Anti-Coronavirus Therapies (ACT) to prevent progression of COVID-19: Randomized trials

The Canadian COVID-19 Collaboration

CLINICAL TRIAL PROTOCOL

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INVESTIGATOR'S AGREEMENT

I,_____, **the investigator**,

have examined this ACT trial protocol and have fully discussed the objectives of this trial and the contents of this amended protocol with the ACT Coordinating Center representative(s) from the Population Health Research Institute at Hamilton Health Sciences Corporation (Sponsor).

I agree to conduct the study according to this protocol and to comply with its requirements, subject to ethical and safety considerations.

I agree to comply with the International Council for Harmonization Tripartite Guideline on Good Clinical Practice (GCP), Tri-Council Policy Statement (TCPS2) and other applicable guidelines, and all applicable laws and regulations.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I agree the Sponsor owns all data and intellectual property generated from this trial. I further agree that the first publication will be led by the trial's Steering Committee, after which I will receive access to the full dataset for internal education and non-commercial research purposes only.

I acknowledge the Sponsor will indemnify my hospital and I for any third party claims resulting directly from PHRI's negligence or willful misconduct in this trial, provided that such claim is not caused by my hospital's or my negligence or willful misconduct.

Investigator Name: _____

Investigator Signature: _____ **Date:** _____

Hospital / Site: _____

City: _____

PROTOCOL APPROVAL

Signature:

Date:
2020-07-15

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Signature

Date:
2020-07-15

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Contents

Study Synopsis

Title	Anti-Coronavirus Therapies to prevent COVID-19 progression trial
Coordinating Investigators	Richard Whitlock, Emilie Belley-Côté, Sanjit Jolly, John Eikelboom
Study Background	COVID-19 is a global pandemic. Various treatments have the potential to prevent disease progression but so far few have been proven to be effective.
Study Aim	This program will evaluate anti-inflammatory and anti-thrombotic therapy to determine whether they prevent clinical progression of COVID-19 in outpatients and inpatients.
Study Population	Outpatient trial: Symptomatic patients outside of hospital with a laboratory diagnosis of COVID-19. Inpatient trial: Symptomatic patients admitted to hospital with a laboratory diagnosis of COVID-19.
Study Design	Parallel group trial with *factorial* randomization (see figure below).
Randomization	Outpatient trial (factorial randomizations): Anti-inflammatory: colchicine vs. control. Anti-thrombotic: acetylsalicylic acid (ASA) vs. control. Inpatient trial (factorial randomizations): Anti-inflammatory: colchicine vs. control. Antithrombotic: combination of ASA and rivaroxaban vs. control.
Eligibility Criteria	Outpatient trial: *Inclusion criteria:* 1) Symptomatic and laboratory-confirmed diagnosis of COVID-19. 2) Age ≥30 years. 3) High risk: either age ≥70 or at least one of the following: male; obesity (BMI ≥30); chronic cardiovascular, respiratory, or renal disease; active cancer; diabetes. 4) Within 7 days (ideally 72 hours) of diagnosis or worsening clinically. *Exclusion criteria (apply to all patients):* 1) General: advanced kidney disease (eGFR <15 mL/min/1.73m^2); advanced liver disease; pregnancy (known or potential) or lactation. 2) Colchicine: allergy or planned use; current or planned use of cyclosporine, verapamil, HIV protease inhibitor, azole antifungal, or macrolide antibiotic (except azithromycin). 3) ASA: allergy or planned use; high risk of bleeding; current or planned use of other anti-thrombotic drugs (e.g., P2Y12 inhibitors, direct oral anticoagulants, vitamin K antagonists, heparins) Inpatient trial: *Inclusion criteria:* 1) Symptomatic and laboratory-confirmed diagnosis of COVID-19. 2) Age ≥18 years. 3) Within 72 hours (ideally 24 hours) of admission or worsening clinically. *Exclusion criteria (apply to all patients):*

<table>
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2) Colchicine: allergy or planned use; current or planned use of cyclosporine, verapamil, HIV protease inhibitors, azole antifungals, or macrolide antibiotics (except azithromycin).
3) ASA and rivaroxaban: allergy or planned used of rivaroxaban; high risk of bleeding; current or planned use of P2Y12 inhibitors or therapeutic doses of anticoagulants* (e.g., direct oral anticoagulants, vitamin K antagonists, heparin, LMWH), current or planned use of strong inhibitors of both CYP 3A4 and P-gp (e.g., lopinavir/ritonavir, carbamazepine, ketoconazole). *Note that prophylactic doses of anticoagulants can be used in patients who are randomized to control.</td></tr>
<tr><td>Dosing</td><td>Colchicine* (outpatient and inpatient)
Outpatient trial: eGFR ≥30 mL/min/1.73m^2: 0.6 mg twice daily for 3 days, then 0.6 mg once daily for 25 days (total 28 days). eGFR 15 to 29 mL/min/1.73m^2: 0.6 mg once daily for 28 days.
Inpatient trial: eGFR ≥30 mL/min/1.73m^2: two 0.6 mg tablets (1.2 mg) followed by 0.6 mg 2 hours later, then 0.6 mg twice daily for 28 days. eGFR 15 to 29 mL/min/1.73m^2: 0.6 mg once daily for 28 days.
(*Depending on availability, 0.6 mg tablets can be substituted by 0.5 mg tablets)
ASA (outpatient and inpatient)
Outpatient trial: 75 to 100 mg once daily for 28 days.
Inpatient trial: 75 to 100 mg once daily for 28 days.
Rivaroxaban (inpatient only)
Inpatient trial: 2.5 mg twice daily for 28 days.</td></tr>
<tr><td></td><td>Outpatient trial (n=3,500)
<table><tr><th></th><th>Colchicine</th><th>Control</th></tr><tr><td>Aspirin</td><td>N=875</td><td>N=875</td></tr><tr><td>Control</td><td>N=875</td><td>N=875</td></tr></table>
Inpatient trial (N=2,500)
<table><tr><th></th><th>Colchicine</th><th>Control</th></tr><tr><td>ASA plus Rivaroxaban</td><td>N=625</td><td>N=625</td></tr><tr><td>Control</td><td>N=625</td><td>N=625</td></tr></table></td></tr>
<tr><td>Primary Outcomes</td><td>Outpatient trial during the first 45 days after randomization:
The primary outcome for colchicine vs. control is the composite of hospitalization or death.
The primary outcome for ASA vs. control is the composite of major thrombosis (myocardial infarction, stroke, acute limb ischemia, pulmonary embolism), hospitalization, or death.
Inpatient trial during the first 45 days after randomization:</td></tr>
</table>

	The primary outcome for colchicine vs. control is the composite of high flow oxygen, mechanical ventilation, or death. The primary outcome for the combination of ASA and rivaroxaban vs. control is the composite of major thrombosis (myocardial infarction, stroke, acute limb ischemia, pulmonary embolism), high flow oxygen, mechanical ventilation, or death.
Total number of subjects and power:	Outpatient trial: Planned sample size is 3,500; this will provide at least 80% power to detect a 30% relative risk reduction (RRR) for each intervention vs. control in the proportion developing the primary outcome, assuming overall rate of the primary outcome of 7.5%. Inpatient trial: Planned sample size is 2,500; this will provide at least 80% power to detect a 20% RRR for each comparison vs. control in the proportion developing the primary outcome, assuming overall rate of the primary outcome of 22%.
Statistical Considerations	Randomization: In both trials, randomization will be stratified by centre, in randomly permuted blocks. Analysis: The primary analysis of efficacy will be conducted under the intention-to-treat principle; all randomized participants will be included in the analyses. Each trial will be analyzed separately with 2-sided level of significance of 0.05.
Duration of Study Period (per subject)	The primary outcome is during the first 45 days after randomization. All participants will be followed for 6 months from randomization in both trials.

1. Background

A novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected over 180 million people with more than 3.8 million deaths worldwide as of June, 2021[1]. The disease that is now known as COVID-19 was first reported to the World Health Organization on December 31, 2019. The disease was declared a pandemic on March 11, 2020 and has had a profound impact on individuals and communities around the world. Exploring therapies potentially of benefit for COVID-19 remains a public health priority.

SARS-CoV-2 enters cells by binding to the angiotensin converting enzyme2 (ACE2) receptor. The most common clinical manifestations of COVID-19 are pneumonia (which can lead to acute respiratory distress syndrome); acute cardiac, cerebral, renal and hepatic dysfunction; and thrombotic events including myocardial infarction (MI), stroke, acute limb ischemia (ALI) and venous thromboembolism VTE)[2]. Disease progression and mortality appear to be related to an intense inflammatory response (cytokine storm) and secondary thrombosis in the pulmonary, cardiac, and cerebral vasculature. Among persons diagnosed with COVID-19, 10-15% require hospital admission, 5% require intensive care unit admission, and 1-3% die[3]. Mortality is greatest among older adults and those with chronic disease. The large number of hospital admissions during disease outbreaks has overwhelmed many healthcare systems.

Vaccines have proven to be the most effective way to tackle the COVID-19 crisis, but many countries do not have access to vaccines and even where the vaccine is widely available, hesitancy is limiting uptake.[4] Discovering effective and safe treatments for COVID-19 therefore remains important.

Recent randomized trials highlight the potential for medical therapies to prevent COVID-19 disease progression. Anti-inflammatory therapy with glucocorticoids and interleukin-6 receptor antagonists reduce mortality in hospitalized patients[5,6], and several other therapies appear promising. However, additional treatments are required to further reduce the burden of morbidity and mortality.

Many infectious diseases require multidrug therapy to target different mechanisms (e.g., tuberculosis, HIV). For COVID-19, we will likely need combinations of several widely available and affordable interventions that target different pathways (e.g., infection, inflammation, thrombosis) to substantially reduce the risk of COVID-19 disease progression. We need to test these treatments as soon as possible after diagnosis, and in patients with mild symptoms (i.e., outpatients) as well as those with more moderate or severe disease (i.e., inpatients) to have the greatest impact.

2. Study Interventions

The Anti-Coronavirus Therapy (ACT) trials have used a *conceptual framework* to identify several interventions that affect the disease at different stages. We are evaluating, in both outpatients and inpatients (mild and moderate/severe disease), several widely available interventions, alone and in combination, that potentially reduce *inflammation* (colchicine) and prevent *thrombosis* (aspirin [ASA], rivaroxaban). Each intervention has been widely used and is safe when used for other indications and has preliminary in-vitro or clinical data suggesting

benefit in patients with COVID-19. We expect that each intervention when used alone will be at best moderately effective, but that their *combinations may be of substantial benefit.*

Anti-inflammatory

Colchicine has powerful anti-inflammatory effects[7]. It accumulates in neutrophils and monocytes, inhibits the NLRP3 inflammasome (which can be activated by SARS-CoV-2) and suppresses blood levels of IL-6. When used at low doses, colchicine is effective in several inflammatory conditions (e.g., gout, Familial Mediterranean Fever, pericarditis) as well as in cardiovascular prevention[7,8]. Based on its mechanism of action and low cost, colchicine is an attractive option to suppress the inflammatory response in COVID-19 disease. Supporting this hypothesis, randomized trials have suggested a benefit of colchicine in both outpatients (COLCORONA, n=4,488)[9] and inpatients (COLCOVID, n=1,279; R Diaz [PI], personal communication), but the results were not definitive and a further trial (RECOVERY, n=11,340; published on pre-print server) did not demonstrate a benefit of colchicine in inpatients with COVID-19. It is unclear whether the lack of benefit in the RECOVERY trial might be explained by the short duration of treatment (up to 10 days, compared with up to 14 days in COLCOVID and 30 days in COLCORONA). We are testing colchicine given for 28 days in outpatients and inpatients with COVID-19.

Antithrombotic

Recent postmortem studies indicate that COVID-19 patients have extensive endothelial dysfunction and microvascular thrombosis in the lungs, the brain, the heart and the kidneys[910]. ASA and rivaroxaban are effective anti-thrombotic drugs when used alone or in combination. When used alone, ASA prevents both venous and arterial thromboembolism, including stroke and MI[11].Low dose rivaroxaban used in combination with ASA is substantially more effective than ASA alone for prevention of arterial events (24% RRR) and venous thromboembolism (39% RRR) and has an acceptable risk of bleeding[12].

Observational data have suggested a benefit of antithrombotic therapies in patients with COVID-19, but randomized trials (NIH multiplatform, n=2,293 [published on pre-print server]; INSPIRATION, n=562[13]; ACTION, n=615[14]) comparing therapeutic or intermediate doses of heparin, low-molecular-weight heparin, or rivaroxaban with prophylactic doses in inpatients have produced inconclusive results. In each of these trials, intensified anticoagulant therapy reduced thrombosis at the cost of more bleeding and did not produce mortality benefits, although in one trial there was an increase in days of organ free support. None of the completed trials has tested antiplatelet therapy alone in outpatients or the combination of antiplatelet and low intensity anticoagulant therapy in inpatients. We are testing ASA in outpatients and in combination with rivaroxaban in inpatients who are at higher risk of thrombosis.

3. ACT study design features

Our program has several unique design features:

I. *Two parallel trials* testing the effects of interventions in complementary populations:
   a. The Outpatient trial in symptomatic patients in the community who are COVID-19 positive and at high risk of disease progression: colchicine is being compared with

control (anti-inflammatory); and ASA is being compared with control (anti-thrombotic); using a 2 x 2 factorial design. The primary outcome for colchicine vs. control is the composite of hospitalization or death. The primary outcome for ASA vs. control is the composite of major thrombosis, hospitalization or death.

b. The Inpatient trial in symptomatic patients who are COVID-19 positive and who are hospitalized: colchicine is being compared with control (anti-inflammatory); and the combination of ASA and rivaroxaban is being compared with control (anti-thrombotic); using a 2 x 2 factorial design. The primary outcome for colchicine vs. control is the composite of high flow oxygen, mechanical ventilation or death. The primary outcome for the combination of ASA and rivaroxaban vs. control is the composite of major thrombosis, high flow oxygen, mechanical ventilation or death. .

The data on the comparison between anti-inflammatory and control, and between anti-thrombotic and control from the two trials are complementary and will be combined in separate analyses. The overall program will provide information on the value of various interventions in a broad range of patients with mild and moderate/severe COVID-19 disease.

II. *Factorial design,* simultaneously testing multiple interventions:
Factorial designs have been widely used for over 50 years in randomized clinical trials and are supported by an extensive literature[15,16]. The best known examples of these are the ISIS-2 trial, which tested the effects of streptokinase vs. its control, and ASA vs. its control in acute MI and demonstrated that each one reduced mortality by 25% and 20% respectively and that the two treatment combined had an additive effect of a 45% risk reduction in mortality[17]. Other notable examples of successful factorial designs are the HOPE study, conducted by our group (approved by Health Canada), which tested the effects of ramipril vs. placebo and vitamin E vs. placebo. This trial demonstrated the value of ramipril in reducing mortality, MI, and stroke, and indicated the neutrality of vitamin E on these outcomes[18,19]. Subsequent to these trials, there have been several trials with factorial designs in a large number of conditions. Trials that we have conducted in Canada with Health Canada approval include HOPE-3[20-22], and the TIPS-3 trial, which used a 2 x 2 x 2 design to test a polypill vs. its control, aspirin vs. its control, and vitamin D vs. its control[23]. Other trials include ISIS-3 and ISIS-4, ORIGIN in patients with diabetes (lantus insulin and fish oil supplements)[24,25], COMPASS (rivaroxaban and pantoprazole)[26,27], and DREAM (ramipril and rosiglitazone)[28,29].

In a factorial design, which simultaneously tests multiple interventions that are not known to interact with each other and can potentially be used together, there is substantial gain in efficacy and also gain in scientific knowledge. For example, below is the design of a 2 x 2 factorial design:

a. A vs. control (no A)
b. B vs. control (no B) in the same patients by randomizing each patient twice.

Using this design, we get the information on A vs. control (vs. B or vs. neither A nor B) and on B vs. control (vs. A or vs. neither A nor B), as well as the combined effects of A plus B vs. control (vs. A alone, vs. B alone or vs. neither A nor B). A 2 x 2 factorial design reduces the required sample size by about one-third compared to a three-arm

design and provides added information on the combined effects of the two treatments being tested (which a 3-arm study would not provide). Factorial designs have been widely used and accepted as valid with substantial efficiency and gain in scientific knowledge. A number of ongoing COVID-19 trials are using parallel designs with multiple interventions; the most important advantage of a factorial design is the ability to efficiently test multiple drug combinations which may be synergistic.

III. *Adaptive design* that enables modifications based on emerging data:
Adaptive designs are used when there is significant uncertainty about key aspects of a disease, treatments, etc. Adaptive designs are generally used in Phase II or early Phase III trials. Given the COVID-19 pandemic, and the lack of strong biological or prior clinical data on many of the interventions being proposed, an adaptive design makes a lot of sense (our study is a combination of Phase 2 and Phase 3 designs)

At the time of designing the ACT trials there was very little data to support the various hypotheses and interventions that we had planned. Accordingly, the projected event rates in ACT were based on very little data. The also trial experienced substantial delays in startup related to administrative challenges and delays in regulatory and ethical approvals as well as delays in importation of study drug. As a result, the trial experienced much slower than expected recruitment.

On June 4, 2021, the ACT Steering Committee reviewed trial progress (blinded to treatment group) and noted the following:

a) Enrollment was progressing smoothly with several hundred patients being recruited into each of the inpatient and outpatient trials each month. In the month of May 2021, the trial enrolled 318 patients in the outpatient trial and 392 into the inpatient trial for a total of 710.
b) Recruitment was being achieved with activity at less than one-half of the originally planned number of sites. An additional 40 sites were still to be activated.
c) The proportion of patients who had experienced a primary outcome was much lower in both the outpatient (6-7% vs 12% originally projected) and inpatient (15% vs 30% originally projected) trials.
d) The proportion of patients under the age of 30 who were experiencing a primary outcome was <2%.

Accordingly, the Steering Committee decided to increase the sample size, modify the primary outcomes for the outpatient and inpatient trials, and introduce a higher age cut-off in the outpatient trial.

The adaptive design used in the ACT trials follows the same principles as the World Health organization (WHO) SOLIDARITY trial, the UK RECOVERY Trial, and several other large trials in patients with COVID-19.

The previous version (Version 15) of the protocol proposed minimum sample sizes (the SOLIDARITY trial did not provide any samples sizes), but left open the possibility of increasing the sample size. Similar to the SOLIDARITY trial, we indicated that new arms could be added, or arms that appear to be ineffective as reviewed by an independent DSMC could be dropped for futility. We are submitting amendments to Health Canada and ethics committees for any adaptations to the protocol. .

The ACT COVID-19 platform capitalizes on some of the experiences and advanced methodologic thinking in clinical trials design and conduct in order to efficiently and rapidly test a range of interventions, and also have the flexibility to modify the protocol while preserving statistical and methodological rigour and validity.

4. Outpatient trial: preventing disease progression in symptomatic COVID-19 positive outpatients

4.1 Study Objectives

4.1.1 Primary objectives

To evaluate if (1) colchicine vs. control prevents hospitalization or death (primary outcome).

To evaluate if (2) ASA vs. control prevents major thrombosis (myocardial infarction, stroke, acute limb ischemia, pulmonary embolism), hospitalization or death (primary outcome).

Primary objectives will be evaluated during the first 45 days after randomization.

4.2 Study Design

4.2.1 Type of study

A multi-centre, open-label, parallel group, randomized controlled trial with a 2 x 2 factorial design in symptomatic outpatients with COVID-19.

4.2.2 Expected number of participants

3,500.

4.2.3 Allocation procedure

Randomization will be via central interactive web randomization system (IWRS). Randomization will occur in 1:1 ratio to colchicine vs. control and in 1:1 ratio for ASA vs. control, stratified by site and using randomly permuted blocks (undisclosed sizes to maintain concealment of allocation).

4.2.4 Duration of the study period for each subject

Total 6 months. Participants will be followed at day 8, day 45 and 6 months.

4.3 Study population

Outpatients will be identified at screening clinics or will be self-referred or referred by health care providers.

4.3.1 Inclusion criteria

1) Symptomatic and laboratory-confirmed diagnosis of COVID-19.
2) Age ≥30 years.
3) High risk: either age ≥70 or at least one of the following: male; obesity (BMI ≥30); chronic cardiovascular, respiratory, or renal disease; active cancer; diabetes) OR age>=70 years.
4) Within 7 days (ideally 72 hours) of diagnosis or worsening clinically.

4.3.2 Exclusion criteria (apply to all patients)

1) General: advanced kidney disease (eGFR <15 mL/min/1.73m^2)*; advanced liver disease; pregnancy (known or potential) or lactation
2) Colchicine: allergy or planned use; current or planned use of cyclosporine, verapamil, HIV protease inhibitor, systemic azole antifungal, or macrolide antibiotic (except azithromycin).
3) ASA: allergy or planned use; high risk of bleeding, current or planned use of other anti-thrombotic drugs (e.g., P2Y12 inhibitors, direct oral anticoagulants, vitamin K antagonists, heparins).

(*Patients >70 years, with known chronic kidney disease, or with a history of diabetes for more than 10 years must have creatinine [eGFR] result available from within 3 months prior to randomization)

4.4 Study Procedures (See Table 1 at end of Section 4)

4.4.1 Interventions

Consenting participants will be randomized to: anti-inflammatory: colchicine vs. control; and anti-thrombotic: ASA vs. control.
Colchicine*
eGFR ≥30 mL/min/1.73m^2: 0.6 mg twice daily for 3 days, then 0.6 mg once daily for 25 days (total 28 days).
eGFR 15 to 29 mL/min/1.73m^2: 0.6 mg once daily for 28 days.
(*Depending on availability, 0.6 mg tablets can be substituted with 0.5 mg tablets).
ASA
75 to 100 mg once daily for 28 days.

We will place no constraints on treating physicians with respect to usual care other than avoidance of potentially interacting non-study treatments.

4.4.2 Data collection

We will collect participant sex, age, comorbidities (e.g., smoking, diabetes, heart disease, lung disease, and immunosuppression), selected medications and trial outcomes.

4.5 Study Outcomes

4.5.1 Primary efficacy outcome

Colchicine vs control: hospitalization or death
ASA vs control: major thrombosis (myocardial infarction, stroke, acute limb ischemia, pulmonary embolism), hospitalization, or death

4.5.2 Secondary efficacy outcomes

Colchicine vs control: Nil

ASA vs control: any thrombosis

4.5.3 *Other outcomes*

Both randomizations:
7-point severity score (ordinal scale):
i) Not hospitalized, no limitations on activities
ii) Not hospitalized, limitation on activities;
iii) Hospitalized, not requiring supplemental oxygen;
iv) Hospitalized, requiring supplemental oxygen;
v) Hospitalized, on non-invasive ventilation or high flow oxygen devices;
vi) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
vii) Death

4.6 Statistical Considerations

4.6.1 Sample size calculation

Minimum sample size required is 3,500 to have at least 80% power to detect to detect a 30% RRR for each intervention vs. control in the proportion developing the primary outcome, assuming overall rate of primary outcome of 7.5%. This makes allowance for 2% loss to follow-up (although we expect this will be <1%). See Appendix 1 for sample size tables.

4.6.2 Statistical analyses

The primary hypothesis of efficacy will be tested under the intention-to-treat principle: all randomized participants will be included in the analyses from the time of randomization to the first occurrence of the outcome.Kaplan Meier curves will be used for a survival analysis and a Cox proportional hazard model will be used to estimate HR and 95% CI. Additional details are provided in a separate Statistical Analysis Plan.

4.6.3 Planned subgroup analyses

We will explore whether the following variables modify treatment effect: age, sex and the presence or absence of comorbidities at baseline.

Table 1: Schedule of study events

	Screen[a]	**Day 1 (Rand)**	**Day 4**	**Day 8**	**Day 45**	**6 months**
Informed Consent	X	X				
Eligibility assessment	X	X				
Serum creatinine[b]	X	X				
Randomization		X				
Medical history		X				
Concomitant medications		X				
Interventions dispensed[c]		X				
Translational substudy[d]		X	X	X		
Adherence assessment				X	X	

Adverse events assessment				X	X	X
Endpoint assessment				X	X	X

a. Screening can also occur on the day of randomization.
b. Outpatient trial: creatinine result within 3 months for patients >70 years of age, known history of kidney disease, or diabetes history for more than 10 years; Inpatient trial: creatinine within 72 hours of randomization.
c. Only for patients randomized to interventions.
d. For patients who consent to participate in the substudy.

5. Inpatient trial: preventing disease progression in symptomatic COVID-19 positive inpatients

5.1 Study Objectives

5.1.1 Primary objectives

To evaluate if (1) colchicine vs. control prevents invasive high flow oxygen, mechanical ventilation or death (primary outcome).

To evaluate if (2) the combination of ASA and rivaroxaban vs. control, prevents major thrombosis (myocardial infarction, stroke, acute limb ischemia, pulmonary embolism), high flow oxygen, mechanical ventilation or death (primary outcome).

Primary objectives will be evaluated during the first 45 days after randomization.

5.2 Study Design

5.2.1 Type of study

A multi-centre, open-label, parallel group, randomized controlled trial with a 2 x 2 factorial design in symptomatic inpatients with COVID-19.

5.2.2 Expected number of participants

2,500.

5.2.3 Allocation procedure

Randomization will be via central IWRS. Randomization will occur in 1:1 ratio to colchicine vs. control and in 1:1 ratio to the combination of ASA and rivaroxaban vs. control, stratified by site and using randomly permuted blocks (undisclosed sizes to maintain concealment of allocation).

5.2.4 Duration of the study period for each subject

Total 6 months. Participants will be followed at day 8, day 45 and 6 months.

5.3 Study population

Inpatients will be referred by health care providers.

5.3.1 Inclusion criteria

1) Symptomatic and laboratory diagnosis of COVID-19
2) Age ≥18 years of age.
3) Within 72 hours (ideally 24 hours) of hospital admission or worsening clinically.

5.3.2 Exclusion criteria (apply to all patients)

1) General: advanced kidney disease (eGFR <15 mL/min/1.73m^2), advanced liver disease, pregnancy (known or potential) or lactation, already ventilated for >72 hours
2) Colchicine: allergy or planned use; current or planned use of cyclosporine, verapamil, HIV protease inhibitor, systemic azole antifungal, or macrolide antibiotic (except azithromycin).
3) ASA and rivaroxaban: allergy or planned use of rivaroxaban; high risk of bleeding; current or planned use of P2Y12 inhibitors or therapeutic doses of anticoagulants* (e.g., direct oral anticoagulants, vitamin K antagonists, heparin, LMWH), current or planned use of strong inhibitors of both CYP 3A4 and P-gp (e.g., lopinavir/ritonavir, carbamazepine, ketoconazole).
*Note that prophylactic doses of anticoagulant can be used in patients who are not randomized to the combination of ASA and rivaroxaban.

(*Patients must have creatinine [eGFR] result available from within 72 hours before randomization).

5.4 Study Procedures (See Schedule of Events Table at end of Section 4)

5.4.1 Interventions

Consenting participants will be randomized to: anti-inflammatory: colchicine vs. control; and anti-thrombotic: combination of ASA and rivaroxaban vs. control

<u>Colchicine*</u>
eGFR ≥30 mL/min/1.73m^2: two 0.6 mg tablets (1.2 mg) followed by 0.6 mg 2 hours later, then 0.6 mg twice daily for 28 days
eGFR 15 to 29 mL/min/1.73m^2: 0.6 mg once daily for 28 days.
(*Depending on tablet availability, 0.6mg tablets can be substituted with 0.5 mg tablets)
<u>ASA</u>
75 to 100 mg once daily for 28 days
<u>Rivaroxaban</u>
2.5 mg twice daily for 28 days

We will place no constraints on treating physicians with respect to usual care other than avoidance of potentially interacting non-study treatments.

5.4.2 Data collection

We will collect participant sex, age, comorbidities (e.g., smoking, diabetes, heart disease, lung disease, and immunosuppression), selected medications and trial outcomes.

5.5 Study Outcomes

5.5.1 Primary outcome

Colchicine vs control: high flow oxygen, mechanical ventilation, or death

ASA vs control: major thrombosis (myocardial infarction, stroke, acute limb ischemia, pulmonary embolism), high flow oxygen, mechanical ventilation, or death
(*Participants already receiving high flow oxygen or mechanical ventilation will be followed for death).

5.5.2 Secondary outcomes

Colchicine vs control: high flow oxygen, mechanical ventilation, or respiratory death
ASA vs control: high flow oxygen, mechanical ventilation, or respiratory death; any thrombosis

5.5.3 *Other outcomes*

Both randomizations:
7-point severity score (ordinal scale)

5.6 Statistical Considerations

5.6.1 Sample size calculation

Minimum sample size required is 2,500 to have at least 80% power to detect a 20% RRR for each intervention vs. control in the proportion developing the primary outcome, assuming overall rate of primary outcome of 22%%. This allows for 1% loss to follow-up. See Appendix 1 for sample size tables.

5.6.2 Statistical analysis methods

Same as Outpatient trial (Section 4.6.2).

5.6.3 Planned subgroup analyses

We will explore whether the following variables modify treatment effect: age, sex, the presence or absence of comorbidities at baseline, disease severity at baseline, admission to ICU at randomization, ventilated at randomization.

6. Translational substudy

The clinical manifestations and laboratory findings in patients with COVID-19 are well described, but we do not know whether changes in blood biomarker levels are related to viral load, predict disease progression and end-organ damage, or can be used to evaluate response to treatment. To address these issues, we will serially collect, in a subset of about 500 ACT outpatients and inpatients, nasal swabs to measure viral load and blood samples to measure soluble ACE2 levels and markers of inflammation, coagulation activation and end-organ damage (e.g., troponin, liver enzymes, and creatinine). We will also collect radiographic information (where possible and already performed as part of usual care) to evaluate disease progression and to correlate changes with viral load and blood biomarkers. Improved understanding of disease mechanisms could facilitate early identification of beneficial treatments and make drug development faster. For details see translational study manual.

7. Program Management and Safety

7.1 Safety Monitoring and Reporting

Colchicine, ASA and rivaroxaban have been extensively studied and used for many years in many thousands of patients (and in some cases millions of patients), and their adverse effects profiles are well described. COVID-19 has been diagnosed in more than 45 million patients, and the clinical manifestations have been described in detail.

7.2 Serious adverse events

For the purposes of this trial, study efficacy and safety outcomes, known adverse effects of study medications (other than those listed below as Events of Special Interest), and events that are expected to occur with high frequency in patients with COVID-19 infection will be captured on the case report forms and will be exempted from expedited reporting. All of these events will be reviewed by the DSMC on an ongoing basis and included in the final study report.

The mechanisms of action of colchicine, ASA and rivaroxaban are independent and the types of adverse events (other than bleeding with ASA and rivaroxaban) that might arise are quite distinct. However, the DSMC will also review the results on efficacy and safety in individual cells based on factorial design.

Events of Special Interest are serious adverse drug reactions known to be related to study interventions (including those resulting from overdose) and pregnancy, and will be reported to regulatory authorities (with copies to Bayer for Bayer study drugs) within 72 hours of the sponsor becoming aware. These include:

a) Colchicine: severe cytopenias.
b) ASA and rivaroxaban combination: intracranial bleeding, fatal bleeds, serious bleed in a major organ.
c) Any severe allergy to study interventions.
d) Study intervention overdose causing severe adverse drug reaction.
e) Pregnancy.

Serious adverse events with a reasonable causal relationship to study interventions, unexpected for the patient population under study or inconsistent with the product information (i.e., SUSARs), and that occur in participants treated with study medication will be reported to the regulatory agencies on CIOMS forms (with copies to Bayer for Bayer study drugs) within 72 hours of the sponsor becoming aware.

All adverse events that lead to permanent discontinuation of study interventions will be recorded and included in the final study report.

7.3 Renal function assessment and management of study interventions when there is deterioration in renal function

In the outpatient trial, we are treating patients for 28 days, and since neither colchicine nor aspirin is nephrotoxic, there is no indication to routinely monitor renal function, even in patients with a baseline eGFR of 15-29 (with or without albuminuria)[30]. At the time of consent, patients

are advised to report side effects that may occur during study treatment, including diarrhea, and all patients will be reassessed at day 8 for side effects.

In the inpatient trial, patients are evaluated clinically on at a least a daily basis and will undergo routine laboratory monitoring of renal function as part of routine clinical care. None of the interventions being tested in the inpatient trial are nephrotoxic and in the COMPASS trial of 27,395 patients with chronic coronary or peripheral artery disease where we tested the same doses of rivaroxaban and aspirin for a mean of 23 months we did not perform routine laboratory testing[14]. Investigators will however be encouraged to check serum creatinine if patients have any sudden worsening of their clinical status that might be expected to cause acute kidney injury (e.g., reduced oral intake, diarrhea, hypotension).

If eGFR drops to 15 to 29 ml/min/1.73m^2 the dose of colchicine will be reduced to once daily. If eGFR drops below 15 ml/min/1.73m^2 or creatinine rises by 60% over 24 hours or 100% over 48 hours, or creatinine rise is accompanied by oliguria or anuria, colchicine and rivaroxaban will be discontinued.

7.4 Data Management

Data management will be performed by the PHRI in accordance with PHRI standards and procedures for collection and validation of data. Data will be collected on electronic case report forms (eCRFs) using an electronic data capture system, based on the availability of data in the site's electronic medical record. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the participant's eCRF. All data will be kept secure and confidentiality of all study participants will be carefully protected. Data will be validated, managed, and stored in a de-identified database on a secure server at PHRI.

7.5 Withdrawal from the Study

Any participant who discontinues study treatment will continue follow-up assessments through to the designated final visit with the exception of those participants who withdraw consent for follow-up. If this occurs, the reason for withdrawal must be documented. Data already collected from participants requesting withdrawal will not be deleted, in order to maintain scientific integrity of the study. Withdrawn participants will not be replaced.

8. Study Organization

8.1 Central coordination and study management

The study will be coordinated through the Population Health Research Institute (PHRI), a joint institute of Hamilton Health Sciences and McMaster University, Hamilton, Canada. Regular meetings will be coordinated between a primary team consisting of the coordinating investigators, central research coordinator, and relevant team members from the PHRI to assess trial progress on an ongoing basis, review recruitment rates by site, and address any potential need for site visits or direct intervention/communication.

8.2 Steering Committee

This group, consisting of the principal and coordinating investigators, study chair, study statistician, involved subject matter experts, and National Leaders (Appendix 2) will meet on

a regular basis to assess study progress and discuss necessary interventions or protocol amendments as required.

8.3 Data Safety Monitoring Committee (DSMC)

An independent DSMC will review the accumulating study data after approximately every 100 patients in each trial have been randomized (the frequency of review can be adjusted at their discretion based on emerging data) and make recommendations to the study leadership about the conduct of the trial, integrity of the data and trial discontinuation to ensure the overall safety of participants. The guiding policies and operating procedures governing the DSMC will be described in a separate DSMC charter. The DSMC will follow a flexible pragmatic monitoring approach for efficacy, considering each trial separately. They will follow a modified Haybittle-Peto boundary of 3 SD at two consecutive time points 2 months apart as a general guideline. They will also be looking for consistency of efficacy results across both trials prior to recommending stopping any trial early. Because these boundaries are extreme, no modification of the level of significance of the final results is necessary. The DSMC will also be monitoring the safety of the participants, focusing on adverse events and other safety indicators.

9. Regulatory Considerations, Ethics and Insurance

Prior to the initiation of a study site, approval from the appropriate regulatory agency to conduct the study in accordance with applicable country-specific regulatory requirements will be obtained as required. The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable privacy requirements, and the guiding principles of the Declaration of Helsinki, including, but not limited to:

- Review Ethics Board (REB)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments
- Patient informed consent prior to inclusion in the study

Indemnification in Canada will be provided by Health Insurance Reciprocal of Canada (HIROC). Separate arrangements are in place for other countries.

9.1 Responsibilities of the investigator(s)

The Investigator(s) undertake(s) to perform the study in accordance with Good Clinical Practice and will provide documentation of their qualifications to the project office prior to study start. The Investigator is required to ensure compliance with respect to the visit schedule and procedures required by the protocol. The Investigator agrees to provide all information requested in the case report forms in an accurate and timely manner according to instructions provided. Random or for cause monitoring visits may be done by PHRI representatives.

9.2 Confidentiality

Any personal health information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. The study personnel, employees of the regulatory agencies, including Health Canada, PHRI (the study sponsor), and its agents may need to review participant medical records in order to accurately record information for this study. If results of this study are reported in medical journals or at meetings, the participant’s identity will remain confidential.

9.3 Record retention

Data will be entered directly from the electronic medical record or from interview with the participant at the time of follow-up visits into the electronic case report forms. Laboratory data will be sent directly to the project office. The Sponsor will maintain study records according to regulatory requirements and ICH guidelines.

9.4 Ownership of Study Data and Results

PHRI Project Office and the Steering Committee of the study have the ownership (on behalf of the steering committee and investigative group) of all data and results collected during this study. These data will be used to develop publications and make any submissions if required to regulatory authorities. The data will be shared publicly after the main study results have been published.

10. Publication Policy

The results of the study will be published rapidly after study completion in the names of the study group and all wholehearted collaborators. A detailed Publications Policy will be developed.

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Appendix 1

Outpatient trial

Table 1.1 Event rate conversion from overall rate to the rate in control group

RRR		Overall event rate=6%	Overall event rate=7%	Overall event rate=8%
25%	Control	0.0686	0.0800	0.0914
30%	Control	0.0706	0.0824	0.0941
35%	Control	0.0727	0.0848	0.0970

Table 1.2 Sample size calculation output by PASS13 when the power is 80% for outpatients using log-rank test (alpha=0.05, total time=45 days, Loss to follow-up rate 2% over the 45 days period, which is converted to the daily loss rate as shown in the table by $L_D = 1 - (1 - 0.02)^{\frac{1}{45}} = 0.0449\%$)

RRR	N1	N2	N	Control Event (M1)	Treatment Event (M2)	Accrual time / Total time	Overall rate	Control loss	Treatment loss
25%	3023	3024	6047	0.0686	0.0514	0 / 45	0.06	0.0004	0.0004
	2563	2564	5127	0.0800	0.0600	0 / 45	0.07	0.0004	0.0004
	2218	2219	4437	0.0914	0.0686	0 / 45	0.08	0.0004	0.0004
30%	1975	1975	3950	0.0706	0.0494	0 / 45	0.06	0.0004	0.0004
	1674	1675	3349	0.0824	0.0576	0 / 45	0.07	0.0004	0.0004
	1449	1450	2899	0.0941	0.0659	0 / 45	0.08	0.0004	0.0004
35%	1361	1361	2722	0.0727	0.0473	0 / 45	0.06	0.0004	0.0004
	1154	1154	2308	0.0848	0.0552	0 / 45	0.07	0.0004	0.0004
	999	999	1998	0.0970	0.0630	0 / 45	0.08	0.0004	0.0004

Inpatient trial

Table 2.1 Event rate conversion from overall to the rate in control group

RRR		Overall Event rate =18%	Overall event rate=20%	Overall event rate=22%
20%	Control	0.2000	0.2222	0.2444
25%	Control	0.2057	0.2286	0.2514
30%	Control	0.2118	0.2353	0.2588
35%	Control	0.2182	0.2424	0.2667
40%	Control	0.225	0.250	0.275
45%	Control	0.2323	0.2581	0.2839

Table 2.2 Sample size calculation output by PASS13 when the power is 80% for outpatients using log-rank test (alpha=0.05, total time=45 days, Loss to follow-up rate 1% over the 45 days period, which is converted to the daily loss rate as shown in the table by $L_D = 1 - (1 - 0.01)^{\frac{1}{45}} = 0.0223\%$)

RRR	N1	N2	N	Control Event (M1)	Treatment Event (M2)	Accrual time / Total time	Overall rate	Control loss	Treatment loss
20%	1445	1445	2890	0.2000	0.1600	0 / 45	0.18	0.0002	0.0002
	1268	1268	2536	0.2222	0.1778	0 / 45	0.20	0.0002	0.0002
	1122	1123	2245	0.2444	0.1956	0 / 45	0.22	0.0002	0.0002
25%	872	872	1744	0.2057	0.1543	0 / 45	0.18	0.0002	0.0002
	765	765	1530	0.2286	0.1714	0 / 45	0.20	0.0002	0.0002
	677	678	1355	0.2514	0.1886	0 / 45	0.22	0.0002	0.0002
30%	569	570	1139	0.2118	0.1482	0 / 45	0.18	0.0002	0.0002
	500	500	1000	0.2353	0.1647	0 / 45	0.20	0.0002	0.0002
	442	443	885	0.2588	0.1812	0 / 45	0.22	0.0002	0.0002
35%	392	393	785	0.2182	0.1418	0 / 45	0.18	0.0002	0.0002
	344	345	689	0.2424	0.1576	0 / 45	0.20	0.0002	0.0002
	305	305	610	0.2667	0.1733	0 / 45	0.22	0.0002	0.0002

Appendix 2

List of Countries and National Leaders

COUNTRY	NAME
Argentina	Rafael Diaz, Andres Orlandini
Brazil	Alvaro Avezum
Canada	Richard Whitlock, Emilie Belley-Cote
Colombia	Patricio Lopez-Jaramillo
Ecuador	Camilo Felix
Egypt	Mohamad Hassany
India	Prem Pais, Denis Xavier
Nepal	Sanjib Sharma
Pakistan	Khawar Kazmi
Philippines	Antonio Dans
Rwanda	Menelas Nkeshimana
Russia	Oxana Drapkina, Anna Kontsevaya
Saudi Arabia	Khalid AlHabib
South Africa	Sean Wasserman, Pat Commerford
United Arab Emirates	Afzalhussein Yusufali