Population Health Research Institute

HEALTH THROUGH KNOWLEDGE

Anti-Coronavirus Therapies to prevent progression of COVID-19 (ACT), a randomized trial

The Canadian COVID-19 Collaboration

CLINICAL TRIAL PROTOCOL

Version: Final 2.0

Date: March 25, 2020

Study Coordinating Centre: Population Health Research Institute,
McMaster University and Hamilton Health Sciences,
DBCVSRI, 237 Barton Street East
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INVESTIGATOR'S AGREEMENT

I, _____, the investigator, have examined this protocol:

ACT Trial

and I 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.

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 Harmonisation Tripartite Guideline on Good Clinical Practice (GCP) and applicable regulations/guidelines and all locally applicable laws.

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.

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Investigator Signature: _____ **Date:** _____

Hospital: _____

City: _____

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Table of Contents

Study Synopsis

Title	Anti-Coronavirus Therapies to prevent COVID-19 progression trial
Coordinating Investigators	Richard Whitlock, Emilie Belley-Côté
Study Background	COVID-19 is a global pandemic. Preliminary data from pre-clinical studies and observations in humans suggest that the combination of chloroquine and azithromycin can suppress virus growth and reduce viral load in infected patients.
Study Aim	This program will determine whether the combination of chloroquine and azithromycin reduces the primary outcome of clinical progression of COVID-19. The program consists of 2 parallel trials in people who have tested COVID-19 positive; 1) the **outpatient trial**, and 2) the **inpatient trial**.
Study Population Main eligibility criteria:	1) **Outpatient trial**: Outpatients with a COVID-19 diagnosis (either individuals at screening clinics, in the emergency room but not admitted to hospital, or health care staff who have tested positive) and 2) **Inpatient trial**: Patients admitted to hospital with a diagnosis of COVID-19 infection. <u>Inclusion criteria</u> 1) Age ≥ 18 years 2) Provision of informed consent 3) Diagnosis of active COVID-19 using established testing <u>Exclusion criteria</u> 1) Known glucose-6-phosphate dehydrogenase (G6PD) deficiency 2) Contra-indication to chloroquine or azithromycin 3) Already receiving chloroquine or azithromycin
Study Outcomes	**1) Outpatient trial** A) Primary outcome: composite of hospital admission or mortality B) Secondary outcomes: 1) Mortality 2) Hospital admission 3) Invasive mechanical ventilation 4) Admission to intensive care unit (ICU) 5) Renal replacement therapy 6) Extracorporeal support C) Translational outcomes (in a subset of patients) 1) Viral titre 2) ACE-2 levels 3) Inflammatory markers D) Safety outcomes

	1) Malignant arrhythmia needing intervention 2) Agranulocytosis 3) Stevens-Johnson syndrome/toxic epidermal necrolysis 4) Retinal toxicity **2) Inpatient trial** A) Primary outcome: composite of invasive mechanical ventilation or mortality B) Secondary outcomes: 1) Mortality 2) Invasive mechanical ventilation 3) Admission to ICU 4) Renal replacement therapy 5) Extracorporeal support C) Translational outcomes (in a subset of patients) 1) Viral titre 2) ACE-2 levels 3) Inflammatory markers D) Safety outcomes: 1) Malignant arrhythmia needing intervention 2) Agranulocytosis 3) Stevens-Johnson syndrome/toxic epidermal necrolysis 4) Retinal toxicity
Study Design	Open-label, randomized trials. A vanguard phase will start as soon as possible in Hamilton and nearby regions. Thereafter study will expand to other centers in Canada and other countries, as necessary and feasible.
Total number of subjects:	**1) Outpatient trial** Minimum total sample size required is **N= 1000** (500 in each arm); it will provide 90% statistical power to detect a 50% relative risk reduction (RRR) in the proportion developing the primary outcome, assuming an usual care risk of progression of 12%. **2) Inpatient trial** Minimum total sample size required is **N=530** (265 in each arm) in order to have 90% statistical power to detect a 40% RRR in the proportion progressing to mechanical ventilation or mortality, assuming an usual care risk of progression of 30%.

Study Intervention (both trials)	Patients will be randomly allocated to an active group that will receive chloroquine for a total of 7 days plus azithromycin for 5 days plus usual care **or** to usual care, as follows: **Chloroquine** Adults with a bodyweight ≥ 50 kg: 500 mg twice daily for 7 days Adults with a bodyweight < 50 kg: 500 mg twice daily on days 1 and 2, followed by 500 mg once daily for days 3 -7 **Azithromycin** 500 mg on day 1 followed by 250 mg once daily for 4 days
Statistical Considerations	**Randomization:** In both trials, randomization will be done within center, in randomly permuted blocks. **Adaptive design features (both trials):** • Adaptive termination: A Data & Safety Monitoring Committee (DSMC) will follow a flexible pragmatic monitoring approach for efficacy and safety, considering each trial separately. They will review accumulating data after every 50 subjects have been randomized (with the ability to modify frequency of their review as dictated by the emerging data) and will only stop the trial if there is proof beyond reasonable doubt of efficacy (modified Haybittle-Peto boundary of 3 standard deviation (SD) for benefit or harm as a general guideline). They will also look for consistency of efficacy results across both trials prior to recommending early stopping for a trial. • Adaptive intervention arms: The DSMC and the Study investigators will keep abreast of other ongoing trials and, if another promising intervention emerges, they may recommend adding (or replacing) one or more arms with the new promising intervention(s). • Adaptive sample size: Sample size calculations are based on disease progression rates that are not well known. We remain flexible, and the DSMC will be monitoring the possibility that the assumptions for sample size calculations may be modified with emerging information from this trial or other ongoing trials. If necessary, sample size may be increased accordingly. **Analysis:** The primary hypothesis 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. No modification of the level of significance is necessary with the 3 SD boundary for the Haybittle-Peto criteria. **Outpatient trial:** The primary analysis will use the Z-test for comparison of proportions. Secondary analyses will include adjusting

	the intervention effect for demographic and exposure characteristics of the participants using logistic regression models. **Inpatient trial:** The primary analysis will use the Z-test for comparison of proportions. Secondary analyses will include adjusting the intervention effect for demographics, exposure characteristics, and severity of disease upon admission, using logistic regression models.
Duration of Study Period (per subject)	Patients will be followed for 45 days from randomization in both trials and will receive a telephone call at 1 year to evaluate vital status.

1. Program Background

A novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected hundreds of thousands of people worldwide. The disease that is now known as COVID-19 was first reported to the World Health Organization on December 31, 2019. The disease is spreading quickly around the globe and has been declared a pandemic on March 11, 2020. Exploring therapies potentially of benefit for COVID-19 is a public health emergency.

Chloroquine and azithromycin in combination have shown promise in treating COVID-19. In vitro, chloroquine increases the endosomal pH required for the virus to fuse with cells, interferes with the glycosylation of SARS-CoV-2 cell receptors, thereby blocking viral infection.[1,2] Investigators performed a time-of-addition assay which showed that chloroquine is effective at both the entry and post-entry stages of the SARS-CoV-2 infection in cells. Azithromycin is a macrolide antibiotic that has been found to inhibit the viral tropism and replication of Zika and Ebola viruses.[3-5]

In a non-randomized, open label clinical experience of 36 patients, the combination of azithromycin and hydroxychloroquine was associated with a significant reduction in viral load and reduction of viral carriage by day 6 compared to controls.[6] Patients treated with the combination of azithromycin and hydroxychloroquine also had shorter carrying duration compared to patients reported in the literature. In the subgroup of patients who were treated with azithromycin for clinical reasons, viral elimination was noted to be faster.

There is sparse information on the effects of both drugs in people with coronavirus infection and little or no clinical symptoms. Preventing clinical disease leading to hospitalizations is of great clinical and public health value. This has led some governments or their spokespersons (e.g., the US, India) to recommend the routine use of chloroquine as prophylaxis, We believe that evaluating the effects of these regimen in a well-designed randomized controlled trial is important, with careful attention to safety (avoiding the use of large loading doses, use of low doses for no more than 7 days), and telephone checks on clinical safety as in person assessments are not practical during this period where physical distancing is recommended) and regular monitoring of both efficacy and safety by an independent group of experts.

We assume hydroxychloroquine and chloroquine have similar anti-viral activity. We will refer to both drugs as chloroquine unless otherwise specified in this protocol (at present it is not known which of the above two drugs will be available in sufficient quantities to conduct the trial rapidly). Although chloroquine and azithromycin prolong the QT interval, it is very rarely associated with clinically important arrhythmias, and usually at higher doses than used in our study.[7-9]

The world needs several trials of existing agents that are repurposed to treat and prevent COVID-19 pneumonia and related complications. Of the currently known agents, chloroquine and azithromycin appear to be promising in the treatment for COVID-19.

Preventing people infected with COVID-19 from developing severe enough symptoms to require hospitalization is as important as treating people with COVID-19 pneumonia from deteriorating and needing ventilation or experiencing death. Therefore, we have established a program that includes two parallel trials; an **outpatient trial** seeking to prevent hospital admission and mortality, and an **inpatient trial** seeking to prevent need for mechanical ventilation or mortality. This program is a priority. If this therapy is proven conclusively to be effective, it will be used around the world. If it proves ineffective, other treatments will be explored emergently using the platform we (and other investigators) will establish.

As we design the trials, we acknowledge that many of the details usually available to design a study are not reliably available. This includes event rates (although we have made the best estimate using available data), potential size of the study or the numbers of cases that can be enrolled within a reasonable period as the number of cases is expected to increase rapidly in Canada and in many other countries). We have therefore designed these trials using the best available data, our judgement and with the goal of recruiting as many patients as possible (but at least 1000 into an outpatient trial and at least 530 into the inpatient trial). We have also built in two key mechanistic substudies testing the effects of the regimen on viral loads and on inflammation – to get an early indication of potential efficacy. During the conduct of the trials, we may need to make adjustments to several aspects of study design. To enable this and to monitor safety, the trial data will be reviewed periodically by an expert and independent data and safety monitoring committee (DSMC). We may also consider adding new arms or replacing existing arms (if they are shown to be ineffective based on emerging data) as promising new treatments emerge.

2. Program Hypothesis

Azithromycin in combination with chloroquine therapy (AZCT) on top of usual care will reduce disease progression of COVID-19 compared to usual care.

3. Outpatient trial: Preventing disease progression in COVID positive outpatients

3.1 Study Objectives

3.1.1 Primary objectives

To evaluate if AZCT compared to usual care results in reduced hospital admission or mortality for outpatients diagnosed with COVID-19.

3.1.2 Secondary efficacy objectives

To evaluate if AZCT compared to usual care results in reductions in mortality, hospitalization, invasive mechanical ventilation, admission to intensive care unit (ICU), renal replacement therapy, and extracorporeal support in outpatients diagnosed with COVID-19.

3.1.3 Tertiary efficacy objectives

To evaluate if AZCT compared to usual care results in reductions in length of ICU stay, length of hospital stay, non-invasive ventilation, and duration of ventilation.

3.1.4 Translational objective (in a subset of participants)

To evaluate if AZCT compared to usual care results in reductions of viral titre and inflammatory markers and to assess whether expression of ACE-2 levels is associated with mortality.

3.1.5 Safety objectives

To evaluate whether the risk of the following is increased in patients with COVID-19 receiving AZCT compared with those receiving usual care: malignant arrhythmia requiring intervention, agranulocytosis, Stevens-Johnson syndrome/toxic epidermal necrolysis, and retinal toxicity.

3.2 Study Design

3.2.1 Type of study

A multi-centre, open-label, parallel group, randomized controlled trial evaluating the efficacy and safety of AZCT plus usual care compared to usual care in outpatients with COVID-19.

3.2.2 Expected number of patients

The minimum sample size for the study is a total of 1000 outpatients. This sample size may change as this trial has an adaptive design.

3.2.3 Allocation procedure

Randomization: Eligible patients that have provided informed consent will be randomized via the central interactive web randomization system (IWRS) at the Population Health Research Institute. The process should take less than 3 minutes. Each patient will be assigned to one of two groups, AZCT plus usual care or usual care, in randomly permuted blocks (undisclosed sizes to maintain concealment of allocation). The allocation will be communicated to site personnel and patients will be made aware of their assignment. It is not practical to use placebo as this would entail considerable delays in starting the trial but the outcomes are likely to occur and be ascertained independent of the knowledge of the treatment allocation. Therefore, the results are likely to be unbiased.

Stratification: We will stratify randomization by site.

3.2.4 Duration of the study period for each subject

Patients will be followed for 45 days from the time of randomization. Data of events occurring in hospital will be obtained from hospital records supplemented by a telephone call or follow up at 7-10 days and at 45 days after randomization. Participants will receive a telephone call at 12 months to determine morbidity and mortality.

3.3 Study population

These patients will be identified at screening clinics and in emergency rooms. This group will also include healthcare workers screened for COVID-19 infection. They will be eligible once a diagnosis of COVID-19 is confirmed by established testing. These patients will not have been admitted to hospital at the time of enrolment.

3.3.1 Inclusion criteria

1) Age ≥ 18 years of age
2) Informed consent
3) Diagnosis of active COVID-19 confirmed by established testing

3.3.2 Exclusion criteria

1) Known glucose-6-phosphate dehydrogenase (G6PD) deficiency
2) Contra-indication to chloroquine or azithromycin
3) Already receiving chloroquine or azithromycin

3.3.3 Adaptive design features

Adaptive intervention arms: The DSMC and the Steering Committee will keep abreast of other ongoing trials and, if a more promising intervention is emerging, may recommend adding (or replacing) one arm with the new promising intervention. They will also assess the results of the translational objectives when available and may add a chloroquine loading dose if a rapid or large reduction in viral titres is not observed with the current regimen.

Adaptive sample size: Sample size calculations are based on disease progression rates that are not well known. The DSMC will monitor the possibility that the assumptions for sample size calculations may be modified with emerging information from this trial or other ongoing trials. If recruitment is going well, the steering committee may decide to extend recruitment as long as the independent DSMC does not terminate the trial for clear evidence of efficacy, futility (or low likelihood) to detect a clinically meaningful difference (e.g. a 20% RRR in events) or concerns about safety.

3.4 Study Procedures

In order to make it possible to implement this protocol where resources are scarce, we have simplified trial procedures, and data collection. Direct electronic data entry is encouraged.

3.4.1 Consenting process

These patients will be consented by a variety of strategies. These can include consent to be contacted in the future which will be obtained at the time of screening (i.e., before the results of testing are available) and consent to participate once a positive test result is received. In all cases, we will explain the trial, answer their questions and document the consent process.

3.4.2 Interventions

Blinding: Patients and healthcare providers will not be blinded to treatment. To account for this, we have objective outcome definitions to minimize the opportunity for bias to influence event assessment.

Consenting participants will be randomized to receive AZCT plus usual care or usual care.

AZCT Arm

Chloroquine

Adults with a bodyweight ≥ 50 kg: 500 mg twice daily for 7 days
Adults with a bodyweight < 50 kg: 500 mg twice daily on days 1 and 2, followed by 500 mg once daily for days 3-7.

Azithromycin

500 mg on day 1 followed by 250 mg daily for 4 days

Usual Care

We will place no constraints for treating physicians with respect to usual care. We will document information on all key co-interventions, including information on drugs at the time of randomization and post randomization/during hospitalization.

3.4.3 Data collection

We will collect patient sex, age, disease severity, comorbidities (smoking, diabetes, heart disease, lung disease, immunosuppression, etc.), other medications, and trial outcomes. A minimum of 50 patients in this trial will be swabbed on days 0, 1, 3, 5, 7, 10, 14 for quantitative polymerase chain reaction (PCR) assessment of viral titre. In addition, a

subset of patients will have blood collected on the date of randomization and on day 3 for biomarker evaluation (targeted at markers of inflammation) and to biobank for later analysis.

3.5 Study Outcomes

3.5.1 Primary efficacy outcome

The primary outcome is admission to hospital or mortality.

3.5.2 Secondary efficacy outcomes

The secondary outcomes are mortality, admission to hospital, invasive mechanical ventilation, admission to ICU, renal replacement therapy, and extracorporeal support.

3.5.3 Tertiary efficacy outcomes

Tertiary outcomes are length of ICU stay, length of hospital stay, noninvasive mechanical ventilation, and duration of mechanical ventilation.

3.5.4 Translational outcomes

The translational outcomes are viral titre, ACE-2 levels and biomarkers.

3.5.5 Safety outcomes

The safety outcomes are malignant arrhythmia requiring intervention, agranulocytosis, Stevens-Johnson syndrome/toxic epidermal necrolysis, and retinal toxicity.

3.6 Safety outcome definitions

Malignant arrhythmia requiring intervention: Life-threatening ventricular arrhythmias: Regular, wide complex tachycardia lasting at least 30 seconds or associated with hemodynamic instability, polymorphic ventricular tachycardia (including torsades de pointes) of any duration, ventricular fibrillation of any duration requiring intervention.

Agranulocytosis: severe neutropenia, neutrophils below 500 cells/mm^3 of blood.

Stevens-Johnson syndrome/Toxic epidermal necrolysis: fever, mucositis, skin tenderness, and blistering.

Retinal toxicity: New onset loss of vision with associated bilateral change of retinal pigmentation (Bull's-eye maculopathy).

3.7 Statistical Considerations

3.7.1 Sample size calculation

The total minimum sample size required is **N=1000** (500 in each intervention arm) in order to have 90% statistical power to detect a rate ratio (RR) of 0.50 in the time to progression to requiring hospitalization or death, assuming a standard-of-care rate of progression of 12%. We also assumed an accrual time of 3-6 months and make allowance for cumulative loss to follow-up of 3% per arm although we expect this will be lower (i.e., <1%).

3.7.2 Statistical analysis methods

The primary hypothesis of efficacy will be conducted under the intention-to-treat principle; all randomized participants will be included in the analyses. All results will be analyzed with 2-sided level of significance of 0.05.

Given the fixed 45 day time period of assessment of the primary outcomes of progression, we will compare the proportions of progression events between the two study arms rather than the times to progression. The primary analysis will use the Z-test for comparison of proportions. We will also secondarily adjust the intervention effect for demographics, and exposure characteristics of participants, using logistic regression models.

Descriptively, Kaplan-Meier curves of the estimated time to hospitalization will be constructed. This secondary analysis will use the Log-rank statistic, stratified by center. Secondary analyses will include adjusting the intervention effect for demographic and exposure characteristics of the participants using Cox proportional hazards regression models.

3.7.3 Planned subgroup analyses

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

4. Inpatient trial: Preventing disease progression in COVID positive inpatients

4.1 Study Objectives

4.1.1 Primary objectives

To evaluate if AZCT compared to usual care results in reduced requirement for invasive mechanical ventilation or mortality for hospitalized patients diagnosed with COVID-19.

4.1.2 Secondary efficacy objectives

To evaluate if AZCT compared to usual care results in reductions in mortality, invasive mechanical ventilation, admission to intensive care unit, renal replacement therapy, and extracorporeal support in outpatients and inpatients diagnosed with COVID-19.

4.1.3 Tertiary efficacy objectives

To evaluate if AZCT compared to usual care results in reductions in length of ICU stay, length of hospital stay, non-invasive ventilation, and duration of ventilation.

4.1.4 Translational objectives

To evaluate if AZCT compared to usual care results in reductions of viral titre and inflammatory markers and to assess whether expression of the ACE-2 receptor is associated with mortality.

4.1.5 Safety objectives

To evaluate the whether the risk of the following is increased in patients receiving COVID-19 compared with those receiving usual care: malignant arrhythmia requiring intervention, agranulocytosis, Stevens-Johnson syndrome/toxic epidermal necrolysis, and retinal toxicity.

4.2 Study Design

4.2.1 Type of study

A multi-centre, open-label, parallel group, randomized controlled trial evaluating the efficacy and safety of the AZCT compared to usual care in inpatients with COVID-19.

4.2.2 Expected number of patients

The minimum sample size for the study is a minimum of 530 patients. However, this sample size may change as this trial has an adaptive design.

4.2.3 Allocation procedure

Randomization: Eligible patients that have provided informed consent will be randomized via the central IWRS at the Population Health Research Institute. Each patient will be assigned to one of two groups, AZCT plus usual care or usual care, in randomly permuted blocks (undisclosed sizes to maintain concealment of allocation). The allocation will be communicated to site personnel and patients will be made aware of their assignment. It is not practical to use placebo. It would likely entail considerable delays in starting the trial but the outcomes are likely to occur and be ascertained independent of the knowledge of the treatment allocation. Therefore, the results are likely to be unbiased.

Stratification: randomization will be stratified by site.

4.2.4 Duration of the study period for each subject

Patients will be followed for 45 days from the time of randomization. Data of events occurring during hospital will be obtained from hospital records supplemented by a telephone call or follow up at 7-10 days and at 45 days after randomization.
Participants will receive a telephone call at 12 months to determine vital status.

4.3 Study population

These patients are admitted (or waiting for admission) to the hospital for COVID-19 at the time of enrolment.

4.3.1 Inclusion criteria

1) Age ≥ 18 years of age
2) Informed consent
3) Diagnosis of active COVID-19 confirmed by established testing

4.3.2 Exclusion criteria

1) G6PD deficiency
2) Contra-indication to chloroquine or azithromycin
3) Already receiving chloroquine or azithromycin

4.3.3 Adaptive design features

Adaptive intervention arms: The DSMC and the Steering Committee will keep abreast of other ongoing trials and if other promising interventions emerge, may recommend adding (or replacing) one arm with the new promising intervention. They will assess the results of the translational objectives when available and may add a chloroquine loading dose if a large reduction in viral titres is not observed with the current regimen.

Adaptive sample size: Sample size calculations are based on disease progression rates that are not well known. We remain flexible, and the DSMC will be monitoring the possibility that the assumptions for sample size calculations may be modified with emerging information from this trial or other ongoing trials. If recruitment is going well, the steering committee may decide to extend recruitment as long as the independent DSMC does not terminate the trial for clear evidence of efficacy, futility (low probability) to detect a clinically meaningful difference (e.g. a 20% RRR in events) or concerns about safety.

Note, the DSMC will review the data from the two trials to make its decisions.

4.4 Study Procedures

In order to make it possible to implement this protocol where resources are scarce, we have simplified trial procedures, and data collection. Direct electronic data entry is encouraged.

4.4.1 Consenting process

All patients capable of consenting will provide informed consent. If the patient is deemed incapable of consenting, their substitute decision maker will be contacted. We will explain the trial, answer their questions and, document the consent process.

4.4.2 Interventions

Blinding: Patients and healthcare providers will not be blinded to treatment. To account for this, we have objective outcome definitions to minimize the opportunity for bias to influence event assessment.

Consenting participants will be randomized to receive AZCT plus usual care or usual care.

AZCT Arm

Chloroquine

Adults with a bodyweight ≥ 50 kg: 500 mg twice daily for 7 days
Adults with a bodyweight < 50 kg: 500 mg twice daily on days 1 and 2, followed by 500 mg once daily for days 3-7.

Azithromycin

500 mg on day 1 followed by 250 mg daily for 4 days

Usual Care

We will place no constraints for treating physicians on the therapies with respect to usual care. We will document information on all key co-interventions, including information on drugs at the time of randomization and post randomization /during hospitalization.

4.4.3 Data collection

We will collect patient sex, age, disease severity, comorbidities (smoking, diabetes, heart disease, lung disease, immunosuppression, etc.), other medications, and trial outcomes. A minimum of 50 patients in this trial will be swabbed on days 0, 1, 3, 5, 7, 10, 14 for quantitative polymerase chain reaction (PCR) assessment of viral titre. A minimum of 50 patients will have a blood sample collected on the day of randomization and on day 3. These samples will be used to measure inflammatory markers and ACE-2 levels and will be stored for future analyses.

4.5 Study Outcomes

4.5.1 Composite primary outcome

The primary outcome is mortality or need for invasive mechanical ventilation*.
*Patients intubated or requiring imminent intubation at the time of randomization will only be followed for the primary outcome of death.

4.5.2 Secondary efficacy outcomes

The secondary outcomes are mortality, invasive mechanical ventilation, admission to ICU, renal replacement therapy, and extracorporeal support.

4.5.3 Tertiary efficacy outcomes

Tertiary outcomes are length of ICU stay, length of hospital stay, noninvasive mechanical ventilation, and duration of mechanical ventilation.

4.5.4 Translational outcome

The translational outcomes are viral titre, inflammatory markers, and ACE-2 receptor levels.

4.5.5 Safety outcomes

The safety outcomes are malignant arrhythmia requiring intervention, agranulocytosis, and Stevens-Johnson syndrome/toxic epidermal necrolysis, and retinal toxicity.

4.5.6 Safety outcome definitions

Malignant arrhythmia requiring intervention: Life-threatening ventricular arrhythmias: Regular, wide complex tachycardia lasting at least 30 seconds or associated with hemodynamic instability, polymorphic ventricular tachycardia (including torsades de pointes) of any duration, ventricular fibrillation of any duration requiring intervention.

Agranulocytosis: severe neutropenia, neutrophils below 500 cells/mm³ of blood.

Stevens-Johnson syndrome/Toxic epidermal necrolysis: fever, mucositis, skin tenderness, and blistering.

Retinal toxicity: New onset loss of vision with associated bilateral change of retinal pigmentation (Bull's-eye maculopathy).

4.6 Statistical Considerations

4.6.1 Sample size calculation

The minimum sample size required is **N=530** (265 in each intervention arm) in order to have 90% statistical power to detect a 40% relative risk reduction (RRR) in the proportion progressing to mechanical ventilation or death, assuming a standard-of-care risk of progression of 30%. Since patients will be hospitalized, we assumed minimal (<1%) loss to follow-up.

4.6.2 Statistical analysis methods

The primary analysis of efficacy will be conducted under the intention-to-treat principle; all randomized participants will be included in the analyses. All results will be analyzed with 2-sided level of significance of 0.05. Given the rapid assessment of the primary outcomes of progression, and the expected absence of loss to follow-up, we will compare the proportions of progression events between the two study arms rather than the times to progressions. The primary analysis will use the Z-test for comparison of proportions. Secondary analyses will include adjusting the intervention effect for demographics, exposure characteristics, and severity of disease upon admission, using logistic regression models.

4.6.3 Planned subgroup analyses

We will explore whether the following variables modify treatment effect: age, sex, disease severity (admission to ICU at randomization versus not) and presence or absence of comorbidities.

5. Program Management and Sub-studies

5.1 Safety Monitoring and Reporting

Chloroquine and azithromycin have been extensively studied and have been used for many years and in many hundreds or thousands of patients, and their adverse effects profiles are well described. COVID-19 has been described in more than 400,000 patients and the clinical manifestations have also been extensively described.

All information concerning adverse events will be systematically collected, all data on safety and outcomes will be reviewed regularly by the independent DSMC and sent to regulatory authorities on a monthly basis.

5.1.1 Serious adverse events

For the purposes of this trial, study efficacy and safety outcomes, known adverse effects of study medications, and events that are expected to occur with high frequency in patients with COVID-19 infection will be captured on the CRF and will be exempted from the expedited reporting. All of these events will be included in the final study report and reviewed by the DSMC on an ongoing basis.

Only those events that are both serious and unexpected for the patient population under study and who are being treated with study medication will be reported to the regulatory agency in an expedited manner.

Adverse events that are not serious, but which lead to permanent discontinuation of study medication will be recorded and included in the final study report.

5.2 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 patient's eCRF. All data will be kept secure and confidentiality of all study patients will be carefully protected. Data will be validated, managed, and stored in a de-identified database on a secure server at PHRI.

5.3 Treatment Compliance Adherence

Participant treatment compliance will be documented.

5.4 Handling of Treatment Modification or Discontinuation

Prescribed study medication should be continued for the full course whenever possible. If the medication is stopped, the investigator should determine if treatment can be modified or re-initiated.

5.4.1 Study Drug Discontinuation

If the medication is discontinued, patients will be followed up according to the study procedures as specified in this protocol, up to the scheduled date of study completion, or up to recovery or stabilization of any serious and unexpected adverse event to be followed-up as specified in this protocol, whichever occurs last.

5.5 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 patients 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 patients will not be replaced.

5.6 Sub-studies

The steering committee may add sub-studies based on participating investigators' interests. Sub-studies of interest may relate to virology, biochemical parameters, imaging, etc.

5.7 Data Safety Monitoring Committee (DSMC)

An independent DSMC will review the accumulating study data after approximately every 50 patients 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 patients. 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 for benefit and harm as a general guideline. They will also be looking for consistency of efficacy results across both trials prior to recommending stopping any trial early. No modification of the level of significance of the final results is necessary with the higher 3 SD boundary for the Haybittle-Peto criteria.

The DSMC will also be monitoring the safety of the participants, focusing on adverse events and other safety indicators. Adverse events will be sent to the DSMC chair on a regular basis (e.g., after the first 50 patients in each trial and every month thereafter).

6. Study Organization

6.1 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.

6.2 Steering Committee

This group, consisting of the coordinating investigators, study statistician, and involved subject matter experts, will meet on a regular basis to assess study progress and discuss necessary interventions or protocol amendments as required.

7. Regulatory and Ethical Considerations Regulatory considerations

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

7.1 Ethics review committees

The protocol and informed consent for this study must be reviewed and approved by an appropriate Research Ethics Board (REB)/Independent Ethics Committee (IEC) before the study commences.

7.2 Responsibilities of the investigator(s)

The Investigator(s) undertake(s) to perform the study in accordance with Good Clinical Practice. 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.

7.2.1 Data collection on electronic case report forms (eCRFs)

It is the responsibility of the Investigator to prepare and maintain adequate and accurate eCRFs which have been provided by the study to record all observations and other data pertinent to the clinical investigation. All eCRFs should be completed in their entirety and in a timely fashion.

7.2.2 Curriculum vitae

An updated copy of the curriculum vitae for each Investigator and co-Investigator will be provided to the PHRI prior to the beginning of the study.

7.2.3 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 and the study sponsor, PHRI, and its agents may need to review patient 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 patient's identity will remain confidential.

7.2.4 Record retention

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

7.2.5 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.

8. Publication Policy

The results of the study will be published rapidly after study completion in the names of all wholehearted collaborators.

9. References

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