Canada. The results of the study will be disseminated to policy-makers, presented at conferences and published in peer-reviewed journals to ensure that findings are accessible to the broader scientific and medical communities. This study was approved by the Unity Health Toronto Research Ethics Board (#22-179) and Clinical Trials Ontario (Project ID 4133).

Trial registration number NCT05614349

INTRODUCTION

While the acute phase of the COVID-19 pandemic has ended, SARS-CoV-2 continues to circulate globally, with over seven million deaths annually attributed to the virus.[1] Vaccines and natural immunity have now substantially reduced hospitalisations and the need for critical care; however, SARS-CoV-2 is endemic and remains a threat to health.[2] New variants of SARS-CoV-2 continue to emerge with the risk that vaccine effectiveness and acquired immunity may decline.[3] Therefore, there will remain an ongoing need for therapeutics that are effective, safe, affordable and suitable for use in community settings.[4]

While several agents have been evaluated for mild to moderate infections in outpatient settings, current guidelines from Canada,[5 6] the USA[7] and international bodies[8 9] primarily have recommended nirmatrelvir/ritonavir (Paxlovid).[9] Other therapeutics, such as fluvoxamine or metformin,[10] have moderate (and mixed) supporting evidence,[11] and inhaled therapeutics have weak evidence to support their use but may be considered.[9 12] Nirmatrelvir/ritonavir is a promising treatment; however, the key randomised controlled trial (RCT) that assessed its efficacy, the Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) study, was conducted in unvaccinated patients before the emergence of more recent variants of SARS-CoV-2.[13] Data from the EPIC-SR study showed no significant difference in time to recovery (12 days for nirmatrelvir/ritonavir vs 13 days for placebo) or hospitalisation/death rates (0.8% vs 1.6%) in vaccinated or unvaccinated non-hospitalised patients with SARS-CoV-2.[14] A recent systematic review and network meta-analysis of antivirals for non-severe SARS-CoV-2 infection highlighted the need for further studies to evaluate nirmatrelvir/ritonavir and other therapeutics in vaccinated populations and against newer variants of SARS-CoV-2.[15] In addition, current antiviral therapies for SARS-CoV-2 infection have limitations, including potential adverse effects ranging from mild symptoms to severe reactions, and eligibility restrictions that limit their use in certain populations. Our systematic review and meta-analysis demonstrated that antioxidant therapy was associated with shorter hospital stays (pooled mean difference (MD): −1.39 days; 95% CI: −2.66 to −0.12; I^2=81%; 9 studies, n=887) and faster symptom resolution compared with controls (pooled MD: −2.43 days; 95% CI: −3.01 to −1.84; I^2=17%; 4 studies, n=412) F.[16] Our findings suggest that antioxidant treatments hold promise, but further evidence from RCTs is needed.

Adaptive platform trials (APTs) are an ideal design to assess multiple therapies simultaneously, with the flexibility to introduce new treatments as they emerge. [17] APTs have played a crucial role in identifying effective treatments for hospitalised COVID-19 patients.[18] RECOVERY identified dexamethasone as significantly reducing mortality in patients requiring oxygen[19] and tocilizumab in severe disease.[20] REMAP-CAP highlighted the efficacy of intravenous steroids in intensive care unit (ICU) patients.[21] Collaborative efforts across APTs, such as ATTACC, REMAP-CAP and ACTIV-IV, demonstrated that therapeutic-dose heparin reduces progression to ICU-level care and mortality in non-critically ill hospitalised patients.[22 23] In the outpatient setting, the PRINCIPLE trial in the UK demonstrated the efficacy of inhaled budesonide.[24]

Given the evolving nature of the virus and the limitations of current therapeutic options, ongoing evaluation of treatments in community settings remains essential to ensure optimal care for patients. The Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings (CanTreatCOVID) is a multiarm APT that aims to evaluate the clinical and cost-effectiveness of multiple therapeutic interventions compared with usual care for non-hospitalised patients with SARS-CoV-2 at high risk of severe complications. The trial uses a flexible design that allows for the assessment of various treatments simultaneously, ensuring that new and promising therapies can be quickly tested and incorporated to improve patient outcomes in community-based settings.

METHODS AND ANALYSIS

Trial design

CanTreatCOVID is an open-label, individually randomised, APT conducted across Canada. The trial currently involves six provinces: Ontario, Québec, Alberta, Manitoba, British Columbia and Newfoundland and Labrador. Each province has a dedicated research hub with a team of research staff, and recruitment occurs through ‘spokes’ in primary

care centres and other community settings, as well as other recruitment methods. The first provincial hub (Ontario) was activated on 16 January 2023, and the remaining five provinces (Newfoundland and Labrador, Quebec, Manitoba, Alberta and British Columbia) were activated by December 2023. Recruitment will continue until 31 March 2026 (funding end date). The primary objective is to evaluate the clinical and cost-effectiveness of multiple therapeutics for non-hospitalised SARS-CoV-2 patients at high risk of severe complications. The trial also aims to address practical challenges related to the implementation of these therapies in diverse healthcare settings. By using an APT design, CanTreatCOVID allows for the continuous evaluation and comparison of treatments, incorporating new interventions as evidence emerges.

RECRUITMENT STRATEGY

We recruit participants through several channels to ensure broad outreach across Canada. Public communications and community partnerships have played a key role, with recruitment materials available in English and French in each province. The trial website (www.CanTreatCOVID.org) provides clear information and supports public engagement, transparency and knowledge sharing, based on insights from previous Canadian trials and the Platform Adaptive trial of NOvel antiviRals for eArly treatment of COVID-19 in the Community (PANORAMIC) study in the UK.[25] Additionally, a toll-free hotline, available from 08:00 to 18:00 ET, Monday to Friday, provides direct support for potential participants, with trained research assistants available to intake participants and answer questions. We have also developed recruitment materials for public advertising (eg, transit, print/online media, traditional media) and digital channels (eg, Google ads, Facebook, Twitter, Instagram).

Primary care practice-based research networks are another source of recruitment. We have engaged primary care practices and physicians, and with their permission, we use existing electronic medical record data to identify patients who meet key eligibility criteria (age and underlying health condition). This has enabled proactive communication with potentially eligible participants should they contract SARS-CoV-2. In outpatient settings, including primary care clinics, urgent care centres, specialty clinics, emergency departments and pharmacies, we disseminate recruitment materials and encourage referrals, particularly for high-risk populations.

We have leveraged institutional and provincial databases to maximise outreach. Our interdisciplinary team is affiliated with institutions that maintain databases of participants from past studies who have consented to be contacted for future research. This has allowed us to connect directly with individuals who have already expressed a willingness to contribute to scientific studies. Additionally, we collaborate with provincial organisations, such as provincial Ministries of Health, to access databases of individuals who have received the COVID-19 vaccine and consented to be contacted for research purposes.

ELIGIBILITY CRITERIA

Eligible participants include individuals aged 50 years and older, or those aged 18–49 with pre-existing comorbidities that increase their risk of severe illness. Participants must also have a positive SARS-CoV-2 test (PCR or RAT) with proof of a positive test provided via a picture of the result. Patients must be enrolled within 5 days of onset of symptoms associated with SARS-CoV-2 infection[5 9] because some therapeutics must be taken early in an infection to be effective. Eligible symptoms include at least one of the following: fever or chills, cough, shortness of breath, decreased or loss of taste or smell, runny nose or nasal congestion, headache, fatigue, sore throat, muscle aches or joint pain, or gastrointestinal symptoms.

Exclusion criteria include participants who have been hospitalised or remained in an emergency department for more than 24 hours, prior enrolment in CanTreatCOVID, current participation in another SARS-CoV-2 therapeutic trial, use of or contraindications to a trial therapeutic or inability of the participant or caregiver to provide informed consent. Patients with contraindications to specific trial drugs are excluded from that particular intervention arm but remain eligible for randomisation into other treatment arms. To participate, patients must be eligible for both the usual care arm and at least one intervention arm of the trial.

SCREENING

Regardless of how the potential participant learnt about the trial, potential participants must speak to a research assistant via telephone call to undergo initial screening. The initial screening process includes reviewing the eligibility criteria and conducting a preliminary assessment of the compatibility of the potential participant's medications based on a list provided by the participant. The initial screen also serves the potential participant by clarifying questions about trial involvement. If English is not the first language, we rely on internal staff if they are able to speak the participant's language, or a certified interpreter within our organisation. In some cases, family members are willing to assist with translation. Study questionnaires are currently available in both English and French. However, we will include additional languages if needed, depending on the number of participants requiring translation support. If a participant speaks a language for which we do not have translation services readily available, we assess feasibility on a case-by-case basis to ensure inclusivity. To mitigate selection bias, we have implemented broad eligibility criteria and a decentralised recruitment strategy. Moreover, participants are not required to complete forms independently. Study staff assist with enrolment and follow-ups via phone if

needed, which reduces barriers for those with limited digital literacy.

If eligible, the research assistant proceeds to engage the potential participant in the process of obtaining written informed consent. The participant also provides consent to having a team member contact their usual community pharmacy and primary care provider, as needed, to clarify any discrepancies in their health status, including their medications. Once these consents are obtained, the study pharmacist conducts a detailed review of the participant's medications using a medication list from the patient's usual pharmacy or provincial repository. If additional information is required to determine eligibility, this is obtained using electronic clinical resources and, if further necessary, the study team contacts the participant's primary care provider for further clarification. Once the detailed medication and eligibility review has been satisfactorily completed, the study pharmacist makes a recommendation (which may include strategies to mitigate potential drug interactions) to the provincial principal investigator (PI) who approves and signs off on the participant's eligibility.

Randomisation and allocation

Following confirmation of eligibility, participants are immediately randomised through an interactive, secure, web-based system maintained by the data management group. Randomisation is conducted using fixed, equal allocation ratios corresponding to the number of active treatment arms for which the participant is eligible. If a participant is eligible for two arms (eg, usual care and one therapeutic), they will be randomised in a 1:1 ratio between these two options. If a participant qualifies for more than two arms, the randomisation ratio will adjust accordingly (eg, 1:1:1 if there are three eligible arms). Initially, participants were randomised in a 1:1 ratio between usual care and the first therapeutic arm (nirmatrelvir/ritonavir). As additional therapeutics are introduced (antioxidant therapy as the second arm), the randomisation ratio adjusts accordingly (eg, 1:1:1). To ensure balance and minimise bias, randomisation is stratified by age group (<65 years vs ≥65 years) and employs permuted blocks of varying sizes.

BLINDING

In this open-label APT, both participants and recruiting clinicians are aware of the assigned intervention. Therefore, no unblinding or code breaking is required. However, trial investigators who are not involved in participant recruitment, as well as the lead statisticians, remain blinded to treatment allocations. Unblinded statisticians, along with independent members of the DSMC, have access to unblinded data. These individuals are responsible for monitoring interim outcomes and will only disclose unblinded information once a decision is reached to stop recruitment for any specific intervention arm.

INTERVENTION

As the trial progresses, the selection of therapeutics to be evaluated for SARS-CoV-2 treatment in outpatient settings is guided by the Canadian COVID-19 Out-Patient Therapeutics Committee. This committee continuously reviews the latest evidence and provides recommendations to the Steering Committee. The decision to include a new therapy is based on several key criteria:

- Strong scientific and biological rationale, supported by compelling evidence or successful independent studies (eg, phase I/II trials) demonstrating efficacy for treating SARS-CoV-2 in outpatient settings.
- Sufficient availability of the therapeutic to ensure consistent supply throughout the trial.
- Scalability of the therapeutic, allowing widespread use if found to be effective.
- The addition of a new arm must not interfere with the completion of ongoing research arms.
- The therapeutic must remain clinically relevant by the time the trial arm is completed.

The adaptive platform design and master protocol structure enable the seamless incorporation of new interventions, ensuring flexibility and responsiveness to emerging evidence. Detailed information for each therapeutic, including dosage, known side effects, adverse reactions, duration of treatment and existing data, is provided to participants along with a patient handout in lay language to ensure clear understanding.

The first intervention arm is nirmatrelvir/ritonavir (Paxlovid), consisting of 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. On randomisation to this arm, participants are urgently provided with a participant pack containing nirmatrelvir/ritonavir, along with dosing instructions and safety information. Participants are advised to complete the full 5-day treatment course, which should be initiated as soon as possible after a diagnosis of SARS-CoV-2 has been made, and ideally within 5 days of symptom onset. Adherence to the study therapeutic is monitored through participant self-reporting.

Participants are eligible for the nirmatrelvir/ritonavir arm if they meet all platform-level inclusion criteria and none of the platform-level exclusion criteria. Additional nirmatrelvir/ritonavir specific exclusion criteria include: a history of clinically significant hypersensitivity to nirmatrelvir/ritonavir or its excipients; known hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption; severe liver impairment (characterised by severe ascites, encephalopathy, jaundice or prolonged INR (patients with liver disease without any of these features are eligible); being a solid organ transplant recipient on immunosuppressants; having moderate or severe renal disease (defined as chronic kidney disease (CKD) stage 3, 4 or 5 or current acute kidney injury or most recent estimated glomerular filtration rate (eGFR) in the past 6 months <60 mL/min); currently taking nirmatrelvir/ritonavir; clinical

requirement to continue taking a drug contraindicated or not recommended for administration with nirmatrelvir/ritonavir; known or suspected pregnancy; breastfeeding or being of childbearing potential without using highly effective contraception.

The second intervention arm is antioxidant therapy (selenium 300 µg, zinc 40 mg, lycopene 45 mg, and vitamin C 1.5 g) administered as three capsules taken once per day for 10 days. Participants are advised to complete the full 10-day treatment course. On randomisation to this arm, participants are promptly provided with a participant pack containing the antioxidant therapy, along with dosing instructions and safety information.

Eligibility for the antioxidant therapy arm also requires meeting all platform-level inclusion criteria and none of the platform-level exclusion criteria. Additional exclusion criteria specific to antioxidant therapy include: known or suspected pregnancy, breastfeeding, childbearing potential without highly effective contraception, allergy or intolerance to any of the ingredients (selenium, zinc, lycopene, vitamin C, ascorbyl palmitate, hypromellose, microcrystalline cellulose or sodium stearyl fumarate), use of warfarin as a preventive measure, advanced CKD (stage 3–5, eGFR<60 mL/min), liver disease awaiting transplantation, a history of calcium oxalate kidney stones, head and neck cancer within the past 5 years, history of non-melanoma skin cancer, current use of supplements with selenium (≥300 µg/day), zinc (≥40 mg/day), lycopene (≥45 mg/day), and vitamin C (≥1500 mg/day), and consumption of omega-3 fatty acids at baseline without willingness to stop during the intervention period.

Primary and secondary outcomes

Our primary outcome is all-cause hospitalisation or death within 28 days from randomisation. This is captured through daily diaries (completed from day 1 to day 14) as well as during participant follow-up at 21 and 28 days. It will also be cross-checked 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,[26] and this outcome has been used in several key studies of SARS-CoV-2 treatments in community settings.[24 27 28] This time frame also corresponds to when hospitalisations due to adverse drug events from therapy (or drug interactions) would be expected to occur.

The secondary outcomes include: (1) time to recovery, defined as the first instance that a participant reports feeling fully recovered. This will be captured through daily diaries (days 1–14) using the questions: “Do you feel recovered today? That is, symptoms associated with illness are no longer a problem”, which has been used in PRINCIPLE[24] and PANORAMIC,[29] and the Flu Pro Plus relevant questions about returning to usual health and activities[30]; (2) time to sustained resolution, defined as the number of days from randomisation to the first of 3 consecutive days of resolution or alleviation (without subsequent relapse by day 28); (3) time to progression of signs or symptoms, defined as the number of days from randomisation to the first of 2 consecutive days of worsening); (4) symptom severity, will be captured through daily diaries 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’; (5) postacute sequelae of SARS-CoV-2, collected at 90 days and 36 weeks, using the WHO clinical case definition[29 31] and the validated Symptom Burden Questionnaire for Long COVID[26]; (6) Quality of life, using the European Quality of Life 5-dimension, 5-level questionnaire (EQ-5D-5L), collected at baseline, 21 days, 28 days, 90 days and 36 weeks and analysed using Canadian reference values; health service use, treatment costs, cost/QALY, analysed using standard trial-based economic evaluation methods[32] and (7) early discontinuation and severe adverse events (table 1).

Data collection and participants’ follow-up procedures

At baseline, we collect data on sociodemographic including date of birth, sex assigned at birth, gender identity, education level, household income, income source, ethnicity, rurality. We also collect healthcare numbers, all phone numbers, an emergency contact, an email address and seek permission to use text messaging, as well as alternative contacts and caregivers (for obtaining follow-up data should the need arise).

All participants receive a call from the trial team 1 day after randomisation to confirm the receipt of study materials and medication (if randomised to a study drug) and to address any questions. For participants randomised to nirmatrelvir/ritonavir, an additional safety call is made on day 4 to monitor for any early side effects and to ensure that no new medications have been taken that may be contraindicated with nirmatrelvir/ritonavir. Similarly, participants randomised to the antioxidant therapy arm receive an additional safety call on day 6 to check for potential adverse drug reactions or any contraindicated medications. These safety calls ensure that participants remain safe while adhering to the study protocol.

Participants in all arms will complete an online daily diary each day for 14 days (online supplemental file 1), a validated approach from similar trials.[24 25 33] Participants self-report symptoms and severity, as well as contact with health services (eg, hospital admissions, ED visits, visits to specialists and primary care), which will be corroborated with administrative data when the data become available. Moreover, 10% of participants are randomised to complete additional Flu Pro Plus questions in the daily diary, which collect detailed information on severity of symptoms (online supplemental file 2). Our primary study outcome is reported by the patient or their alternative contact and does not rely on administrative data for publication and timely dissemination of results.

Participants are prompted to complete online follow-up surveys using REDCap Cloud electronically through

Table 1 Study outcomes in CanTreatCOVID Trial

Primary outcome measures	Data source	Time point(s)
Emergency department visits/hospital admission/death	Patient or study partner self-report and medical record review	Within 28 days of enrolment
Secondary outcome measures		
Time to recovery	Participant or study partner report using online diary or telephone call	Daily online diary (days 1–14) or telephone at days 21 and 28
Symptom severity	Participant or study partner report using online diary or telephone call	Daily online diary (days 1–14) or telephone at days 21 and 28
Health service use	Participant or study partner report and medical record review	Within 28 days
Postacute sequelae of SARS-CoV-2	Participant or study partner report using online survey or telephone call (WHO clinical case definition[29 41] and the recently validated Symptom Burden Questionnaire for Long COVID[26])	Online surveys and telephone calls at day 90 and week 36
Quality of life	EQ-5D-5L	Telephone calls at days 21, 28, 90 and week 36
Early discontinuation		
Severe adverse events	Participant or study partner report	

CanTreatCOVID, Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings; E-5D-5L, European Quality of Life 5-dimension, 5-level questionnaire.

automated emails sent through the survey software. Research staff call participants with no internet access, as well as those who prefer to complete surveys over the phone. Participants who have not completed their diary for at least two consecutive days before day 7 or again before day 14 will be contacted by staff by email, phone or text. Staff make 3 attempts over 3 days before considering it missing data.

Research staff contact patients at 21 days and 28 days, focusing on the primary outcome, and at 90 days and 36 weeks from randomisation, with a focus on post-acute sequelae of SARS-CoV-2. The EQ-5D-5L[34] will be administered at baseline, 21 days, 28 days, 90 days and 36 weeks. Adverse events will be assessed throughout the study period; data on serious adverse events considered by the investigator to be related to the assigned regimen will be collected through the end of study participation.

Statistical analysis

Primary analysis population

The primary intention-to-treat (ITT) analysis population is defined as all randomised participants according to the group they were randomly allocated to, regardless of deviation from protocol. The ITT population is typically the primary population for the analysis of efficacy parameters. A subset of efficacy parameters will be evaluated for the per protocol (PP) population, defined as randomised patients who adhered to more than 80% of the assigned therapy. For patients who have an early outcome, 80% applies to the expected number of doses by that time and not the total number. For the usual care group, PP will be defined as not receiving an investigational product for the duration corresponding to the PP duration needed for the investigational product. The Safety Population, defined as randomised patients who received at least 1 dose of study drug, is the primary population for the analysis of safety endpoints, compared with the usual care group.

Primary and secondary outcome(s) analysis

For our primary outcome analysis, we use a Bayesian logistic regression model which includes the randomised treatment group, age and vaccination status as covariates. We will calculate and report model-based estimates of the difference in hospitalisation/death rates between each treatment arm and the usual care, along with 95% credible intervals. If data for the primary outcome are missing for more than 5% of the study population, we will conduct a sensitivity analysis in which missing data will be imputed using multiple imputation. For the secondary endpoints, we will use a Bayesian piecewise exponential model and Bayesian logistic regression, depending on the endpoint data type. Covariates will include randomised group, age and vaccination status. For Bayesian logistic regression, we will report ORs for each pairwise treatment arm comparison with the usual care group, along with corresponding credible intervals. For continuous outcomes, we will report the mean and SD for each treatment arm, along with the adjusted difference in means and its 95% credible interval for each pairwise comparison with the usual care group.

The interim analysis plan will be determined by using a series of clinical trial simulations to ensure that satisfactory operating characteristics in terms of controlling the

type I error rate in cases where all treatment arms are the same, while attempting to maximise the statistical power in cases where one or more treatment arms yield meaningful treatment benefits. Before any unblinded analyses are performed by an independent statistician, the simulations will be performed by the Methods and Statistical Analysis Committee (SAC) who will be blinded to the knowledge of group assignments.

The interim analysis will determine (a) the superiority of the treatment arm in comparison with the Standard of Care (SOC); (b) switching the SOC arm to another treatment arm with significant superiority; (c) futility and suspension of a treatment arm and (d) adding additional treatment arms.

Interim futility determines whether a treatment arm should be suspended, ie, halted from receiving new patients for the next cohort. We compute the model-based hospitalisation/death rate for each treatment arm, denoted as p_j, with the stratification covariates being set to the respective populational averages. Using Markov chain Monte Carlo sampling, we compute the Bayesian posterior probability that hospitalisation/death rate of treatment arm j is smaller than that of the SOC by at least a margin of 1%, $\Pr(p_{SOC} - p_j > 0.01)$, and if it is smaller than a precalibrated stopping boundary, for example, 0.001, the interim futility rule for hospitalisation/death endpoint is satisfied. If interim futility rules are satisfied for a treatment, then it will be suspended over the next cohort. If the two interim futility rules are no longer satisfied in the next interim analysis in the light of new data in other treatment arms, the suspension might be cancelled.

Subgroup analyses will be performed on several populations, including age, sex, gender, body mass index, income, race and ethnicity, rurality, medical conditions (multimorbidity and immunocompromised), number of vaccine doses received (< 2vs ≥2) and place of recruitment (emergency departments vs other settings). We will also examine the moderating effects of concomitant medications, such as corticosteroids. For each subgroup, we will calculate model-based estimates of the difference in rates of emergency visits, death and hospitalisation between the treatment arms and the usual care, accompanied by 95% Bayesian credible intervals computed using the primary analysis model.

Sample size

Given the open, 'perpetual' trial structure, the trial does not have a finite ending based on sample size. We have determined our estimated sample size per arm based on Bayesian logistic regression to estimate the adjusted OR for hospitalisation or death at 28 days for a pairwise comparison of treatment arm (initially nirmatrelvir/ritonavir) versus comparator (initially usual care). Assuming a conservative 5% comparator event rate of hospitalisation or death,[35 36] we deemed that a reduction from 5% to 3.35% would be clinically meaningful, based on the current published evidence.[13 24 27] We estimate that approximately 2413 participants per arm will be required to provide 90% power for detecting a 25% reduction in the relative risk of hospitalisation/death.

Ethics and dissemination

The CanTreatCOVID master protocol and subprotocols have been approved by Health Canada and the following research ethics boards in the participating provinces across Canada: Unity Health Toronto Research Ethics Board—St. Michael's Hospital (Ontario); McGill University Health Centre Research Ethics Board (Quebec); The Conjoint Health Research Ethics Board, University of Calgary (Alberta); The University of Manitoba Biomedical Research Board—Research Ethics Bannatyne (Manitoba); University British Columbia Children's & Women's Research Ethics Board (British Columbia); Newfoundland and Labrador Health Research Ethics Board (Newfoundland and Labrador). All participants provide informed consent, which can be completed online, via email or verbally via telephone. An independent Data Monitoring and Safety Committee oversees safety data, reviews interim analyses provided by the SAC and communicates recommendations to the Trial Steering Committee (TSC). The TSC provides guidance and oversight to the Trial Management Group. The results of the study will be disseminated to policymakers, presented at conferences and published in peer-reviewed journals to ensure that findings are accessible to the broader scientific and medical communities.

Patient and public involvement

Patients and members of the public have contributed to the development of the CanTreatCOVID study by providing valuable input on recruitment strategies and patient-facing materials, such as consent forms and study posters, to ensure clarity and accessibility. The trial's community engagement specialists hold monthly meetings with patient partners to gather feedback on implementation and identify potential barriers to participation. Their perspectives have been essential in refining communication strategies and promoting inclusivity across diverse populations.

While patient partners and the public are not directly involved in data analysis, they will play a key role in reviewing the findings and contributing to the development of lay summaries and outreach initiatives to foster broader community engagement. Patient and public involvement will continue to guide subsequent phases of this trial, with a particular focus on expanding their participation in planning dissemination and knowledge translation activities.

DISCUSSION

CanTreatCOVID is an open-label, individually randomised, APT designed to evaluate therapeutics for SARS-CoV-2 infection in high-risk outpatient populations. Eligible participants include those aged 50 years or older, or those aged 18–49 with at least one chronic

medical condition or immunosuppression. Patients must be enrolled within 5 days of symptom onset. The trial evaluates therapeutics against usual care and may compare treatments directly as new interventions are added. The Canadian COVID-19 Out-Patient Therapeutics Committee oversees the selection of investigational therapies based on emerging evidence, ensuring that relevant and promising treatments are assessed in real-time.

CanTreatCOVID's adaptive design allows modifications based on interim analyses of primary outcome data, enabling the removal of interventions deemed futile or successful. This structure also facilitates the integration of findings from international trials and the addition of new treatment arms as they become available. This flexible approach ensures the trial remains responsive to the evolving nature of the COVID-19 pandemic and the therapeutic landscape, while contributing to the broader knowledge base on outpatient management of SARS-CoV-2.

Comparison with other studies

Several other APTs share similar objectives and methodologies. The multicentre, adaptive, randomised platform trial to evaluate the effect of repurposed medicines in outpatients with early COVID-19 and high risk for complications (TOGETHER) trial [37] is multicentre APT assesses repurposed medicines for treating high-risk COVID-19 outpatients in early stages of infection. The study was conducted in Brazil and recruited over 10 000 participants. The trial has concluded investigations on six medications including hydroxychloroquine, lopinavir/ritonavir, ivermectin, fluvoxamine maleate, metformin and doxazosin; and currently has four treatments (peginterferon lambda, fluvoxamine, fluvoxamine plus molnupiravir and fluvoxamine plus inhaled corticosteroid) under investigation. The trial ability to test a range of inexpensive, repurposed drugs has offered valuable data on treatments that are scalable, especially in low-income and middle-income countries. While TOGETHER shares CanTreatCOVID's focus on early treatment in outpatients, it differs in its geographic scope and focus on repurposed drugs.

The PANORAMIC,[27] conducted in the UK, is one of the largest APTs for outpatient COVID-19 therapeutics. It is an open-label APT that assessed the safety and efficacy of antiviral treatments vs usual care in patients at increased risk of COVID-19-related morbidity and mortality. PANORAMIC has enrolled over 29 000 participants across 65 sites. The trial evaluated both molnupiravir[25] and nirmatrelvir/ritonavir. Recruitment for both treatments has now concluded, with the trial playing a significant role in confirming the real-world effectiveness of these antiviral agents in highly vaccinated populations. PANORAMIC shares CanTreatCOVID's community-based approach, but it is primarily focused on antiviral treatments, while CanTreatCOVID aims to evaluate a broader range of therapies.

The Accelerating COVID-19 Treatment Interventions and Vaccines (ACTIV-2 and ACTIV-6) were launched by the US National Institutes of Health to assess outpatient treatments for mild-to-moderate COVID-19 cases in individuals at risk of severe disease progression.[38] ACTIV-2, a phase II/III trial, evaluates monoclonal antibodies, oral antivirals and inhaled interferons and has enrolled 4044 participants across 172 sites worldwide, including locations in Argentina, Brazil and the USA.[38 39] ACTIV-6, a phase III platform trial, examines the effectiveness of widely available prescription and over-the-counter medications in managing COVID-19 symptoms in outpatients.[38] With a focus on repurposed medications, such as ivermectin and fluvoxamine, ACTIV-6 has enrolled over 10 000 participants across 110 sites within the USA.[38] Similar to TOGETHER, ACTIV-6 aims to provide data on accessible, affordable treatments, but focuses on medications readily available to the public. Both ACTIV-2 and ACTIV-6 provide valuable insights into outpatient management of SARS-CoV-2, though they differ from CanTreatCOVID by targeting specific therapeutic classes rather than a broad spectrum of treatments.

Strengths and limitations

One of CanTreatCOVID's major strengths is its community-focused approach, which prioritises early intervention for patients in outpatient settings. By allowing enrolment without the need for in-person visits, the trial maximises accessibility and reduces barriers to participation. This approach captures a broader, more diverse patient population and also ensures that therapeutics are tested during the early, milder stages of COVID-19, where timely intervention may yield the greatest benefits. This emphasis on community care reflects the growing recognition that managing SARS-CoV-2 in outpatient settings is critical to reducing the burden on healthcare systems and preventing severe outcomes. Another key strength is the trial's adaptive design, which allows for real-time flexibility. As new data become available, treatments that show promise can be added, while ineffective ones can be removed. This adaptability is essential in a rapidly evolving pandemic, where new variants and therapies continue to emerge.

A key limitation of the trial is its open-label design. Without blinding, both participants and study clinicians are aware of the intervention being administered, which introduces the potential for bias. However, the decision to forgo placebo control was made deliberately, as usual care in the community does not typically include placebo administration. Additionally, creating placebo equivalents for multiple investigational drugs in a large-scale platform trial would be logistically challenging and may delay the rapid evaluation of potentially life-saving treatments. While the open-label design could impact subjective outcomes, it remains the most feasible and practical option given the trial's scale and the urgency of the pandemic. Furthermore, previous open-label trials have shown no difference in subjective outcomes, specifically, time

to recovery between different intervention arms and usual care,[40] indicating that the absence of a placebo did not impact participants' perception of being fully recovered.

Another potential limitation is the reliance on self-reported data for adherence to the study medications, which may introduce variability in how accurately participants follow the therapeutic regimen. To address this, the trial uses online questionnaires and regular check-ins with study staff to support accurate reporting and help participants stick to the regimen.

CanTreatCOVID represents a robust, APT designed to address the urgent need for effective therapeutics in the outpatient management of SARS-CoV-2. By focusing on high-risk populations and leveraging real-world healthcare settings, the trial offers the potential to identify treatments that can significantly improve outcomes in the community. The adaptive design enables the trial to evolve in response to emerging evidence. While challenges such as the open-label design and self-reported adherence exist, these are outweighed by the trial's strengths in accessibility, scalability and responsiveness to the changing pandemic landscape.

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REFERENCES

1 World Health Organization. WHO coronovirus disease (COVID-19). 2024. Available: https://data.who.int/dashboards/covid19/deaths?n=c
2 Ashton J. COVID-19 and herd immunity. *J R Soc Med* 2022;115:76–7.
3 Telenti A, Arvin A, Corey L, *et al*. After the pandemic: perspectives on the future trajectory of COVID-19. *Nature New Biol* 2021;596:495–504.
4 McCullough PA, Kelly RJ, Ruocco G, *et al*. Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection. *Am J Med* 2021;134:16–22.
5 Public Health Agency of Canada. COVID-19 treatments. 2022.
6 Ontario COVID-19 Science Advisory Table. Ontario COVID-19 drugs and biologics clinical practice guidelines working group. clinical practice guideline summary: recommended drugs and biologics in adult patients with covid-19.
7 COVID-19 Treatment Guidelines Panel - National Institutes of Health. Coronovirus disease 2019 (COVID-19) treatment guidelines. 2022.
8 Siemieniuk RA, Bartoszko JJ, Zeraatkar D, *et al*. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020;370:m2980.
9 World Health Organization. Therapeutics and COVID-19: living guideline. 2022.
10 Lee TC, Boulware DR. Is there room for metformin at COVID-19's dinner table? updated analysis of clinical trials. *Clin Infect Dis* 2025;80:487–8.
11 Lee TC, Vigod S, Bortolussi-Courval É, *et al*. Fluvoxamine for Outpatient Management of COVID-19 to Prevent Hospitalization. *JAMA Netw Open* 2022;5:e226269.
12 Lee TC, Bortolussi-Courval É, Belga S, *et al*. Inhaled corticosteroids for outpatients with COVID-19: a meta-analysis. *Eur Respir J* 2022;59:2102921.
13 Hammond J, Leister-Tebbe H, Gardner A, *et al*. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *N Engl J Med* 2022;386:1397–408.

14 Hammond J, Fountaine RJ, Yunis C, *et al*. Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with Covid-19. *N Engl J Med* 2024;390:1186–95.
15 Pitre T, Van Alstine R, Chick G, *et al*. Antiviral drug treatment for nonsevere COVID-19: a systematic review and network meta-analysis. *CMAJ* 2022;194:E969–80.
16 Sharma R, Patel A, Ojha T, *et al*. Role of antioxidant therapy in the treatment and prognosis of covid-19: a systematic review and meta-analysis of randomized controlled trials. *Curr Dev Nutr* 2024;8.
17 The Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat Rev Drug Discov* 2019;18:797–807.
18 Vanderbeek AM, Bliss JM, Yin Z, *et al*. Implementation of platform trials in the COVID-19 pandemic: A rapid review. *Contemp Clin Trials* 2022;112:106625.
19 Recovery Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021;384:693–704.
20 RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:1637–45.
21 Angus DC, Derde L, Al-Beidh F, *et al*. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19. *JAMA* 2020;324:1317.
22 The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med* 2021;385:777–89.
23 The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med* 2021;385:790–802.
24 Yu L-M, Bafadhel M, Dorward J, *et al*. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (Principle): a randomised, controlled, open-label, adaptive platform trial. *The Lancet* 2021;398:843–55.
25 Butler CC, Hobbs FDR, Gbinigie OA, *et al*. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet* 2023;401:281–93.
26 Hughes SE, Haroon S, Subramanian A, *et al*. Development and validation of the symptom burden questionnaire for long covid (SBQ-LC): Rasch analysis. *BMJ* 2022;377:e070230.
27 Reis G, Dos Santos Moreira-Silva EA, Silva DCM, *et al*. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health* 2022;10:e42–51.
28 Ganatra S, Dani SS, Ahmad J. Oral Nirmatrelvir and Ritonavir in Non-hospitalized Vaccinated Patients with Covid-19. *Clin Infect Dis* 2022.
29 Munblit D, O'Hara ME, Akrami A, *et al*. Long COVID: aiming for a consensus. *Lancet Respir Med* 2022;10:632–4.
30 Richard SA, Epsi NJ, Lindholm DA, *et al*. COVID-19 Patient-Reported Symptoms Using FLU-PRO Plus in a Cohort Study: Associations With Infecting Genotype, Vaccine History, and Return to Health. *Open Forum Infect Dis* 2022;9:ofac275.
31 Soriano JB, Murthy S, Marshall JC, *et al*. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis* 2022;22:e102–7.
32 Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: A non-parametric approach to confidence interval estimation. *Health Econ* 1997;6:327–40.
33 Lee TC, Morris AM, Grover SA, *et al*. Outpatient Therapies for COVID-19: How Do We Choose? *Open Forum Infect Dis* 2022;9:ofac008.
34 Reenen M, Oppe M. EQ-5D-3L user guide: basic information on how to use the EQ-5D-3L instrument. *EuroQol Research Foundation* 2015;22.
35 Richardson S, Hirsch JS, Narasimhan M, *et al*. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020;323:2052.
36 Gold JAW, Wong KK, Szablewski CM, *et al*. Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19. 2020;69.
37 Butler C, Investigators P. Platform Adaptive trial of Novel antivirals for early treatment of COVID-19 in the Community (PANORAMIC): Study protocol. 2022.
38 Keshtkar-Jahromi M, Adam SJ, Brar I, *et al*. ACTIV trials: cross-trial lessons learned for master protocol implementation. *J Clin Transl Sci* 2024;8:e152.
39 Currier JS, Moser C, Eron JJ, *et al*. ACTIV-2: A Platform Trial for the Evaluation of Novel Therapeutics for the Treatment of Early COVID-19 in Outpatients. *J Infect Dis* 2023;228:S77–82.
40 Hayward G, Butler CC, Yu L-M, *et al*. Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE): protocol for a randomised, controlled, open-label, adaptive platform, trial of community treatment of COVID-19 syndromic illness in people at higher risk. *BMJ Open* 2021;11:e046799.
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