An Adaptive Randomized Platform Trial to Investigate the Efficacy of Novel Agents for Treatment of SARS-CoV-2 Infection Among High-Risk Outpatient Adults in Low and Middle Income Countries

|  |  |
| --- | --- |
| Study code | Tx for SARS-CoV-2 |
| Short title | Outpatient Management of SARS-CoV-2 for High-Risk Adults in LMICs |
| Initial investigational products for Brazil | Hydroxychloroquine (HCQ)  Lopinavir/ritonavir (LPV/r) |
| Initial investigational products for South Africa | LPV/r  Azithromycin |
| Other potential investigational products | Other chloroquine-based therapies, other antivirals, and other candidate regimens |
| Initial comparator | Ascorbic acid (placebo) |
| Date of protocol | 09 May 2020 |
| Protocol version | 1.0 |
| Protocol registry number | TBD |
| Trial Website | www.TogetherTrial.com |
| Summary of revision history | Not applicable |
| Sponsor | McMaster University |
| Funder | Bill and Melinda Gates Foundation |

**Signature Page**

The present trial protocol was subject to critical review and is approved in its present version by the following individuals:

|  |  |
| --- | --- |
| Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_ | Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
|  | Name: Edward J Mills, McMaster University |
|  | Role: Principal Investigator |
| Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_ | Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
|  | Name: Gilmar Reis, Pontifícia Universidade Católica de Minas Gerais |
|  | Role: Brazil Principal Investigator |
| Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_ | Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
|  | Name: Mark Cotton, Stellenbosch University |
|  | Role: South Africa Principal Investigator |

**Contact Information**

|  |  |
| --- | --- |
| Principal investigator | Dr. Edward Mills, Cytel  Phone: +1 778 317 8530; Email: [millsej@mcmaster.ca](mailto:millsej@mcmaster.ca) |
| Brazil Principal Investigator | Prof. Mark Cotton, Stellenbosch University  Email: [mcot](mailto:edecloedt@sun.ac.za)@sun.ac.za |
| South Africa Principal Investigator | Prof. Mark Cotton, Stellenbosch University  Email: [mcot](mailto:edecloedt@sun.ac.za)@sun.ac.za |
| South African Co-Principal Investigator/Lead Investigator | A/Prof. Eric Decloedt, Stellenbosch University  Email: [ericdecloedt@sun.ac.za](mailto:ericdecloedt@sun.ac.za) |
| South Africa Co-Principal Investigators | Prof. Jean Nachega, University of Stellenbosch  Email: jnacheg1@jhu.edu  Prof. Landon Myer, University of Cape Town  Email: [landon.myer@uct.ac.za](mailto:landon.myer@uct.ac.za) |

Table of Contents

[1. Synopsis 8](#_Toc38818733)

[2. Schedule of Activities 13](#_Toc38818734)

[3. Introduction 14](#_Toc38818735)

[3.1. Background 14](#_Toc38818736)

[3.2. Study Rationale 15](#_Toc38818737)

[3.2.1. COVID-19 and Antiviral Approaches 15](#_Toc38818738)

[3.2.2. Antiviral Effects of Chloroquine Analogues Against COVID-19 16](#_Toc38818739)

[3.2.3. Antiviral Effects of Azithromycin Against COVID-19 17](#_Toc38818740)

[3.2.4. Antiviral Effects of Lopinavir and Ritonavir Analogues Against COVID-19 17](#_Toc38818741)

[3.2.5. Antiviral Effects of Atazanavir Analogues Against COVID-19 17](#_Toc38818742)

[3.2.6. Rationale for Ascorbic Acid Control as a Comparator 18](#_Toc38818743)

[3.2.7. Rationale for Dosing Selection of Experimental Interventions 18](#_Toc38818744)

[3.3. Benefit/Risk Assessment 18](#_Toc38818745)

[4. Objectives and Endpoints 20](#_Toc38818746)

[5. Study Design 22](#_Toc38818747)

[5.1. Overall Design 22](#_Toc38818748)

[5.2. Participant and Study Completion 23](#_Toc38818749)

[6. Study Population 24](#_Toc38818750)

[6.1. Inclusion Criteria 24](#_Toc38818751)

[6.2. Exclusion Criteria 25](#_Toc38818752)

[6.3. Screen Failures 25](#_Toc38818753)

[6.4. Recruitment 26](#_Toc38818754)

[6.5. Co-enrollment Guidelines 26](#_Toc38818755)

[7. Treatments 27](#_Toc38818756)

[7.1. Treatments Administered 27](#_Toc38818757)

[7.2. Risks to the Participants 27](#_Toc38818758)

[7.2.1. Risks Associated Administration with experimental therapies 27](#_Toc38818759)

[7.2.2. Risks Associated with COVID-19 Diagnosis 28](#_Toc38818760)

[7.2.3. Management of Participants to Limit Risks of SARS-CoV-2 Transmission 28](#_Toc38818761)

[7.3. Dose Modification and Toxicity Management 28](#_Toc38818762)

[7.4. Method of Treatment Assignment 29](#_Toc38818763)

[7.5. Blinding 29](#_Toc38818764)

[7.6. Preparation/Handling/Storage/Accountability 30](#_Toc38818765)

[7.7. Treatment Compliance 30](#_Toc38818766)

[7.8. Concomitant Therapy 30](#_Toc38818767)

[7.8.1. Prohibited Medications 31](#_Toc38818768)

[7.8.2. Precautionary Medications 31](#_Toc38818769)

[7.9. Treatment After the End of the Study 31](#_Toc38818770)

[8. Discontinuation/Withdrawal Criteria 32](#_Toc38818771)

[8.1. Discontinuation of Study Treatment 32](#_Toc38818772)

[8.2. Withdrawal from the Study 32](#_Toc38818773)

[8.3. Lost to Follow-up 32](#_Toc38818774)

[9. Study Encounters 34](#_Toc38818775)

[9.1. Screening/Baseline Evaluation: Day 0/1 34](#_Toc38818776)

[9.2. Day 2 Through Day 13 35](#_Toc38818777)

[9.3. Days 3, 8 and 14 (+/-1 day) 35](#_Toc38818778)

[9.4. Day 14 35](#_Toc38818779)

[9.5. Optional Day 56: DBS for antibody development 36](#_Toc38818780)

[Participant Reimbursement 36](#_Toc38818781)

[10. Study Assessments and Procedures 37](#_Toc38818782)

[10.1. Efficacy Assessments 37](#_Toc38818783)

[10.1.1. Mid-nasal Swab 37](#_Toc38818784)

[10.1.2. Participant Survey 37](#_Toc38818785)

[10.2. Adverse Events 38](#_Toc38818786)

[10.2.1. Serious Adverse Events 38](#_Toc38818787)

[10.2.2. AE and SAE Attribution to HCQ or LPV/r 38](#_Toc38818788)

[10.3. Treatment of Overdose 38](#_Toc38818789)

[10.4. Safety Assessments 38](#_Toc38818790)

[10.5. Dried Blood Spot Optional Sub-study 39](#_Toc38818791)

[10.6. Biohazard Containment 40](#_Toc38818792)

[11. Statistical Considerations 41](#_Toc38818793)

[11.1. Sample Size Determination 41](#_Toc38818794)

[11.2. Populations for Analyses 42](#_Toc38818795)

[11.3. Statistical Analyses 42](#_Toc38818796)

[11.3.1. Efficacy Analyses 43](#_Toc38818797)

[11.3.2. Secondary endpoints 44](#_Toc38818798)

[11.3.3. Pharmacokinetic Analysis 45](#_Toc38818799)

[11.3.4. Exploratory Exposure-Response Analyses 45](#_Toc38818800)

[11.3.5. Combined Study Analysis 45](#_Toc38818801)

[12. References 46](#_Toc38818802)

[13. Appendices 49](#_Toc38818803)

[Appendix 1: Abbreviations and Terms 49](#_Toc38818804)

[Appendix 2: Protocol Structure 51](#_Toc38818805)

[Appendix 3: Study Governance Considerations 52](#_Toc38818806)

[Appendix 4: Pharmacokinetic Sample Collection and Analysis 57](#_Toc38818807)

[Appendix 5: Site-Specific Protocol Addendum Template 62](#_Toc38818808)

[Appendix 6: The inFLUenza Patient-Reported Outcome Instrument (Flu-PRO) – Modified for SARS-COV-2 70](#_Toc38818809)

[Appendix 7: WHO Ordinal Scale for Clinical Improvement 73](#_Toc38818810)

[Appendix 8: Hydroxychloroquine 74](#_Toc38818811)

[Appendix 9: Lopinavir-ritonavir 77](#_Toc38818812)

[Appendix 10: Azithromycin 79](#_Toc38818813)

[Appendix 11: Experimental intervention 82](#_Toc38818814)

# Synopsis

Expanded Title:

**TOGETHER Trial:** An Adaptive Randomized Platform Trial to Investigate the Efficacy of Novel Agents for Treatment of SARS-CoV-2 Infection Among High-Risk Outpatient Adults in LMICs

Short Title:

Outpatient Management of High-Risk Adults with SARS-CoV-2

Rationale:

Despite the fact that most hospitals are already overwhelmed and hospitalization will not be feasible even for severe COVID-19 cases in most of low- and middle-income countries (LMICs), the majority of current clinical trials is taking place in hospital settings and in high-income countries (HICs) ([www.covid19-trials.org](http://www.covid19-trials.org)). Many of these trials are also excluding marginalized population groups such as people living with HIV (PLHIV) and people with active or latent tuberculosis (TB) who are key populations of interest for LMICs. The burden of HIV and TB in LMICs is generally much higher than in HICs. For instance, the prevalence of HIV in LMICs is generally much higher with 13% HIV prevalence in South Africa and 0.5% in Brazil (UNAIDS, 2018). The incidence of TB in South Africa is 520 per 100,000 and 45 cases per 100,000 in Brazil (WHO, Global TB Report 2019).

There is a need to immediately start the clinical investigation of outpatient strategies in these resource-limited regions that are inclusive of these marginalized groups.

This protocol is for an adaptive platform trial for the treatment of high-risk adults with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection not requiring hospital admission for Brazil and South Africa, hereafter referred to as TOGETHER 2 and TOGETHER 3, respectively. This proposal builds on an US-based adaptive platform trial for high-risk SARS-CoV-2 adult outpatients (hereafter referred to as TOGETHER 1).

The primary research question is to the efficacy of experimental interventions to prevent LRTI among persons with SARS-CoV2 infection who are at high risk of progression. The primary outcomes of trial will include progression to LRTI, defined by SpO2<93% or 6% decrease in Sp02 from baseline; and presence of viral shedding from nasal swabs at day 10 of treatment. Other agents are rapidly being screened and developed for SARS-CoV-2 infection and could be incorporated into this protocol as additional arms. The flexible platform trial design will allow additional agents to be added and tested with standardized eligibility criteria, outcomes, and measurements. If an intervention is shown to be effective, this design would allow replacement of the placebo group with the effective intervention as the comparator.

Design:

This is an international multi-center adaptive randomized platform trial for the treatment of SARS-CoV-2 infection in high-risk adults not requiring hospital admission. Stratified randomization will be stratified based on country location, time since symptom onset (<48 vs. >48 hours) and HIV status at baseline.

Other chloroquine-based therapies, antiviral therapies, and other affordable candidate drug regimens that can be repurposed for COVID-19 may also be considered for this trial. The decision to add new therapeutic strategies will be made based on external findings with consultations of the local stakeholders. Therapies that can be repurposed for COVID-19 (e.g. lopinavir-ritonavir) will be prioritized since they offer more affordable and scalable therapeutic options for LMICs. The added arm may be tested with standardized eligibility criteria, outcomes, and measurements, as the other experimental interventions.

**Population:**

Men and women 18 years of age to 80 who test positive for SARS-CoV-2.

Eligible participants will be at increased risk of developing LRTI based on established risk factors for severe COVID-19 disease (at least one of the following):

* + Age ≥60
  + Presence of pulmonary disease, specifically moderate or severe persistent asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, emphysema, or tuberculosis
  + Diabetes mellitus (type 1 or type 2), requiring oral medication or insulin for treatment
  + Hypertension, requiring at least 1 oral medication for treatment
  + Coronary artery disease with history of graft or stent
  + Cardiac failure, Class 2 or greater using New York Heart Association functional class
  + History of organ or stem cell transplant
  + Immunocompromised status due to disease (e.g., those living with human immunodeficiency virus, confirmed malignancy)
  + Immunocompromised status due to medication (e.g., persons taking 20 mg or more of prednisone equivalents a day, anti-inflammatory monoclonal antibody therapies, or cancer therapies)
  + Body mass index ≥30

For evaluations of experimental interventions compared to control, a total of 165 persons per arm will be enrolled.

A second cohort of participants aged 18-59 without identified risk factors for progression to LRTI will be enrolled for the virologic endpoint (n=45 persons per arm).

Participants will be counselled about the preliminary *in vitro* data of the activity of interventions against SARS‑CoV-2 and equipoise regarding efficacy in humans given that there are only limited data at this time.

If additional data emerge on alternative potentially effective agents for SARS-CoV-2, additional arms can be added to the study as a new intervention appendix to the protocol. The standardized operating procedures and comprehensive statistical analysis plans will allow for integration of new arms.

Interventions:

* **Placebo**: Ascorbic acid 1000 mg orally twice daily for 1 day then 500 mg orally twice daily for 9 days
* **Hydroxychloroquine (HCQ):** HCQ 400mg twice on day 1, then 200mg twice a day for an additional 9 days
* **Lopinavir/ritonavir (LPV/r)**: LPV/r 800 mg-200 mg orally twice daily x 1 day, then 400 mg-100 mg twice daily for an additional 9 days
* **Azithromycin**: Azithromycin 1000mg orally daily x 1 day, then 500mg daily for an additional 9 days

Objectives and Endpoints:

|  |  |
| --- | --- |
| Objectives | Endpoints |
| Primary | |
| * To test the efficacy of experimental interventions to prevent progression to LRTI, among persons with SARS-CoV-2 infection who are at high risk of progression, compared to ascorbic acid. * To test the efficacy of experimental interventions to reduce SARS-CoV-2 viral shedding | * LRTI, defined by SpO2<93% or decline from baseline of 6% in 2 measurements at least 2 hours apart.   *Trial is statistically powered for this endpoint in both the high-risk and low-risk populations. Lower-risk population is included as an exploratory analysis and will be analyzed separately to the high-risk cohort.*   * Time to clearance of nasal SARS-CoV-2, defined as 1 negative swab. |
| Secondary | |
| * To test the safety of experimental interventions for treatment of high-risk outpatients with SARS‑CoV-2 infection | * Serious adverse events (including death, hospitalization) and adverse events resulting in treatment discontinuation |
| * To test whether any of the experimental interventions has an effect on hospitalization and describe the duration of hospitalization among persons who become hospitalized with COVID-19 disease | * Proportion hospitalized * Days of hospitalization |
| * To test whether any of the experimental interventions decrease resolution rate for symptomatic SARS-CoV-2 infection / COVID-19 disease | * Proportion of days with fever after randomization * Proportion of days with respiratory symptoms after randomization * Proportion of days with SpO2<93% for >1 hour/day after randomization |
| * To test whether any of the experimental interventions is associated with decreased viral shedding from self-collected nasal swabs over 14 days (Day 1, Day 3, Day 5, Day 7, Day 10 and Day 14)\*   \*Swab collection may be decreased to Day 1, Day 5 and Day 10 in participants where multiple swabbing is not feasible. | * Proportion of days with SARS-CoV-2 detected from mid-nasal swabs by PCR * Median quantity of SARS-CoV-2 detected from mid-nasal swabs by PCR |
| Exploratory (optional) | |
| * To assess pharmacokinetics of experimental interventions and potential associations with clinical and virologic outcomes | * Blood concentration of each experimental intervention in DBS |

Sample size:

The study will initially enroll 165 high-risk participants per arm to achieve 90% statistical power at 2-sided type I error rate of 5% for a pairwise comparison against the control to detect a treatment effect of relative risk reduction of 50% for the primary outcome(s) assuming control event rate of 30% for the primary outcome and 5% dropout rate.

A smaller cohort of 45 participants per arm aged 18 to 59 years and without risk factors for progression to LRTI will be enrolled for the co-primary virologic outcome.

Eligible participants will be randomized at an equal allocation ratio to study experimental interventions or placebo. If a second eligible patient is in the same household, both will be assigned to the same regimen. A blinded sample size re‑assessment may be done to possibly increase the target sample size up to 240 participants per arm in the high-risk cohort, based on observed control event rate, drop-out rate, and within household correlation (if any). As there is uncertainty in the recruitment rate, the decision on the timing for blinded assessment and the possible increase in sample size will be made by the DSMB that will monitor recruitment rate starting the start of second week.

During the sample size re-assessment, a blinded assessment of the observed CER of proportion of viral clearance and hospitalization will also be done. If the CER of viral clearance and hospitalization are adequately high to achieve adequate statistical power (e.g. 80 to 90%) at 5% type I error rate within the feasible sample size target range, switching the endpoint to either viral clearance and hospitalization for possible interim analyses and adaptations may be considered by the TSC.

Should a new intervention be added, allocation ratio will be adjusted to favor the new arm ensuring that control arm participants are still enrolled concurrently with active arms. An empirical Bayesian information borrowing method may be used to supplement the comparison of new intervention that is added later using past data collected.

Duration:

14 days of clinical follow-up per participant

Enrollment and completion TBD based on the observed recruitment rate

**Proposed sites:** Concurrent with the US site (TOGETHER 1), Brazil (TOGETHER 2) and South Africa (TOGETHER 3), we will work together to generative comparative data. Interventions for TOGETHER 1, 2 and 3 may differ depending on feasibility, evolving epidemiology and the evidence on interventions, and appropriateness of interventions in the local environments.

# Schedule of Activities

| Procedure | Screening | Self-Quarantine | | | | | | |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Treatment Period | | | | | | |
| Day 0a | Day 1a | Day 2a | Day 3a | Days  4 to 8 | Day 9a | Days  9 to 13 | Day 14a | Day 56 |
| Informed consent | X |  |  |  |  |  |  |  |  |
| Demography | X |  |  |  |  |  |  |  |  |
| Past and current medical conditions, including known pregnancy and/or lactation status | X |  |  |  |  |  |  |  |  |
| Concomitant medications | X |  |  |  |  |  |  |  |  |
| Laboratory documentation of COVID-19 testing | X |  |  |  |  |  |  |  |  |
| Inclusion and exclusion criteria | X |  |  |  |  |  |  |  |  |
| Randomization | X |  |  |  |  |  |  |  |  |
| Mid-nasal swaba |  | X |  | X | X |  | X | X |  |
| Study therapies |  | X | X | X | X | X | Xc |  |  |
| Daily Survey (including dosing and swab adherence, concomitant medications) |  | X | X | X | X | X | X | X |  |
| WURSS-11 Upper Respiratory Symptom Scale | X | X | X | X | X | X | X | X |  |
| Participant collected daily vitals (include temperature, pulse, SaO2, QT monitoring if indicated by the safety profile of the investigational drug, respiratory rate) |  | X | X | X | X | X | X |  |  |
| Contact with study clinicianb |  | X | X | X | X | X | X | X |  |
| Exit Contact Survey (including concomitant medications, symptoms, etc.) |  |  |  |  |  |  |  | X |  |
| Adverse Event review |  | X | X | X | X | X | X | X |  |
| Dried blood spot sample for investigational drug concentrations and anti-SARS-CoV-2 antibodies |  | X | 1 to 5 samples (no more than 1 per day) after dosing start | | | | | | X |
| SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. WURSS: Wisconsin Upper Respiratory Symptom Survey-11  Note: Depending on group assignment, the dosing regimen will vary.  a Screening and Day 1 evaluations will be conducted with participants physically present at the study site, Day 2 to 14 evaluations will be conducted through a web-based screening tool, HIPAA-compliant video conference (Telehealth), telephone, or text messaging. Screening and Day 1 evaluations may occur on the same day. Self mid-nasal swab for viral assessment will be done on Day 1, Day 3, Day 5, Day 7, Day 10 and Day 14. Swab collection may be decreased to Day 1, Day 5 and Day 10 in participants where multiple swabbing is not feasible.  b These evaluations will be as needed/requested by study participant.  c Last day of study medication will be administered on Day 10 | | | | | | | | |  |

# Introduction

This is an international multi-center adaptive randomized platform trial for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in high risk adults not requiring hospital admission. This protocol builds upon the US-based outpatient treatment platform trial.

The trial will initial start with placebo-equivalent (ascorbic acid) as a control in the clinical evaluation of the experimental interventions. Additional arms will be added as new agents or combinations are prioritized. In addition, if one of the agents is found to be superior over placebo, it may become the control group against which new interventions are measured. Evaluations include safety and tolerability, SARS-CoV-2 viral shedding, and development of lower respiratory tract infection (LRTI).

Initially, 165 patients per arm will be recruited and randomized (at the level of household) at an equal allocation. If more than one participant in the same household, all will be assigned to the same randomized group, preserving some degree of masking. The control data (ascorbic acid) from the US trial may be used to in conjunction with the control data from TOGETHER 2 and 3. A second group of 45 individuals per arm (18 to 59 years of age) without risk factors for progression to LRTI will be randomized at an equal allocation to the same experimental and control interventions.

* In the US for TOGETHER 1, the trial started with three arms: 1A) Placebo; 1B) HCQ; and 1C) LPV/r.
* In Brazil for TOGETHER 2, the trial will start with four arms: 2A) Placebo; 2B) HCQ; and 2C) LPV/r.
* In South Africa for TOGETHER 3, the trial will start with three arms: 3A) Placebo; 3B) LPV/r; and 3C) Azithromycin

During the study participants will perform the following:

* Collect mid-nasal swabs for viral detection for the co-primary trial endpoint
* Complete daily assessments for symptoms of LRTI and measurement of temperature, respiratory rate, pulse, and SpO2.
* Complete surveys that will include questions about symptoms from both the drug regimen and respiratory and systemic symptoms, review of concomitant medications, and other pertinent topics

During the 14 study days, participants take medication, complete surveys, and collect mid‑nasal swab for viral quantification and will assess symptoms for progression to LRTI. Physical assessments will include daily temperature, SpO2 assessment using a pulse oximeter.

## Background

SARS-CoV-2 is a coronavirus novel to the human population discovered in December 2019; it is currently the cause of a global pandemic.[1-3](#_ENREF_1) The World Health Organization (WHO) named the novel coronavirus SARS-CoV-2 and the disease caused by SARS-CoV-2 COVID-19. Person-to-person transmission has occurred in China, across temperate Asia, Europe, and North America, with sporadic cases in Africa and person-to-person transmission in the southern hemisphere. Accurate reporting is limited by availability of diagnostic testing. The WHO declared the COVID-19 pandemic a Public Health Emergency of International Concern on 30 January 2020.[4](#_ENREF_4)

Most deaths and severe pneumonitis have occurred in the elderly or in persons with underlying pulmonary or cardiac comorbidities or diabetes. In healthy adults, including pregnant women, it can cause a febrile, self-limited pneumonia. Infection appears less symptomatic in children and younger adults.[5](#_ENREF_5) Nevertheless, the burden of this pandemic to the global health and economic systems is expected to be substantial. No acquired immunity to this novel viral infection appears to exist in the human population globally, and no effective treatment or preventative agent is licensed at this time.

As with many infectious epidemics, household contacts, first responders, caregivers, and medical personnel attending persons with COVID-19 are at high risk of infection. The incubation time requires 14 days of quarantine for exposed individuals not wearing personal protective equipment [6](#_ENREF_6), and on 03 March 2020, WHO declared a global shortage of personal protective equipment leaving doctors, nurses, and other frontline workers dangerously ill-equipped to care for COVID-19 patients.[7](#_ENREF_7) Extensive absences from the care network and health system will degrade the ability to care not only for those with COVID-19 but also for routine healthcare issues as well. At the height of local epidemic, the health care system becomes overburdened with patients with respiratory illness. To date, rigorous self-isolation and lockdown have been required to contain the SARS-CoV-2, leaving entire societies to abruptly stop normal life. Interventions are urgently needed to stop viral spread and to decrease the morbidity and mortality cause by the infection. The ability to stop viral replication to prevent transmission of the virus and to prevent LRTI, which is associated with need for hospitalization and possibly mechanical ventilatory support, will be of benefit to the individual, the hospital system, and the health of the public. In addition, targeting those at highest risk of progression to LRTI and hospitalization will have the greatest impact on the pandemic. Including a cohort without risk factors for LRTI for the co-primary virologic outcome will provide additional data to inform whether the intervention is likely to have a public health benefit by reducing transmission in situations where self-isolation is not feasible.

## Study Rationale

### COVID-19 and Antiviral Approaches

SARS-CoV-2 is a novel betacoronavirus of zoonotic origin, similar to the coronaviruses severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS). Based on current evidence, case fatality rate for SARS-CoV-2 is about 3%, which is significantly lower than SARS-CoV (10%) and MERS-CoV (40%).[8](#_ENREF_8) However, SARS-CoV-2 has potentially higher transmissibility (R0: 1.4-5.5) than both SARS-CoV (R0: 2‑5) and MERS-CoV (R0: <1).[8](#_ENREF_8)

Our understanding of the viral pathogenesis of SARS-CoV-2 remains limited. However, it appears that the virus cell entry depends on binding of the viral spike (S) proteins to cellular receptors and on S protein priming by host cell proteases. SARS-CoV-2, like SARS-CoV, uses the same receptor angiotensin converting enzyme 2 (ACE2) on pulmonary epithelial cells for entry and the transmembrane serine protease 2 for S protein priming.[9](#_ENREF_9) The receptor binding domain of lineage B betacoronaviruses is a single, continuous domain that contains all of the structural information necessary to interact with the host receptor. Fusion is mediated at the cell membrane, delivering the viral nucleocapsid inside the cell for subsequent replication. ACE2 expression is found in the lung epithelial cells, vascular endothelium, renal tubular epithelium, and epithelia of the small intestine. Viral shedding has been localized primarily to respiratory droplets and fecal samples.[2](#_ENREF_2)

Medications to treat and/or prevent SARS-CoV-2 need to inhibit aspects of the viral life cycle, ultimately blocking replication. Already-approved and available medications are ideal for immediate evaluation for SARS-CoV-2 infection treatment and prevention. Two potential targets for anti-SARS-CoV-2 medications are viral polymerases and proteases.[10](#_ENREF_10) Pilot clinical studies are already ongoing for SARS-CoV-2 using various repurposed antiviral medicines (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov>). Similarities between SARS-CoV-2 with SARS-CoV and MERS suggest that antivirals with *in vitro* efficacy against SARS-CoV and MERS may be promising agents as SARS-CoV-2 PEP.[10](#_ENREF_10)

### Antiviral Effects of Chloroquine Analogues Against COVID-19 (TOGETHER 1 & 2)

TOGETHER 1 and TOGETHER 2 are studying hydroxychloroquine (HCQ). Chloroquine (CQ) was discovered in 1934 by Bayer and was used in 1945 as an antimalarial to become one of the most prescribed drugs globally, prior to the emergence of widespread drug resistance in *Plasmodium falciparum*.[11](#_ENREF_11) CQ was found to be effective against rheumatoid tenosynovitis in 1951.[12](#_ENREF_12) HCQ was licensed in the United States in 1955 as an antimalarial and as a drug for rheumatoid arthritis, and it was widely marketed for the latter due to a favorable safety profile with chronic use.[13](#_ENREF_13) The mechanisms of action for HCQ for treatment of rheumatoid arthritis and other autoimmune diseases are still not fully understood despite widespread use over the past 60 years.[14](#_ENREF_14)

CQ and HCQ have been proposed as potential agents for treatment and prevention against other infectious agents beyond malaria.[15](#_ENREF_15),[16](#_ENREF_16) The mechanism of action differs according to the pathogen: against intracellular bacteria and fungi by alkalinizing vacuoles containing the microorganisms, restoring the activity of other antibiotics, and against viral replication through alkalization of acidic organelles, namely endosomes, lysosomes, and Golgi vesicles.

CQ is effective *in vitro* against SARS-CoV coronavirus in Vero E6 cells with the EC50 ~8µM[17](#_ENREF_17) and had shown evidence of prevention activity in vivo.[18](#_ENREF_18) Hence, these re-purposed drugs were obvious hits for testing against SARS‑CoV-2. *In vitro* inhibition in Vero E6 cells against the novel coronavirus, SARS-CoV-2, has been published in recent weeks. Wang et al (2020) showed that the EC50 and EC90 for CQ in Vero E6 cells is 1.13 µM and 6.90 µM, respectively.[19](#_ENREF_19) Yao et al (2020) showed that the EC50 for CQ treatment of infected cells at 48 hours was 5.47 µM, whereas HCQ appeared slightly more potent, with EC50 of 0.72 µM at 48 hours.[20](#_ENREF_20) These levels appear to be within the range of exposures that could be achieved with standard HCQ treatment, and likely prophylaxis, due to concentrations of the drug achieved in the lung tissue.[20](#_ENREF_20) No *in vitro* data in the lung epithelial cells are available nor are any animal model data.

Multiple observational and small Investigator-initiated COVID-19 pneumonia treatment trials using CQ, HCQ, and variety of other medications are ongoing in China (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov>). Gao et al reported anecdotal efficacy of CQ as treatment for COVID‑19–associated pneumonia.[21](#_ENREF_21)

Antivirals of relevance to TOGETHER 3:

### Antiviral Effects of Azithromycin Against COVID-19

Azithromycin is a broad‑spectrum azalide antibiotic used to treat a number of bacterial infections, including pneumonia. Azithromycin has shown antiviral activity *in vitro* against Zika, Ebola, rhinoviruses, and other respiratory viruses.[22](#_ENREF_22),[23](#_ENREF_23) Although the mechanism of its antiviral activity is not clear, some findings suggest it may be associated with augmentation of interferon response.[23](#_ENREF_23) Alternatively, azithromycin may convey antiviral activity by increasing the pH of cell organelles such as endosomes and the *trans*-Golgi network.[24](#_ENREF_24) Changing the pH of intracellular vesicles may alter the glycosylation of ACE2, a key receptor for cell entry for SARS‑CoV-2.[25](#_ENREF_25),[26](#_ENREF_26) PK modelling supports the azithromycin regimen will include an additional loading dose on day 1 to allow earlier achievement of azithromycin concentrations in lung that consistently achieve the EC50 determined for SARS-CoV-2.

### Antiviral Effects of Lopinavir and Ritonavir Analogues Against COVID-19

Lopinavir-ritonavir (LPV/r), is a combination medication that has been used to treat HIV/AIDS. Lopinavir is a HIV type 1 aspartate protease inhibitor that is usually “boosted” with ritonavir to increase the plasma half-life of lopinavir through the inhibition of cytochrome P450. Lopinavir has been shown to have in-vitro inhibitory activity against SARS‑CoV [28, 29, 30]. Compared to ribavirin as a historical control group, it has been previously shown that lopinavir–ritonavir (400 mg and 100 mg, respectively) can reduce the risks of adverse clinical outcomes such as acute respiratory distress syndrome and death as well as viral load among patients with SARS. [29, 31, 32] Based on *in vitro* testing and previous clinical evaluation, LPV/r is an important treatment regimen that should be tested for SARS‑CoV-2. Although a recent open-label clinical trial did not show efficacy of LPV/r to decrease days of hospitalization or viral shedding, this trial focused on patients who were already hospitalized, likely due to LRTI and used a suboptimal dosing strategy. The proposed trial will treat participants earlier in the illness, and supported by PK modelling, will use a higher loading doses on day 1, which will allow earlier achievement of LPV concentrations exceeding SARS-CoV-2 EC50 values in the lung.

### Rationale for Ascorbic Acid Control as a Comparator

In healthy adults, COVID-19 disease is likely to present as an upper respiratory viral infection, characterized by a febrile disease with cough and fatigue.[30](#_ENREF_30) Symptom reporting may vary based on participants’ perception as to whether they are taking investigational antivirals or ascorbic acid, but the primary study endpoints of LRTI and viral shedding are not affected. There is no rigorously‑proven therapy for individuals with outpatient COVID-19 disease, although multiple therapies are under investigation.

Because there is not established therapy, use of a control is acceptable and ethical both for participants’ health and safety as well as ensuring the most rigorous trial design to evaluate an intervention for COVID-19 disease caused by SARS-CoV-2. As there are multiple intervention regimens with different dosing schedule and route, full blinding for patients and clinicians will not be feasible. Participants will be blinded to their allocation to the extent possible. If >1 individual from the same household is enrolled, all will be assigned to the same randomized group.

The dose of ascorbic acid chosen for this protocol is considered to be safe and well tolerated. All participants, regardless of assigned group, will be able to take additional ascorbic acid (e.g., over the counter vitamins, or through food) should they choose, as there is no known maximum daily safe dose of ascorbic acid. Clinical trial evidence has demonstrated that ascorbic acid, alone or in combination with other micronutrients, does not substantially reduce the risk of upper respiratory infections or severe consequences of infectious processes; thus, ascorbic acid is not expected to have a prevention effect for SARS-CoV-19 and is considered a placebo-equivalent product for this study.

### Rationale for Dosing Selection of Experimental Interventions

As the COVID-19 epidemic remains very fluid and new data are emerging from observational and clinical trials daily, this protocol is written to allow adaptation to incorporate additional medications throughout the trial. The rationale for dosing selection of each experimental interventions will be provided in each of the corresponding appendix. This modular structure of protocol is used for this platform trial that may end up adding new experimental interventions during the trial.

## Benefit/Risk Assessment

**There is equipoise as to whether the *in vitro* efficacy of any drug will translate into efficacy to prevent LRTI.** COVID-19 disease can be unpredictable in its severity, but a 3.4% mortality rate has been observed among clinical pneumonia cases. The elderly (>60 years) and those with medical comorbidities are at highest risk of poor outcomes.[1-3](#_ENREF_1) Moreover, transmission in younger persons amplifies infection in communities, putting susceptible persons at risk. There is no proven drug for treatment of those with COVID-19 disease.

**QT prolongation:** Azithromycin and LPV/r are widely used throughout South Africa without the requirement of QT measurements prior to initiation. LPV/r has been reviewed by CredibleMeds (crediblemeds.org) but the evidence available at this time did not result in a decision for it to be placed as a risk medicine for QT prolongation and Torsades de Pointes. Azithromycin has been associated with QT prolongation.  However we will exclude patients with a baseline QTc interval of > 470 ms in males, and > 480 ms in females.

**LPVr use in undiagnosed HIV-positive patients:**Ten days of LPV/r monotherapy is unlikely to cause resistance (high barrier to resistance) and is effective for viral suppression. The risk of HIV-associated immune reconstitution inflammatory syndrome (IRIS) is possible, and the time of onset varies from days to months after antiretroviral initiation. Ten days of LPV/r potentially carries a low risk of unmasking IRIS in undiagnosed HIV-positive patients. Should IRIS occur, it will be recorded as a serious adverse event (SAE). Testing for HIV prior to enrolment is not pragmatic as it exposes health care workers to SARS-CoV-2 infection and there is no referral pathway for newly diagnosed HIV-positive patients with SARS-CoV-2 co-infection. In this study we minimise interaction between study staff and patients using Telehealth.

**Drug interactions between study arms and rifampicin-treated and ART treated patients:**We included an explicit exclusion criteria to exclude patients with potentially clinically significant pharmacokinetic and pharmacodynamic drug interactions as determined by the study clinical pharmacologist. As far as possible, we want to study HIV-positive and patients treated for pulmonary tuberculosis as they are potentially a high risk for severe disease who could benefit from an early treatment. If one of the study experimental drugs are considered to put the patient at increased risk due to drug interactions, randomization for such patients will be limited to the study arms that are deemed to be safe by the study clinical pharmacologist.

**Misclassification as low-risk:** We thoroughly question participants about their medical history to best as possible correctly classify them as high- or low-risk for co-morbidities. We will also request participants for consent to access their medical records to review for co-morbidities.

# Objectives and Endpoints

|  |  |
| --- | --- |
| Objectives | Endpoints |
| Primary | |
| * To test the efficacy of experimental interventions to prevent progression to LRTI, among persons with SARS-CoV-2 infection who are at high risk of progression, compared to ascorbic acid. * To test the efficacy of experimental interventions to reduce SARS-CoV-2 viral shedding | * LRTI, defined by SpO2<93% or decline from baseline of 6% in 2 measurements at least 2 hours apart. *Trial is statistically powered for this endpoint in both the high-risk and low-risk populations. Lower-risk population is included as an exploratory analysis and will be analyzed separately to the high-risk cohort.* * Time to clearance of nasal SARS-CoV-2, defined as 1negative swab. |
| Secondary | |
| * To test the safety of experimental interventions for treatment of high-risk outpatients with SARS‑CoV-2 infection | * Serious adverse events (including death, hospitalization) and adverse events resulting in treatment discontinuation |
| * To test whether any of the experimental interventions has an effect on hospitalization and describe the duration of hospitalization among persons who become hospitalized with COVID-19 disease | * Proportion hospitalized * Days of hospitalization |
| * To test whether any of the experimental interventions decrease resolution rate for symptomatic SARS-CoV-2 infection / COVID-19 disease | * Proportion of days with fever after randomization * Proportion of days with respiratory symptoms after randomization * Proportion of days with SpO2<93% for >1 hour/day after randomization |
| * To test whether any of the experimental interventions is associated with decreased viral shedding from self-collected nasal swabs over 14 days (Day 1, Day 3, Day 5, Day 7, Day 10 and Day 14)\*   \*Swab collection may be decreased to Day 1, Day 5 and Day 10 in participants where multiple swabbing is not feasible. | * Proportion of days with SARS-CoV-2 detected from mid-nasal swabs by PCR * Median quantity of SARS-CoV-2 detected from mid-nasal swabs by PCR |
| Exploratory | |
| * To assess pharmacokinetics and exposure-response relationship of experimental interventions | * Blood concentration of each experimental intervention in DBS |

# Study Design

## Overall Design

The overarching goal of this study is to assess the effectiveness of interventions on the incidence of LRTI progression among high-risk adult outpatients with SARS-CoV-2 infection to inform public health control strategies.

This is an international multi-center adaptive randomized platform trial for the treatment of SARS-CoV-2 infection in high-risk adults not requiring hospital admission. Randomization will be stratified on country location, time since symptom onset (<48 hours or >48 hours), and HIV status at baseline.

Initially, this study will enroll up to 495 eligible adults (18 to 80 years of age) with high-risk for LRTI progression at baseline who are PCR-confirmed SARS-CoV-2 infection (165 per arm). An additional cohort of 45 eligible adults per arm (18 to 59 years of age) without risk factors for LRTI progression will also be enrolled for the co-primary virologic outcome. Eligible participants will be enrolled and randomized at an equal allocation. Recruitment rate will be assessed on a weekly basis starting at the end of second week after the first eligible patient is recruited and randomized.

* In the US for TOGETHER 1, the trial started with three arms: 1A) Placebo; 1B) HCQ; and 1C) LPV/r.
* In Brazil for TOGETHER 2, the trial will start with four arms: 2A) Placebo; 2B) HCQ; 2C) LPV/r and 2D) HCQ + LPV/r.
* In South Africa for TOGETHER 3, the trial will start with three arms: 3A) Placebo; 3B) LPV/r; and 3C) Azithromycin

The control data (ascorbic acid) from the US study may be used in conjunction with the control data from Brazil and South Africa.

Other chloroquine-based therapies, antiviral therapies, azithromycin, and other affordable candidate drug regimens that can be repurposed for COVID-19 may also be considered for this trial. The decision to add new therapeutic strategies will be made based on external findings with consultations of the local stakeholders. Therapies that can be repurposed for COVID-19 will be prioritized since they offer more affordable and scalable therapeutic options for LMICs. The added arm will be tested with standardized eligibility criteria, outcomes, and measurements, as the other experimental interventions.

An independent data and safety monitoring board (DSMB) will be convened for this study with expertise in COVID-19 or respiratory viruses and emerging epidemics as well as biostatistics. The purpose of the DSMB is to monitor the study for operational futility, social harms, and efficacy. The DSMB will also review the blinded sample size re-assessment plan, proposed sample size changes, and make recommendations on the allocation ratio, in case the new intervention arms are added.  If additional data emerge on alternative effective agents, the protocol could be modified through an amendment to alter its sample size and evaluate alternative therapies.

A blinded sample size re-assessment will be done to potentially increase the sample size target during the trial, should a lower control event rate (CER) and/or higher drop-out rate be observed. The decision on the timing of the sample size re-assessment will be made by the independent DSMB during the trial based on the observed recruitment rate. The DSMB will also decide on a possible interim analysis during the trial after the sample size re-assessment based on the information on the observed recruitment rate, the CER, the drop-out rate, and the final sample size target, if applicable.

The decision for interim analysis will be made in a blinded manner (e.g., based on pooled number of events). The interim monitoring plan (written by the Study Statistician) will define monitoring bounds to maintain the two‑sided type I error rate at the desired 5% (e.g. 97.5% or higher probability of superiority over the control group). Should a new experimental candidate be added during the trial, allocation ratios will be adapted to favor the new arm.

If additional data emerge on alternative potentially effective agents for SARS-CoV-2, additional arms can be added to the study as a new intervention appendix to the protocol. The standardized operating procedures and comprehensive statistical analysis plans will allow for integration of new arms.

## Participant and Study Completion

As an initial target, up to 165 high risk participants and 45 low risk participants per arm will be randomly assigned to study treatment or control. This sample size target will likely increase based on the blinded sample size re-assessment.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA). The clinical evaluation of each experimental intervention will be considered completed when sufficient number of participants complete the study to enable appropriate evaluation of the primary endpoint.

# Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

High-risk cohort:

1. Men or women 18-80 years, inclusive, at the time of signing the informed consent
2. Willing and able to provide informed consent
3. Laboratory confirmed SARS-CoV-2 infection, with test results within past 72 hours
4. At increased risk of developing severe COVID-19 disease (at least one of the following)
   * Age ≥60
   * Presence of pulmonary disease, specifically moderate or severe persistent asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, emphysema, or tuberculosis on treatment
   * Diabetes mellitus (type 1 or type 2), requiring oral medication or insulin for treatment
   * Hypertension, requiring at least 1 antihypertensive oral medication for treatment
   * Coronary artery disease with history of graft or stent
   * Cardiac failure, Class 2 or greater using New York Heart Association functional class
   * History of organ or stem cell transplant
   * Immunocompromised status due to disease (e.g., those living with human immunodeficiency virus, confirmed malignancy)
   * Immunocompromised status due to medication (e.g., persons taking 20 mg or more of prednisone equivalents a day, anti-inflammatory monoclonal antibody therapies, or cancer therapies)
   * Body mass index ≥ 30 kg/m2

Low-risk cohort:

1. Men or women, 18-59 years, inclusive without any risk factors for developing severe COVID-19 disease (point 5 above)
2. Willing and able to provide informed consent
3. Laboratory confirmed SARS-CoV-2 infection, with test results within past 72 hours
4. Body mass index < 30 kg/m2

## Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Known hypersensitivity to any of the study drugs
2. Currently hospitalized
3. Signs of respiratory distress prior to randomization, including respiratory rate >24 per minute and/or SpO2 < 93%
4. Chronic kidney disease (Stage IV or receiving dialysis)
5. Known liver disease or cirrhosis
6. Known personal or family history of long QT syndrome
7. Taking chronic medications associated with prolonged QT and may induce Torsades de Pointes as per CredibleMeds.org, including certain antipsychotic medications or antidepressants (e.g., citalopram, venlafaxine, and bupropion) and unable to stop during the trial
8. Baseline QTc interval of > 470 ms in males, and > 480 ms in females
9. Potentially clinically significant pharmacokinetic and pharmacodynamic drug interactions as determined by the study clinical pharmacologist\*

Note:

\*If one of the study experimental drugs are considered to put the patient at increased risk due to drug interactions, randomization for such patients will be limited to the study arms that are deemed to be safe by the study clinical pharmacologist. As it is likely that only the HIV-infected participants may have negative drug interactions with the experimental drugs, this reduced randomization is important to allow participation of HIV-infected participants on treatment and rifampicin-treated participants.

Pregnant and lactating persons will be eligible for enrollment into this study. TOGETHER 3 study drugs have been shown to be safe in pregnant women.

## Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened if there is a change in their eligibility.

## Recruitment

Each site will establish local recruitment and screening methods that operationalize protocol‑specified requirements for eligibility determination in a manner that is tailored to and most efficient for the local study setting and target study population. Each site will use a variety of recruitment approaches, including direct recruitment at clinics, referrals from other providers and SARS-CoV-2 testing sites and laboratories, and use of online and social networking websites and apps. Recruitment materials will educate participants about COVID-19, transmission within households, and epidemiology in the community. *See Appendix 5.*

The proposed sites have established track records of high-quality clinical research integrated into clinical care settings; annual retention rates in clinical trials conducted in these sites exceed 90%. The sites have large COVID-19 epidemics with regulation limiting contact to reduce infectious spread.

## Co-enrollment Guidelines

Participants may be co-enrolled in other research studies, provided that these are observational studies only. Any other exception requires approval of the Principal Investigators; if a participant clinically worsens, such as requiring hospitalization, it is expected that an exception will be automatically granted and participation in treatment studies permitted. The study team should be consulted for co-enrollment in studies that do not meet this guidance or if there are questions about eligibility for co-enrollment. For any co-enrolled study, combined blood draws should not exceed current Red Cross phlebotomy guidance.

# Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

## Treatments Administered

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **Dosage formulation** | **Route of Administration** | **Manufacturer** | **Instructions** |
| Ascorbic acid | 500 mg tablets | Oral | Ranbaxy Be-Tabs | 2 tablets every 12 hours for the first day and 1 tablet twice daily for the subsequent 9 days, for a total of 10 days of treatment. Take at approximately the same time each day with a meal. If a dose is missed, it should be taken as soon as possible. If it is less than 4 hours before the next dose, the dose should be skipped. |

Packaging and label: The medication will be dispensed in an otherwise-unmarked container with the study label. The container will be labeled with a unique identifier.

For the experimental interventions, the details on the dosage formulation, route of administration, manufacturer, and instruction are provided in their corresponding Appendix.

## Risks to the Participants

### Risks Associated Administration with experimental therapies

The safety of experimental therapies for treatment of patients with COVID-19 disease is unknown. However, their side effect profiles are well described, and these drugs are generally well tolerated. This protocol is using a short loading dose, not a sustained one.

COVID-19 may regardless be associated with cardiac effects. The proposed regimens may prolong QT, resulting in arrhythmias. Participants will be screened for QT prolongation. Long-term manifestations of LPV/r and other regimens, including hepatic disease, are not likely in short term exposure.

The risks associated with administration of each experimental intervention is provided in their corresponding appendix.

### Risks Associated with COVID-19 Diagnosis

Enrollment in this protocol will not impact the public health department’s advice for self‑quarantine. Enrollment may improve morale during quarantine for COVID-19 infection. COVID-19 may be associated with anxiety, and the ability to monitor for LRTI and interact with study clinicians may allay anxiety.

### Management of Participants to Limit Risks of SARS-CoV-2 Transmission

To limit the transmission of SARS-CoV-2, participants will receive visits via secure Telehealth in order to limit the movement of persons with potential SARS-CoV-2 and leave clinical space free for ill patients requiring care. Also, to limit exposure in waiting rooms clinical specimens will be self-collected and collected by a study driver. This will also eliminate exposure of study personnel to SARS-CoV-2.

## Dose Modification and Toxicity Management

If a study therapy dose is missed, it should be taken as soon as possible. If it is less than 4 hours before the next dose, the dose should be skipped.

Modification for toxicities is discussed below. Only toxicities related to study medications provided through the study will be considered in the toxicity management section.

**Grade 1 or 2**

Participants who develop Grade 1 or 2 toxicity (per division of acquired immunodeficiency syndrome [DAIDS] adverse event [AE] Grading Table; see: <https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf>) that is considered to be related to the study medication may continue study treatment at the discretion of the site Investigator with close follow-up. If a participant chooses to discontinue study treatment, the site should notify the study protocol team within 7 days. These participants will remain on study, off study treatment, and have all evaluations performed.

**Grade 3**

* Participants who develop a Grade 3 symptomatic toxicity thought by the site Investigator to be related to study drug should have study product withheld, and the site should consult with the Core Protocol team. The participant should be reevaluated every 2 days until the AE returns to Grade ≤2, at which time study drug may be reintroduced at the discretion of the site Investigator in consultation with the protocol team.
* Participants experiencing Grade 3 toxicity requiring permanent discontinuation of study product should be followed up weekly until resolution of the toxicity. Participants will have premature study treatment discontinuation evaluations performed. These participants will remain on study, off study treatment, and have all evaluations performed per the SoA.

**Grade 4**

* Participants who develop a Grade 4 symptomatic toxicity will have study product permanently discontinued, and the site should notify the Principal Investigator within 72 hours.
* Participants experiencing Grade 4 toxicity requiring permanent discontinuation of study product should be followed up weekly until resolution of the AE or return to baseline. These participants will remain on study, off study treatment, and have all evaluations performed per the SoA.

**Specific Management of Toxicities Related to Study-Provided Drugs**

Specific management details of toxicities related to study provided drugs are provided in their corresponding appendix.

## Method of Treatment Assignment

Participants will be randomized at an equal allocation ratio between experimental intervention and control groups at the level of the household (all eligible participants in 1 household will receive the same intervention). The randomization plan will be overseen by the Study Statistician. The randomization code and resulting allocation list will be generated and overseen by the Study Statistician. The list will be blocked and stratified by site and risk level.

## Blinding

As there are multiple intervention regimens with different dosing schedule and route that make blinding for patients and clinicians will not be feasible. The medications are not identical-appearing and dosing is different for the active agents so blinding will operate in different ways across those involved in the study. This study will preserve blinding for the laboratory testing and study statisticians.

* The bottle of medication they receive will not identify the treatment allocation, only the number and frequency of pills to be taken. If >1 participant per household is randomized, all will receive the same treatment. However, full blinding of patients will likely not be possible.
* While the study medication will be dispensed directly to participants, full blinding of the treating clinicians will not be feasible given that there are multiple intervention regimens.
* Laboratory testing for viral shedding will be blinded, as laboratory staff will not be informed of randomized assignment. The viral shedding endpoint of the trial is an objective one, unlikely to be altered by unmasking, should it occur.
* Study pharmacy staff will be unblinded, as they will prepare the study medication.
* The study statistician will be blinded for analysis purposes.

LPV/r and other regimens have a different dosing schedule and a different shape but participants in a household will all receive the same assignment and study clinicians will not see the study medication, to mimic some blinding.

The participants will be blinded to their randomization group once assigned. At enrollment, the unblinded Study Pharmacist will use the randomization code revealed at the point of randomization to provide the participant with their group assignment and dispense the allocated study medication in a bottle marked with the study label. The medication and medication information, mid-nasal swabs sufficient to complete the study procedures, *DBS sampling kit, if within the sub-study,* and study instructions will be provided to the participant.

## Preparation/Handling/Storage/Accountability

Drugs should be stored at room temperature, as per package insert. Records must be maintained that document receipt, release for dosing, disposal, or return to the sponsor.

## Treatment Compliance

The participant will be contacted to ensure that they received the box of study supplies; were able to collect the mid-nasal swab and store it appropriately; and took their medication as prescribed. Participants will be asked to complete a survey that includes information regarding treatment administration. *In a sub-study, azithromycin and lopinavir-ritonavir concentrations via a DBS will also be evaluated.*

Consultation via Telehealth, text messaging, or telephone will be available to provide support to the participant to complete study procedures.

## Concomitant Therapy

Participants will be asked about concomitant medications at the screening/baseline evaluation visit. During the study, participants will be asked to complete Surveys (Daily Survey and Exit Contact Survey) that include information regarding any medication or vaccine (including over‑the‑counter or prescription medicines, vitamins, and/or herbal supplements) that the participant receives during the study. At each contact, the Investigator should question the participant about any medication taken. Participants taking hormonal contraceptives to prevent pregnancy will be educated that they will need to use a backup form of birth control during the study period.

## Treatment After the End of the Study

No additional treatment will be provided at the end of the study.

# Discontinuation/Withdrawal Criteria

## Discontinuation of Study Treatment

Study treatment will be discontinued for the following reasons:

* Hospitalization
* Requirement for prohibited concomitant medications or other contraindication to study product
* Occurrence of an AE requiring discontinuation of study product
* Request by participant to terminate study treatment
* Clinical reasons believed to be life-threatening by the physician, even if not addressed in Section 7.2

Participants who stop study product should continue study participation off study product with continued evaluations as per the SoA. The reason for study product discontinuation should be recorded.

## Withdrawal from the Study

* A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time for the following reasons:
  + At the request of the primary care provider if he/she thinks the study is no longer in the best interest of the participant
  + Participant is judged by the Investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
  + At the discretion of the Institutional Review Board/Ethics Committee or government agencies as part of their duties, Investigator, or industry supporter
* If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent.
* If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
* See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

## Lost to Follow-up

A participant will be considered lost to follow-up if he/she is unable to be contacted by the study site.

The following actions must be taken if a participant fails to comply with required study procedures:

* The site must attempt to contact the participant as soon as possible and counsel the participant on the importance of maintaining the assigned procedure schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
* Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s medical record.
* Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

# Study Encounters

The current COVID-19 pandemic has placed a significant burden on the healthcare system. For this study, specimen and data collection will be conducted to minimize impact of non-ill participants within the healthcare system.

Participants will be instructed to seek clinical care should they manifest any signs or symptoms of LRTI requiring medical intervention.

## Screening/Baseline Evaluation: Day 0/1

Screening and enrolment will be done with the participant physically present.

**Day 0 evaluations are as follows:**

* Informed consent
* Collection of demographic information
* Collection of past and current medical conditions, including known pregnancy and/or lactation status
* Collection of concomitant medication information
* Collection of information regarding exposure to the index case
* Check of inclusion and exclusion criteria
* Collect mid-nasal swab for PCR

Eligible participants will be randomized. Participants will receive a monitoring kit at enrolment, which will include thermometer and SpO2 device. Participants will be instructed how to self-assess respiratory rate, temperature and oxygen saturation. A study driver wearing personal protective equipment will deliver and collect study related mid-nasal swabs and DBS cards as needed.

**The participant will do the following on Day 1:**

* Take study therapy (as assigned)
* Complete Daily Survey (online, telephone, or text messaging). This Survey will include confirmation of adherence to study therapy dosing and daily swab collection, concomitant medication review, and symptoms review and objective measures including SpO2, respiratory rate, temperature and pulse. In addition, the Baseline Dyspnea Index survey will be completed.

*Instructions for skin puncture and DBS sample preparation are provided in Appendix 4. A study team member will be available via Telehealth, telephone, or text messaging to provide support for completion of this study procedure.*

**Screening/Day 0 and Day 1 procedures can occur on the same day.**

The SARS-CoV-2 positive test results will be confirmed through laboratory records.

## Day 2 Through Day 13

The participant will do the following every day from Day 1 through Day 13, inclusive:

* Collect mid-nasal swab for PCR on Day 3, Day 5, Day 7 and Day 10. (Swab collection may be decreased to Day 5 and Day 10 in participants where multiple swabbing is not feasible.)
* Take study therapy (as assigned)
* Complete Daily Survey (online, telephone, or text messaging). This Survey will include confirmation of adherence to study therapy dosing and daily swab collection, concomitant medication review, AEs, and symptoms review and objective measures including SpO2, respiratory rate, temperature and pulse. In addition, the Transitional Dyspnea Survey will be completed.
* *If in DBS Sub-study, collect DBS samples for analysis of concentration of assigned experimental intervention at any time during this period (1 to 5 times) after study drug dosing has commenced. No more than 1 sample per day should be collected.*

A study team member will be available via Telehealth, text messaging, or telephone to provide support for completion of study procedures. The driver will collect the swabs as required.

## Days 3, 8 and 14 (+/-1 day)

Contact with study clinician or staff will be conducted via telemedicine (Telehealth) or telephone. Participants will be clinically assessed for signs and symptoms of respiratory distress and will have in person assessment of AEs. As needed, additional contact with the study clinician or staff will be conducted at the request of the participant (e.g., if developing concerning symptoms or an adverse event) or if needed to clarify study procedures or follow-up symptoms.

## Day 14

The participant will do the following on Day 14:

* Collect mid-nasal swab for PCR (May be omitted in participants where multiple swabbing is not feasible).
* Complete Daily Survey (online, telephone, or text messaging). This Survey will include confirmation of adherence to study therapy dosing and daily swab collection, concomitant medication review, and symptoms review and objective measures including SpO2, temperature and pulse.
* *If in DBS Sub-study*, *collect DBS samples for analysis of concentration of assigned experimental intervention, if not already collected.*

A study team member will be available via Telehealth, text messaging, or telephone to provide support for completion of study procedures.

Clinical outcomes will be confirmed through the electronic health record, if possible.

## Optional Day 56: DBS for antibody development

## Participant Reimbursement

Participants will be reimbursed on Day 14. No reimbursement will be provided to index cases for questionnaire completion and referral of their close contacts. No reimbursement will be provided for unscheduled Telehealth visits requested by the participants for support with study procedures.

# Study Assessments and Procedures

* Study procedures and their timing are summarized in the SoA.
* Protocol waivers or exemptions are not allowed.
* Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
* Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
* All baseline evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
* Procedures conducted as part of the participant’s routine clinical management and obtained before signing of the informed consent form may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
* *Blood samples will only be collected as a part of a sub-study. The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 10 mL.*

## Efficacy Assessments

### Mid-nasal Swab

Participants will collect mid-nasal swabs for viral detection at Day 1, Day 5 and Day 10. If the preliminary reports prove reproducible, these could be replaced by saliva samples which would be preferable for a number of reasons.

Participants will receive a swab kit.

Participants will collect and store their nasal swabs in a box for pick up.

The used swabs will be collected by the study drivers.

Swabs will be subjected to quantitative RNA amplification and tested for SARS-CoV‑2.

### Participant Survey

Participants will be asked to complete Surveys (Daily Survey and Exit Contact Survey) that will include questions about symptoms from both the drug regimen, review of concomitant medications. A modified baseline and transitional dyspnea index survey will be utilized on a daily basis to assess dyspnea.

## Adverse Events

Participants will be asked to complete Surveys (Daily Survey and Exit Contact Survey) that include information on any symptoms that they are experiencing. In addition, AE review by a staff member (via telephone, Telehealth, or text messaging) will be performed.

All AEs must be recorded on electronic case report forms (eCRFs) if any of the following criteria have been met:

* All AEs meeting SAE definition

### Serious Adverse Events

An SAE is defined as any untoward medical occurrence that:

* Results in death
* Is life-threatening
* Requires inpatient hospitalization or prolongation of existing hospitalization
* Results in persistent or significant disability/incapacity
* Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above

All AEs that are recorded must have their severity graded. To grade AEs, sites should refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS Regulatory Support Center website at <https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf>.

### AE and SAE Attribution to LPV/r or azithromycin

In those randomized to receive LPV/r or azithromycin, all AEs and SAEs should have attribution recorded as LPV/r or azithromycin related or not related, in the judgment of the site Investigator.

## Treatment of Overdose

Overdose of experimental regimens should be managed according to the labeling information (see appendices)

Ascorbic acid exhibits low toxicity; risks from overdose are expected to be minimal.

## Safety Assessments

Safety will be assessed via participant Surveys, as shown in the SoA.

Participants will be asked to complete Surveys (Daily Survey and Exit Contact Survey) that include questions about their health, healthcare seeking, symptoms, illness within their household, contact, and mobility. Qualifying events will be recorded on the eCRF and reported as AEs, as described in Section 10.2.

## Dried Blood Spot Optional Sub-study

Participants will be invited to provide a dried blood spot (DBS) sample for therapy concentration and pharmacokinetics of the medications as well as for SARS-CoV-2 antibody testing. These samples will be collected and stored. For participants not wishing to participate in the DBS sub‑study, this will not be considered a protocol deviation. Participants will receive instructions for DBS self-collection in writing, with telephone, Telehealth, and text messaging options as support. Once cards have been dried, they will be collected by the study courier and returned to the laboratory. The aim of the DBS Sub-study is to evaluate investigational drug concentrations as an adherence measure and the PK of LPV/r azithromycin. If serological assays for SARS-CoV-2 are available, stored DBS may be tested for SARS-CoV-2 antibodies.

***Pharmacokinetics***

The exposure-response relationship of investigational therapies of treated for SARS-CoV-2 has not been established. Population PK analyses can be used to further inform dose selection in other populations and support concentration-response investigations with efficacy and safety outcomes. To accomplish this, sparse PK sampling techniques can be employed. This would involve collection of whole blood at 1 to 5 times after dosing has commenced. The time of collection post-dose can be random; however, no more than 1 sample per day should be collected.

The basic requirements for PK sampling are as follows:

1. Accurate record of time of the dose prior to the blood sampling (dd:mm:yy; hh:mm)
2. Accurate recording of time of blood sampling (dd:mm:yy; hh:mm) for each blood sampling.
3. Whole blood can be obtained by venipuncture or capillary blood by skin puncture using a lancet.
4. Approximately 100 µL of blood is then applied to filter paper as outlined in the appendix.

The DBS analysis will be performed by the Division of Clinical Pharmacology, Stellenbosch University.

***Anti-SARS-CoV-2 Antibody Testing***

DBS sample for serology will be collected at Day 56 and tested for SARS-CoV-2 antibodies provided that an appropriate test is available. The relevant permits including a material transfer agreement (MTA) will be applied for / drafted should SARS-CoV-2 analysis be performed outside Stellenbosch University.

## Biohazard Containment

As the transmission of SARS-CoV-2 and other respiratory droplet pathogens can occur through contact with respiratory droplets and contaminated surfaces, precautions will be employed by all personnel in the handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

# Statistical Considerations

## Sample Size Determination

The sample size required to show a 50% treatment efficacy (i.e. relative risk reduction of 50%) is entirely dependent on the control event rate (CER). Sample size calculations used an estimated 30% CER.

The table below shows the sample size required at various treatment effects, CER, and drop-out rates for operating characteristics of 90% statistical power and two-sided type I error rate of 5%. Power may be lower depending on CER and drop-out rate (Table 1). As the initial sample size target, 165 per arm has been initially chosen for each experimental group to achieve 90% power with 0.05 two‑sided Type 1 error for a pairwise comparison against the control (ascorbic acid) to detect at least 50% treatment efficacy in reducing the progression to LRTI (primary endpoint) assuming a CER of 30% and 5% drop-out rate.

Table 1 Sample Size Per Arm Required to Detect a Relative Risk Reduction of 40% to 60% Under Various Control Event and Drop-out Rates

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **RRR** | **Drop-out rate = 0%** | | | **Drop-out rate = 5%** | | | **Drop-out rate = 20%** | | |
| **CER=10%** | **CER=20%** | **CER=30%** | **CER=10%** | **CER=20%** | **CER=30%** | **CER=10%** | **CER=20%** | **CER=30%** |
| 40% | 962 | 437 | 261 | 1013 | 460 | 275 | 1202 | 546 | 327 |
| 50% | 578 | 263 | 158 | 609 | 277 | **165** | 723 | 329 | 198 |
| 60% | 375 | 171 | 103 | 395 | 180 | 108 | 469 | 214 | 128 |

**Acronyms**: CER: Control event rate; RRR: Relative risk reduction.

Sample size calculation was done with the desired operating characteristics of 90% statistical power and 5% type I error rate (two-sided).

As illustrated in the table above, the statistical power will depend heavily on the observed CER. Given uncertainty of the target population, the final target sample size will be re-estimated after four weeks after the first patient is randomized using the observed CER and drop-out rate in the control group as a blinded sample size re-assessment. As it is difficult to predict the enrollment rate, the recruitment rate will be assessed on a weekly basis starting at the end of second week.

The sample sizes for TOGETHER 2 and 3 were determined based on the sample size calculation for TOGETHER 1 (US trial). The initial sample size target for TOGETHER 1 is 165 patients per arm that will achieve 90% power with 0.05 two‑sided Type 1 error for a pairwise comparison against the control group (ascorbic acid) to detect treatment effect of 50% relative risk reduction (RRR) in reducing the progression to LRTI (primary endpoint) assuming a control event rate (CER) of 30% and 5% drop-out rate.

Given uncertainty of the target population, a blinded sample size re-assessment will be done to potentially increase the sample size target during the trial, should a lower control event rate (CER) and/or higher drop-out rate be observed. The decision on the timing of the sample size re-assessment will be made by the independent data safety monitoring board (DSMB) during the trial based on the observed recruitment rate. The statistician part of the DSMB will assess the CER and drop-out rate (at time to be determined) and re-calculate the sample size required to achieve 90% statistical power at 5% two-sided type I error rate to detect a treatment effect size of 50% RRR.

During the time of sample size re-assessment, a blinded assessment of the observed CER of proportion of viral clearance and hospitalization will also be done. If the CER of viral clearance and hospitalization are adequately high to achieve adequate statistical power (e.g. 80 to 90%) at 5% type I error rate within the feasible sample size target range, the TSC may consider switching the endpoint to either viral clearance and hospitalization for possible interim analyses and adaptations.

This will be done with proper firewall to maintain blinding of the information on the re‑calculated sample size.

## Populations for Analyses

For analysis purposes, the following populations are defined and will be described in greater detail in the trial Statistical Analysis Plan:

|  |  |
| --- | --- |
| Population | Description |
| Intention to Treat (ITT) | All enrolled participants: high-risk group for the primary clinical endpoint; high- and low-risk groups (separately) for the primary virologic endpoint. |
| PK evaluable | Participants from the DBS Sub-study with at least 1 interpretable PK sample |

DBS: dried blood spot; PK: pharmacokinetic;

## Statistical Analyses

The Statistical Analysis Plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, the detailed analytical plans with endpoints and procedures for accounting for missing, unused, and spurious data. An Interim Monitoring Plan will also be developed to describe approaches for re-estimation of sample size and any planned interim analyses. This section presents a brief summary of the planned statistical analyses of the primary and secondary endpoints (these are listed in Section 4).

### Efficacy Analyses

Demographic characteristics (age, sex, race) of each study group will be tabulated.

The mean age (plus range and standard deviation) by sex of the enrolled participants, as a whole and per group, will be calculated.

**Primary analyses:**

The primary analyses will be conducted on the ITT population overall and by cohort. Participants randomized to each active arm will be compared to participants randomized to placebo (ascorbic acid). The primary analysis will make use of all participants randomized to placebo, whether contemporaneously enrolled or not using an Empirical Bayesian information borrowing method (described below). Due to anticipated heterogeneity in risk of disease progression, pre-specified baseline variables, including age, weight, and days of symptoms at time of enrollment will be included in the model to increase precision.

**Sensitivity analysis:**

The primary analyses will be repeated replacing randomization arm by actual treatment to account for possible off-label use of and noncompliance to the investigational products.

**Subgroup analyses:**

All subgroup analyses will be pre-specified in the Statistical Analysis Plan. Any further subgroups will be considered ad hoc.

**Empirical Bayesian information borrowing method:**

In the case that a new experimental treatment is added into this platform trial, there will already be data collected from patients who are enrolled prior (past data). To incorporate the past control data with the concurrent control data from patients who are concurrently enrolled, empirical Bayesian information borrowing method will be used[32](#_ENREF_32). Instead of using concurrent data only, combining past data with the concurrent data can potentially be advantageous in terms of statistical power and lower number of participants that are needed to be randomized to the control arm. This is particularly important for possible improved ethics and feasibility for the context of conducting a platform trial for SARS-CoV-2. Additionally, in the case that relevant external trial data become available, this empirical information borrowing method may be used. The DSMB, which will contain clinical experts, will make on whether to include or ignore the external trial data. The Study Statistician will assess the similarities of the external trial(s) to this clinical trial in terms of eligibility criteria, trial location, data collection procedures, and the reliability and comprehensiveness of the available dataset. If deemed appropriate, the empirical Bayesian information borrowing method will be used to determine the degree of the information that can be “borrowed” from the external dataset and be used for the statistical comparison.

As there are multiple randomized clinical trials that are either ongoing or being planned right now for SARS-CoV-2 with potentially relevant interventions, it is important to plan for an approach, such as this empirical Bayesian borrowing method, that can potentially incorporate these external data with the internal data. An important feature of this method is the avoidance of use of any subjective or informative prior distributions that may become a point of dispute in certain schools of thought. To our knowledge, there are currently two published clinical trials with potentially relevant interventions as the ones that are proposed for this adaptive platform trial. [36, 37] In the Chinese trial registry, there are more than 300 interventional trials that have been registered for SARS-CoV-2. It is very likely that external data source will become available during the trial.

The full technical details on the empirical Bayesian information borrowing method will be described in the Statistical Analysis Plan.

**Missing Data:**

Due to the design of the study and retention activities, we expect to be able measure outcomes on all participants. However, in the unlikely event of a missing test result, the missing data will be imputed.

**Interim Analysis:**

The DSMB will decide on a possible interim analysis during the trial after the sample size re-assessment based on the information on the observed recruitment rate, the CER, the drop-out rate, and the final sample size target, if applicable. The decision for interim analysis will be made in a blinded manner (e.g., based on pooled number of events). The interim monitoring plan (written by the Study Statistician) will define monitoring bounds to maintain the two‑sided type I error rate at the desired 5% (e.g. 97.5% or higher probability of superiority over the control group). Should new experimental candidates be added during the trial, allocation ratios will be adapted to favor the new arms.

### Secondary endpoints

All secondary endpoints will be assessed in the Intention-to-Treat population overall and by cohort.

#### Safety Analyses

All safety analyses will be performed on the Intention-to-Treat population. AEs will be compared by study group.

#### Hospitalization

Hospitalization rates between the groups will be compared using logistic regression stratified by site. Number of days hospitalized will be described graphically and by median and interquartile rage.

#### Symptom Resolution

Days with fever after randomization, respiratory symptoms after randomization and Sp02<93% after randomization will be modeled using Poisson regression stratified by site with an offset for number of days of observation.

### Pharmacokinetic Analysis

Sparse PK from DBS will be analyzed using standard population PK analysis methodologies using standard software such as NONMEM® V7.4 or Phoenix NLME V8.2.

### Exploratory Exposure-Response Analyses

PK-evaluable participants will have post-hoc individual concentration profiles and exposure estimates determined for exploratory exposure-response analyses against primary and secondary efficacy and safety endpoints. Exploratory PK/pharmacodynamic analyses will be performed as the data allow.

### Combined Study Analysis

This protocol is being published as a model protocol for other institutions to consider as they undertake studying treatments to prevent development of LRTI among outpatients with SARS-CoV-2 infection. It is hoped that individual patient data from similar studies can be pooled into a combined study analysis. De-identified data from the present study will be made available for these purposes in accordance with the funder’s open access policy (<https://www.gatesfoundation.org/how-we-work/general-information/open-access-policy>).

# Reimbursement

The South African Health Products Regulatory Authority Clinical Trial Participant Time, Inconvenience and Expense (TIE) compensation model will be followed, dated June 2018.

<https://www.sahpra.org.za/wp-content/uploads/2020/02/7_Clinical-Trial-Participant-Time-Inconvenience-and-Expense_TIE_Compensation_Model_May18_v1-1.pdf>

# References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**(10223): 497-506.

2. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**(8): 727-33.

3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**(10223): 507-13.

4. Release WN. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). 30 January 2020 2020. <https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov>).

5. Cai J, Xu J, Lin D, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis* 2020.

6. Linton NM, Kobayashi T, Yang Y, et al. Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation: A Statistical Analysis of Publicly Available Case Data. *J Clin Med* 2020; **9**(2).

7. Release WN. Shortage of personal protective equipment endangering health workers worldwide. 2020. <https://www.who.int/news-room/detail/03-03-2020-shortage-of-personal-protective-equipment-endangering-health-workers-worldwide>.

8. Chen J. Pathogenicity and transmissibility of 2019-nCoV-A quick overview and comparison with other emerging viruses. *Microbes Infect* 2020; **22**(2): 69-71.

9. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020.

10. Li CC, Wang XJ, Wang HR. Repurposing host-based therapeutics to control coronavirus and influenza virus. *Drug Discov Today* 2019; **24**(3): 726-36.

11. Slater AF. Chloroquine: mechanism of drug action and resistance in Plasmodium falciparum. *Pharmacol Ther* 1993; **57**(2-3): 203-35.

12. Mackenzie AH. An appraisal of chloroquine. *Arthritis Rheum* 1970; **13**(3): 280-91.

13. Shippey EA, Wagler VD, Collamer AN. Hydroxychloroquine: An old drug with new relevance. *Cleve Clin J Med* 2018; **85**(6): 459-67.

14. Schrezenmeier E, Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol* 2020; **16**(3): 155-66.

15. Rolain JM, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. *Int J Antimicrob Agents* 2007; **30**(4): 297-308.

16. Savarino A, Shytaj IL. Chloroquine and beyond: exploring anti-rheumatic drugs to reduce immune hyperactivation in HIV/AIDS. *Retrovirology* 2015; **12**: 51.

17. Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochem Biophys Res Commun* 2004; **323**(1): 264-8.

18. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J* 2005; **2**: 69.

19. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; **30**(3): 269-71.

20. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020.

21. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020; **14**(1): 72-3.

22. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020: 105949.

23. Menzel M, Akbarshahi H, Bjermer L, Uller L. Azithromycin induces anti-viral effects in cultured bronchial epithelial cells from COPD patients. *Sci Rep* 2016; **6**: 28698.

24. Poschet JF, Perkett EA, Timmins GS, et al. Azithromycin and ciprofloxacin have a chloroquine-like effect on respiratory epithelial cells. 2020. bioRxiv preprint. doi: <https://doi.org/10.1101/2020.03.29.008631>.

25. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses* 2012; **4**(6): 1011-33.

26. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020; **367**(6483): 1260-3.

27. Furst DE, Lindsley H, Baethge B, et al. Dose-loading with hydroxychloroquine improves the rate of response in early, active rheumatoid arthritis: a randomized, double-blind six-week trial with eighteen-week extension. *Arthritis Rheum* 1999; **42**(2): 357-65.

28. Collins KP, Jackson KM, Gustafson DL. Hydroxychloroquine: A Physiologically-Based Pharmacokinetic Model in the Context of Cancer-Related Autophagy Modulation. *J Pharmacol Exp Ther* 2018; **365**(3): 447-59.

29. Tett SE, Cutler DJ, Day RO, Brown KF. Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol* 1989; **27**(6): 771-9.

30. Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA* 2002; **288**(6): 715-21.

31. Packaging UM. Biological Substance Category B. 2020. <https://www.un3373.com/category-biological-substances/category-b>.

32. Schoenfeld D, Zheng H, Finkelstein D. Bayesian design using adult data to augment pediatric trials. *Clinical Trials* 2009; **6**: 297-304.

# Appendices

Appendix 1: Abbreviations and Terms

|  |  |
| --- | --- |
| Term | Definition |
| ACE2 | Angiotensin converting enzyme 2 |
| AE | Adverse event |
| COVID-19 | Coronavirus disease |
| CQ | Chloroquine |
| DAIDS | Division of Acquired Immunodeficiency Syndrome |
| DAIDS | Division of acquired immunodeficiency syndrome |
| DBS | Dried blood spot |
| DSMB | Data and safety monitoring board |
| EC50 | Half-maximal effective concentration |
| eCRFs | Electronic case report forms |
| Eligible | Qualified for enrollment into the study based upon adherence to inclusion/exclusion criteria |
| GFR | Glomerular filtration rate |
| HCQ | Hydroxychloroquine |
| HIPAA | Health Insurance Portability and Accountability Act |
| IATA | International Air Transport Association |
| ICF | Informed consent form |
| Index case | Term used throughout the protocol to denote the person with confirmed or suspected SARS‑CoV‑2 infection to whom the study participant was exposed |
| IRB | Institutional Review Board |
| MERS-CoV | Middle East respiratory syndrome coronavirus |
| Participant(s) | Term used throughout the protocol to denote the enrolled individual(s) |
| PCR | Polymerase chain reaction |
| PEP | Post-exposure prophylaxis |
| PK | Pharmacokinetic |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SARS-CoV | Severe acute respiratory syndrome coronavirus |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SoA | Schedule of Activities |
| WHO | World Health Organization |

Appendix 2: Protocol Structure

The protocol for this trial will be structured to be modular organized around the main protocol.

The main protocol will contain all the background and rationale for this trial and all generic information to the trial, the research approach, the trial design and conduct, and the overall trial governance, and ethical considerations. Other appendices for study governance, site-specific protocol addendum template, intervention-specific labels, pharmacokinetic modelling, and pharmacokinetic sample collection and analysis are provided below. The Intervention-Specific Appendices (e.g. LPV/r label appendix) will contain the information about the interventions. There will be a specific appendix for each of the intervention arm with features of the given intervention strategy and how it will be delivered, and any additional endpoints and data collection that are not covered in the main protocol. Given the perpetual nature of this trial, there may be modifications and/or additions to the main protocol. Each modification and/or addition to the main protocol will be subject to the Trial Steering Committee who will receive recommendation from other study committees (see Appendix 3).

Appendix 3: Study Governance Considerations

**Committees Structure**

The Trial Steering Committee will take the overall responsibility for the trial design and conduct. All committees will act in accordance to the International Clinical Harmonization Guidelines for Good Clinical Practice (GCP) Principles.



Figure 1: Administrative Structure

Study Team Monitoring

The study team will monitor the conduct of the study through monthly summary reports of arms of accrual and baseline characteristics and quarterly reports of data pooled over treatment arms of data completeness, specimen collection, and adverse events (AEs). The study team will review individual participant-level safety data frequently to assess the relation of all reported AEs to study treatment. On a weekly basis, the study team will review by-arm summaries of premature study discontinuations and premature study treatment discontinuations (and reasons) and AEs.

Independent Monitor

Study conduct will be monitored by an independent monitor. Monitors will visit participating clinical research sites to review the individual participant records, including consent forms, electronic case report forms, supporting data, laboratory specimen records, and endpoints through laboratory and medical records (physicians’ progress notes, nurses’ notes, individuals’ hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect the sites’ regulatory files to ensure that regulatory requirements are being followed and the sites’ pharmacies to review product storage and management.

Data and Safety Monitoring Board

An independent data and safety monitoring board (DSMB) will be convened for this study with expertise in coronavirus disease (COVID-19) or respiratory viruses, antiviral therapies and shedding, and emerging epidemics and a biostatistician. The purpose of the DSMB is to monitor the study for operational futility, social harms, and efficacy. The DSMB will evaluate the progress of the project, including periodic assessments of accrual, retention, safety, performance and variation of the project sites, and other factors that can affect project implementation.

The DSMB will review and approve modifications to the overall enrollment target based on the event rate. Due to the anticipated rapid speed of enrollment and the short duration of the study, it is unlikely that pre-specified stopping rules for efficacy and futility in terms of the efficacy of interventions will be reached before all participants are enrolled. The DSMB will review severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) endpoints.

The DSMB will conduct interim reviews (if specified) when adequate data have been accrued and convene by teleconference. Open reports containing accrual and retention rates, participant characteristics, and serious adverse events will be sent to the protocol team and DSMB members the week prior to the DSMB meeting. Only the DSMB members and the unblinded biostatistician will receive password-protected closed reports of SARS-CoV-2 endpoints by randomization arm.

**Regulatory and Ethical Considerations**

The study will be conducted according to GCP, the Belmont Report, and the Declaration of Helsinki. The study protocol, site-specific informed consent forms (ICFs), participant education and recruitment materials, and other requested documents—including any subsequent modifications—will be reviewed and approved by Western Institutional Review Board (WIRB), as the single IRB of record, responsible for oversight of research conducted at the study sites. Subsequent to initial review and approval, the WIRB will review the study at least annually.

**Informed Consent Process**

The principles of informed consent in the current edition of the Declaration of Helsinki will be implemented in each clinical study before any protocol-specified procedures or interventions are carried out. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, and this fact will be documented in the participant’s record.

A participant who is rescreened is not required to sign another ICF; eligibility for the study must be re-checked prior to enrollment.

**Study Records**

Each study site will establish a standard operating procedure for confidentiality protection. Each site will ensure that study records including administrative documentation and regulatory documentation as well as documentation related to each participant enrolled in the study, including ICFs, locator forms, case report forms, notations of all contacts with the participant, and all other source documents are stored in a secure manner.

**Confidentiality**

Participants’ study information will not be released without their written permission, except as necessary for oversight by:

* The protocol Principal Investigators or designees
* Study funders
* South African Health Products Regulatory Authority (SAHPRA)
* Stellenbosch University Health Research Ethics Committee (SU HREC)

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. The exceptions are SARS-CoV-2 testing results, which are subject to local and state reporting which is name-based. Local public health may contact participants diagnosed with SARS-CoV-2 for the purpose of surveillance and contact notification. Participants will be informed prior to SARS-CoV-2 testing that results are reportable and may lead to contact by local public health if results are positive for infection.

All records will be kept locked. All computer entry and networking programs will be done with coded numbers only.

Appendix 4: Pharmacokinetic Sample Collection and Analysis

**Collection of Blood**

Skin puncture

1. Put on a pair of disposable gloves.
2. Before skin puncture, the participant should warm his/her hands. The finger is massaged anterogradely to enrich the blood flow toward the puncture site.
3. Clean the skin of the palmar side of the tip of the distal phalanx of the third or fourth finger of the non-writing hand with a suitable disinfectant, for example, 70% isopropyl alcohol. Puncture the skin by a single-use safety lancet. The finger should be held in such a position that the gravity facilitates the collection of blood from the fingertip.
4. When collection of capillary blood by skin puncture is complete, place a bandage on the fingertip.

Venipuncture

To be conducted by trained personnel per standard procedures.

**Preparation of Blood Spots**

Preparation from blood collected by skin puncture

1. Wipe off the first drop of blood with a gauze pad because it may contain excess tissue fluids. Massage the finger again to increase blood flow at the puncture site. Transfer the following drop to one of the circles of a filter card without touching the surface directly with the fingertip. Allow the blood to be soaked into the texture of the filter by capillary forces only.
2. Let the next large drop of capillary blood form on the fingertip and collect it in the next circle. Continue this procedure until all necessary circles are filled or blood flow stops.
3. Do not squeeze or “milk” the finger excessively if the blood flow is not sufficient to fill all the required circles of the filter card. If blood flow stops, place a bandage on the fingertip. Perform a second skin puncture on another finger if more blood is needed for the examination.
4. For blood obtained by venipuncture, use syringe to apply approximately 100 µL of blood on the filter paper.

**Drying of Blood Spots**

To dry the blood spots, put the filter cards on a clean paper towel and let them dry, preferably overnight (but for at least 4 hours), at room temperature in the absence of any external source of heat. When the drying process is complete, the blood spots have a uniformly dark brownish color and no red areas are visible anymore.

**Storage and Transportation of Dried Blood Spots (DBS)**

NOTE: Processing of the blood spots can be interrupted after drying. The filter cards can now be stored.

1. For storage, put the filter paper card in a single, gas-impermeable zipper bag, containing 1 to 2 desiccant sachets to protect the specimens from moisture. Optionally, add a humidity indicator card.
2. Transfer this bag to a freezer as soon as possible. If freezers are not available under field conditions, storage at -4°C or even at ambient temperature is feasible for up to 14 days.
3. Transport frozen DBS specimens on dry ice. For filter cards initially kept at ambient temperature, use a triple packaging system, which consists of the zipper bag(s) as the inner container(s) as well as an inner and an outer envelope. No content markings are required on the outer envelope for shipment by regular mail, but the international biohazard symbol must be affixed to the primary inner container.
4. Exclude the filter cards from further processing if the desiccant packs and/or the additional humidity indicator card changes to a pink color.

On the filter paper, the participant should record the following:

1. His/her name and date of birth
2. Date and time of sample
3. Date and time of last dose

Samples that appear to be collected according to the schedule of activities, which have the required amount of blood for a 5- to 6-mm punch and have the minimal required information (1 through 3 above), will be processed for investigational drug concentrations.

Appendix 5: Site-Specific Capacity

**Study Personnel and responsibilities**

**Study leads**

*PI:* Prof Mark Cotton, Stellenbosch University, [mcot@sun.ac.za](mailto:mcot@sun.ac.za)

*Co-PI and Lead:* Prof Eric Decloedt, Stellenbosch University, [ericdecloedt@sun.ac.za](mailto:ericdecloedt@sun.ac.za)

*Co-PI:* Prof Jean Nachega, Stellenbosch University, [jnacheg1@jhu.edu](mailto:jnacheg1@jhu.edu)

*Co-PI:* Prof Landon Myer, University of Cape Town, [landon.myer@uct.ac.za](mailto:landon.myer@uct.ac.za)

**Clinical Pharmacology**

*Co-I:* Dr Roland van Rensburg, Stellenbosch University, [rolandmed@gmail.com](mailto:rolandmed@gmail.com)

*Co-I:* Dr Veshni Pillay Fuentes-Lorente, Stellenbosch University, [14847795@sun.ac.za](mailto:14847795@sun.ac.za)

*PK analytical analysis:* Dr Tracy Kellermann, Stellenbosch University, [tkellermann@sun.ac.za](mailto:tkellermann@sun.ac.za)

*Co-I:* Prof Helmuth Reuter, Stellenbosch University, [hr@sun.ac.za](mailto:hr@sun.ac.za)

**Infectious Diseases (Clinical liaison)**

*Co-I:* Prof Helena Rabie, Stellenbosch University, [hrabie@sun.ac.za](mailto:hrabie@sun.ac.za)

*Co-I:* Dr Jantjie Taljaard, Stellenbosch University, [jjt@sun.ac.za](mailto:jjt@sun.ac.za)

*Co-I:* Dr Arifa Parker, Stellenbosch University, aparker@sun.ac.za

*Co-I:* Dr Hans Prozesky, Stellenbosch University, [hwp@sun.ac.za](mailto:hwp@sun.ac.za)

*Co-I:* Dr Marije van Schalkwyk, Stellenbosch University, [marije@sun.ac.za](mailto:marije@sun.ac.za)

**FAMCRU**

*Co-I:* Dr Shaun Barnabas, Stellenbosch University, [barnabas@sun.ac.za](mailto:barnabas@sun.ac.za)

*Co-I:* Dr Samantha Fry, Stellenbosch University, [fry@sun.ac.za](mailto:fry@sun.ac.za)

*Co-I:* Dr Maria Magdalena Groenewald

*Co-I:* Dr Yasmeen Alkhalwaya

*Co-I:* Dr Caro-lee Saal

*Manager:* Mr George Fourie, Stellenbosch University, [georgef@sun.ac.za](mailto:georgef@sun.ac.za)

*Pharmacist:* Ms Sonja Pieterse, Stellenbosch University, [sonjap@sun.ac.za](mailto:sonjap@sun.ac.za)

*Study co-ordinator:* Ms Caroldine Neal, Stellenbosch University, [neal@sun.ac.za](mailto:neal@sun.ac.za)

*Data manager:*  Mr Brian Grey, Stellenbosch University, [briang@sun.ac.za](https://eur03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fbriang%40sun.ac.za%2F&data=02%7C01%7C%7C02ca10d135d644e30dd008d7f40daaca%7Ca6fa3b030a3c42588433a120dffcd348%7C0%7C0%7C637246211858393699&sdata=V%2B4NCXXov2cbkHNXiqvLpgeF7ekTCMcx2veREFjv2D8%3D&reserved=0)

*Sample processing:* Mr K Smith, Stellenbosch University, [smith@sun.ac.za](mailto:smith@sun.ac.za)

**Stellenbosch University Immunology Research Group**

*Co-I:* Dr Stephanus Malherbe, Stellenbosch University, malherbe@sun.ac.za

*Co-I:* Dr Andriette Hiemstra, Stellenbosch University, ahiemstra@sun.ac.za

*Co-I:* Dr Candice Macdonald, Stellenbosch University, [macdonald@sun.ac.za](mailto:macdonald@sun.ac.za)

*Co-I:* Dr Jane Shaw, Stellenbosch University, [janeshaw@sun.ac.za](mailto:janeshaw@sun.ac.za)

*Co-I:* Dr Donald Simon, Stellenbosch University, [donaldsimon@sun.ac.za](mailto:donaldsimon@sun.ac.za)

*Co-I:* Dr Tracy Cummins, Stellenbosch University, [cummins@sun.ac.za](mailto:cummins@sun.ac.za)

**Virology**

*Co-I:* Prof Wolfgang Preiser, Stellenbosch University, [preiser@sun.ac.za](mailto:preiser@sun.ac.za)

**Child and adolescent studies** (independent submission)

*Co-I:* Dr Marieke van der Zalm, Stellenbosch University, [mariekevdzalm@sun.ac.za](mailto:mariekevdzalm@sun.ac.za)

**Study site and infrastructure**

The primary research site will be the **Family Centre for Research with Ubuntu (FAMCRU)** situated in Tygerberg Hospital (TBH) (<http://www.famcru.org.za/>). FAMCRU will serve as the primary study site and provide study related infrastructure. FAMCRU’s director Mark Cotton, PI, established FAMCRU to conduct prospective studies of research questions relevant to sub-Saharan Africa systematically in collaboration with other academic institutions both inside and outside South Africa and to serve as a research unit for clinical trials. In 2002 FAMCRU received NIH funding to become a Pediatric AIDS Clinical Trials Group (PACTG, later renamed IMPAACT) research site and the Comprehensive International Program for Research in AIDS (CIPRA). The latter was in collaboration with the Universities of Cape Town (UCT) and the Witwatersrand (Wits) to develop local research facilities and to undertake protocols specifically to answer questions relevant to resource-constrained settings. In addition, the Rockefeller Foundation funded a joint proposal with UCT to investigate the prophylaxis of tuberculosis Pneumocystis jerovici pneumonia in HIV-infected children. FAMCRU affiliated to the AIDS Clinical Trial Group (ACTG) in 2013 to conduct adult HIV and tuberculosis trials and has the necessary infrastructure, staff and support to perform this research as well as developing the protocols. FAMCRU has experience in conducting both adult and paediatric pharmacokinetic studies. FAMCRU is also funded through PENTA-ID and the EDCTP. It has 1000m2 space. We have identified 4 potential additional study sites: **Stellenbosch University Immunology Research Group (SU IRG)** is located on the same premises as TBH, but on the SU Faculty of Medicine and Health Sciences campus. The IRG clinical space has 7 consulting rooms, 2 waiting areas, 2 bathrooms and 2 sputum booths with HEPA filters in converted shipping containers that are air conditioned and serviced daily. The containers have 3 telephone lines, basins and separate entrances as well as UV air sterilizer filters with fans. We have existing clinical and research collaborations with the following community sites: Médecins Sans Frontières (Doctors Without Borders) situated in the Khayelithsha community, Gugulethu community and Paarl community. We have budgeted to allow for the setup of 2 mobile research sites in high prevalence COVID-19 communities. We will monitor the SARS-CoV-2 spread to identify the most appropriate community sites.

**Virology:** The Division of Medical Virology at Tygerberg was the second public sector laboratory in South Africa to perform routine testing for SARS-CoV-2 by real-time PCR. From initially small numbers it has ramped up testing to several hundred of patient samples per day, 7 days a week. The platform used is a commercial multi-target (located in the viral RdRP, E, and N genes) real-time PCR (Seegene, Inc. Allplex 2019-nCoV assay, Korea MFDS-EUA - CE-IVD). As fall-back, if test kit supplies are not delivered in time, the Division has established an in-house method based on the Charité, Germany, protocol (cf. [https://www.who.int/docs/default-source/coronaviruse/protocol-v2-1.pdf](https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.who.int%2Fdocs%2Fdefault-source%2Fcoronaviruse%2Fprotocol-v2-1.pdf&data=02%7C01%7C%7C4240142180e14a19af7e08d7e08a5001%7Ca6fa3b030a3c42588433a120dffcd348%7C0%7C0%7C637224757013713338&sdata=89Lq7qV41WPdZO%2FyfDVfrK2oYlEMa9efUswjlfr%2FUSo%3D&reserved=0)). Diagnostic testing follows national (NICD) and international (WHO) guidelines and recommendations ([https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance](https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.who.int%2Femergencies%2Fdiseases%2Fnovel-coronavirus-2019%2Ftechnical-guidance%2Flaboratory-guidance&data=02%7C01%7C%7C4240142180e14a19af7e08d7e08a5001%7Ca6fa3b030a3c42588433a120dffcd348%7C0%7C0%7C637224757013713338&sdata=8yIVQgsjVW5GN5qToumd5lqDv8%2FvwCzDUODHMqEVbsY%3D&reserved=0)), including confirmatory testing of a certain number of positive and negative specimens by a previous established laboratory. The Division has semi-automated platforms for RNA extraction and thermocyclers for real-time PCR and is in line to receive an automated high-throughput platform for RNA extraction and a pipetting robot which will allow for testing more samples from late April 2020 onwards. It has substantial expertise in data handling and specimen storage under optimal conditions.

**Analytical laboratory:** The Division of Clinical Pharmacology houses a Tygerberg Hospital laboratory for therapeutic drug monitoring (which is in the process of obtaining SANAS accreditation), as well as several analytical laboratories. The unit houses a Shimadzu 8040 liquid-chromatography tandem mass spectrometry (LC-MS/MS) instrument managed by the Central Analytical Facility, as well as two high pressure liquid chromatography (HPLC) instruments, together with various instrumentation used in sample extraction and purification. The Division has been awarded a further R1.8 million designated for upgrade of laboratory infrastructure. A quality system exists within the analytical facility ensuring compliance with good clinical laboratory principles (GCLP), and HPLC/LC-MS/MS methods are validated according to industry guidelines (EMA, FDA). A sample management facility comprising of ultra-low freezers, -20°C freezers and 4°C fridges, all connected to external temperature monitoring systems, house all clinical samples according to industry guidelines. Together with extensive staff expertise, the analytical laboratory is well equipped to perform bioanalysis for clinical trials. The laboratory is managed by Dr Tracy Kellermann who will be responsible for method development and study drug concentration analysis.

**Local Recruitment Procedures**

We have recruitment infrastructure on all levels of health care in Cape Town, South Africa. The South African collaborating universities will be Stellenbosch University and the University of Cape Town. The primary research site will be the Family Centre for Research with Ubuntu (FAMCRU) situated in TBH (<http://www.famcru.org.za/>). The primary recruitment will be from Tygerberg hospital (TBH) and its referring hospitals and clinics. TBH is the largest public-sector tertiary referral hospital in the Cape Town Metropole and serves over 3.4 million people, mostly vulnerable populations from densely populated low-income communities and rural areas. TBH is the designated provincial COVID-19 centre preparing for the imminent community outbreak of COVID-19. The additional study sites will be set up in the following community sites: Khayelithsha community, Gugulethu community and Paarl community. We will monitor the SARS-CoV-2 spread to identify the most appropriate community sites.

FAMCRU has a standard operating procedure concerning the informed consent process that states:

* Informed consent process will be conducted in a private room in the participants’ language of choice.
* Informed consent will be obtained by qualified study personnel i.e. counselors or study nurses.
* Prospective participants will be given ample time to ask questions about the study, and if requested, be allowed to discuss participation with partners/family members.
* The sub-investigators will verify that the participant or their guardian has enquired adequate knowledge about the study and fully understands the Informed consent.
* As part of the quality assurance process, a quality controller will verify the signature of the informed consent prior to the participant leaving the site, and will also ensure that the participant receives a copy of the signed document.
* The consent remains an ongoing process until the participant discontinues the study.

Appendix 6: The inFLUenza Patient-Reported Outcome Instrument (Flu-PRO) – Modified for SARS-COV-2

DAILY SURVEY (D1-14)

inFLUenza patient-reported outcome (Flu-PRO): 32 items validated, can score across domains.

\*\*\*FYI: This takes about 5 minutes to complete

How are you feeling today?

FLU-PRO Not at all A little bit Somewhat Quite a bit Very much

Nose

Runny or dripping

Congestion or stuffy

Sneezing

Sinus pressure

Lack of smell

Throat

Sore throat

Scratchy or itchy throat

Difficulty swallowing

Lack of taste

Eyes

Teary or watery eyes

Sore or painful eyes

Eyes sensitive to light

Chest/Respiratory

Trouble breathing

Chest congestion

Chest tightness

Dry or hacking cough

Wet or loose cough

Sputum (coughing up sputum or phlegm)

Wheezing

Gastrointestinal

Felt nauseous

Stomach ache

Vomit

Diarrhea

Body/Systemic

Felt Dizzy

Head congestion

Headache

Lack of appetite

Sleeping more than usual

Body aches or pains

Weak or tired

Chills of shivering

Felt cold

Felt hot

Sweating

How are you feeling today?

0 no symptoms 1 Mild 2 Moderate 3 Severe 4 Very severe

Please rate interference in daily activities due to illness:

1 Not at all 2 A little bit 3 Somewhat 4 Quite a bit 5 Very much

How is your general health?

1 Poor 2 Fair 3 Good 4 Very good 5 Excellent

Have you returned to your usual health today? Yes/no

Have you returned to your usual activities today? Yes/no

TAKE MEDS, TAKE SWAB (Copy post-exposure prophylaxis)

Take your vitals:

* Oxygen level
* Pulse
* Temperature
* Respiratory rate
* Electrocardiogram monitor

PM Time:

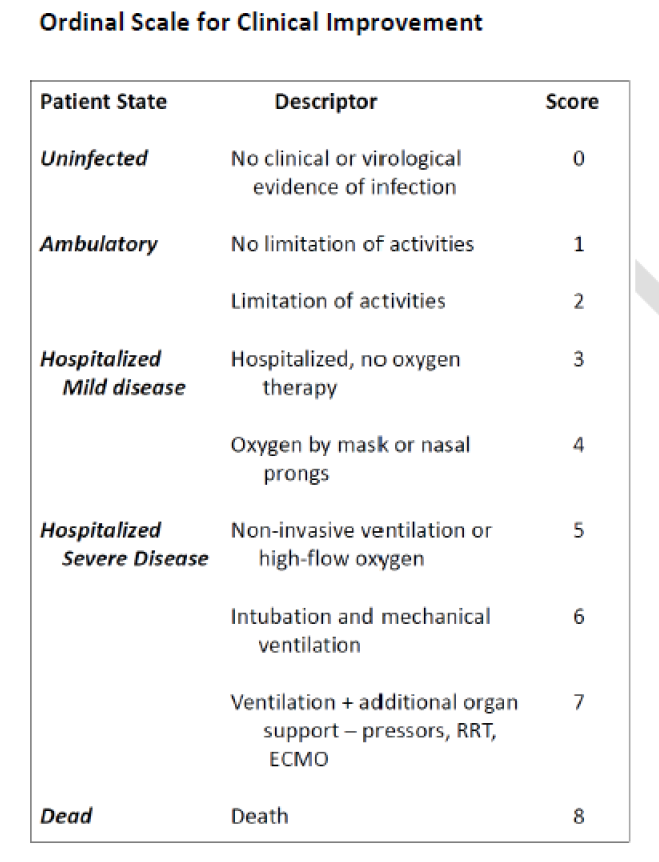
* Take meds
* Take vitals
* Oxygen level
* Pulse
* Temperature
* Respiratory rate

Anxious mood Not at all mild moderate severe very severe

Yu J, Powers JH, Vallo D, et al. Evaluation of efficacy endpoints for a Phase IIb study of a respiratory syncytial virus vaccine in older adults using patient-reported outcomes with laboratory confirmation. Value Health. 2020 Feb;23(2):227-235.

Appendix 7: WHO Ordinal Scale for Clinical Improvement

WHO COVID-19 Core Protocol  
SOLIDARITY Trial  
Version 10.0, March 22, 2020



Appendix 8: Hydroxychloroquine

**Dosing rationale for HCQ**

HQC is a long-acting drug with a terminal half-life of approximately 40 days. It is well absorbed, moderately protein bound, and will accumulate in tissues including the lung, heart, liver, and kidneys. It is typically given with a loading dose of approximately 2-fold the standard dose to accelerate achieving steady state drug concentrations.[27](#_ENREF_27) Since the drug will be used in those with SARS-CoV-2 upper respiratory tract infection, it is desirable to achieve adequate drug levels quickly to decrease viral replication.

A PBPK model was built (SIMCYP simulator v.18) using physical and chemical parameters of HCQ obtained from the literature;[28](#_ENREF_28) PK parameters (liver intrinsic clearance, fa, ka) were determined from clinical data.[29](#_ENREF_29) This PBPK model was used to simulate HCQ concentrations in plasma and lung fluid following 5 proposed dosing regimens in order to select an optimal regimen for the Peking University Third Hospital’s ongoing trial of HCQ in China. The combination of *in vitro* antiviral concentration-effect and predicted drug concentrations in this study were used to propose a loading dose of 400 mg HCQ twice a day on Day 1, followed by HCQ 200 mg twice a day on Day 2 through Day 5.

A second study (BYSY-DCTC-CPPO-HCQ-PBPKAR) was undertaken to simulate HCQ concentration-time profiles in plasma, whole blood, and lung in Chinese healthy populations. Since elderly patients have reduced glomerular filtration rate (GFR), simulations were conducted using a healthy Caucasian healthy population with renal injury (GFR 30 to 60 mL/min) and compared to a population with normal renal function to support the study design of therapeutic use of HCQ.

This protocol will investigate a single dosage of HCQ. Participants will receive a loading dose of 400 mg BID for 1 days followed by 400mg for 9 days. Subsequent investigations will be encouraged to undertake a more rigorous exposure-response assessment to define optimal dosing, including exploration of the lowest possible effective dose, and possible alternate dosing schedules (i.e., weekly instead of daily). Daily dosing has the highest likelihood to achieve sustained required drug levels for viral inhibition, as shown in the physiologically based PK (PBPK) modeling (Appendix 4). HCQ is commonly used daily in doses up to 600 mg of HCQ sulfate (465 mg base) per day for rheumatoid arthritis or systemic lupus erythematosus initially, with a usual maintenance dose 200 mg (155 mg base) for maintenance therapy. HCQ and CQ are both commonly used in a weekly dosing schedule for malaria chemoprophylaxis.

HCQ is associated with a better safety profile for daily and chronic use than CQ, including 5 decades of experience with use in these dose ranges in adults and the elderly. It is on the WHO Essential Medicines List for use in rheumatic disorders and is widely prescribed as an anti‑inflammatory for rheumatoid arthritis, systemic lupus erythematosus, and other autoimmune syndromes. Based on the limited *in vitro* data available, HCQ appears to be slightly more potent than CQ against SARS-CoV-2.[20](#_ENREF_20)

**Treatment administration**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **Dosage formulation** | **Route of Administration** | **Manufacturer** | **Instructions** |
| HCQ | 400 mg (300 mg base) tablets | Oral | Novartis | Take 2 tablets twice on Day 1 and 1 tablet twice a day for the subsequent 9 days, for a total of 10 days of treatment. Take at approximately the same time of the day with a meal or a glass of milk. If a dose is missed, it should be taken as soon as possible. If it is less than 4 hours before the next dose, the dose should be skipped. |

Packaging and label: The medication for home delivery will be dispensed in an otherwise-unmarked container with the study label. The container will be labeled with a unique identifier. The container will be packed in a standard box used for mail delivery of medications as needed.

**Risks associated with HCQ**

With tens of millions of doses of HCQ administrated for malaria and autoimmune diseases, the side effect profile of HCQ is well described and the drug is generally well tolerated. With short‑term administration (as opposed to chronic/year-long use in rheumatologic disease management), the major AEs are gastrointestinal (nausea, vomiting, dyspepsia, abdominal cramps, and diarrhea) and transient skin rashes. The gastrointestinal symptoms may vary by specific generic manufacturer of HCQ and are best managed by taking the drug with food or a glass of milk. A transient rash, most commonly morbilliform or psoriasiform, can develop in 10% of participants, often with a sustained loading dose, and is often managed by lowering the dose. To avoid this potential side effect, this protocol is using a short loading dose, not a sustained one. Uncommonly, idiosyncratic leukopenia/thrombocytopenia can occur and the drug should not be given to those with underlying bone marrow disorders. Lastly, hypoglycemia can occur and those taking insulin or glucose-lowering drugs are at risk; blood glucose should be monitored.

The safety of HCQ for treatment of patients with COVID-19 disease is unknown. COVID-19 may be associated with cardiac effects. HCQ may prolong QT, resulting in arrhythmias. Participants will be monitored for QT prolongation and counseled about this risk.

Long-term manifestations of HCQ, including retinitis, renal and hepatic disease, and cardiomyopathy, are not likely in short-term exposure.

**Specific Management of Toxicities Related to HCQ**

Gastrointestinal disturbance

Gastrointestinal disturbance (nausea, vomiting, diarrhea) is a common known possible side effect of HCQ. Taking with food or milk may improve tolerability.

Visual disturbances

Suspected visual changes should be evaluated for possible etiologies–if an HCQ-associated visual disturbance is suspected, HCQ should be stopped.

Allergic reactions

HCQ should be discontinued permanently if a serious allergic reaction is suspected. These participants will remain on study, off study treatment, and have all evaluations performed per the standard operating procedure(s).

QT prolongation

HCQ is associated with QT prolongation. QT will be assessed during the study using a portable monitor that can transmit arrhythmias to a central location which will be monitored.

**HCQ label**

Generic hydroxychloroquine label (current as of June 2018) is available online at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b82bbda6-64f2-4426-b4ec-254eeea895ae>.

Appendix 9: Lopinavir-ritonavir

**Dosing rationale for LPV/r**

The trial will test a daily regimen of LPV/r for 10 days for treatment of SARS-CoV-2. Daily dosing after a large loading dose has the highest likelihood to achieve sustained required drug levels for viral inhibition. LPV/r is commonly used daily in regimens of combination antiretroviral therapy for the treatment of HIV infection. LPV/r is associated with a favorable safety profile. Short-term drug toxicities includes gastrointestinal side effects: moderate nausea and diarrhea. It is on the WHO Essential Medicines List for use in HIV infection and is widely available throughout the world.

A population pharmacokinetic model (POPPK)1 was used to simulate time-course of plasma concentrations of lopinavir after adjusting the model for time-varying lopinavir clearance informed by the summary basis of approval for LPV/r (Kaletra®) and Klein et al.2 Total LPV concentration in plasma values from the pharmacokinetic model were translated total LPV concentration in epithelial lining fluid (ELF). Total ELF to total plasma concentration was reported in one treated individual.3 Free ELF to free plasma concentration was calculated based on physiochemical properties of LPV.4 Both ratios are aligned, suggesting 1.5- to 2-fold higher total ELF concentration relative to total plasma concentration.

A LPV/r regimen of 800mg/200mg x 2 doses on day 1, followed by 400mg/100mg 12 hourly for another 9 days is projected to result in lung concentrations exceeding a SARS-CoV-1 in vitro EC50 of 4µg/mL in all subjects across the 10 day treatment duration.5 Owing to the autoinduction of its LPV metabolism, concentrations are higher earlier in the treatment interval. This also corresponds when viral load is likely to be highest.

**Figure 1.** Pharmacodynamic simulations showing % patients projected to achieve lung concentrations >1, 1-5 and >5x an in vitro EC50 of 4µg/mL for SARS-CoV-1.

A screenshot of a cell phone

Description automatically generated

The loading dosing regimen is well covered from clinical safety margin perspective during the development program for LPV/r (Kaletra®), and the subsequent dosing from day 2 is the standard dosing regimen used in treatment of HIV.

**Treatment administration**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **Dosage formulation** | **Route of Administration** | **Manufacturer** | **Instructions** |
| Lopinavir‑ritonavir (LPV/r) | 200mg-50mg tablets | Oral | AbbVie | Take 4 tablets every 12 hours for the first day, then take 2 tablets twice daily for 9 days. Take at approximately the same time each day with a meal. If a dose is missed, it should be taken as soon as possible. If it is less than 4 hours before the next dose, the dose should be skipped. |

**Specific Management of Toxicities Related to LPV/r**

Gastrointestinal disturbance

Nausea, vomiting, and diarrhea are common known possible side effects of LPV/r. Taking with food may improve tolerability.

QT prolongation

LPV/r is associated with QT prolongation. QT will be assessed prior to enrolment to assess eligibility.

**LPV/r label**

The lopinavir-ritonavir label (current as of Dec 2019) is available online at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8290add3-4449-4e58-6c97-8fe1eec972e3>.

**References**

1. López Aspiroz, E. *et al.* Population Pharmacokinetics of Lopinavir/Ritonavir (Kaletra) in HIV-Infected Patients. *Ther. Drug Monit.* 1 (2011). doi:10.1097/FTD.0b013e31822d578b

2. Ng, J. *et al.* Population pharmacokinetic/pharmacodynamic analysis of lopinavir and ritonavir in subjects receiving the tablet formulation. *J. Int. AIDS Soc.* **11**, P245 (2008).

3. Atzori, C., Villani, P., Regazzi, M., Maruzzi, M. & Cargnel, A. Detection of intrapulmonary concentration of lopinavir in an HIV-infected patient. *AIDS* **17**, 1710–1711 (2003).

4. Kiem, S. & Schentag, J. J. Interpretation of Antibiotic Concentration Ratios Measured in Epithelial Lining Fluid. *Antimicrob. Agents Chemother.* **52**, 24–36 (2008).

5. Chu, C. M. *et al.* Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* **59**, 252–6 (2004).

Appendix 10: Azithromycin

**Dosing rationale for Azithromycin**

The efficacy and safety of azithromycin monotherapy in the treatment of COVID-19 has not been established. The dose regimen of 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5 in combination with hydroxychloroquine was used in a recently published study of HCQ and azithromycin in patients with COVID-19.1

There are a range of possible dosages in the US product labels, depending on the indication. For example, one single 2 gram oral dose of azithromycin is indicated for gonococcal urethritis and cervicitis. For mild community-acquired pneumonia, the recommended dose is 500 mg on Day 1, followed by 250 mg once daily on Days 2 through 5. For community-acquired pneumonia in patients who require initial intravenous therapy for susceptible organisms, 500 mg is administered intravenously for Days 1 and 2, followed by an oral daily dose of 500 mg to complete a 7- to 10-day course of therapy.

A loading dose of azithromycin 1 gram on Day 1, followed by a maintenance dose of 500 mg daily to complete a 10-day course of therapy facilitates a more efficient achievement of pseudo-steady state concentrations. The maintenance dose of 500 mg daily to complete the 10-day course is consistent with labeled dosing.

The most common adverse reactions to azithromycin are diarrhea, nausea, abdominal pain, or vomiting. Severe side effects include serious allergic reactions, including, but not limited to, anaphylaxis, angioedema, and dermatologic reactions such as Stevens-Johnson syndrome. Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Azithromycin can cause abnormal changes in the cardiac electrophysiology that may lead to a potentially fatal irregular heart rhythm. It may increase the risk of death, especially in those with heart problems, compared with those on other antibiotics such as amoxicillin or no antibiotic. Patients with pre-existing conditions are at particular risk, such as those with QT interval prolongation, proarrhythmic conditions, low blood levels of potassium or magnesium, a slower than normal heart rate, or those who use certain drugs to treat abnormal heart rhythms. Elderly patients may be more susceptible to development of Torsades de Pointes arrhythmias.

**Physiological based PK model for Azithromycin Dose Regimen**

A physiologically based pharmacokinetic (PBPK) model for azithromycin was developed previously and verified against clinical data.2 With the exception of the B:P ratio which was set at 2.28, the input parameters for the azithromycin model remained the same.3 This updated model was then used to predict exposures in plasma and lung after administration of 1 gram for 1 day and 500 mg daily for 9 days. Based on physicochemical data, the predicted lung to tissue ratio (Kp) was 16.44, which was lower than the observed ratio of 50.5 determined for lung tissue following a single oral dose of either 500 or 2000 mg azithromycin.4 Both predicted and observed ratios were used in simulations (100 participants aged 20 – 80 years; 50% female) of plasma and lung concentration-time profiles which were then compared against in vitro values of 2.12 (EC50) and 8.65 µM (EC90) reported for inhibition of SARS-CoV-2 by azithromycin (**Figure 1**).5 It should be noted that the unbound fraction in plasma (fu) was set at 0.69 and the predicted fu in lung tissue was 0.82 (intracellular fu=0.16). Thus, unbound and total concentrations were similar in both plasma and lung.

A picture containing screenshot

Description automatically generated

**Figure 1**. Predicted concentration-time profiles for azithromycin in the plasma and lung based on Kp values of 16.33 and 50 in the lung.

Based on the simulations shown, it appears that the dosing regimen of 1 gram for 1 day followed by 500 mg daily for 9 days, is able to attain concentrations of azithromycin in the lung that are higher than the in vitro EC90 value determined for azithromycin.

**Specific Management of Toxicities Related to Azithromycin**

Gastrointestinal disturbance

Gastrointestinal adverse reactions (nausea, vomiting, abdominal pain, and diarrhea) are common side effect of azithromycin. Most gastrointestinal side effects do not require treatment discontinuation and participants may receive treatment for symptoms (e.g., antiemetics).

Allergic reaction

Serious allergic reactions, including, but not limited to anaphylaxis, angioedema, and dermatologic reactions such as Stevens-Johnson syndrome have been reported with azithromycin treatment. Azithromycin should be discontinued immediately in the event of a hypersensitivity reaction.

QT prolongation

Azithromycin is associated with QT prolongation. QT will be assessed prior to enrolment prior to enrolment to assess eligibility.

**Azithromycin label**

Generic Azithromycin label (current as of June 2019) is available online at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=41e2163b-af61-4323-8b9c-2d44fc122fd9>

**References:**

1. Gautret, P. *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int. J. Antimicrob. Agents* 105949 (2020). doi:10.1016/j.ijantimicag.2020.105949

2. Johnson, T. N., Jamei, M. & Rowland-Yeo, K. How Does In Vivo Biliary Elimination of Drugs Change with Age? Evidence from In Vitro and Clinical Data Using a Systems Pharmacology Approach. *Drug Metab. Dispos.* **44**, 1090–1098 (2016).

3. Pene Dumitrescu, T. *et al.* Development of a Population Pharmacokinetic Model To Describe Azithromycin Whole-Blood and Plasma Concentrations over Time in Healthy Subjects. *Antimicrob. Agents Chemother.* **57**, 3194–3201 (2013).

4. Lucchi, M. *et al.* Pharmacokinetics of azithromycin in serum, bronchial washings, alveolar macrophages and lung tissue following a single oral dose of extended or immediate release formulations of azithromycin. *J. Antimicrob. Chemother.* **61**, 884–891 (2008).

5. Touret F, Gilles M, Barral K, NougairédeA, Decroly E, de Lamballerie X, Coutard B. In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. bioRxiv preprint doi: <https://doi.org/10.1101/2020.04.03.023846>.

Appendix 11: Experimental intervention to be added as part of adaptive design

**Dosing Rationale**

**Treatment Administration**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **Dosage formulation** | **Route of Administration** | **Manufacturer** | **Instructions** |
|  |  |  |  |  |

Packaging and label: The medication for home delivery will be dispensed in an otherwise-unmarked container with the study label. The container will be labeled with a unique identifier. The container will be packed in a standard box used for mail delivery of medications as needed.

**Risks Associated with Experimental Intervention**

**Specific Management of Toxicities Related to Study-Provided Drug**

**Drug label**