

Azithromycin for COVID-19 Trial in Outpatients Nationwide (ACTION)

Manual of Operations and Procedures

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Table of Contents

| | | |
|----------|--|-----------|
| 1 | Chapter 1: Overview | 5 |
| 1.1 | <i>Executive Summary</i> | <i>5</i> |
| 2 | Background | 5 |
| 2.1 | <i>Preliminary Studies</i> | <i>5</i> |
| 2.2 | <i>Objectives.....</i> | <i>6</i> |
| 3 | Chapter 2: Trial Design..... | 6 |
| 3.1 | <i>Randomization.....</i> | <i>7</i> |
| 3.2 | <i>Trial Profile.....</i> | <i>8</i> |
| 3.3 | <i>Sub Studies</i> | <i>9</i> |
| 3.4 | <i>Outcomes.....</i> | <i>11</i> |
| 3.4.1 | <i>Primary Outcome.....</i> | <i>11</i> |
| 3.4.2 | <i>Secondary Outcomes</i> | <i>11</i> |
| 3.5 | <i>Sample Size.....</i> | <i>12</i> |
| 3.6 | <i>Masking.....</i> | <i>12</i> |
| 3.7 | <i>Study Period.....</i> | <i>13</i> |
| 3.8 | <i>Main Study Timeline.....</i> | <i>14</i> |
| 4 | Chapter 3: Study Eligibility..... | 14 |
| 4.1 | <i>Inclusion Criteria</i> | <i>14</i> |
| 4.2 | <i>Exclusion Criteria</i> | <i>14</i> |
| 5 | Chapter 4: Study Methods | 15 |
| 5.1 | <i>Recruitment</i> | <i>15</i> |
| 5.2 | <i>Enrollment.....</i> | <i>16</i> |
| 5.2.1 | <i>Informed Consent</i> | <i>16</i> |
| 5.3 | <i>Baseline Assessment.....</i> | <i>18</i> |
| 5.4 | <i>Treatment</i> | <i>18</i> |
| 5.5 | <i>Day 3 Assessment.....</i> | <i>18</i> |
| 5.6 | <i>Day 7 Assessment.....</i> | <i>19</i> |
| 5.7 | <i>Day 14 Assessment.....</i> | <i>19</i> |
| 5.8 | <i>Day 21 Assessment.....</i> | <i>19</i> |
| 5.9 | <i>Reminders.....</i> | <i>19</i> |
| 5.10 | <i>Kit Preparation</i> | <i>20</i> |
| 6 | Sample Collection Procedures..... | 21 |
| 6.1 | <i>Nasal Swab Collection</i> | <i>21</i> |

| | | |
|-----------|---|-----------|
| 6.2 | <i>Saliva Collection</i> | 22 |
| 6.3 | <i>Rectal Swab Collection</i> | 22 |
| 7 | Laboratory Procedures | 24 |
| 8 | Duties and Responsibilities of Staff | 25 |
| 8.1 | <i>Principal Investigators</i> | 25 |
| 8.2 | <i>Co-Investigators</i> | 25 |
| 8.3 | <i>Study Coordinators</i> | 25 |
| 8.4 | <i>Biostatistician</i> | 26 |
| 8.5 | <i>Data Analyst</i> | 26 |
| 8.6 | <i>Laboratory Technicians</i> | 26 |
| 9 | Statistical Methods | 26 |
| 10 | Study Medication | 26 |
| 10.1 | <i>Description</i> | 27 |
| 10.2 | <i>Dosage</i> | 27 |
| 10.3 | <i>Medication Procurement/Donation</i> | 27 |
| 10.4 | <i>Medication Quality Control</i> | 28 |
| 10.4.1 | <i>Drug Storage</i> | 28 |
| 10.5 | <i>Concurrent Medications</i> | 29 |
| 10.6 | <i>Measures of Treatment Compliance</i> | 29 |
| 11 | Adverse Event Monitoring and Safety Assessment | 29 |
| 11.1 | <i>Adverse Events</i> | 29 |
| 11.2 | <i>Adverse Event Monitoring</i> | 30 |
| 11.3 | <i>Serious Adverse Events</i> | 31 |
| 12 | Protection of Human Subjects | 32 |
| 12.1 | <i>Institutional Review Board Approval</i> | 32 |
| 12.2 | <i>Informed Consent</i> | 32 |
| 12.3 | <i>Risks and Benefits of Study Procedures</i> | 33 |
| 13 | Study Monitoring | 33 |
| 13.1 | <i>Protocol Violations</i> | 33 |
| 14 | Data Collection, Management, and Security | 34 |
| 14.1 | <i>Scope of the Data</i> | 34 |
| 14.2 | <i>Data Storage, Management, and Security</i> | 34 |
| 14.3 | <i>Electronic Data Collection Forms</i> | 34 |

| | | |
|-----------|--|-----------|
| 14.4 | <i>Data Review</i> | 34 |
| 14.5 | <i>Data Entry</i> | 34 |
| 14.6 | <i>Data Transfer</i> | 35 |
| 14.7 | <i>Data Entry Errors</i> | 35 |
| 14.8 | <i>Data Consistency and Validity</i> | 35 |
| 14.9 | <i>Data Preparation and Cleaning</i> | 35 |
| 14.10 | <i>Monitoring</i> | 36 |
| 14.11 | <i>Data Analysis</i> | 36 |
| 14.12 | <i>Data Storage and Security</i> | 36 |
| 15 | Data and Safety Monitoring Committee Charter | 37 |
| 15.1 | <i>DSMC Membership</i> | 37 |
| 15.2 | <i>Conflicts of Interest</i> | 37 |
| 15.3 | <i>Timing and Purpose of the DSMC Meetings</i> | 37 |
| 15.4 | <i>Procedures to Ensure Confidentiality and Proper Communication</i> | 38 |
| 15.5 | <i>Statistical Monitoring Guidelines</i> | 39 |
| 15.6 | <i>DSMC Contact Information</i> | 39 |

Abbreviations

COVID-19: Coronavirus Disease 2019
DCC: Data Coordinating Center
DSMC: Data and Safety Monitoring Committee
SAE: Serious Adverse Event
SARS: Severe Acute Respiratory Syndrome
SC: Steering Committee
UCSF: University of California, San Francisco
WHO: World Health Organization

1 Chapter 1: Overview

1.1 Executive Summary

Identification of a safe, effective treatment for individuals with mild or moderate COVID-19 that prevents disease progression and reduces hospitalization would reduce the burden on the health system. High dose hydroxychloroquine is being evaluated for SARS-CoV-2 prevention and COVID-19 disease treatment but has a high risk of a number of potentially severe adverse events. Recent evidence has indicated that the broad-spectrum macrolide azithromycin may have some activity against coronaviruses. A large community randomized trial in Niger demonstrated reduced viral load among children with commensal coronaviruses (prior to the emergence of SARS-CoV-2) in communities receiving biannual mass azithromycin distribution compared to placebo (submitted). In SARS-CoV-2 patients in France, the addition of azithromycin to a hydroxychloroquine regimen appeared to decrease SARS-CoV-2 positivity by PCR compared to hydroxychloroquine-only and control patients.[6] Azithromycin is generally well-tolerated and may be an attractive option for treating patients with mild disease.[7–10]

2 Background

2.1 Preliminary Studies

Azithromycin has activity against RNA viruses *in vitro*.

*Azithromycin reduces rhinovirus replication in cultured primary bronchial epithelial cells*¹. Schogler and colleagues (2015) showed that rhinovirus viral load was decreased in both bronchial epithelial cells isolated from healthy controls and from patients with cystic fibrosis when pretreated with azithromycin. This antiviral action is associated with the induction of interferon pathways. Furthermore, treatment with azithromycin did not induce cell toxicity in primary cystic fibrosis bronchial cells.

*Azithromycin reduces Zika proliferation and virus-induced cytopathic effects in glial cell lines and human astrocytes*². Retallack and colleagues (2016) showed that Zika infection of cultured glial cells was inhibited with azithromycin in a dose-dependent manner. The EC₅₀ ranges from 2.1 μM to 5.1 μM, all within the plasma levels for the current dosing of azithromycin in humans. Azithromycin also decreased viral production.

*Azithromycin inhibits Zika infection in Vero cells*³. Li and colleague (2019) showed that Vero cells treated with azithromycin inhibited Zika infection at a late stage of the viral cycle. The inhibitor concentration (IC₅₀) ranged from 1.23 to 4.97 μM. The pretreatment of azithromycin increased interferon pathway responses after Zika infection.

Reduction of Alpha- and Betacoronavirus viral burden is associated with mass azithromycin treatment

Nigerien children treated with biannual oral azithromycin had reduced coronavirus viral burden (MORDOR Group, under review). At 24 months, NP swabs from children that underwent 4 azithromycin treatments had an 8-fold reduction in Alphacoronavirus and a 14-fold reduction in Betacoronavirus (prior to SARS-CoV-2 identification) compared to NP swabs from children treated with placebo.

Preliminary evidence has suggested that azithromycin may reduce viral load in patients with SARS-CoV-2 infection. Two non-randomized studies from France evaluated hydroxychloroquine in combination have been reported^{4, 5}, one of which is unpublished. In the first study, patients received 600 mg hydroxychloroquine daily for ten days or no treatment. Six patients receiving hydroxychloroquine additionally received azithromycin (500 mg on Day 1, followed by 250 mg per day on Days 2 through 5). The primary outcome was virologic clearance at Day 6. At the end of the study, 70% of patients receiving hydroxychloroquine achieved virologic cure compared to 12.5% in the control group. Of those receiving azithromycin, 100% achieved virologic control at Day 6. While these results are hypothesis-generating that azithromycin may have effect on virologic outcomes in SARS-CoV-2 patients, this was a small non-randomized study with significant methodological limitations. The second study is an observational cohort study of 80 patients receiving hydroxychloroquine plus azithromycin. Of these, 81% had a favorable outcome, 15% required oxygen therapy, 3.8% were transferred to the ICU, and one patient died. Viral load decreased over time, and 93% had no detectable virus at Day 8. Taken together, these studies are hypothesis-generating that azithromycin may have some activity against SARS-CoV-2 infection. Randomized placebo-controlled trials are required to definitively evaluate the efficacy of azithromycin for COVID-19 disease progression.

2.2 Objectives

1: To determine if a single oral dose of azithromycin is effective for improving recovery in patients with a positive SARS-CoV-2 PCR test with mild or moderate disease. We will define improved recovery as symptom free at Day 14 post enrollment.

3 Chapter 2: Trial Design

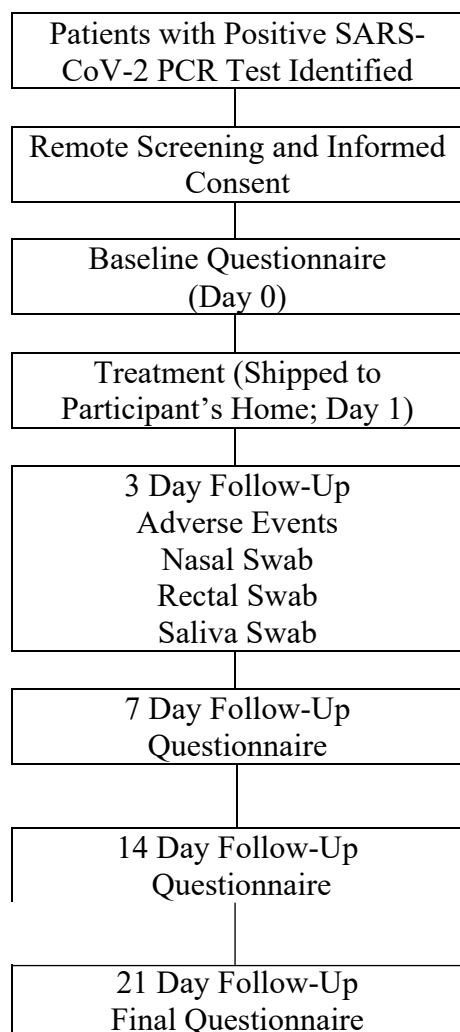
This trial will be a scalable, remote trial to evaluate the efficacy of azithromycin for the prevention of COVID-19 disease progression and hospitalization. The entire trial will be

conducted remotely via mail, telephone, and email to minimize infection risk to patients and study staff.

3.1 Randomization

Participants will be randomized in a 2:1 fashion to one of two arms. Participants will be randomized to receive either a single oral dose of azithromycin (1.2 g) or oral placebo. Participants will be randomized by the study biostatistician. The randomization will be implemented into REDCap. The randomization will be masked by treatment letters: AAA, BBB,CCC, HHH, TTT, or VVV. The masked study coordinator will send the participant their corresponding study treatment. The coordinator will determine the participant's allocation by the patient's REDCap record ID. Packaged study treatment will not identify whether the patient received azithromycin or placebo. Every attempt will be made to preserve masking and we will use a matching placebo to ensure masking of investigators and participants. Laboratory staff will be masked for all laboratory outcomes. The use of a 2:1 ratio results in a small loss in statistical power, however the increased probability of receiving study drug balances the loss in power with ethics if azithromycin were shown to be efficacious and may make enrollment in the trial more acceptable to patients.

3.2 Trial Profile



TRIAL AT A GLANCE

Randomization: Individually randomized 2:1, azithromycin : placebo

Intervention Arms:

- A single, oral 1.2 g dose of azithromycin, OR
- A single oral dose of placebo

Patient Population: Patients in the United States with a positive SARS-CoV-2 PCR test with mild or moderate symptoms who are not hospitalized at enrollment

Primary Outcome: Hospitalization by or before Day 14

3.3 Sub Studies

Swab Sub-Study

We will randomly select participants to collect additional swab samples in a sub-study. In addition to the regular treatment and questionnaire activities, the participants of the sub-study may be asked to:

1. Self-collect a nasal, rectal, and/or saliva swab at baseline, days 3, 7, and/or 14

Participants may participate in the main study swabs at Day 3 or the swab sub-study or they may opt not to collect swabs at all. Participants in the sub-study will not collect double swabs at day 3. Swabs will only be collected once.

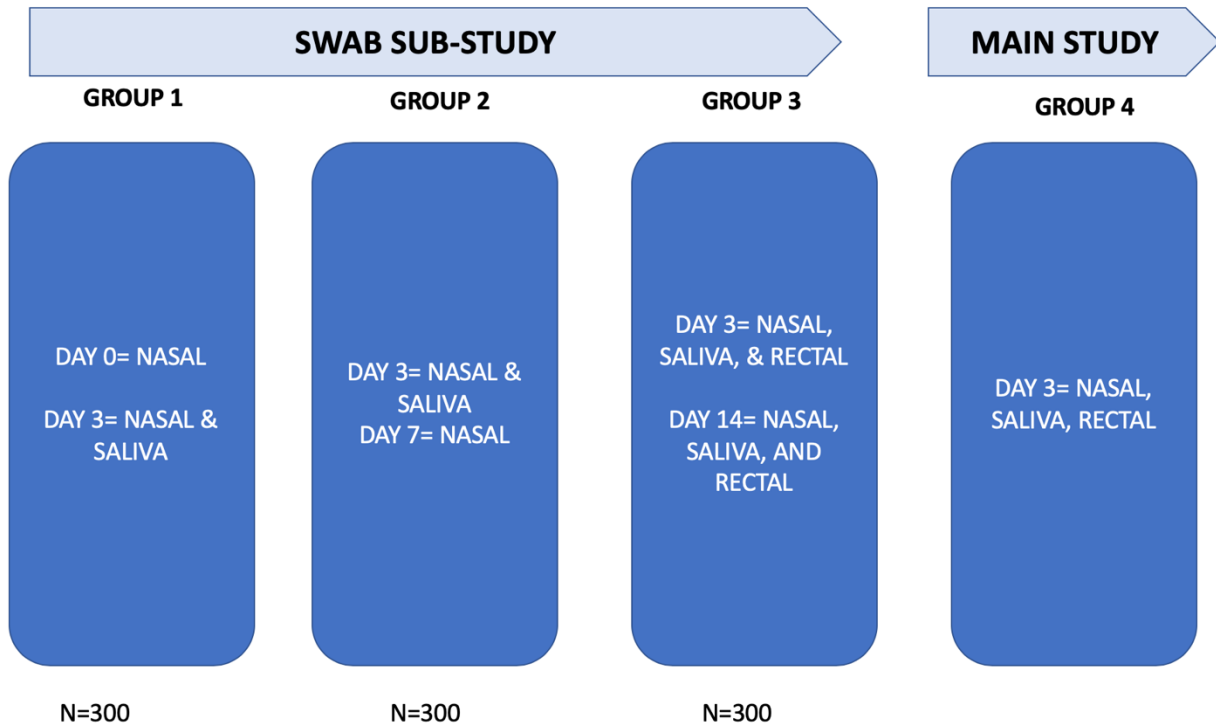
The figure below outlines the possible paths for participants interested in collecting swabs.

Participants may:

- 1) Only collect swabs at Day 3 as part of the main study. These participants will collect up to 3 swabs total.
- 2) Collect swabs at Baseline, Day 3, Day 7, and/or Day 14 as part of the sub-study. These participants will collect up to 4 nasal swabs, 4 rectal swabs, and 4 saliva swabs (up to 12 swabs total).

Patients may also opt not to collect swabs. All patients will be randomized in the same fashion as one group, despite the patient's decision to collect swabs or not.

Figure 1:



We plan to place patients into one of three groups for the swab sub-study or a fourth group into the main study. The first 300 participants agreeing to take part in the sub-study will be in Group 1. The next 300 will be in Group 2. The last 300 will be in Group 3. All other willing participants will be placed in Group 4 as part of the main study. The groups are outlined below:

Group 1=

- Nasal Swab at Day 0
- Nasal & Saliva Swab at Day 3

Group 2=

- Nasal & Saliva Swab at Day 3
- Nasal Swab at Day 7

Group 3=

- Nasal, Saliva, Rectal Swab at Day 3
- Nasal, Saliva, Rectal Swab at Day 14

Participants who are willing to take part in the main study swabs but not in the sub-study swab group will be placed in Group 4 automatically.

Group 4=

- Nasal, Saliva, Rectal Swab at Day 3

Hospitalization Verification Sub-Study

Proof of hospitalization in a sub-set of participants would be beneficial to validate the primary outcome. Therefore, we will randomly select participants who have been hospitalized for the hospitalization verification sub-study. We will request to access patient medical records for these selected patients. All participants for the trial will be requested to sign the UCSF HIPAA Authorization form for permission to use personal health information for research. We will also use the US National Death Index to link patient deaths to our study.

3.4 Outcomes

3.4.1 Primary Outcome

The primary outcome will be a symptom-based outcome. We will conduct a binary assessment of whether the participant is symptom free at Day 14 (yes or no) post enrollment.

3.4.2 Secondary Outcomes

Secondary outcomes will include

- **Hospitalization:** Defined as any visit to the emergency room or other hospital setting that resulted in a stay of 24 hours or more.
- **Adverse events:** we will conduct an adverse event survey at Day 3 after treatment, including gastrointestinal side effects (nausea, vomiting, diarrhea, abdominal pain) and rash. We note that some COVID-19 patients report gastrointestinal symptoms, and this survey will provide data on whether azithromycin causes additional gastrointestinal effects beyond those symptoms.
- **Prevalence of positive swabs:** we will compare the prevalence of SARS-CoV-2 positive swabs at Day 3 after treatment in self-collected nasal, saliva, and rectal swabs in azithromycin compared to placebo-treated participants.
- **Viral load:** we will assess viral load by RT-PCR in self-collected nasal, saliva, and rectal swabs at Day 3 after treatment.
- **Mortality:** we will collect emergency contact/next of kin information during the baseline questionnaire. We will follow-up with the emergency contact if participants are lost to follow-up at the Day 14 questionnaire to assess mortality and hospitalization outcomes.
- **Genetic macrolide resistance determinants:** We will evaluate the prevalence of genetic macrolide resistance determinants *ermB*, *mefA/E*, and *mphA* by targeted PCR in rectal samples collected at Day 3 after treatment.
- **COVID-19 symptoms:** we will ask patients about COVID-19 symptomology during each online questionnaire, including cough, fever, myalgia, anosmia, shortness of breath (and related abilities such as ability to walk across a room or up a flight of stairs), fatigue, conjunctivitis, and orthostatic symptoms.

- **Number of emergency room visits:** during each online questionnaire we will survey patients about any emergency room visits (with stays <24 hours) that occurred since their last survey.
- **Number of household members with COVID-19 (confirmed or symptomatic):** during each online questionnaire we will ask participants how many of their household members have symptoms of COVID-19 or confirmed disease.
- **Death:** we will attempt to link deaths among participants to the National Death Index.

3.5 Sample Size

The COVID-19 epidemic is changing rapidly over time. We propose a group sequential design with a flexible sample size that is adaptive to changing trial parameters over time with no maximum sample size. These designs are used in outbreak trials due to uncertainty with respect to parameters such as incidence and severity of outcomes. Full details on the sample size are provided in the Statistical Analysis Plan. In brief, the trial will employ a committee that is masked to results by arm that will evaluate the sample size on a weekly basis to evaluate the sample size based on the probability of hospitalization and enrollment.

On December 2, 2020 the DSMC members agreed to revise the sample size and primary outcome of the trial. Our re-estimated sample size of N=455 would allow for detection of a 15% absolute difference in probability of being symptom free at 14 days assuming that 50% in the placebo arm are symptom free (this is based on the current overall percent of participants who are symptom free at 14 days in ACTION). Because ACTION is enrolling more slowly than we had anticipated and we are planning a smaller sample size and we are also planning a single interim analysis at approximately 50% enrollment (N=230 participants), testing for efficacy at $p=0.001$, and then assess the final outcome at $p=0.049$.

3.6 Masking

Investigators and participants will be masked to the treatment allocation. The following study procedures will be in place to ensure double-blind administration of study treatments.

- Access to the randomization code will be controlled
- A taste-matching placebo will be utilized
- Packaging and labeling of test and control treatments will be identical to maintain the blind.

The study blind will be broken upon completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken only in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the investigators should discuss the emergency with the Medical Monitor prior to unblinding.

3.6.1 Unmasking Protocol

If a patient and/or their doctor is concerned about a potential drug interaction or other medical issue, a discussion regarding a decision to unmask may come up.

If the patient has already taken the study medication:

1. Dr. Thuy Doan (PI) speaks with the patient and/or their treating doctor about the specific case. The decision will be made between the patient, the treating physician, and Dr. Doan about whether unmasking is necessary.
2. If no unmasking is required at the time, the issue is resolved. The patient and treating doctor can get back in touch if necessary.

3. If unmasking is required, we will take the following steps:

- a. We will only unmask a treating physician who is responsible for the patient's COVID care if deemed to be necessary for the care and safety of that patient. We will not directly unmask a patient. However, the treating physician may unmask the patient. The study team should advise the patient that it is very important that they do not inform us of what their study treatment was. As we are not involved in the patient's care, there is no reason for us to know their treatment assignment.
- b. The study team will inform Dr. Ben Arnold (ACTION biostatistician) of the patient's ID number and their treatment letters.
- c. Dr. Arnold will call the patient's physician and relay this information to the physician. He will reiterate that the patient's physician should not disclose the treatment assignment to anyone on the study team except for him. Dr. Arnold will have information available to him including the study dosing (1.2 g single dose as powder for oral suspension), when the patient was enrolled, and when the patient took the study drug (if known).
- d. Dr. Arnold or his delegate will document the incident in an event log.
- e. Study staff will check in with the patient, encourage the participant to continue participating in the study, and remind them not to inform the study team of their treatment assignment.

If the patient has not yet taken the study medication:

1. Dr. Doan will speak with the patient and/or the patient's treating physician about the study. The decision will remain with the patient and their doctor as to whether the patient takes the study medication. No unmasking will occur, as any potential concerns can be avoided by simply not taking the study medication. We will ask the patient to document that they did not take the study medication on their follow-up form and the study team will document the event and the study team will encourage the patient to continue in the trial.

3.7 Study Period

Each participant will be in the study for a total of 21 days.

3.8 Main Study Timeline

| Timepoint | Activity |
|-----------|--|
| Day 0 | <ul style="list-style-type: none"> • Eligibility Screening • Informed Consent • Baseline Questionnaire • Randomization |
| Day 1 | <ul style="list-style-type: none"> • Treatment |
| Day 3 | <ul style="list-style-type: none"> • Adverse events questionnaire • Self-collected nasal swab (opt-in) • Self-collected saliva swab (opt-in) • Self-collected rectal swab (opt-in) |
| Day 7 | <ul style="list-style-type: none"> • Hospitalization and symptoms questionnaire |
| Day 14 | <ul style="list-style-type: none"> • Hospitalization and symptoms questionnaire (primary endpoint) |
| Day 21 | <ul style="list-style-type: none"> • Hospitalization and symptoms questionnaire |

4 Chapter 3: Study Eligibility

4.1 Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for this study:

- Evidence of a positive SARS-CoV-2 test and test results received within the previous seven days
- Not currently hospitalized
- Willing and able to receive study drug by mail
- Willing and able to return the internet-based study questionnaires at baseline, day 3, 7, 14, and 21 days via email or over the phone.
- No known allergy or other contraindication to macrolides
- No known history of prolongation of the QT interval (eg. History of torsades de pointes, congenital long QT syndrome, bradyarrhythmia).
- No recent use of hydroxychloroquine within the past 7 days for participants >55 years of age.
- Not currently taking nelfinavir or warfarin (Coumadin)
- Age 18 years or older at the time of enrollment
- Not currently pregnant
- Provision of informed consent

4.2 Exclusion Criteria

Participants will be excluded if they meet any of the following criteria:

- Negative or no SARS-CoV-2 test and test results not received within the previous seven days
- Currently hospitalized
- Not willing and able to receive study drug by mail
- Not willing and able to return the internet-based study questionnaires at baseline, 3, 7, 14 and 21 days via email or over the phone
- Known allergy or contraindication to macrolides
- History of known prolongation of the QT interval (e.g., history of torsades de pointes, congenital long QT syndrome, bradyarrhythmia)
- Recent use of hydroxychloroquine (past 7 days) for participants >55 years of age
- Currently taking nelfinavir or warfarin
- Younger than 18 years old at the time of enrollment
- Currently pregnant
- No provision of informed consent

5 Chapter 4: Study Methods

5.1 Recruitment

We will employ several recruitment methods for this trial.

A. Stanford University Clinical Virology Laboratory

The primary method of recruitment is in partnership with laboratories performing SARS-CoV-2 testing. Patients with a positive SARS-CoV-2 test will be identified from the laboratory, and with receipt of a positive test, patients will be sent an email or letter inviting them to contact the study staff for screening and enrollment if interested.

The Clinical Virology Laboratory at Stanford University, which conducts the vast majority of Northern California's SARS-CoV-2 testing will be our first laboratory partner. Recruitment could be expanded to include additional laboratories nationwide.

B. Flyers/Social Media

We will also use flyers to advertise the study at COVID-19 testing locations and public spaces. Social media platforms will also be used such as Facebook, Twitter, and Instagram. We will also use social media to create an online ad campaign for the study. Please see the appendix for a template of the social media documents.

C. Study Website

We will create a study specific website designed to recruit participants and provide more information about the study. The website can be found here: <https://proctor.ucsf.edu/action-trial>. The link to the REDCap screening questionnaire can be found directly on the website. The website also contains contact information, frequently asked questions, and eligibility criteria.

Participants can contact study staff if they are interested by phone at 415-326-3761 or by emailing ACTIONTrial@ucsf.edu.

D. Open Door Health, Rhode Island

Open Door Health in Providence, Rhode Island will also assist with recruitment activities for this project. Open Door Health is one of the first primary care centers in Rhode Island that is dedicated to serving LGBTQ+ Rhode Islanders. The facility serves a large Black, Hispanic/Latinx, and immigrant population. The coordinators at Open Door Health will help recruit participants by passing out flyers and providing COVID positive patients with the study email and phone number.

E. Every Door Direct Mail with USPS

Every Door Direct Mail, or EDDM, is targeted marketing with the US postal service. We will create a postcard advertising the study. We will then work with the US postal service to deliver the postcard to residences along mail routes in selected zip codes. The postcard will contain study info, the study website, and the study contact info. Interested participants can call or email us directly or visit the study website. See the appendix for an example of the postcard used.

F. WebMD

WebMD is an online platform for news and information regarding human health. WebMD publishes COVID-19 specific information which reaches approximately 14 million people per month. Advertising ACTION on WebMD's COVID content pages enables us to reach potential participants nationwide. We will place electronic ads as banners on their website. Interested participants can click 'learn more' and then they will be directed to the study screening form.

5.2 Enrollment

Interested participants will be remotely screened for eligibility prior to enrollment. Participants can be screened by phone or by an electronic REDCap form accessible from the study website. If eligible, study staff will call the participant and collect informed consent electronically via DocuSign. Upon determining eligibility and signing electronic informed consent documents, study staff will ask the participant to provide their mailing address. Study staff will then mail the participant their randomized treatment allocation, self swabbing materials, and email an electronic baseline questionnaire. No contact between study staff and participants in this trial will take place as to minimize risk of infection spread. At the end of the screening questionnaire, we will collect phone number and email information from the eligible participants. We will also require patients to provide proof of their positive test result by uploading documentation through REDCap.

The data analyst will inform the coordinator daily of the new eligible participants. Coordinators will then call participants to review the study and informed consent form.

5.2.1 Informed Consent

Consent scripts will be submitted and approved by the UCSF IRB committee in San Francisco, California prior to study implementation. The informed consent document will be sent electronically to eligible participants with the Experimental Subject's Bill of Rights. Children under the age of 18 will not be eligible. All participants will be informed about the possible risks

and benefits of treatment. If the participant wishes to withdraw themselves from the study, they may do so at any time.

The informed consent form will be sent electronically to the participant's email address via DocuSign while the coordinator is on the phone with the patient. The coordinator will review the form with the patient. If the patient wishes to participate, they will sign the form electronically. Electronic signed consent forms will be uploaded to the UCSF Box account for ACTION.

5.2.1.1 Informed Consent for Spanish Speaking Participants

We will utilize the UCSF IRB's "preferred method" of informed consent for Spanish speakers. A qualified translator will translate all study documents including the informed consent document, the study surveys, the patient instructions, and all study documents. Spanish speaking participants will be called over the telephone with a study staff member and a qualified medical interpreter. The communication plan is outlined below:

1. If a participant submits a screening form, the study staff will contact the medical interpreter to set up a time to call the participant. Once a time is established, the study staff will call or text the participant in Spanish to confirm the time.
2. If a Spanish speaking potential participant calls the study phone number, the study staff member will attempt to communicate that we will call back with the interpreter. A follow-up text will be sent in Spanish confirming a time the medical interpreter will call back to review the study and informed consent.
3. If a participant submits an English screening form, we will follow the steps from item #1 listed above and move this participant into the Spanish REDCAP project for ACTION. The English record ID for this participant will be deleted after transferring their information to the Spanish REDCAP project. This ensures that the participant will receive all study documents in Spanish throughout the study.

5.2.1.2 Informed Consent for Non-English and Non-Spanish Speakers

We will utilize the IRB's "short form method" to consent non-english and non-spanish speakers. The Experimental Subject's Bill of Rights form will be presented to the subject in their primary language. An interpreter will translate the UCSF IRB approved consent form to the subject. The consent discussion will occur with the study staff member, interpreter, and subject on the phone simultaneously. The subject will sign the Bill of Rights form and the interpreter obtaining consent will sign the English consent form.

5.2.1.3 Informed Consent for Computer Illiterate Participants

Some participants may be unable to navigate email and DocuSign to provide their electronic signature on the consent document. In this case, several steps will be taken in order to obtain informed consent from these participants.

1. The translator or coordinator will review the steps from the document “How to use DocuSign” over the phone with the participant. See appendix for this document.
2. If the participant is still unable to use email and/or DocuSign, we will ask if there is anyone in the subject’s household who could assist them with using the computer to open the ICF document. The participant will sign on their own.
3. If the subject is still unable to navigate the consent form, we will explain that we will mail them two paper copies of the consent form with FedEx Priority First Overnight mail. We will call the participant back when they have received the package and review the consent form with them while they have the paper copy in front of them. We will then ask them to sign one copy of the consent form and mail it back to us in a provided pre-paid FedEx envelope. The participant will place the package outside their front door and the UCSF coordinator will organize the FedEx pick up for them. The participant keeps the second copy of the ICF.

5.3 Baseline Assessment

Once a participant is determined eligible for the study and informed consent has been signed, they will be asked to complete an electronic baseline questionnaire via REDCap. Participants will be asked to provide information about their health and contact information in order to facilitate follow-up. Next of kin information will be collected in the event that the patient is unresponsive due to hospitalization or death. Please see the questionnaire in the appendix.

Participants unable or unwilling to electronically complete the questionnaires themselves may call the study coordinator who can fill out the survey on their behalf over the phone. Participants may also utilize a designated alternate, such as a family member, to fill out the electronic questionnaire on their behalf. The coordinator will make a note on the patient Masterfile if they filled out a questionnaire on the subject’s behalf.

A sub-set of participants in the swab sub-study will be asked to collect a nasal swab at baseline.

5.4 Treatment

Participants will receive a single oral dose of azithromycin (1.2 g) or placebo in the mail directly to their home. The treatment will come as an oral suspension. The patients will receive instructions for how to administer the treatment. Participants will be unaware if they have received azithromycin or placebo. Details on study medication are outlined in Chapter 7. Only eligible participants will be treated.

5.5 Day 3 Assessment

Three days after treatment, participants will be asked to complete a brief adverse event survey. They will also be asked to self-collect sample specimens, if they are willing to. The first will be a nasal swab. The second will be a saliva swab. The third swab will be a rectal swab. The swab

kits will be mailed to the patient directly. Patients will have detailed instructions outlining how to collect the swabs. The swab procedure is outlined in Chapter 6. After collecting the swabs, the patient will mail the specimens back to the UCSF Proctor Foundation for analysis. Directions for shipping the samples back to the Proctor Foundation will be provided. We will mail participants pre-assembled category B biological substance shipping materials and a pre-paid shipping slip. Participants will call FedEx directly to schedule a pick-up or they will contact the study coordinator to schedule the pick-up for them.

Participants may opt out of the swab collection if they wish to do so. During the initial screening questionnaire, we will ask if participants are willing to collect the swabs. Participants can still participate in the trial, opting to only receive the medication and not perform the swabs.

Some participants may be willing to participate in the swab sub-study (determined at consent). These patients will be asked to collect saliva, rectal, and nasal swabs at Day 3. They will only collect these swabs once, and they will not collect Day 3 swabs as part of the main study.

5.6 Day 7 Assessment

Participants will complete a questionnaire 7 days post baseline. The questionnaire will ask about the patient's health status and hospitalization status. The REDCap questionnaire will be sent electronically to the patient's email address.

A small subgroup of patients (100 per arm) will be asked to collect a rectal, saliva, and nasal swab at the Day 7 timepoint.

5.7 Day 14 Assessment

Participants will complete an electronic follow-up questionnaire at 14 days post treatment. This is our primary endpoint. We will contact the next of kin provided by the participant during enrollment for vital status and hospitalization information for participants who do not return their electronic questionnaire within 4 days of the due date.

A small subgroup of patients (100 per arm) will be asked to collect a rectal, saliva, and nasal swab at the Day 14 timepoint.

5.8 Day 21 Assessment

A final electronic REDCap survey will be sent to participants at day 21. This is the final study questionnaire. The questionnaire will be similar to the Day 14 survey. Information about the patient's health and hospitalization status will be collected.

5.9 Reminders

Participants will be sent reminders if the questionnaires are not completed. The first reminder will be sent via email 1 day after non-completion. A text reminder will be sent 2 days after non-completion. A study coordinator will call the participant if the questionnaire is not completed within 3 days. If the respondent fails to answer the 14-day timepoint questionnaire, the study coordinator will call the next-of-kin emergency contact if the questionnaire is not completed within 4 days of the due date.

5.10 Kit Preparation

Laboratory staff at the F.I Proctor Foundation will prepare the patient kits to be sent to the participant's residence. Each kit will include all materials necessary for the trial. The kit will include:

- The treatment allocation
- Swabs
- Cryogenic tubes with Zymo media
- Gloves
- Scissors
- Instructions for each swab collection procedure and patient handbook
- Parafilm
- Ziploc bags
- Category B Biological Substance Packaging for UN3373 materials
- Pre-paid shipping labels
- Patient Healthcare Provider Cards

The coordinator will sign out kits by scanning a barcode on a REDCap form when the kit is mailed to the patient. Study laboratory staff will sign in kits when they arrive from the participant. A barcode will once again be scanned into a REDCap form. Each kit will have a color coded sticker on the outside to identify which swab group the participant is in. The color scheme is:

Red: Group 1

Green: Group 2

Yellow: Group 3, Day 3

Blue: Group 3, Day 14

Blank: Group 4

Patient ID numbers will be generated by REDCap. The patient ID number will link the participant to the study questionnaires, treatment allocation, and swabs.

Each sample will be coded with a unique number. Swabs will be coded as a 6 digit number starting with a letter. For example, nasal swabs will be coded as N123456. Rectal swabs will be coded as R123456. Saliva swabs will be coded as S123456. These codes will also be generated by Zhaoxia Zhou.

Healthcare provider cards will be provided in each kit. Participants will be instructed to provide this card to their healthcare provider in the event that they seek medical attention while in the study. The card will contain contact information that the provider may call to find out which medication, azithromycin or placebo, the patient has received as part of this study.

5.11 Drawing Prizes

A random drawing will be included in this study. The drawing will be open to all individuals in the study, individuals who are invited to participate in the study but decline, prospective subjects who are ineligible, subjects who withdraw from the study, and any individual who asks to be included. Winners will receive a gift card valued at \$100.00. We will select one winner after every 500 people are included in the drawing. Winners will be notified by telephone or email, and the gift card will be mailed to their home address.

The odds of winning will be about 1 in 500. We will continue to do the drawing throughout the time that we are recruiting participants for this study.

For any drawing, the odds of winning a prize depend on how many people are entered in the drawing. As we do not know how many people will participate in this study related drawing, we cannot predict what will be the odds of winning a prize.

5.12 Emergency Room Follow-Up

Participants who report an emergency room visit during their follow-up surveys will be re-contacted by the study team by phone or email. The participant will be asked to provide more detail regarding their emergency room visit. The study team member will ask the participant the primary reason for their emergency room visit, which interventions they received, and any other relevant information such as how long they were in the ER for. The participant's responses will be recorded in RedCap.

6 Sample Collection Procedures

6.1 Nasal Swab Collection

Willing participants will collect a self nasal swab on Day 3 of the study. A small group of 200 participants will be asked to collect a nasal swab at day 7 and day 14 too.

Participants will be instructed to:

1. Wash hands with soap and water.
2. Place the collection tube (labeled "NASAL") that is half-filled with clear liquid into the Styrofoam block and loosen but do not remove the cap.
3. Blow your nose to get rid of excess mucus.
4. Insert swab into one nostril, not too far, just so the cotton tip is inside your nose.

5. Rotate the swab against the nostril wall. Turn the swab a full 360° a total of two times.
6. Using the same swab, repeat steps 4 and 5 in the other nostril.
7. Open the tube and place the cotton end of the swab into the tube up to the marked line.
8. Break the swab stick by bending to snap the swab.
9. Put the cap back on the tube, making sure it is closed tightly and will not leak or spill and remove the tube from the Styrofoam block.
10. Gently stretch the parafilm around the seal on the tube. The film should stretch and stick to itself as you wrap the film around the tube.
11. Place the sealed tube back inside the provided kit bag and seal it shut.
12. Place the sealed kit bag into the provided biohazard bag.
13. Wash hands with soap and water.

6.2 Saliva Collection

Participants will also self collect a saliva swab on Day 3 of the study. The instructions will be included in the kit mailed to the participant's home. A small group of 200 participants will be asked to collect saliva at Day 7 and Day 14 as well. The instructions to collect a saliva swab are:

1. Wash hands with soap and water.
2. Place the collection tube (labeled "SALIVA") that is half-filled with clear liquid into the Styrofoam block and loosen but do not remove the cap.
3. Open the swab and place the cotton end of the swab beneath your tongue.
4. Keep the swab under your tongue for one (1) minute. Do not move the swab to other parts of the mouth.
5. Open the tube and place the cotton end of the swab into the tube.
6. Cut the swab using the provided scissors one finger width above the end of the cotton (~1 inch from cotton tip). See handout for scale (if needed). Allow the cotton end of the swab to gently fall the rest of the way into the tube. Dispose of the swab handle in the trash.
7. Put the cap back on the tube, making sure it is closed tightly and will not leak or spill and remove the tube from the Styrofoam block.
8. Gently stretch the parafilm around the seal on the tube. The film should stretch and stick to itself as you wrap the film around the tube.
9. Place the sealed tube back inside the provided kit bag and seal it shut.
10. Place the sealed kit bag into the provided biohazard bag.
11. Wash hands with soap and water.

6.3 Rectal Swab Collection

A rectal sample will be collected from a small subset of about 300 participants. The first 300 participants included in the study will be asked to collect a rectal swab during day 3 of the study. Additionally, a small group of 200 participants will be asked to collect a rectal swab at day 7 and day 14 as well. The steps for collection, processing, and storage include:

1. Take the provided swab package.

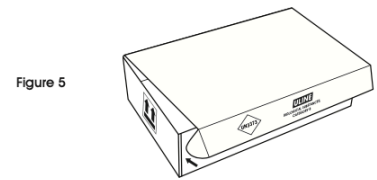
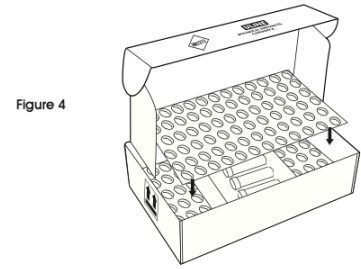
2. Position for the swab
 - a. The patient should stand in a squatting position.
3. Carefully remove the swab from the package and be sure the cotton tip is not touched.
4. Insert the tip of the swab into the patient's anus only as far as needed to make contact with fecal material (1 to 3 cm). Rotate the swab 180 degrees.
5. The tip should be a brownish color when removed from the patient.
6. Place the swab into the preservative into the collection tube. Be sure the swab is fully submerged in the liquid preservative and then break the swab off using the pre-scored breaking point.
 - a. If the swab cannot be broken off while the tip is fully submerged in the liquid, twirl the swab in the liquid first.
7. Tightly screw the cap back on the collection tube.
8. Wrap the area where the cap meets the tube with Parafilm to ensure the sample will not leak.
9. Place the tube in the rectal swab container.

All samples will be sent to the Coordinating Center. These samples are stored and shipped at ambient temperature using Category B Biological Substance shippers and pre-paid packaging slips. The instructions for shipping will be clearly marked in the instruction packet given to participants.

Packing Instructions:

1. Make sure the ULINE 6 cell absorbent sheet (white pouch) contains each of the samples you have collected. Make sure each sample is in a separate pouch. (See Figure 1).
2. Insert fully prepared absorbent sheet into the provided biohazard bag (See Figure 2).
3. Seal specimen bag by following instructions printed on the front of the bag.
4. Insert one sheet of the provided bubble wrap inside the bottom of the ULINE shipping box.
5. Place sealed biohazard bag should be placed on top of the bottom layer of bubble wrap.
6. Place the second sheet of bubble wrap on top of the sealed specimen bag.
7. Fold the top of the box down and insert each of the tabs into the sides of the box to fully close. (See Figure 5).

8. Seal the box with tape to make sure it does not open during shipping.
9. On top of the ULINE shipping box, remove or black out the old shipping label.
10. Take the new shipping label, provided with the kit and fill out your **NAME, ADDRESS, AND PHONE NUMBER** under the **FROM** section (Section 1). Be sure to press hard with a ballpoint pen. Everything else on the shipping label will be filled out for you.
11. Remove the top sheet of the shipping label to keep for your records. There should be two sheets remaining on the shipping label. **Do not remove the FedEx copy.**
12. Flip the label over and peel the backing off of the label. The back of the label should be sticky.
13. Stick the new label over the old label. Press down firmly on all corners to make sure it sticks.
14. Proceed to the shipping instructions to send your samples back to UCSF.



Shipping Instructions:

There are two ways to ship your samples back to UCSF. Each are described below:

1. Coordinator Assisted Shipping
 - a. Contact the **UCSF study coordinators** at **415-326-3761** or **ACTIONTrial@ucsf.edu**
 - b. The coordinators will take down your information and schedule a pickup at your house. Prepare to receive another call for further information about your samples' pick up.
2. Self-Schedule Shipping
 - a. Call **FedEx** at **1-800-463-3339**
 - b. Say "schedule pick-up".
 - c. Say "I don't have an account number, use tracking number"
 - d. Continue scheduling a time that works for you. When you are finished, leave your package outside your door.
The total process should take five to ten minutes. If you are uncomfortable with this method please call the study coordinators instead as mentioned above.

7 Laboratory Procedures

All laboratory processing will be done at the conclusion of the trial. Samples will be de-identified. All laboratory personnel will be masked and samples will be processed in a randomized fashion.

Nasal swabs are placed in Zymo, which inactivated all infectious agents, including SARS-CoV-2. RNA will be extracted and subjected to RT-PCR to detect the E gene of SARS-CoV-2.

E Gene Primers and Probes

| | Sequence (5' to 3') |
|------------------|----------------------------|
| SARS-CoV-2 E Fwd | ACAGGTACGTTAATAGTTAATAGCGT |
| SARS-CoV-2 E Rev | ATATTGCAGCAGTACGCACACA |

| Probe | Sequence (5' to 3') |
|-----------------------|----------------------------|
| SARS-CoV-2_E_Prpb-FAM | ACACTAGCCATCCTTACTGCGCTTCG |

8 Duties and Responsibilities of Staff

8.1 Principal Investigators

The principal investigators of this trial are Thuy Doan, MD, PhD and Catherine Oldenburg, ScD.

- Develop study design, specific aims, and outcome measurements, with the help of the biostatistician, study coordinators, and partners
- Obtain grant funding with help of partners
- Ensure that the staff follow the protocol and properly execute all areas of research
- Ensure that all ethical approvals are maintained
- Write or add major contributions to all study-related publications
- Ensure proper masking procedures for staff involved in the study
- Supervise all aspects of the study

8.2 Co-Investigators

- Assume responsibility for the study in the absence of the Principal Investigators
- Supervise team members to ensure conformity to study procedures
- Assist in study design and development of statistical analysis plan
- Contribute to major decisions regarding the study

8.3 Study Coordinators

- Ensure the execution of the study per protocol
- Coordinate with outside laboratory sites
- Manage correspondence with participants
- Maintain all ethical clearances for the study, including IRB renewals, DSMC approvals, and FDA requirements
- Prepare all forms and documents needed
- Screen potentially eligible participants
- Collect informed consent from participants
- Arrange logistics for mailing participants their study kits
- Purchase, maintain, and organize study supplies
- Maintain communication and partnership with Principipl Investigators regarding all study activities and plans

- Appropriately back up forms and data

8.4 Biostatistician

- Create the statistical analysis plan (SAP)
- Prepare the randomization allocation list
- Receive all study data and review for quality control purposes
- Ensure appropriate masking
- Prepare data analysis plan for DSMC meetings, oversee analysis and prepare all presented data for DSMC meetings, reports, publications, and FDA reports.

8.5 Data Analyst

- Create and maintain the database for all collection and results related data for the study
- Monitor correct receipt of data after each collection visit
- Develop consistency checks in the data management
- Verify data inconsistencies with study coordinator
- Analyze and provide data regarding collection and results for study staff when needed, such as for publications, DSMC meetings, or other reports
- Back up all data appropriately
- Follow up on any missing data or lab results

8.6 Laboratory Technicians

- Prepare patient study kits with all materials needed for the study
- Organize study supplies
- Prepare patient information sheets and swab instructions
- Scan swabs received from the participants into the REDCap database
- Assist with laboratory analysis of samples
- Assist with biobanking and storage of specimens

9 Statistical Methods

Please see the Statistical Analysis Plan for details on pre-specified statistical methods for this trial.

The primary analysis will estimate the risk difference (RD) and risk ratio (RR) comparing azithromycin to placebo. We will estimate these parameters using a logistic regression model with a single covariate for treatment arm. We will estimate the RD and RR from the logistic regression using marginal standardization, and a bootstrap for 95% confidence intervals [5,6]. We will compute *P*-values for differences between arms using a permutation test with the difference between arms as the test statistic and 10,000 iterations.

The secondary analysis of viral load will compare log transformed values of relative read and number of reads using a t-test. We will compute *P*-values for differences between arms using a permutation test with the difference between arms as the test statistic and 10,000 iterations.

Determination of statistical significance for the primary and secondary analysis will follow the final alpha-spending function determined by the group sequential design.

10 Study Medication

The study drug product will be obtained from Pfizer, Inc. Participants enrolled in the study will be offered a dose of oral azithromycin or placebo determined by their randomization allocation. We will monitor adverse events following treatment as described in Chapter 9.

10.1 Description

Azithromycin, or Zithromax, is supplied as an oral suspension in bottles containing azithromycin dehydrate powder equivalent to 1200 mg per bottle and the following inactive ingredients: sucrose, tribasic anhydrous sodium phosphate, hydroxypropyl cellulose, xanthan gum; FD&C Red #40, and flavoring including spray dried artificial cherry, crème de vanilla, and banana. After constitution, a 5 mL suspension contains 200 mg of azithromycin. This study will utilize the European Union formulation of the drug, which is comparable to the United States formulation.

10.2 Dosage

Azithromycin and placebo will be administered as a single oral 1.2 g dose. Individuals who are allergic to macrolides/azalides will not be enrolled in the study. We propose providing a 1.2 gm oral dose depending on immediate availability and formulation for azithromycin and placebo. A single 1 g dose of azithromycin in adults is approved for many common indications, including *Chlamydia trachomatis* urethritis and chancroid. This is also the dose used for treatment of trachoma, an ocular infection caused by *Chlamydia trachomatis*.

The efficacy of azithromycin for prevention of COVID-19 progression in SARS-CoV-2 positive patients is unknown, as is optimal dosing. Approved oral dosing for other indications includes:

- 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5
- A single dose, give from 1 gm to 2 gm

Single dose regimens have clear advantages in adherence and regimen completion. The long half-life of azithromycin (68 hours for a single oral 500 mg dose) facilitates single dosing. However, this may come at the cost of increased risk of gastrointestinal symptoms.

The comparator group for this trial will be a masked placebo. We propose to use placebo due to the lack of safety and efficacy data for azithromycin in COVID-19 patients and because data generated by uncontrolled studies is unreliable.

10.3 Medication Procurement/Donation

Azithromycin and the placebo have been donated by the Pfizer Corporation. There will be no costs to acquiring the study medication. Pfizer, Inc. will ship azithromycin and placebo to the Proctor Foundation and study staff will send the treatment directly to patients. The lot numbers from the first shipment of drug are:

Placebo: P9640004

Azithromycin: 838900

10.4 Medication Quality Control

Medication will be stored at the Proctor Foundation between the temperature of 15°C to 30°C. The study coordinator and other staff will regularly check and record the study medication expiration dates. Expired medication will be discarded. The drug expires on November 30, 2021.

10.4.1 Drug Storage

The initial drug shipment from Pfizer, Inc. on May 22, 2020 will include 4,707 bottles of azithromycin (98 cartons) and 2,352 bottles of placebo (49 cartons). The drug will be stored at the UCSF Proctor Foundation at 513 Parnassus Avenue MedSci S347 San Francisco, CA 94143. The drug will be kept between 59°F and 85°F in a locked room. Temperature will be monitored using a data logger. Data from the temperature data logger will be uploaded on a monthly basis.

The coordinator will maintain a smaller supply of drug stock at her place of residence until the shelter-in place order is lifted. The coordinator will keep at least 15 bottles of each treatment letter in stock at 487 Sherwood Drive Sausalito, CA 94965. Temperature will be monitored at this location using a data logger. The temperature information will be uploaded monthly.

Logs will be maintained at both locations regarding stock and drug delivery on a weekly basis.

10.5 Packaging and Labeling

The study drug will be relabeled and packaged by UCSF laboratory personnel. Laboratory staff will completely remove the Zithromax labels and place the study label stickers on the bottle. The labels will indicate one of 6 letters: AAA, BBB, CCC, HHH, TTT, or VVV.

Labeling Example:

| | |
|---|--|
| ACTION Study Use before: 30 November 2021 For Oral Use Only Azithromycin 1200 mg (200 mg/5 ml) or Placebo Store at room temperature Caution: New Drug-- Limited by Federal law to investigational use Investigator Name: Thomas Lietman, MD UCSF FI Proctor Foundation 513 Parnassus Avenue, MedSci S309 San Francisco, CA 94143 ACTIONTrial@ucsf.edu Tel: 415-326-3761 | Treatment Group TTT - Rx Only |
|---|--|

Once re-labeled, the drug will be given to the study coordinator. The study coordinator will place the corresponding treatment allocation into each participant's kit prior to sending it to the participant's address. The coordinator will use REDCap to determine each participant's treatment allocation letter.

10.6 Concurrent Medications

Participants are free to seek treatment for their COVID-19 symptoms outside of the study. Participants will be advised to avoid antacids containing aluminum or magnesium while in the study. Participants will be asked about concurrent medications taken at the follow-up questionnaires.

10.7 Measures of Treatment Compliance

Subjects will be asked to confirm if they took the study drug and on which date during the Day 3 questionnaire.

11 Adverse Event Monitoring and Safety Assessment

11.1 Adverse Events

Azithromycin has been extensively studied in humans for many indications, including community-acquired pneumonia and urethritis and cervicitis caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Azithromycin is generally well-tolerated. The most common adverse events following azithromycin are diarrhea (5 to 14%), nausea (3 to 18%), abdominal pain (3 to 7%), and vomiting (2 to 7%). Rarer side effects include abnormal liver function, allergic

reactions, and prolongation of the QT interval. Diarrhea due to *Clostridium difficile* has been reported in rare cases.

Participants who are over 55 years of age and have taken hydroxychloroquine within the past 7 days will be excluded from this study due to concerns of QT prolongation.

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.

Azithromycin is also contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

The common adverse reactions that may occur will be explained in detail to the participants during the informed consent process. Participants will report any adverse events they have experienced during the Day 3 questionnaire. If a participant has a serious adverse event or any other concerns, they will be advised to contact their healthcare provider and/or 911. Participants can also email or call the study staff if they have any concerns.

Some adverse reactions were reported with azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established. These symptoms include:

Allergic: Arthralgia, edema, urticaria, and angioedema.

Cardiovascular: Arrhythmias including ventricular tachycardia and hypotension. There have been reports of QT prolongation and *torsades de pointes*.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and reports of tongue discoloration.

General: Asthenia, paresthesia, fatigue, malaise, and anaphylaxis.

Genitourinary: Interstitial nephritis and acute renal failure and vaginitis.

Hematopoietic: Thrombocytopenia.

Liver/Biliary: Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure. [see *Warnings and Precautions (5.2)*]

Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation, and syncope.

Psychiatric: Aggressive reaction and anxiety.

Skin/Appendages: Pruritus serious skin reactions including erythema multiforme, AGEP, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and DRESS.

Special Senses: Hearing disturbances including hearing loss, deafness and/or tinnitus, and reports of taste/smell perversion and/or loss

11.2 Adverse Event Monitoring

Adverse events will be formally monitored using an electronic questionnaire at Day 3. Participants will be asked to report any adverse events they have experienced since taking the

study drug. Participants will be asked if they have experienced the following adverse events since they last completed the study questionnaire:

- Nausea
- Vomiting
- Diarrhea
- Rash
- Abdominal pain
- Other

During the informed consent procedure, participants will be instructed that participation in the trial does not replace or represent their medical care. While there will be a study email address which participants can use to contact study investigators, it is not monitored full-time and is not a replacement for medical care, nor can the study staff offer medical advice. Participants will be instructed to contact their medical care provider for medical advice or call 911 in case of emergency.

Participants do not have to wait until the Day 3 questionnaire to report adverse events. Participants will be encouraged to contact the study staff at any time for any adverse events or concerns.

11.3 Serious Adverse Events

A Medical Monitor for the trial will be designated by the study lead investigators. The Medical Monitor will review all SAE's that occur and evaluate the likelihood of an association to the study drug. If deemed possibly related to the study drug by the Medical Monitor, the SAE will be forwarded to the DSMC and IRB if necessary. The Medical Monitor for this study will be Dr. Dan Kelly, an internal medicine and infectious disease specialist at UCSF. The Medical Monitor will review serious adverse event cases ideally within 24 to 48 hours. Other adverse events will be analyzed by arm at the end of the study or per request from the DSMC.

Any serious adverse events will be reported to Pfizer. An ISR SAE Form (Investigator-Sponsored Research Serious Adverse Events Form) will be completed by study personnel for each event and sent to SAEFaxmailbox@Pfizer.com.

An SAE is defined as any adverse event that:

- Results in death
- Is life-threatening (i.e., causes an immediate risk of death)
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Changes the risk/benefit ratio of the study
- Any cardiovascular related or unrelated serious adverse event

Or that is considered to be:

- An important medical event

Serious adverse events will be reported to Pfizer, the Data and Safety Monitoring Board and the Institutional Review Board at the University of California, San Francisco. Any event deemed to be definitely, probably, or possibly related and is serious or unexpected will be reported to the IRB within 5 days. Deaths and life-threatening events will be reported immediately.

UCSF will be responsible for discerning which medical occurrences meet the serious adverse event criteria. UCSF personnel will then fill out an ISR SAE form and submit to Pfizer no later than 48 hours from UCSF's awareness date. UCSF awareness date should be noted on the ISR form. UCSF will report SAEs around the clock, 7 days a week. UCSF should not report duplicate reportings of SAEs and provide the causality determined by the Medical Monitor.

Serious adverse events will also be reported to the Food and Drug Administration (FDA). UCSF will be in compliance with the FDCA (21 USC 301 et seq) and Title 21 of the code of federal regulations. UCSF will report any unexpected fatal or life-threatening suspected adverse reactions to the FDA no later than 7 days after initial receipt. UCSF will also report SAEs, findings suggesting significant human risk, and/or clinically important events that increase the rate of SAEs within 15 days after determining the information qualifies for reporting. UCSF must always cite the IND number 149526 on all correspondence. Additionally, UCSF will submit an annual progress report within 60 days of the anniversary of the IND active date (4/18/2020).

12 Protection of Human Subjects

The research team will obtain formal ethical approval prior to the study start. Informed written consent will be collected from all participants electronically due to the remote nature of the study. A research team member will describe the study to participants in depth including information about the treatment and study activities. If, at any time, a participant wishes to withdraw from the study, they will be free to do so.

A Data and Safety Monitoring Board (DSMB) will be empaneled to review patient data throughout the course of the study. The Board will meet to review and approve study procedures prior to trial commencement and will review reports of serious adverse events and interim safety and efficacy analyses. Members of the DSMB will have expertise in infectious disease, epidemiology, biostatistics, and randomized controlled trials.

12.1 Institutional Review Board Approval

UCSF Committee on Human Research

UCSF's Committee on Human Research will review the study protocol for ethical approval.

12.2 Informed Consent

As described in section 4.1.1, all participants will electronically sign an informed consent form. Consent scripts will be submitted to the UCSF Committee on Human Research prior to the study start for ethical approval. Young adults and children under 18 years of age, who cannot give

consent by law, will not be included in the study. Participants will be able to ask the research team questions about the study procedures and withdraw from the study at any time.

12.3 Risks and Benefits of Study Procedures

There are minimal risks to the participant during this trial. Participants may experience some mild or rare side effects as described in Chapter 7 due to the treatment. Adverse effects will be monitored. If any question on the questionnaire makes the participant uncomfortable, and they do not wish to answer, then they may skip the question. The patient may withdraw from the study at any time.

The swabbing procedures present minimal risk to the study participants as well. The participants will self collect a nasal, saliva, and rectal swab. Temporary discomfort may occur. Adverse events such as nose bleeds are possible, but uncommon.

13 Study Monitoring

The project will be continuously monitored by the supervisory team, which will consist of members from UCSF. The supervisory team will run daily and weekly monitoring reports.

The study analyst will daily update the list of eligible participants based on the REDCap screening form. The coordinator will then contact these eligible participants to explain the study in detail, collect informed consent, and obtain the participant's place of residence. The analyst will also inform the coordinator of participants who are late in filling out their questionnaires so that the coordinator may follow-up with them.

A weekly data quality report will be sent to the entire supervisory team, which will include enrollment counts, follow-up data, primary outcome data, and other study statistics.

13.1 Protocol Violations

A protocol violation occurs when the subject, investigator, or study staff fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Changes in the conduct of the research protocol without prior IRB approval
- Any violation that has harmed, or posed significant risk of harm, to the research participant

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files for FDA reporting purposes. Any protocol violation must be reported the UCSF IRB as well.

14 Data Collection, Management, and Security

The project will be continuously monitored by the supervisory team, which will consist of members from the UCSF F.I. Proctor Foundation. The supervisory team will communicate with participants and monitor the data daily. This section discusses how the data are collected, entered into the database, stored, and transferred to the Data Coordinating Center under the supervision of Dr. Benjamin Arnold.

14.1 Scope of the Data

Mortality and morbidity data will be collected in this trial. Participant vital status will be collected at day 3, day 7, day 14 and 21 day follow-ups. Hospitalization and COVID-19 status will also be collected during follow-ups via an electronic questionnaire.

14.2 Data Storage, Management, and Security

Data will be recorded electronically using REDCap. Data will be stored in a secure directory on Box, which maintains HIPAA-level compliance and encryption for UCSF accounts (details here: <https://it.ucsf.edu/services/ucsf-box/additional/how-does-box-protect-your-data>). Rapid transfer of electronically captured data will allow nearly real-time monitoring of activity at the study site. All handheld devices and data entry coordinating centers will be password protected, and all changes in data will be noted, including the date of the change, and the person who made the change. All information collected will adhere to HIPAA compliance rules.

14.3 Electronic Data Collection Forms

All forms for this study will be created electronically on REDCap. These forms will be tested by the UCSF investigators prior to using them for the study. All REDCap forms are electronic and should be completed in their online version. Paper copies will be available to be downloaded, printed, and completed by hand if necessary, but electronic data entry is preferred. Study personnel should communicate any clarifications or updates to the study forms to all participants.

14.4 Data Review

The study coordinator will review all REDCap forms for accuracy and completion prior to submitting them to the REDCap database. If issues are identified post-submission, the study coordinator will contact the appropriate person at the Coordinating Center to address the issue. Only the Coordinating Center is authorized to add missing data or make any changes to submitted data in REDCap. The Coordinating Center may conduct further investigations if certain fields are associated with a higher rate of form errors.

14.5 Data Entry

Once the study coordinator has reviewed the completed REDCap forms, they will submit the electronic forms to the REDCap database. The data manager at the Coordinating Center will review the data for accuracy and completion.

14.6 Data Transfer

The Coordinating Center will access the data through a secure, online REDCap database system. The database manager will download the data sets and conduct checks for completeness and validity. Any queries generated will be communicated by secure encrypted email to the study coordinator for resolution.

14.7 Data Entry Errors

The data manager at the CC will assess study data using an automated program in REDCap (with a goal of completing within 2 days of data entry), searching for missing and contradicting data fields. Wherever there is a mismatch, an error file is generated with relevant data such as the form, field name, and data for which discrepancy is found. The data manager will then contact the study coordinator to verify the forms. Discrepancies and missing values will be assessed by the data manager, and resolved by queries sent to the study coordinator and appropriate observers (e.g., clinician). A logfile will preserve the date and time of any changes, together with who entered the changes.

14.8 Data Consistency and Validity

Through range checks, the data entry software helps prevent inconsistencies or invalid data. The database program will check for the following errors: (1) improper entry of the patient ID based on the checksum, (2) data fields that are out of range, (3) inconsistent or illogical entries, (4) incompleteness, and (5) numerical values that are far outside the range of those previously entered. The software will create an error file with relevant data such as the form identification, field names and the data. Automated checks will be made to ensure consistency and that each variable in the analysis set has in-range values (protecting against negative ages, spelling errors in categorical factors, and similar errors). The data manager will contact the study coordinator about any errors in order to resolve the inconsistencies.

14.9 Data Preparation and Cleaning

Datasets for analysis will be produced in comma separated values (.csv) files containing a single header line whose variable names match the REDCap database. Each analysis set will be in the form of a rectangular table in which each column corresponds to a single variable and each row to an observation. All missing values will be coded explicitly using the string "NA" (as used in the R software). Codes for categorical variables (such as 1 for male, and 2 for female) will be avoided in favor of self-documenting character strings or factor variables (such as Male, Female).

A detailed codebook will be prepared, containing for each variable, (a) the form from which the variable derived, (b) the text of the question, (c) all possible values for the variable, and (d) summary statistics for the variable. Note that all codes and character strings that represent categorical factors will be clearly defined in the codebook. Units for each continuous variable will be unambiguously indicated for each variable. Each release of the analysis set will be accompanied by the corresponding version of the codebook. Version numbering with dates will be strictly observed.

14.10 Monitoring

We will maintain a record of changes to the REDCap database. Database errors include (a) missing information, (b) erroneous information, and (c) errors arising from difficulties with the electronic forms themselves. Weekly quality assurance reports will summarize the number of each of these. Most importantly, we will closely monitor the time between the study visit date and submission of the electronic forms to REDCap to ensure that this time is less than 3 days. If entry times exceed 5 days, then this will trigger a response, which may include investigation and/or reassignment.

14.11 Data Analysis

Following data checks by the data analyst, the Data Analysis Committee will be responsible for analyzing the data from the REDCap database. It will merge the masked data with the randomization list, perform statistical analyses and prepare reports.

Standard report-generation software included with the R statistical and data analysis package will be used to ensure consistency of the codebook and analysis set at all times.

Data monitoring reports will be prepared based on analysis data sets. These will be prepared using report-generation software. Monitoring reports will include (a) recruitment reports for each center, (b) compliance reports, (c) retention reports, and (d) data quality reports. These will be reviewed by the Coordinating Center on a weekly basis.

14.12 Data Storage and Security

Electronic forms will be completed on an encrypted electronic device, requiring a passcode to unlock the device and additional separate login credentials to access the REDCap forms. Copies of the electronic forms will not be stored on the device itself but rather within the secured REDCap database.

All electronic storage will be subject to standard security procedures in compliance with established enterprise information security standards. Each computer will be hardware-firewalled and will not be accessible outside the Local Area Network. Hard-disk encryption will be used for each machine, and the machine will not be accessible without a network account and password. Only study-specific personnel will have password access to the encrypted Box directory. Accounts will be immediately deactivated for data entry or other personnel who leave the study.

15 Data and Safety Monitoring Committee Charter

This charter is for the Data and Safety Monitoring Committee (DSMC) for the *Azithromycin for COVID-19 Treatment in Outpatients Nationwide (ACTION)* Trial.

The Charter will define the primary responsibilities of the DSMC, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and communication, statistical monitoring guidelines to be implemented by the DSMC, and an outline of the content of the Open and Closed Reports that will be provided to the DSMC.

The DSMC will be advisory to the trial leadership group, hereafter referred to as the Steering Committee (SC). The SC will be responsible for promptly reviewing the DSMC recommendations and determining, whether to continue or terminate the trial, and to determine whether amendments to the protocol are required. If needed, the DSMC may seek the advice of a content expert outside of the committee.

15.1 DSMC Membership

The DSMC is an independent multidisciplinary group consisting of epidemiologists, biostatisticians, bioethicists, and clinicians that collectively has experience in the management of infectious diseases and in the conduct and monitoring of randomized clinical trials.

The DSMC membership has been restricted to individuals free of apparent conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory. Thus, neither study investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DSMC.

15.2 Conflicts of Interest

The DSMC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organizations (CRO), or with other sponsors having products that are being evaluated or that are competitive with those in the trial. The DSMC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DSMC members will be responsible for advising fellow members of any changes in any of the membership requirements that occur during the course of the trial. It may be appropriate for DSMC members who develop significant conflicts of interest resign from the DSMC.

DSMC membership is to be for the full duration of the trial. If any members leave the DSMC, the SC, in consultation with the DSMC, will promptly appoint a replacement.

15.3 Timing and Purpose of the DSMC Meetings

Organizational Meeting

The initial meeting of the DSMC will be an Organizational Meeting. This is during the final stages of protocol development and the purpose is to provide advisory review of scientific and ethical issues relating to study design to discuss the standard operating procedures and to discuss the format and content of the Open and Closed Reports that will be used to present trial results.

The Organizational Meeting will be attended by all DSMC members, lead trial investigators, and the trial biostatistician.

Formal Interim Analysis Meetings

One or more 'Formal Interim Analysis' meetings will be held to review data relating to treatment safety and efficacy, and quality of trial conduct.

15.4 Procedures to Ensure Confidentiality and Proper Communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DSMC has access to all emerging information from the trial regarding comparative results of efficacy and safety, aggregated by treatment arm.

Closed Sessions

Sessions involving only DSMC members and, where appropriate, those unmasked trial investigators (on the Data Coordinating Committee) who generate the Closed Reports (called Closed Sessions) will be held to allow discussion of confidential data from the trial, including information about the relative efficacy and safety of interventions.

At a final Closed Session, the DSMC will develop a consensus on its list of recommendations, including that relating to whether the trial should continue.

Open Session

In order for the DSMC to have access to information provided, by study investigators, or members of regulatory authorities, a joint session between these individuals and DSMC members will be held between the Closed Sessions.

Open and Closed Reports

For each DSMC meeting, Open and Closed Reports will be provided. Open Reports, will include data on recruitment and baseline characteristics, pooled data on eligibility violations, and completeness of follow-up and compliance. The study statistician (TCP) will prepare these Open Reports.

Closed reports, available only to those attending the Closed Sessions of the meeting, will include analyses of primary and secondary efficacy endpoints, including subgroup and adjusted analyses, AEs and symptom severity, and Open Report analyses that are displayed by intervention group. These Closed Reports will be prepared by the study biostatistician.

The Open and Closed Reports should provide information that is accurate, with follow-up that is complete to within two months of the date of the DSMC meeting. The Reports should be provided to DSMC members approximately three days prior to the date of the meeting.

Minutes of the DSMC Meeting

The research team will prepare minutes for the open portion of the meeting, including the DSMC's recommendations.

Recommendations to the Steering Committee (SC)

At each meeting of the DSMC during the trial, the committee will make a recommendation to the Steering Committee to continue or terminate. This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this Charter.

Recommendations to amend the protocol or conduct of the study made by the DSMC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue or to stop the trial based on the DSMC recommendations.

The DSMC will be notified of all changes to the protocol or to study conduct. The DSMC concurrence will be sought on all substantive recommendations or changes to the protocol or study conduct prior to implementation.

The SC may communicate information in the Open Report to the sponsor and may inform them of the DSMC recommended alterations to study conduct or early trial termination in instances in which the SC has reached a final decision agreeing with the recommendation. The SC will maintain confidentiality of all information it receives other than that contained in the Open Reports until after the trial is completed or until a decision for early termination has been made.

15.5 Statistical Monitoring Guidelines

The SC will propose statistical rules for a futility stopping rule (requested by the sponsor) and an efficacy stopping rule at the first DSMC meeting.

15.6 DSMC Contact Information

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Dave Glidden: david.glidden@ucsf.edu

Emily Gower: egower@email.unc.edu

APPENDIX

Appendix 1: Original manual of procedures

REVISION HISTORY

4/9/2020: Addition of 21 day follow up timepoint, added additional details to the Study Methods Chapter.

4/10/2020: Addition of Pfizer information to Medication Chapter, addition of Chapter 12 Study Monitoring.

4/19/2020: New eligibility criteria added (QT prolongation + chloroquine over 55).

4/20/2020: Chapter 5 and 6: addition of a sub-study where 100 patients per arm are asked to collect nasal, saliva, and rectal swabs at days 3, 7, 14. Addition of chapter 8: Staff responsibilities.

4/21/2020: Addition of adverse events and SAE information per request of Pfizer.

4/24/2020: Addition of Pfizer SAE reporting requirements.

4/27/2020: Addition of section 3.3 Sub-Studies. Addition of Death as a secondary endpoint. Addition of eligibility criteria (not currently taking nelfinavir or warfarin). Section 5.10 change of patient ID number to REDCap based.

4/28/2020: Addition of figure 1 in 3.3. Change in main study swabs from first 300 participants to all participants will be asked to collect rectal swab at day 3.

5/4/2020: Specification that we will exclude pregnant women. Addition of FDA reporting criteria to SAE section.

5/5/2020. Addition of protocol violation section, drug storage section, concurrent medications section

5/6/2020: Specification of cardiovascular related events for reportable serious adverse events to Pfizer

5/12/2020: Removal of rectal swab in group 1 & group 2 in swab sub-study section.

5/26/2020: Addition of Dr. Seitzman and Dr. Redd to the protocol. Addition of color-coded sticker scheme for kits to section 5.10. Addition of lot numbers from drug to 10.4.

6/3/2020: Addition of online social media ad campaign under recruitment.

6/8/2020: Expansion of eligibility criteria “positive test within past 3 days” to “positive test within past 7 days”. Specified that participant can fill out questionnaires via email or over the phone in eligibility criteria.

7/8/2020: Addition of unmasking protocol to 3.6.1.

8/24/2020: Addition of protocol for short form method of consent.

9/23/20: Addition of Rhode Island Open Door Health as recruitment site. Addition of EDDM to recruitment methods. Addition of random drawing lottery.

11/13/20: Addition of WebMD to recruiting methods. Addition of language for obtaining informed consent from computer illiterate participants.

12/7/20: Change primary outcome. Moved hospitalization to secondary outcome.

- The investigators edited the primary outcome to a symptom based outcome. Instead of a hospitalization at Day 14 post enrollment, the primary outcome will be a binary assessment of whether the participant is symptom free at Day 14 (yes or no) post enrollment. This change was made because the trial will not have enough statistical power for the original hospitalization outcome. The event “hospitalization” is much rarer

in the study population than anticipated and enrollment is slower than planned. This change was approved by the trial's Data Safety Monitoring Committee and Institutional Review Board.

12/18/20: Updated objective and sample size.

4/5/21: Addition of section 5.12 Emergency Room Follow-Up.

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