Official Title: Hydroxychloroquine vs. Azithromycin for Hospitalized Patients With Suspected or Confirmed COVID-19 (HAHPS): A Prospective Pragmatic Trial

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CLINICAL STUDY PROTOCOL

Hydroxychloroquine vs. Azithromycin for Hospitalized Patients with Suspected or Confirmed COVID-19 (HAHPS): A prospective pragmatic trial

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STATEMENT OF COMPLIANCE

This study will be carried out in accordance with Good Clinical Practice (GCP) and information privacy/security as required by the following:

- United States (US) Code of Federal Regulations (CFR) 45 CFR Part 46 (The Common Rule)
- International Council on Harmonization (ICH) E6 (R2)
- 45 CFR Part 160 and Part 164, Subparts A, C, and E

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

KEY ROLES

Individuals:

Principal Investigator: SM Brown

Medical Monitor: J Bledsoe

Institutions:

Data Management Core: Intermountain Medical Center

Clinical Coordinating Center: Intermountain Medical Center

Biostatistics Core: University of Utah

Protocol Committee Chair Declaration

TITLE: Hydroxychloroquine vs. Azithromycin for Hospitalized Patients with Suspected or Confirmed COVID-19 (HAHPS)

This study protocol has been critically reviewed by protocol committee members including myself. The protocol is consistent with current best knowledge of risks and benefits of study drug and with the ethical, moral, and scientific principles for clinical research as contained in ICH E6 standards and relevant US regulations.

_____ _____

Samuel M. Brown, MD MS Date of signature

Site Principal Investigator Declaration

TITLE: Hydroxychloroquine vs. Azithromycin for Hospitalized Patients with Suspected or Confirmed COVID-19 (HAHPS)

I have reviewed this study protocol and relevant associated training documents. I agree to abide the protocol requirements and follow Good Clinical Practice. The study will not commence without approval of the relevant Institutional Review Board (IRB). No changes will be made to the study without prior written approval from the protocol committee and the IRB unless it is necessary to control or eliminate an immediate risk to study subject(s).

_____

Name (Printed)

_____ _____

Signature Date of signature

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1.0 Abbreviations and Definitions

CCC = Clinical Coordinating Center
DCC = Data Coordinating Center
DSMB = Data Safety and Monitoring Board
ER = Emergency Room
ICU = Intensive Care Unit
IMC = Intermountain Medical Center
ITT = Intention to Treat
LAR = Legally Authorized Representative
SUSAR = Suspected Unexpected Serious Adverse Reaction

Definitions

Eligible patients: All patients who meet all inclusion criteria and no exclusion criterion.

Enrolled participants: All eligible patients who have completed the consenting process. The time of enrollment will be the time informed consent was signed by the patient or legally authorized representative.

Intention-to-treat (ITT): All randomized patients, regardless of whether they received study drug or completed study procedures. This is the primary analysis set.

Legally Authorized Representative (LAR): An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.

Randomized participants: Enrolled participants who undergo randomization, regardless of whether they receive any study drug.

Serious adverse event (SAE) or serious suspected adverse reaction or serious unexpected suspected adverse event (SUSAR). An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (cf. 21 CFR 312.32(a)). Events that are serious and unexpected and have a reasonable possibility that the event was due to a study procedure are considered SUSARs.

Study day: The day of enrollment is study day zero. The next day is study day one, and so on.

Study hospitals: The hospitals where the patient is enrolled.

Study withdrawal: Permanent withdrawal from the study before the completion of study activities. Study procedures will cease upon withdrawal from the study. Data recorded up to the time of withdrawal will be included in the study analysis, unless consent to use that data has also been withdrawn. If a patient (or LAR) requests withdrawal from the study after completion of study procedures, study endpoints will be determined unless consent to do so has also been withdrawn.

2.0 Study Summary

2.1 Study Title: Hydroxychloroquine vs. Azithromycin for Hospitalized Patients with Suspected or Confirmed COVID-19 (HAHPS).

2.2 Study Objective: Assess the efficacy and safety of hydroxychloroquine (HCQ) as opposed to azithromycin for suspected or confirmed COVID-19.

2.3 Study Hypothesis: Hydroxychloroquine is superior to azithromycin in improving outcomes among patients with suspected or confirmed COVID-19.

2.4 Study design: Phase 2 prospective, randomized, open-label active comparator trial.

2.5 Inclusion criteria

- Adult (age ≥ 18 years)
- Confirmed OR suspected COVID-19,
    - Confirmed: Positive assay for COVID-19 within the last 10 days
    - Suspected: Pending assay for COVID-19 WITH high clinical suspicion
- Scheduled for admission or already admitted to an inpatient bed

2.6 Exclusion criteria

- Allergy to hydroxychloroquine or azithromycin
- History of bone marrow transplant
- Known G6PD deficiency
- Chronic hemodialysis or glomerular filtration rate < 20ml/min
- Psoriasis
- Porphyria
- Concomitant use of digitalis, flecainide, amiodarone, procainamide, propafenone, cimetidine, dofetilide, phenobarbital, phenytoin, or sotalol
- Known history of long QT syndrome
- Current known QTc>500 msec
- Pregnant or nursing
- Prisoner
- Weight < 35kg
- Seizure disorder
- Severe liver disease
- Outpatient use of hydroxychloroquine for treatment of a disease other than COVID-19 OR has received more than 2 days of hydroxychloroquine or azithromycin for suspected or confirmed COVID-19
- Patient has recovered from COVID-19 and/or is being discharged from the hospital on day of enrollment.
- Treating physician refuses to allow patient participation in the study
- Unable to obtain informed consent
- Prior enrollment in this study

2.7 Sample size: The study will enroll as many as 300 patients.

2.8 Primary Endpoint:

- COVID Ordinal Outcomes Scale at 14 days

2.9 Interim Monitoring. A Data Safety Monitoring Board will oversee this trial according to a DSMB Charter.

3.0 STUDY DESCRIPTION

3.1 Background

COVID-19 is pandemic with high mortality among hospitalized patients despite a benign course in the large majority of patients infected. Efficacious therapies are desperately needed. Hydroxychloroquine and chloroquine have antiviral and immune-modulating effects.[1] Hydroxychloroquine is thought to be better tolerated and is used extensively in mild auto-immune disease.

3.1.1 Evidence supporting possible efficacy for hydroxychloroquine.

In cell models, chloroquine both interferes with terminal glycosylation of the ACE2 receptor (the cell surface receptor by which SARS-CoV2 enters human cells) and increases endosomal pH, which interferes (at least *in vitro*) with a crucial step in viral replication.[1,2] Hydroxychloroquine is 5x more potent than chloroquine in a Vero cell model of SARS-CoV-2 infection.[3] In independent experiments, chloroquine has confirmed in vitro activity against SARS-CoV-2.[4] Additionally, hydroxychloroquine has in vitro efficacy against SARS-CoV-1.[5] An informal (and methodologically inadequate) report from a case series of 20 patients in France suggested the possibility of more rapid viral clearance with both hydroxychloroquine and azithromycin, suggesting azithromycin may be a useful comparator for hydroxychloroquine.[6] (The data have been widely misinterpreted in popular discussions as demonstrating efficacy and suggesting synergy; neither appears to be the case on the basis of the data presented.) According to news releases, an as-yet-unpublished set of case series in China (N reportedly 120) suggests the possibility of rapid viral clearance and low rates of progression to critical illness. In addition to in vitro anti-viral effects chloroquine and hydroxychloroquine appear to have immune-modulatory effects, especially via suppression of release of TNF and IL6, especially in macrophages.[1,7-10]

3.1.2 Evidence against efficacy for hydroxychloroquine.

Chloroquine and hydroxychloroquine have been promoted as extremely broad anti-infective agents for decades. The reported effects include suppression of fungi, atypical bacteria, and viruses. Other than the effects on ACE2 glycosylation, the mechanisms invoked as evidence for efficacy against SARS-CoV-2 have also been invoked for a wide range of viruses. However, when chloroquine and hydroxychloroquine have been studied in humans, neither agent has demonstrated consistent efficacy in clinical trials, including in HIV, influenza, hepatitis, and Dengue.[11] In one trial, hydroxychloroquine even increased HIV viral load.[12] Expert opinion advises against hydroxychloroquine for MERS, another serious coronavirus.[13] The long history of clinical failure despite in vitro anti-viral activity suggests that in vitro evidence may not suggest clinical efficacy for hydroxychloroquine.

The ANZICS guidelines emphasize that novel treatments should be administered within clinical trials; the Surviving Sepsis Campaign guidelines (http://bit.ly/SSCCOVID-19) also affirm the lack of evidence to support the clinical use of (hydroxy)chloroquine. WHO guidance (https://apps.who.int/iris/bitstream/handle/10665/331446/WHO-2019-nCoV-clinical-2020.4-eng.pdf) also strongly affirms that “investigational anti-COVID-19 therapeutics should be done under ethically approved, randomized, controlled trials.” The evidence thus strongly favors equipoise.[14]

3.1.3. Relevance of azithromycin.

Azithromycin, a macrolide antibiotic with anti-inflammatory properties has a longstanding, well established safety record. In a secondary analysis of an ARDS trial population (N=235) azithromycin was associated with higher survival.[15] A retrospective study (with propensity matching) of 125 patients with sepsis-associated ARDS suggested lower 60-day mortality.[16] A secondary analysis of a prospective cohort (N=873) suggested higher survival with azithromycin.[17] While azithromycin is commonly recommended in combination with a beta-

lactam for community-acquired pneumonia (which can be confused with COVID-19), randomized trial evidence suggests that omitting the macrolide is in fact non-inferior.[18]

3.1.4. Role for an active comparator arm

Given (1) the likelihood that COVID-19 will occur in pandemic waves, (2) clinicians and investigators have identified many treatments with early suggestions of benefit but no solid evidence for efficacy, (3) the good safety profile of hydroxychloroquine and azithromycin, and (4) the low probability that more than one will be effective, it is reasonable to rapidly evaluate the range of proposed candidates, favoring commonly used and non-toxic treatments for control groups. A pragmatic, comparative effectiveness trial of two active, nontoxic agents in current popular use during the COVID-19 pandemic is urgently indicated.

3.2 Study Design

Phase 2 prospective, randomized, open-label, active comparator trial.

3.3 Study Objective

Assess the efficacy of hydroxychloroquine (HCQ) as opposed to azithromycin for suspected or confirmed COVID-19.

3.4 Study Hypothesis

Hydroxychloroquine is superior to azithromycin in improving clinical outcomes among patients with suspected or confirmed COVID-19.

3.5 Primary endpoint

The WHO proposed (https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf) a slight modification of a preexisting COVID-19 ordinal endpoint, adding an extra status relevant only to prevention trials (no disease), and adding an extra status to reflect the difference between simple invasive ventilation and invasive ventilation plus additional organ support (ECMO, CRRT, or vasopressors). In the interest of synchronization, we will collect data to allow comparison with either the WHO or NIAID version of the scale. For analysis purposes, our primary endpoint is the WHO COVID Ordinal Outcomes Scale at day 14 (with the recognition that no patients are expected to have the status of never having developed a respiratory illness). The details of the endpoint are displayed in Table 1.

Table 1. WHO COVID Ordinal Outcomes Scale *

Patient State	**Descriptor**	**Score**
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized, mild disease	No oxygen therapy	3
	Oxygen by mask or nasal cannulae	4
Hospitalized, severe disease	Non-invasive ventilation or high-flow oxygen	5
	Invasive mechanical ventilation without other organ support	6

	Invasive mechanical ventilation with other organ support (e.g., ECLS, CRRT, vasopressors)	7
Death	Dead	8
ECLS: extracorporeal life support; CRRT: continuous renal replacement therapy *The score for the day reflects the worst status for the given calendar day		

3.6 Secondary endpoints

Hospital-free days at 28 days (calculated as a worst-rank ordinal)
Ventilator-free days at 28 days (calculated as a worst-rank ordinal)
ICU-free days at 28 days (calculated as a worst-rank ordinal)
Time to a 1-point decrease in the WHO ordinal recovery score

The composite endpoints (-free days) will be calculated according to standard procedures (using the "last off" method) and using the worst-rank ordinal approach by which death is counted as -1 days.

4.0 Study Population and enrollment

Our goal is to enroll all hospitalized patients at study hospitals with suspected or confirmed COVID-19 in a pragmatic randomized design.

4.1 Screening

Daily screening in hospitals to identify hospitalized patients with the diagnosis of suspected or confirmed COVID-19. Patients who meet all inclusion criteria and no exclusion criteria will be asked to provide written informed consent (often via a legally authorized representative [LAR]), after which, the patient will be considered an enrolled participant.

4.2 Inclusion criteria

- Adult (age ≥ 18 years)
- Confirmed OR suspected COVID-19,
    - Confirmed: Positive assay for COVID-19 within the last 10 days
    - Suspected: Pending assay for COVID-19 WITH high clinical suspicion*
- Scheduled for admission or already admitted to an inpatient bed

*The suspected COVID-19 criterion is intended to help match clinician behavior during the pandemic at the time that clinical decisions are being made. Delays in testing may force clinicians to make treatment decisions before all data are known. The fundamental notion of the suspected COVID-19 criterion is the experienced clinician's belief that the patient has a high likelihood of being positive for COVID-19. The objective data supporting that belief will be updated regularly via FAQ and communication to study personnel and clinical pharmacists.

At trial launch, these objective data are

- Known COVID-19 exposure with a credible incubation period before disease onset OR
- All of the following
    - ≤ 10 days of new cough or obvious worsening of a chronic cough

  - Bilateral infiltrates consistent with COVID-19 OR new hypoxemia (<92% on room air or use of supplemental oxygen)
  - No alternative explanation for the acute illness presentation

Given the dynamic nature of testing, the performance of the suspected COVID-19 criteria will be monitored at least weekly. If substantial rates of enrollment are observed among patients who are subsequently shown to be COVID-19 negative, the suspected COVID-19 criteria may be adjusted based on consultation with the protocol committee and the DSMB. If rapid turnaround time is achieved at a given site for COVID-19 testing, the suspected COVID-19 criterion may be suspended, as treatment based on positive test results would likely become clinical practice. Such changes will be communicated via a FAQ document and will not require a formal protocol amendment as long as they are consistent with the principles outlined herein. The IRB will be provided with copies of the FAQ as it is updated.

4.3 Exclusion criteria

- Allergy to hydroxychloroquine or azithromycin
- History of bone marrow transplant
- Known G6PD deficiency
- Chronic hemodialysis or glomerular filtration rate < 20ml/min
- Psoriasis
- Porphyria
- Concomitant use of digitalis, flecainide, amiodarone, procainamide, propafenone, cimetidine, dofetilide, phenobarbital, phenytoin, or sotalol
- Known history of long QT syndrome
- Current known QTc>500 msec
- Pregnant or nursing
- Prisoner
- Weight < 35kg
- Seizure disorder
- Severe liver disease
- Outpatient use of hydroxychloroquine for treatment of a disease other than COVID-19 OR has received more than 2 days of hydroxychloroquine or azithromycin for suspected or confirmed COVID-19
- Patient has recovered from COVID-19 and/or is being discharged from the hospital on day of enrollment.
- Treating physician refuses to allow patient participation in the study
- Unable to obtain informed consent
- Prior enrollment in this study

Severe liver disease is defined as clinical diagnosis of cirrhosis plus presence or history of ascites, varices, hepatic encephalopathy, or hospital admission for liver failure.

5.0 Study Procedures

Note that given the high contagiousness of SARS-CoV-2, the limited supply of personal protective equipment, and risk to coordinators' health, study visits, procedures, and monitoring will be performed in a no-touch mode. This also applies to the consenting process, which will be performed via a consenting mechanism that confirms the identity of the patient, provides access to the consent form, and obtains a signature to complete documentation, without requiring physical proximity of research staff and the study subject.

5.1 Study commencement. After informed consent and enrollment, coordinators will complete the baseline CRF, and initiate study procedures, including randomization (variable permuted block randomization by hospital).

5.2 Study drug. This is an open label, randomized, active comparator trial. Patients who are discharged home will not continue treatment after hospital discharge. If the patient has already received azithromycin or hydroxychloroquine prior to randomization (no more than 2 days), the prior doses will count toward the 5-day total dose. For enrolled patients whose laboratory testing returns negative for SARS-CoV-2, if the clinical team believes that another cause of the patient's presentation is more likely than COVID-19 in light of the negative laboratory testing, the clinical team may stop study drug. Such discontinuation will be recorded. Since the fundamental clinical question is whether to start treatment in patients with suspected or confirmed COVID-19, these patients will remain in the primary analytic cohort.

The trial will be temporarily suspended for enrollment at a given site in the event that no study drug is available at that site.

5.2.1. Hydroxychloroquine. Patients in the hydroxychloroquine arm will receive hydroxychloroquine 400mg po BID x 1 day, then 200mg po BID x 4 days[3] (dose reductions for weight < 45kg or GFR<50ml/min). For patients < 45kg, doses will be halved. For patients with GFR<50ml/min, the final dose of hydroxychloroquine will not be administered. The drug dose chosen falls at the lower end of doses proposed in various international trials, but it has proven in vitro efficacy, with a ratio of lung tissue trough concentrations to the EC50 (effective concentration to suppress 50% of viral activity) of >20.[3] Given in vitro confirmation of the adequacy of the dose and likely superior safety profile at the lower dose, we chose the total dose of 2.4gm over 5 days.

Note: if the clinical attending physician believes that bacterial pneumonia is likely and requires a second antibacterial agent for "atypical" infection (an uncommon occurrence in COVID-19), patients may receive another agent (e.g., doxycycline or levofloxacin) as appropriate at the clinician's discretion.

5.2.2. Azithromycin. Patients in the azithromycin arm will receive azithromycin 500mg on day 1 plus 250mg daily on days 2-5 (may be administered IV per clinician preference).

5.3 Study Assessments. Coordinators and/or data queries will classify the COVID Ordinal Outcomes Scale on days 1–7, 14. They will also review for adverse events, including especially rash, self-report of visual changes, or symptomatic hypoglycemia. They will ensure that an EKG is performed at 24 to 48 hours post-randomization time. If a clinical EKG is not performed during this timeframe, a research EKG will be performed. In addition, ventilator status and ICU and hospital stay (using the last-off method) will be used to determine ventilator- and ICU-free days at 28 days using the worst rank ordinal technique, whereby death is scored as -1 days. In addition, coordinators and/or data queries will classify the COVID Ordinal Outcomes Scale on day 14. If this cannot be determined from the medical record, the patient will be contacted via telephone, mail, or electronic methods to determine their status on day 14.

5.2.4 Six-month assessment. A brief visit will ascertain the EQ-5D-5L to measure quality of life. Mortality and readmissions will also be assessed at that visit, which may be performed by telephone, electronic means, or in-person, depending on the subject's needs and preferences.

5.4 Approach to potential risks. Hydroxychloroquine has been used in many thousands of patients as an anti-malarial agent and in systemic lupus erythematosus and rheumatoid arthritis as a mild anti-inflammatory agent. The safety has been well established. Azithromycin has been used in millions of patients and is effective against the causes of bacterial pneumonia. Its immunomodulatory effects are also of interest in a variety of syndromes. While both agents have known side effects, such side effects are generally rare and well-tolerated.

This pragmatic study protocol is designed to optimally protect patients against risk through careful choice of exclusion criteria, pragmatic monitoring for common adverse events, and careful oversight by a DSMB.

5.4.1 Potential risks and risk mitigation. The package insert for hydroxychloroquine lists visual impairment, cardiac impairment, QTc prolongation, worsening of psoriasis or porphyria, proximal myoneuropathy, suicidality, and hypoglycemia. Other reported risks include nausea, diarrhea, vomiting, abdominal pain, headache, dizziness, allergic reactions, rash, low blood counts, seizures, and death. All of these risks are quite rare and where observed are seen after prolonged administration, generally in the range of years. While ocular examinations are recommended after a year (and for acute symptoms), routine ocular examinations have never been recommended for brief duration of therapy. While QTc prolongation has been described, it is generally modest, and routine EKG monitoring is not normally practiced with administration of hydroxychloroquine. In addition, there is some concern that in patients with very low body weight or with low GFR the risk of adverse events may be increased. The potential risks of azithromycin primarily relate to QTc prolongation and *Clostridioides difficile* infection (CDI). Both are clearly described but quite rare with azithromycin.[19] Additional risks include nausea, diarrhea, vomiting, and abdominal pain, allergic reactions, rash, infusion site reaction when given through a vein, abnormal liver function, drug interactions, development of drug-resistant bacteria, heart problems, muscle weakness, cardiac arrest, death. When hydroxychloroquine and azithromycin are co-administered, a modest prolongation in QTc may be observed, which is why we chose the more conservative threshold of 500msec rather than 550msec as an exclusion criterion.

In order to mitigate these risks, we have defined eligibility criteria that exclude patients with elevated risk, keep dosage low, and restrict treatment to just 5 days and avoid outpatient therapy. Patients are monitored within the hospital during treatment. Research coordinators and/or data queries will monitor for adverse events.

5.4.1.1 Monitoring EKG. An EKG will be performed between 24 and 48 hours after randomization (if no clinical EKG has been performed, then the EKG will be performed as a study procedure). This EKG is performed to determine whether the QTc is prolonged after the loading dose. If the QTc is > 500 ms, study drug will be stopped and an assessment made. If there are no other contributors than study drug to prolonged QTc, study drug will be stopped permanently. If there are contributors to QTc that can be reversed (e.g., electrolytes or other QT-prolonging drugs), these will be reversed at the discretion of the clinical team, with a follow-up EKG performed at the clinical team's discretion. If the QTc is again <500 ms, the study drug will be resumed, with another EKG the day after resumption of study drug. If QTc is again >500 ms, study drug will be permanently discontinued.

5.4.1.2 Daily medication review. For the 5 days of therapy, study personnel and/or clinical pharmacists will review medications being prescribed for patients on study. If a medication is being prescribed that is known to prolong QTc, study personnel and/or clinical pharmacists will contact the prescribing clinician to discuss whether the new medication is necessary and important and to make a clinical determination whether study drug and the new medication should be continued. This review will highlight especially the two classes of medications enumerated in Appendix 5.

5.4.2 Reporting and Regulatory Compliance. All relevant information will be reported in compliance with relevant regulations and Good Clinical Practice. This is not a registrational trial but will be performed under an IND exemption, which was obtained before study launch.

5.4.3 ClinicalTrials.gov registration. An appropriate entry in Clinicaltrials.gov will be created before any patient enrollments occur. Updates to the Clinicaltrials.gov entry will be made in compliance with relevant regulations.

5.4.4 Records retention. Study sites will arrange for the retention of raw data as per institutional protocol but for a minimum of 5 years after receipt of any applicable regulatory notification relevant to this study. All data and

documents will be made available when requested by appropriate authorities. Records will be maintained to verify the existence of each patient in the study, as per standard protocol.

5.4.5 Protection against loss of privacy. In order to protect a potential subject's privacy, we will take multiple steps to protect the study subject from breach of confidentiality. The list linking the subject's name and medical record number will be kept behind the hospital firewall in a password-protected file. This file will only be accessible through the hospital server to those individuals given password approval to access the file. Furthermore, the electronic database (REDCap) will be coded with a unique study identifier rather than with individually identifiable PHI (other than certain dates of service, as indicated above).

5.5 Cohort retention techniques. Study follow-up will incorporate published, validated techniques for maximizing cohort retention.[20-23] These retention techniques include careful logging of contact attempts, confirmation of contact information at each encounter, multi-modality contact approaches (e.g., letters, emails, phone calls, social media, spontaneous home visits) as necessary. We anticipate minimal difficulty with cohort retention.

5.6 Data collection. Research coordinators and/or investigators will collect data and record them on paper and/or electronic CRFs. Data quality will be reviewed using front-end range and logic checks at the time of data entry and back-end monitoring of data using electronic reports. Patient records and case report forms will be examined locally (including, as appropriate, duplicate data entry) on a random basis to evaluate the accuracy of the data entered into the database and monitor for protocol compliance with expanded quality assurance efforts if the non-congruence rates exceed 5%. The coordinating center will maintain these data according to relevant regulations and security standards within a REDCap database. Note that given concerns for contagion during the pandemic, coordinators will practice "no-touch" practices for data collection and entry.

5.7 Analysis and interpretation of data. A formal statistical analysis plan (SAP) will be written and finalized before the conclusion of enrollment and before the beginning of data analysis. The principles of this SAP are outlined here.

General. Descriptive summaries will be produced for subject disposition, demographic and clinical characteristics by the randomized hydroxychloroquine and azithromycin groups. The primary analysis and other secondary analyses of efficacy outcomes will be performed in accordance with the intention-to-treat (ITT) principle, with all patients analyzed according to their randomized treatment assignment, irrespective of compliance. In addition to the formal statistical analyses described below, the proportions of subjects with each level of the 8-point COVID scale will be displayed in frequency tables and in graphical summaries for each day, from day 0 (baseline) through day 14 of follow-up. Other ordinal secondary outcomes will be summarized using medians, 10^{th}, 25^{th}, 75^{th}, and 90^{th} percentiles and plots of cumulative distribution functions.

Adherence to the study medications will be summarized by providing the distributions of the number of days (0, 1, 2, 3, 4, or 5) for which study medication is taken in the two randomized groups.

Analysis Sets. The primary analysis and analyses of secondary efficacy outcomes will be performed in the ITT population which consists of all randomized patients. Summaries of safety outcomes will be performed in the safety population consisting of all patients who receive at least one dose of study medication.
We will also perform secondary analyses of efficacy and safety within the subsets of the ITT and safety populations restricted to patients who were confirmed to have COVID-19 (following an approach used in e.g., the VIOLET trial[24]).

Primary Analysis. The prespecified primary analysis will compare the day 14 assessment of the 8-level COVID Ordinal Outcomes Scale between the randomized hydroxychloroquine and azithromycin groups. This analysis will be performed using a proportional odds logistic regression model, with randomized treatment group as the

independent variable and patient age and the baseline level of the COVID Ordinal Outcomes Scale as covariates. Due to restriction of the cohort to hospitalized patients, the baseline COVID Ordinal Outcomes Scale distribution will include patients with levels 3 through 7. Under this model, the treatment effect is expressed as the odds ratio comparing the odds of a score > k vs. a score ≤ k between the hydroxychloroquine and azithromycin groups, so that an odds ratio less than 1 represents treatment benefit. The primary analysis using the proportional odds model is closely linked to the Wilcoxon-rank-sums test, and is thus expected to provide approximately valid inference even if the proportional odds assumption is violated.

The primary analysis will be performed using a Bayesian framework, with a slightly conservative but relatively diffuse normal prior distribution assumed for the log transformed odds ratio. The normal prior will be assigned a mean of 0 (thus taking an agnostic position as to the direction of the treatment effect), and a standard deviation of 0.5415. This prior distribution assigns a probability of 0.80 to an odds ratio between 0.5 and 2.0, with a probability of 0.10 that the odds ratio is below 0.50 and also a probability of 0.10 that the odds ratio is greater than 2.0. The prior distributions for the intercept parameters and covariate regression coefficients in the proportional odds model will be defined in the SAP.

The results of the Bayesian analysis will be expressed as 1) a graphical display of the posterior distribution of the odds ratio, 2) the posterior mean, median and mode with 95% credible intervals, and 3) the following probabilities of clinical relevance based on the posterior distribution of the odds ratio (OR) given the data:

P1 = Pr(OR < 1), indicating the evidence for any benefit;
P2 = Pr(OR < 1/1.25), indicating the evidence for a moderate benefit or greater;
P3 = Pr(OR > 1), indicating the evidence for any harm;
P4 = Pr(OR > 1.25), indicating the evidence for a moderate harm or greater;
P5 = Pr(1/1.2 < OR < 1.2), indicating the evidence for similarity between the two treatments.

Secondary Analyses. We will apply similar Bayesian proportional odds models to evaluate the effectiveness of the hydroxychloroquine vs. azithromycin interventions on each of the following secondary outcomes: ventilator-, ICU-, and hospital-free days through day 28 (with death assigned as a worst-rank ordinal level[25,26] to avoid survivorship bias). We will also apply a primary proportional odds model similar to that used for the primary analysis at day 14 to evaluate the effect of the randomized treatments on the COVID Ordinal Outcomes Scale at day 7.

Missing Data. We expect less than 5% of subjects will have missing data on either the primary or key secondary outcomes listed above. Hence, our primary analyses will be restricted to non-missing observations, without imputation. For the primary outcome, a sensitivity analysis will be performed by applying multiple imputation, in which the imputation model will incorporate non-missing measurements on the COVID Ordinal Outcomes Scale obtained prior to the day 14 assessment as auxiliary variables.

Safety. The safety of both the hydroxychloroquine vs. azithromycin treatments being evaluated in this study is already well established in studies of thousands of patients and in post-marketing surveillance. Safety will however be evaluated in the context of COVID-19 by providing counts (proportions) of adverse events, with special attention to those listed in the package insert for hydroxychloroquine and azithromycin and careful investigation of any SUSARs.

Interim Monitoring. Under the Bayesian design, the posterior distribution describing the accumulating evidence provided by the data for treatment benefit or harm can be updated repeatedly as the trial proceeds, without the requirement for formal adjustments to type-1 error to account for multiple looks as is required by frequentist interim analysis. The coordinating center will work with the DSMB to identify a threshold for the posterior probability of benefit such that a posterior probability of benefit exceeding this threshold would lead to early termination for efficacy. The Bayesian interim monitoring approach will allow the DSMB flexibility in its choice

of times for interim looks. Additional details on the interim monitoring plan will be provided in the DSMB charter.

The general strategy employed would potentially stop early for efficacy but not for futility, as we anticipate that the data from this trial could be patient-level meta-analyzed with other trials in similar populations. Given the nature of the COVID-19 pandemic (with sudden and transient numbers in a given location), it may be difficult for any single trial to answer a question definitively on its own. We will also include feasibility evaluations to allow us to determine when the first wave of COVID19 has resolved, such that further enrollment in the trial is unlikely. Given the potentially cyclic nature of COVID19, the DSMB and the PI and trial statistician may make a determination, given the totality of the evidence, whether to suspend or halt the trial if there is clear evidence that the first wave is over in Utah, with the option to resume enrollment during a second wave of illness.

5.8 Power and sample size analysis

We provide an approximate sample size and power calculation by providing the largest odds ratios (corresponding to the minimum detectable treatment effects, which are indicated by odds ratios less than 1, reflecting treatment benefit) which can be detected in a frequentist analysis under of the primary outcome under a proportional model without covariate adjustment. The target sample size of this trial is 300 randomized subjects; the table also considers smaller sample sizes to indicate the power the trial will reach under optimistic scenarios for controlling the COVID-19 outbreak. The power calculations were performed using statistical simulation (N=10,000 simulations per combination), and provide results very close to those provided by an approximation provided by Whitehead.[27] We consider three scenarios for the distribution in the azithromycin group for the 8 categories of the COVID Ordinal Outcomes Scale: Scenario 1: Uniform distribution with probabilities of 0.125 for each score level, Scenario 2: Overall probabilities at 14 days averaging across both groups of the recent COVID-19 trial by Cao et al.[28] (1= 0, 2= 0.36, 3=0.16, 4=0.23, 5=0.05, 6=0.02, 7=0.02, 8=0.16), and Scenario 3, with probabilities averaged between Scenarios 1 and 2.

Maximum Detectable Odds Ratios (below 1) with 80% Power, 2-sided α= 0.05, Assuming 95% Follow-up			
Sample size	Scenario 1 (uniform)	Scenario 2	Scenario 3
100	0.34	0.32	0.33
150	0.43	0.41	0.42
200	0.48	0.46	0.48
250	0.52	0.50	0.52
300	0.55	0.54	0.55

We note that when expressed as risk ratios the minimum detectable effects are closer to 1 than the odds ratios in the table. For example, in Scenario 3 with N = 300, the detectable odds ratio of 0.55 for a COVID Ordinal Outcomes Scale score > 3 translates to a detectable risk ratio of 0.702 = 0.337/0.48. Thus the target sample size of 300 provides good power to detect an important signal for superiority of hydroxychloroquine over azithromycin. In any case, we anticipate that the data from this study can meaningfully contribute to future meta-analyses of therapeutics for COVID-19.

6.0 Human Subjects Considerations

6.1 Pandemic considerations.

The exponentially rapid spread of COVID-19 across the globe and the very high rate of contagion, especially in healthcare environments, necessitates flexibility in specific logistical details that is nevertheless robustly consistent with the ethical mandates of clinical research. The key aspects of this pragmatic trial special to the

pandemic circumstance are (1) time-sensitivity of trial launch and (2) the need for no-touch operations on the part of research staff to protect their safety. Time-sensitivity and the emotional valence of proposed therapies for a frightening pandemic infection—plus the need to rapidly evaluate a large number of proposed therapies, many of which are already entering clinical practice in advance of evidence—motivate the use of an expeditious, pragmatic, real-world, open-label, active comparator design for this evaluation of the efficacy of hydroxychloroquine. The mandate to protect research staff while assuring that informed consent is obtained drives the choice of electronic consent. “No-touch” consenting procedures will abide by Intermountain guidelines and standards for consenting in pandemic circumstances, including a HIPAA waiver as appropriate.

6.2 Institutional Review Board oversight.

Institutional Review Board (IRB) approval is required and will be secured before any subject is enrolled at the study site. IRB notices will be written and dated. The investigator will promptly report to IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazard to human subjects.

6.3 Selection of subjects.

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The sites will be evaluated to determine whether patient eligibility criteria are met, drawing on routine clinical data. No protocol-specific tests nor procedures will be performed as part of the screening process. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals for participation in the research.

6.4 Justification for including vulnerable subjects.

The present research aims to investigate patients with COVID-19. Due to the nature of the condition, many of these patients will have impaired decision-making capabilities. Moreover, those with intact decision-making capacities likely have milder disease than those with impaired capacity, creating substantial risk of sampling bias. Therefore, this study could not be conducted if limited to enrolling only those subjects with retained decision-making capacity. Hence, subjects recruited for this trial are not being unfairly burdened with involvement in this research simply because they are easily available. They are the core group of patients most likely to experience benefit from hydroxychloroquine or azithromycin.

6.5 Informed consent.

Federal regulations at 21 CFR 50.20 and 45 CFR 46.111(a)(5) require that informed consent be sought from each prospective subject or the subject’s LAR. Each study participant or LAR must sign and date an IRB-approved informed consent form. The consent form (via a HIPAA authorization) will also indicate that protected health information (PHI) may be released to relevant study personnel and regulatory agencies.

Some of the patients approached for participation in this research protocol will be decisionally impaired due to their critical illness. Hence, some patients will not be able to provide informed consent. Accordingly, informed consent will be sought from the participant’s LAR, as defined at 45 CFR 46.102(c): “an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedures(s) involved in the research.” In this study, LARs will be identified as stipulated by relevant regulations and statutes, as per the standards defined for clinical decision making, as is the standard practice in human subjects research.

According to a previous President’s Bioethics Committee (National Bioethics Advisory Committee (NBAC)), an investigator should accept a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place.[29] Finally, OHRP has stated in their determination letters that a surrogate could serve as a LAR for research decision

making if such an individual is authorized under applicable state law to provide consent for the "procedures" involved in the research study.[30]

In cases of LAR consent, study personnel obtaining informed consent are responsible for ensuring that the LAR understands the risks and benefits of participating in the study, answering any questions the LAR may have throughout the study and sharing any new information in a timely manner that may be relevant to the LAR's willingness to permit the subject's continued participation in the trial. The study personnel obtaining consent will make every effort to minimize coercion, whether actual or perceived. All study participants or their LARs will be informed of the objectives of the study and the potential risks. The informed consent document will be used to explain the risks and benefits of study participation to the LAR in simple terms before the patient is enrolled in the study, and to document that the LAR is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The electronic consent form will document the receipt of informed consent.

6.6 Continuing consent.

For subjects for whom consent was initially obtained from a LAR but who subsequently regain decisional capacity while in hospital, sites will seek reconsent for continuing participation. Reconsent will also use electronic consenting methods; in the event that reconsent is not able to be obtained before 6-month followup, then consent for that telephone call will be obtained via oral consent, as the only additional study procedure at that point is a brief telephone call.

6.7 Withdrawal of consent.

Patients may withdraw or be withdrawn (by their LAR) from the study at any time. Data recorded up to the time of withdrawal will be included in the study analysis, unless consent to use data has also been withdrawn. If a patient (or LAR) requests withdrawal from the study after completion of study treatments, study endpoints will be determined unless consent to do so has also been withdrawn.

6.8 Confidentiality.

Federal regulations at 45 CFR 46.111(a)(7) require, when appropriate, adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, reports will be identified only by a coded study number. Only the study team will have access to the codes. All records will be kept in a locked, password protected computer. All computer entry and networking programs will access coded numbers only. All paper CRFs will be maintained in locked offices. Information shared outside Intermountain will be deidentified in accordance with federal regulations, e.g., HIPAA, except as otherwise indicated. Any data sharing will be regulated by appropriate data use agreements, where required. For the purposes of reporting, PHI may be disclosed to relevant regulatory agencies.

6.9 Protocol deviations and violations.

The investigator will not implement any deviation from, or changes of the protocol without prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of telephone number(s)). Any deviation from the approved protocol will be documented and explained by the investigator or a person designated by the investigator. The investigator may implement a deviation from, or a change to, the protocol to eliminate immediate hazard(s) to trial subjects without prior IRB approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and if appropriate, the proposed protocol amendment will be submitted to the IRB.

7 Adverse Events

Patient safety is central to this study protocol.

7.1 Adverse event reporting. The following adverse events will be collected in the adverse event case report forms:

- Serious adverse events
- Nonserious adverse events that are considered by the investigator to be related to study drug or study procedures or of uncertain relationship
- Adverse events that lead to permanent discontinuation of the study drug.

A clinical trial adverse event is any untoward medical event associated with the use of a drug or study procedure in humans, whether or not it is considered related to a drug or study procedure (see Appendix 4).

After randomization, adverse events related to protocol procedures or occurring after the patient receives the first dose of study drug must be evaluated by the study investigator. If the adverse event is judged to be reportable, the investigator will report to the DSMB his/her assessment of the potential relatedness of each adverse event to study drug or study procedure. Investigators will assess whether there is a reasonable possibility that the study drug or procedure caused the event, based on the criteria outlined in Appendix 4. Investigators will also consider whether the event is unanticipated or unexplained given the patient's clinical course, previous medical conditions, and concomitant therapies.

Adverse events that will be collected prospectively as part of the study-specific outcome (and thus would not be separately reported as adverse events) are listed in Appendix 4. Study-specific outcomes will be reported as adverse events if they are both serious and Definitely or Possibly Related to study drug.

7.2 Serious Adverse Events

Serious adverse event collection begins after the patient or LAR has signed informed consent and has received study drug or undergone study procedures. If a patient experiences a serious adverse event after consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a study procedure.

Investigators must alert the DSMB of any **serious and study drug or study procedure related** adverse event within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form. See Appendix 4 for reporting timelines for serious, unexpected, study related events (SAEs) and serious, unexpected suspected adverse reactions (SUSARs).

As per federal definitions (primarily in 21 CFR 312.32(a)), a **serious** adverse event is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening event, one that places the subject at immediate risk of death (this does not include an event that, had it been more serious, would have placed the subject at immediate risk of death)
- Prolonged inpatient hospitalization or rehospitalization
- Persistent or significant disability/incapacity, indicating a substantial disruption of a person's ability to conduct normal life functions (i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events will be collected during the first five days, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be reported unless the investigator feels the events were related to study drug or a protocol procedure.

APPENDICES

Appendix 1. Visit schedule

	Visit						
Procedure	**Baseline**	**24-48 hours post-randomization**	**Daily through 5 days**	**14 days**	**Hospital discharge**	**28 days**	**6 months**
Screening procedures	X						
Informed consent and LAR identification	X						
Patient reconsent (where necessary)					X		
Data collection	X				X		
EKG (research or clinical)		X					
Study drug			X				
Active Adverse Event review			X				
Passive Adverse Event review					X		
WHO ordinal scale				X*			
VFD, ICUFD, HFD						X	
EQ-5D-5L							X
LAR: legally authorized representative; WHO: World Health Organization; VFD: Ventilator-free days; ICUFD: ICU-free days; HFD: hospital-free days; EQ-5D-5L: EuroQol-5 dimensions-5 level *measured daily, days 1–7, 14 on all patients; measured days 1–14 on patients still hospitalized on day 14.							

Appendix 2: Screening logs

Screening activities will be carried out pursuant to 45 CFR 46.116(g) and 45 CFR 164.512(i). Patients in study hospitals will be entered into the screening log on the basis of an ordered COVID-19 test. Those who meet criteria for suspected or confirmed COVID-19 will be evaluated for all inclusion and all exclusion criteria. If all eligibility criteria are met, an informed consent conversation will occur. A HIPAA authorization waiver will be sought for this screening activity as per 45 CFR 164.512(i).

Appendix 3. Authorship criteria and management plan

After the conduct of the Main Study, the following policy will guide authorship decisions.
The ICMJE criteria for authorship will be followed. An author must make:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (a minimum of at least 2 of the above is needed) AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributors who do not meet all 4 of these criteria for authorship will be listed as collaborators rather than authors.

For publications related to the Main Study (Main publications):
The overall PI will direct the authorship decisions for Main publications and will determine the following:

- Whether the results related to the aims are published as part of one manuscript or divided into multiple publications.
- To which journals the manuscript(s) will be submitted
- Any revisions and revision decisions for resubmission to journals for publication
- The order of authorship for the main publications in order of contribution as determined by the Protocol Committee according to the ICMJE recommendations within the following parameters:
    - The first and senior author should be members of the Protocol Committee. The first and senior author can make preliminary decisions about the scope of the manuscript, write the initial draft and decide on journal for submission and then present the plan to the rest of the Protocol Committee for approval.
    - All members of the Protocol Committee will be authors on the Main publications, as long as they meet ICMJE criteria.
    - Among Site PIs who contributed equally to the analysis and write-up of the Main publications, authorship order will be according to the number of patients recruited from the Site PI's site to the Main Study, with higher enrolling sites coming before lower enrolling sites.
    - If the journal limits the number of authors that can be listed, then the study will be attributed to the Protocol Committee and the Study Group, and the Site PIs and their sites will be listed in the acknowledgments, as collaborators, based on the number of patients enrolled from their site. In the event of ties, authorship order will be determined alphabetically, by site name.
    - Secondary site investigators from each site will not be included as authors unless they are on the protocol committee, but they will be listed as collaborators, based on the number of patients enrolled from their site. In the event of ties, authorship order will be determined alphabetically, by site name.

For publications of ancillary studies:

- Any Site Investigator or member of the Protocol Committee can propose an ancillary study to be considered by the Protocol Committee. The Protocol Committee must evaluate the proposal for appropriateness and overlap with other proposals.
- The ancillary study proposal should include the following:
    - Background or Rationale
    - Study Objective or Hypothesis
    - Proposed methods:
        - Study Design
        - Study Population

    - Data Requested: List data needed for analysis of exposure, outcomes, and associated covariates.
    - New Data or Intervention requested: List all data to be collected solely for the purpose of the proposed Ancillary Study.
    - Proposed statistical approach
- Ancillary studies will be opened for other investigators to enlist as authors if they are interested. Lists of ancillary studies will be distributed periodically for review and sign up.
- The order of authorship will be decided by the investigator who proposed and leads the Ancillary Study, guided by the general principles outlined above and consistent with the ICMJE criteria.
- All abstracts and manuscripts from ancillary studies must be submitted to protocol committee for approval prior to submission.

Appendix 4.

As noted in section 7.2, investigators will report all adverse events that are serious and study drug or study procedure related to the DSMB. The DSMB and the PI will then notify the IRB.

The PI, in consultation with the DSMB, will determine whether a SAE has a reasonable possibility of having been caused by the study drug or procedure, as outlined in 21 CFR 312.32**(a)**(1). The PI, in consultation with the DSMB, will also determine whether the event is unexpected. An adverse is considered "unexpected" if it is not listed in the investigator brochure or the study protocol (21 CFR 312.32(a)). If a determination is made that a serious adverse event has a reasonable possibility of having been caused by the drug, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a serious unexpected suspected adverse reaction (SUSAR).

The PI will report all unexpected and study related deaths, SAEs, and SUSARs to the DSMB within 24 hours of learning of the event. The PI and the DSMB will report their findings from review to the IRB within 7 days after report of the event to the DSMB. A final written report will be provided to the DSMB and IRB within 15 calendar days. The DSMB will also review all adverse events and clinical outcomes during scheduled interim analyses.

A4.1. UNANTICIPATED PROBLEMS (UP)

Investigators must also report Unanticipated Problems, regardless of severity, associated with the study drug or study procedures within 24 hours. An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

A4.2. DETERMINING RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG OR PROCEDURES

Investigators will grade the strength of the relationship of an adverse event to esmolol or study procedures as follows:

• Definitely Related: The event follows: (a) a reasonable, temporal sequence from study drug or a study procedure; and (b) cannot be explained by the known characteristics of the patient's clinical state or other therapies; and (c) evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.

• Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Related". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.

• Probably Not Related: The event occurred while the patient was receiving esmolol or undergoing study procedures but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.

• Definitely Not Related: The event is definitely produced by the patient's clinical state or by other therapies administered to the patient.

• Uncertain Relationship: The event does not meet any of the criteria previously outlined.

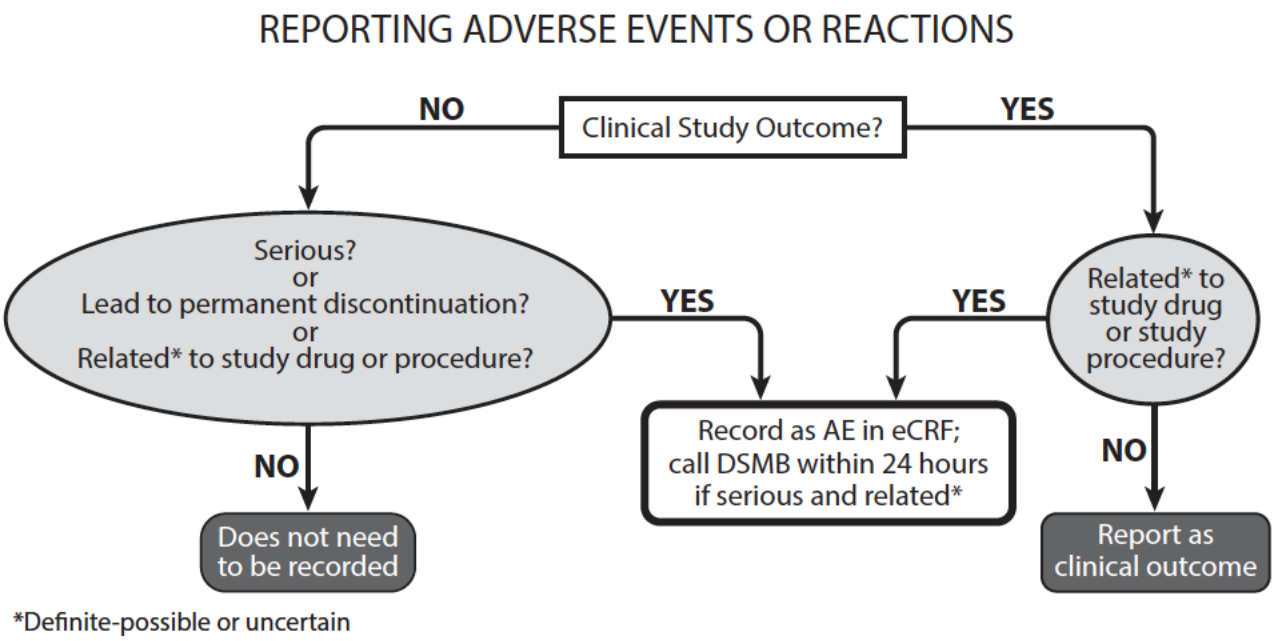
A4.3. CLINICAL OUTCOMES THAT MAY BE EXEMPT FROM ADVERSE EVENT REPORTING

Study-specific clinical outcomes of COVID-19 or ARDS are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study drug or the conduct of study

procedures (or of uncertain relationship). The following are examples of events that will be considered study-specific clinical outcomes

- Death (unless Definitely or Probably related to study drug or procedures)
- Respiratory events: Changes in degree of hypoxemia or its treatment
- Cardiovascular events: changes in doses of vasoactive drugs; cardiac arrest; cardiac arrhythmias.
- Organ dysfunction events: changes in the SOFA score or its constituents.
- ICU admission
- Rash
- Hypoglycemia
- Seizure
- Elevations in ALT, AST, lipase, and amylase
- Acute Kidney injury and dialysis
- Cytopenias
- Nausea/vomiting
- Impaired vision
- *C. difficile* infection

A4.4. DECISION TREE FOR REPORTING ADVERSE EVENTS



Adapted from Ranieri VM, Thompson BT, Barie PS et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012 May 31;366 (22):2055-64. Epub 2012 May 22. PubMed PMID: 22616830 with permission of Dr. Thompson.

Appendix 5. Potential medication interactions with hydroxychloroquine

A. Medications considered contraindicated, which if ordered on an inpatient during the 5-day study period will prompt study personnel or clinical pharmacists to discuss with treating clinicians whether stopping the study drug is appropriate or whether this medication could be stopped or substituted: amiodarone, cimetidine, dofetilide, phenobarbital, phenytoin, sotalol.

B. Medications considered to present a potential interaction with hydroxychloroquine, which if ordered on an inpatient during the 5-day study period, will prompt study personnel or clinical pharmacists to discuss with treating clinicians the risk-benefit assessment of this medication and potential need for additional monitoring: ampicillin, antacids, cyclosporine, digoxin, flecainide, mefloquine, methotrexate, mexilitine, rifampicin, rifapentine.

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