Tool Revision History:

Version Number	Version Date	Summary of Revisions Made
0.1	3/28/20	Original version
0.2	4/1/20	Andrea and IRB edits
0.3	4/2/20	Mark edits, additional pharmacy info, Hochman suggestions, title changed
1.0	4/3/20	Peds placbo added, qTC cutoffs confirmed
	4/4/20	Version reviewed at initial IRB review
1.1	4/5/20	Edits made per IRB suggestion. Pediatric population removed from the protocol entirely
1.2	4/7/20	Further edits per IRB suggestion
2.0	4/7/20	Adding inclusion of pregnant women into study population, adding REDCap e-consenting procedures
3.0	4/16/20	Adding SUNY Downstate as additional site. Removing future storage of specimen. Revising patient reimbursement. Edited amount of blood drawn for research labs as total volume instead of a list. Adding stool collection as part of research sample collection. Clarified use of minimal PHI as link between REDCap and source documents. Changed composite endpoint and exclusion criteria to remove non-rebreather. Added Stephanie Sterling to protocol
4.0	4/20/20	Adding inclusion of Legal Authorized Representative to consent. Including pediatric patients. Editing qT exclusion criteria for adults. Adding Colin Phoon, MD to study team.
5.0	4/28/20	Allowing co-enrollment for participants – removing exclusion criteria of participating in other clinical trials; made other DSMB recommend changes
6.0	5/10/20	Adding D-dimer as laboratory assessment in End of Treatment visit. Changing pediatric placebo compounding so total volume matches that of HCQ.

Title: Treating COVID-19 with Hydroxychloroquine (TEACH)
NCT: NCT04369742
Study Number: 20-00463

TREATING COVID-19 WITH HYDROXYCHLOROQUINE: A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED CLINICAL TRIAL IN HOSPITALIZED ADULTS AND CHILDREN

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NYULMC Study Number:	s20-004463
Funding Sponsor:	NYU Grossman School of Medicine Others: TBD
Study Product:	Hydroxychloroquine sulfate
Study Product Provider:	New York State Department of Health
ClinicalTrials.gov Number	Pending registration

Initial version: 4/4/20

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CQ	Chloroquine
CRF	Case Report Form
CRS	Cytokine Release Syndrome
D	Day
DHHS	Department of Health and Human Services
DOH	Department of Health
DSMB	Data and Safety Monitoring Board
EC	Effective Concentration
EOT	End of Therapy
ECMO	Extracorporeal Membrane Oxygenation
FDA	Food and Drug Administration
G6PD	Glucose-6-Phosphate Dehydrogenase
HCQ	Hydroxychloroquine
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IL	Interleukin
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention to Treat
LOS	Length of Stay
MOP	Manual of Procedures
MERS	Middle Eastern Respiratory Syndrome virus
N	Number (typically refers to participants)
NIH	National Institutes of Health
NRB	Non-rebreather
NYU	New York University
NYS	New York State
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
PTE	Post-treatment Evaluation (day 14)

QA	Quality Assurance
QC	Quality Control
qTC	Q-T Interval, Corrected (Bazett Formula)
SAE	Serious Adverse Event/Serious Adverse Experience
SARS	Severe Acute Respiratory Syndrome
SOP	Standard Operating Procedure
US	United States

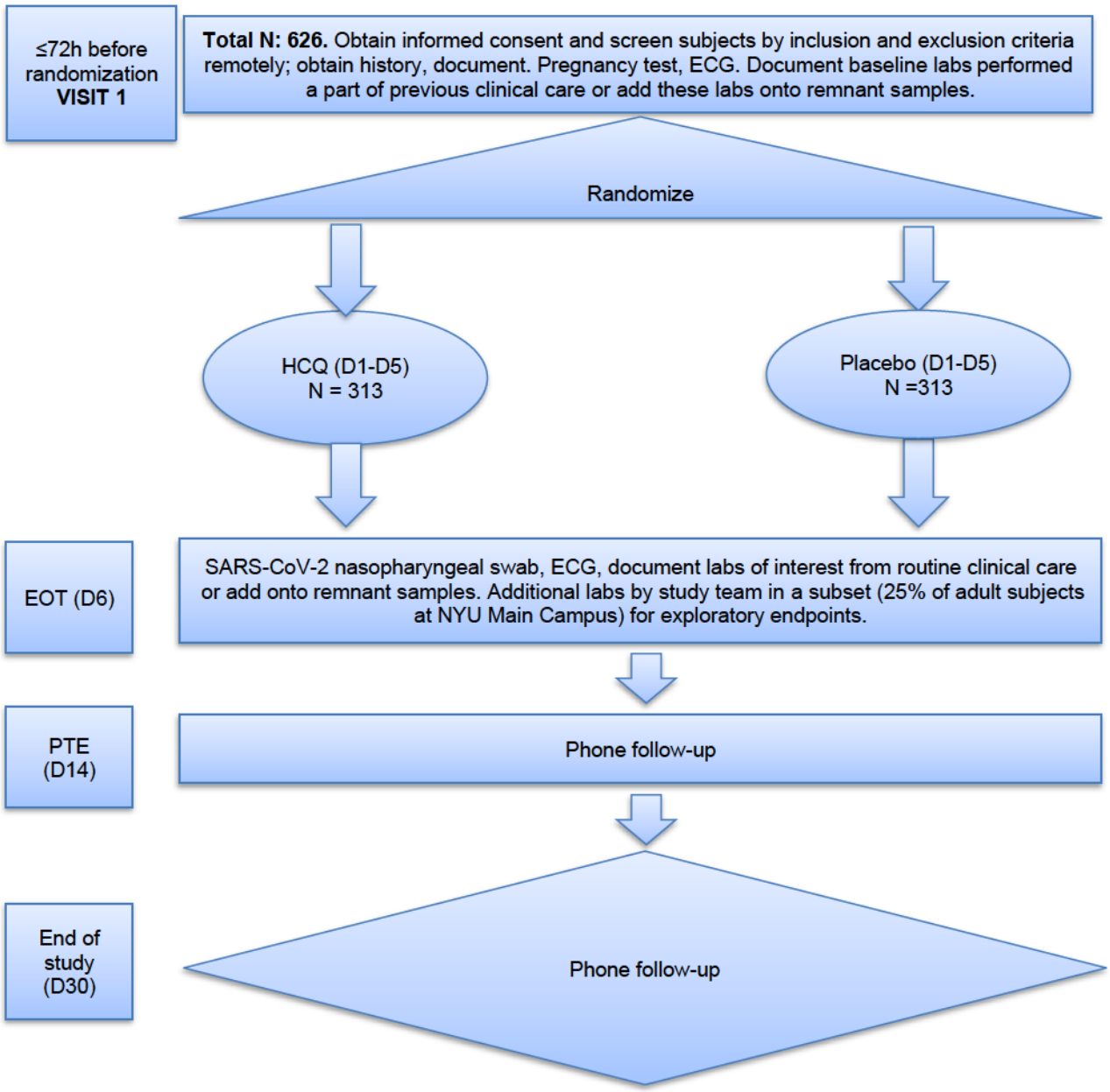
Protocol Summary

Title	**Treating COVID-19 with Hydroxychloroquine: A Multicenter Randomized, Double-blind, Placebo-controlled Clinical Trial in Hospitalized Adults and Children**
Short Title	**Treating COVID-19 with Hydroxychloroquine (TEACH)**
Brief Summary	Treatments for COVID-19 are urgently needed. Hydroxychloroquine (HCQ) is an antimalarial and immunomodulatory agent being repurposed for COVID-19 therapy based off *in vitro* data suggesting a possible antiviral effect. However, HCQ's effect on COVID-19 in human infection remains unknown. To fill this knowledge gap, we will enroll 626 adult and pediatric patients hospitalized with laboratory-confirmed COVID-19 and randomize them 1:1 to a five-day course of HCQ or placebo. Notable exclusion criteria include ICU admission or ventilation on enrollment, prior therapy with HCQ, and baseline prolonged qTC. Our primary endpoint is a severe disease progression composite outcome (death, ICU admission, mechanical ventilation, ECMO, , and/or vasopressor requirement) at the 14-day post-treatment evaluation. Notable secondary clinical outcomes include 30-day mortality, hospital length of stay, noninvasive ventilator support, and cytokine release syndrome (CRS) grading scale. Secondary exploratory objectives will examine SARS-CoV-2 viral eradication at the EOT, changes in COVID-19 putative prognostic markers and cytokine levels, and titers of anti-SARS-CoV-2 antibodies. This randomized trial will determine if HCQ is effective as treatment in hospitalized non-ICU patients with COVID-19.
Objectives	**PRIMARY OBJECTIVE** To determine if treatment of COVID-19 with hydroxychloroquine is superior to placebo in preventing a severe progression composite outcome of death, ICU admission, mechanical ventilation, ECMO, and/or vasopressor requirement at 14 day post-treatment evaluation (PTE) in hospitalized patients. **SECONDARY CLINICAL OBJECTIVES** To compare HCQ to placebo for the treatment of COVID-19 with respect to composite outcome at 30 days post-therapy, individual components of the severe progression composite outcome (death, ICU admission, mechanical ventilation, ECMO, and/or vasopressor requirement), hospital length-of-stay, days of fever, CRS grading scale, respiratory severity score(8-point scale), and qTC prolongation. **SECONDARY LABORATORY OBJECTIVES** To compare HCQ to placebo association with clearance of nasopharyngeal SARS-CoV-2 RNA detection at EOT (D6), changes in baseline liver function tests and inflammatory markers, and changes in COVID-19 prognostic labs and cytokine levels. **EXPLORATORY OBJECTIVES** Compare the effects of HCQ to placebo on the serum anti-SARS-CoV-2 antibody titers, stool microbiome, and antigen-specific T and B cell responses during COVID-19 in a subset of patients.
Methodology	Double-blind, Placebo-controlled, Randomized Clinical Trial

Endpoints	**Primary Safety Endpoint:** Safety and tolerability within each treatment arm defined as cumulative incidence of SAEs through day 30, Cumulative incidence of grade 3 or 4 AEs through day 30, and/or discontinuation of therapy (for any reason). **Primary Efficacy Endpoint**: A severe disease progression composite outcome including any of the following: mortality, ICU admission, invasive mechanical ventilation, ECMO, and/or hypotension requiring vasopressor support by the 14-day post-treatment evaluation (PTE). **Secondary Clinical Endpoints** • Severe disease progression composite endpoint (mortality, ICU admission, invasive mechanical ventilation, ECMO, and/or hypotension requiring vasopressor support) within 30 days of therapy. • Individual components of the severe disease progression composite endpoint (mortality, ICU admission, invasive mechanical ventilation, ECMO, or hypotension requiring vasopressor support) by end-of-treatment (EOT, D6), PTE (D14), and end of study (D30 day). • Hospital length of stay: LOS is defined as the interval (in days) that the patient was admitted to a non-rehabilitation floor, categorized as short (<7 days), moderate (7-10 days), or extended (>10 days). • Days of fever: defined as number of days with temperature >100.4 degrees Fahrenheit. • Days of non-invasive ventilator support (CPAP/BiPAP): defined as days the patient is placed on non-invasive ventilator support (CPAP or BiPAP), excluding routine CPAP use for sleep apnea. • Days of non-rebreather mask O2 support: defined as the number of days the subject was on a non-rebreather mask. • Cytokine release syndrome (CRS) grading scale [1]: calculated on day of randomization (D1), D3 and EOT (D6). • Percentage of subjects reporting each severity score on 8-point ordinal scale at D1 and EOT: ○ The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or ECMO; 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities. • Increase from normal to prolonged qTC (>500 milliseconds, gender neutral)) on electrocardiogram at EOT (D6). **Secondary Laboratory Endpoints** • SARS-CoV-2 viral eradication from nasopharyngeal specimens at EOT, measured by RT-PCR. • Change from baseline AST, ALT, creatinine, glucose, white blood cell count, lymphocyte percentage, hemoglobin, platelets, total bilirubin, LDH, CRP, and IL-6 at EOT. **Exploratory Laboratory Endpoints (25% at NYU Main Campus, N~50)** • Titers of serum anti- SARS-CoV-2 antibodies. • Antigen-specific T and B cell responses, in a subset of participants • Stool microbiome.

Study Duration	8 weeks
Participant Duration	30 days
Duration of IP administration	5 days
Population	Male and female pediatric and adult patients admitted to the hospital with a laboratory confirmed diagnosis of COVID-19
Study Sites	1. NYU Langone Main Campus (Tisch Hospital and Kimmel Pavilion) 2. NYU Langone Brooklyn Hospital 3. NYU Langone Winthrop Hospital 4. Bellevue Hospital Center 5. State University of New York (SUNY) Downstate
Number of participants	626
Description of Study Agent/Procedure	Hydroxychloroquine sulfate 400mg BID (day 1) and 200mg PO BID (days 2-5). Oral (tablet) administration.
Reference Therapy	Placebo: Calcium citrate 400mg BID (day 1) and 200mg BID (days 2-5). Oral (tablet) administration.
Key Procedures	**≤72h prior to enrollment (baseline) and at EOT (D6):** 12 lead ECG, SARS-CoV-2 nasopharyngeal swab, baseline labs recorded from those done during clinical care or added on to remnant clinical samples. In a subset (25%, N~50) of adult participants at NYU Langone Main Campus, blood draws by study team for exploratory laboratory endpoints. **PTE (D14) and End-of-study (D30):** Phone follow-up.
Statistical Analysis	The primary analysis will be a comparison between the two arms (HCQ and placebo) of the primary endpoint rate. The primary outcome will be analyzed using a generalized linear model with binomial link function, with a binary indicator for treatment and adjustment for hospital and age group (the stratification factors). Randomization should obviate the need for additional adjustment factors but if demographic or clinical characteristics are unbalanced with respect to treatment group, we will consider adjustment. The hypothesis will be tested using a Wald test for the statistical significance of the coefficient of the treatment indicator. We will estimate the probability of the primary endpoint for patients in the placebo and hydroxychloroquine groups, derive a relative risk ratio, and present this with its associated 95% confidence interval. Secondary outcomes will be analyzed with similar approaches; the link function used in the generalized linear model will be dictated by the outcome. Binary outcomes such as 30-day all-cause mortality will use the binomial link function as described above. Total hospital length of stay (LOS) will be analyzed using an identity link function (note that LOS will likely be log-transformed to address its skewed distribution). Continuous measures such as FiO2 and cytokine levels will also be analyzed using the identity link.

Schematic of Study Design



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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

In December 2019, a new pneumonia syndrome (COVID-19) caused by a novel coronavirus (SARS-CoV-2) was first detected in Wuhan, a city with 11 million people in central China [2]. Over a two-month period, COVID-19 became pandemic, and SARS-CoV-2 is now responsible for over 960,000 infections and 49,000 deaths worldwide [3]. Therapies for SARS-CoV-2 are urgently needed, so attempts at repurposing drugs have blossomed. However, the efficacy of these therapies in SARS-CoV-2 have not been proven in well-designed clinical trials.

The antimalarial and immunomodulatory drug hydroxychloroquine (HCQ) is one candidate for treatment of SARS-CoV-2.[4] HCQ is hypothesized to decrease the dangerous cytokine storm during COVID-19 by reducing T-cell activation [5], Toll-like receptor (TLR) activation [6], and cytokine expression [7]. The antiviral mechanisms of HCQ **(Fig. 1)** are similar to closely-related chloroquine (CQ), which increases endosomal pH, reducing viral-host membrane fusion [8] and interferes with terminal glycosylation of the viral receptor, ACE2, in the original SARS virus (SARS-CoV) [9]. Importantly, ACE2 is also the cellular receptor bound by SARS-CoV-2 [10].

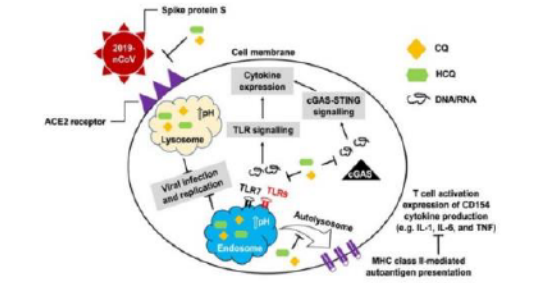

Figure 1 A graphical illustration of the antiviral mechanisms of CQ and HCQ. Both chemicals can interfere with the glycosylation of ACE2 and reduce the binding efficiency between ACE2 on the host cells and the spike protein on the surface of the coronavirus. They can also increase the pH of endosomes and lysosomes, through which the fusion process of the virus with host cells and subsequent replication are prevented. When HCQ enters APCs, it prevents antigen processing and MHC class II-mediated autoantigen presentation to T cells. The subsequent activation of T cells and expression of CD154 and other cytokines are repressed. In addition, HCQ disrupts the interaction of DNA/RNA with TLRs and the nucleic acid sensor cGAS and therefore the transcription of pro-inflammatory genes cannot be stimulated. As a result, administration of CQ or HCQ not only blocks the invasion and replication of coronavirus, but also attenuates the possibility of cytokine storm.

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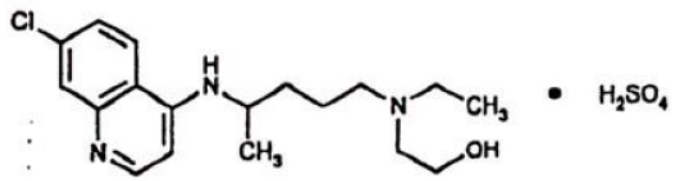
Azithromycin is a macrolide used to treat common bacterial infections, and in viruses there is in vitro data suggesting decreased viral replication of influenza [11]. In coronaviruses, clinical data consists of 1) a retrospective observational study suggesting azithromycin did not benefit during MERS [12] infection and 2) a small study out of France showing higher rates of SARS-CoV-2 clearance with azithromycin and HCQ (N=6) compared to HCQ alone (N=14) [13]. We believe that the existing clinical data do not justify a dedicated azithromycin arm in our study, and we will recommend discontinuing this medication on enrollment into the trial (see 7.5.1).

2.2 Name and Description of the Investigational Agent

Hydroxychloroquine sulfate (HCQ). The chemical name for hydroxychloroquine sulfate is 2-[[4-[(7-Chloro-4-quinolyl) amino]pentyl] ethylamino]ethanol sulfate (1:1). The structure (from package insert) is shown below.



HCQ meets IND exemption criteria:

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
    - Drug safety is explained in 2.4.1.
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

2.2.1 Preclinical Data

- *In vitro:* CQ has activity against SARS-CoV [14], Middle East respiratory virus (MERS) [15], and SARS-CoV-2 [9] replication. Although CQ has in vitro data against more coronaviruses than HCQ, the favorable side effect profile [4], potency (EC50) against SARS-CoV-2 [16], and better availability in the US make HCQ a preferred choice for this clinical trial.
- *In vivo:* CQ did not protect mice from SARS-CoV infections [17].

2.2.2 Clinical Data to Date

- Despite promising *in vitro* results, in chikungunya virus CQ did not protect against severe disease and worsened arthralgias and number of joints affected [18].
- A small study out of France characterized the response of 26 COVID-19 patients treated with HCQ (+/- azithromycin), suggesting HCQ may lead to more rapid SARS-CoV-2 clearance [13]. However, this small study suffered from a poor comparator group, high loss to follow-up rates, and a primary outcome of unclear relevance towards patient outcomes.
- A pilot study from China randomized 30 patients to HCQ vs. conventional therapy group. No difference in viral eradication or clinical outcomes between these groups. Conclusion is that larger studies need to be done to examine the effect of HCQ on COVID-19 [19].
- A small randomized trial out of China published as a pre-print examined 60 patients, finding possible benefit with shorter time to fever resolution and cough improvement, but underpowered to make significant conclusions (Chen et al., pre-print, https://doi.org/10.1101/2020.03.22.20040758).

In order to prove clinical benefit, HCQ needs to be evaluated in a randomized clinical trial. This is especially germane considering other repurposed medications for SARS-CoV2 have shown in vitro and anecdotal promise, but failed during rigorous clinical trials [20].

2.2.3 Dose Rationale

Hydroxychloroquine 400mg PO BID (day 1) and 200mg PO BID (days 2-5). We chose this dosing as HCQ is shown to be more potent than CQ and modeling of HCQ levels in the lung found 400mg BID for one day followed by 200mg BID for four days maximizes drug benefit while minimizing side effects [16].

Calcium citrate is a readily over the counter supplement that is a white, oval tablet that is slightly larger than HCQ but otherwise resembles HCQ. Decision about the placebo agent was made in close collaboration with the NYU research pharmacy. The proposed dose is within the recommended daily allowance of dietary calcium.

2.3 Rationale

COVID-19 is a pandemic respiratory virus that has caused over 3,275,000 infections and 233,000 deaths worldwide [3]. There are no FDA-approved medications for COVID-19, and empiric therapies include repurposed drugs used for other indications. The evidence for repurposing HCQ is based off decreased viral replication *in vitro*. The clinical data is scant and contradictory. Additionally, paradoxical (*in vitro* benefits but harms when tested *in vivo*) HCQ worsening of viral infection is possible similar to the effect CQ had on chikungunya virus. Many upcoming clinical trials will be confounded by a lack of a comparator arm due to widespread use of HCQ and other antivirals empirically. Therefore, a placebo arm is necessary to fill the knowledge gap surrounding the efficacy of HCQ against COVID-19. Our hypothesis is that HCQ is superior to placebo in preventing severe progression of COVID-19.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

HCQ is extensively used as a rheumatologic treatment of systemic lupus erythematosus and other inflammatory diseases and was used for many years as an antimalarial prophylactic agent. Overall, HCQ is well tolerated with a limited side effect profile. The most common HCQ side effects are nausea, vomiting, and diarrhea [21]. Severe ADRs of concern, including cardiomyopathy [22] and retinopathy [23], have primarily been reported in patient's taking HCQ chronically. Retinopathy screening for patients on HCQ is recommended after 5 years of therapy. Hemolysis with G6PD deficiency is mentioned in the package insert, although studies have refuted any association [24]. Nevertheless, we have included a history of G6PD in the exclusion criteria. Prolongation of the qT interval has been reported, primarily with chronic (i.e. years) HCQ use [25]. We include a baseline EKG with non-prolonged qTC as an entry criterion, and will follow qTC prolongation as a secondary endpoint. There are no recommended dose adjustments of HCQ for renal or hepatic impairment. HCQ has been used safely in pregnancy and pediatric populations (see 5.3).

Of note, in the setting of the COVID pandemic, some subjects may be co-enrolled in trials of other investigational agents. We are not excluding any participants who are partaking in other trials studying COVID-19 treatments. The potential risks of those drug interactions with HCQ is unknown, but projected to be minimal in addition to the risks of each independent therapy. Our current safety monitoring plan allows us to detect unknown harms as they occur.

2.4.2 Known Potential Benefits

The preclinical data described above suggests a possible benefit in preventing SARS-CoV-2 replication. At this time, there are no *known* potential benefits of HCQ in COVID-19. We hypothesize that HCQ will benefit the patient by decreasing COVID-19 severe progression to death, ICU admission, mechanical ventilation, ECMO, and/or hypotension requiring vasopressor support.

3 Objectives and Purpose

3.1 Primary Objective

PRIMARY OBJECTIVES

To determine if hydroxychloroquine is superior to placebo for treatment of COVID-19 in hospitalized patients.

- **Primary Efficacy Endpoint**: A severe disease progression composite endpoint defined by the occurrence of any of the following: mortality, ICU admission, invasive mechanical ventilation, ECMO, and/or hypotension requiring vasopressor support by the 14 day post-treatment evaluation.
- **Primary Safety Endpoint:** Safety and tolerability within each treatment arm.

3.2 Secondary Objectives

SECONDARY CLINICAL OBJECTIVES

To compare treatment of SARS-CoV-2 with hydroxychloroquine to placebo with respect to:

- Composite outcome (mortality, ICU admission, invasive mechanical ventilation, ECMO, and/or hypotension requiring vasopressor support) at 30 days
- Individual components of the composite endpoint (mortality, ICU admission, invasive mechanical ventilation, ECMO, and/or hypotension requiring vasopressor support) by EOT, PTE and 30 days of treatment.
- Hospital length of stay.
- Days of fever.
- Days of non-invasive ventilator use.
- Days of non-rebreather mask oxygen supplementation
- Cytokine release syndrome grading scale.
- Percentage of subjects reporting each severity score on 8 point ordinal scale D1 and EOT.
- Percentage of subjects with qTC prolongation at EOT.

SECONDARY LABORATORY OBJECTIVES

To compare SARS-CoV-2 treatment with hydroxychloroquine to placebo with respect to laboratory markers:

- SARS-CoV-2 viral eradication from nasopharyngeal specimens.
- Change of baseline laboratory values with a focus on those related to COVID-19 prognosis.

EXPLORATORY LABORATORY OBJECTIVES

To compare SARS-CoV-2 treatment with hydroxychloroquine to placebo with respect to laboratory markers in a subset (25%, N~50) of adult patients at NYU Main Campus:

- Titers of serum antibodies against SARS-CoV-2.
- Antigen specific T and B cell responses.

3.3 Justification for Inclusion of Children

The study population will include children of all ages. Children have been affected by COVID-19 and while the majority of pediatric patients appear to have mild disease, severe cases have been reported in children. As COVID-19 is affecting children and adults differently, knowledge gleaned from adult medication treatment trials for COVID-19 may not be representative of expected treatment responses among pediatric patients with COVID-19. Despite the majority of pediatric patients with COVID-19 manifesting mild symptoms, pediatric patients are being hospitalized at NYU Langone facilities due to COVID-19 and several pediatric patients had disease manifestations that progressed in severity to the extent ICU level of care was required. Therefore, whether or not hydroxychloroquine can decrease the frequency of progression to severe disease is pertinent to this population. Given that New York represents the epicenter of the COVID-19 outbreak in the United States and the population density of our area, New York City represents the optimal location to perform pediatric COVID-19 treatment trials. New York City is one of the few locations where the burden of pediatric patients requiring hospitalization will be high enough in the United States to enroll sufficient pediatric patients in COVID-19 treatment trials to provide meaningful results.

Data from adult hydroxychloroquine studies that are published or in pre-print to date are insufficiently powered to assess with hydroxychloroquine treatment results in clinical improvement of COVID-19. Multiple in vitro studies demonstrate hydroxychloroquine has inhibitory effects on SARS-CoV-2 (Liu et al Cell Discov. 2020, Wang et al Cell Res 2020, Yao et al Clin Infect Dis. 2020). No data on the effects of hydroxychloroquine in pediatric patients has been published to date. Given the lack of pediatric data on the

effect of hydroxychloroquine treatment for preventing severe outcomes and the pandemic nature of COVID-19, including infection of children, the research objectives of this study are relevant to pediatric populations worldwide and children will be included in the study population.
Hydroxychloroquine is FDA-approved for use in infants, children, and adolescents for chemoprophylaxis and/or treatment of malaria as well as for rheumatological disorders. Hydroxychloroquine dosing of children is based on weight and when dosed appropriately, the use of hydroxychloroquine in pediatric populations does not pose any additional risks exceeding those described in adults. An enhanced safety monitoring plan for cardiac complication associated with hydroxychloroquine use will be implemented for pediatric participants. This plan specifies that:

- Pediatric participants must have documentation of normal electrolytes levels for electrolytes in which low levels may cause pro-arrhythmogenic effects on the heart (potassium, calcium, and magnesium) within 72 hours of enrollment to qualify for this study.
- Pediatric patients with history of congenital QT prolongation, history of cardiac arrest, or family history of congenital QT prolongation will be excluded from study participation.
- Daily 12-lead EKGs for pediatric participants while they remain hospitalized through day 6 (end of treatment) will be performed to closely monitor for QTc prolongation with parameters established for discontinuation of study drug if specific QTc parameters are met.
    - Study drug will be discontinued if QTc ≥ 500 ms or ΔQTc (change from baseline QTc) ≥ 60 ms.
    - This level of monitoring exceeds that normally provided for off-label use of hydroxychloroquine for COVID-19 in pediatric patients, in which a baseline EKG is changed and a repeat EKG may or may not be obtained once during the treatment course.

4 Study Design and Endpoints

4.1 Description of Study Design

We will conduct a multi-center, double-blind, placebo-controlled randomized clinical trial to determine if HCQ (400mg BID on day 1, then 200mg BID days 2-5) is superior to placebo for the treatment of hospitalized patients with laboratory confirmed COVID-19.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Primary Efficacy Endpoint: A severe disease progression composite endpoint defined by the occurrence of any of the following: mortality, ICU admission, invasive mechanical ventilation, ECMO, and/or hypotension requiring vasopressor support by the 14-day post-treatment evaluation (PTE).

Primary Safety Endpoint: Cumulative incidence of SAEs through day 30, Cumulative incidence of grade 3 or 4 AEs through day 30, Discontinuation of therapy (for any reason).

4.2.2 Secondary Study Endpoints

- **Secondary Clinical Endpoints**
    - Composite endpoint (mortality, ICU admission, invasive mechanical ventilation, ECMO, and/or hypotension requiring vasopressor support) within 30 days after treatment.
    - Individual components of composite endpoint (mortality, ICU admission, invasive mechanical ventilation, ECMO, and/or hypotension requiring vasopressor support) by end-of-treatment (EOT), PTE, and 30 days after treatment.
    - Hospital length of stay (in days): LOS is defined as the interval (in days) that the patient was admitted to a non-rehabilitation floor, categorized as short (<7 days), moderate (7-10 days), or extended (>10 days).
    - Days of non-invasive ventilator support (CPAP or BiPAP): defined as days the patient is placed on non-invasive ventilator support (CPAP or BiPAP), excluding routine CPAP use for sleep apnea.
    - Days of fever: defined as number of days with temperature >100.4 degrees Fahrenheit.

- Days of non-rebreather mask O2 support: defined as the number of days the subject was on a non-rebreather mask.
- Cytokine release syndrome (CRS) grading scale [1]: calculated on day of randomization (D1), D3 and EOT.
- Percentage of subjects reporting each severity score on 8-point ordinal scale D1 and EOT
  - The scale is as follows: 1) Death; 2) Hospitalized, on ECMO; 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities.
- Increase from normal to prolonged qTC (>500 milliseconds, gender neutral) on electrocardiogram at EOT.
- All cause mortality

- **Secondary Laboratory Endpoints**
  - SARS-CoV-2 viral eradication from nasopharynx at EOT, as measured by RT-PCR.
  - Change from baseline AST, ALT, creatinine, glucose, hemoglobin, platelets, total bilirubin, CRP, IL-6, white blood cell count at EOT.
  - Change from baseline to long (>500 milliseconds, gender neutral) qTC as measured by electrocardiogram at EOT.

4.2.3 Exploratory Endpoints

- **Exploratory Laboratory Endpoints (in 25% of adult participants on NYU Main Campus)**
  - Titers of serum anti- SARS-CoV-2 antibodies at EOT, measured by ELISA.
  - Antigen-specific T and B cell responses at EOT.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Hospitalized with symptoms consistent with COVID-19 including but not limited to any of the following: fever (documented or subjective), cough, dyspnea, diarrhea, nausea, diffuse myalgias, and/or anosmia
2. Informed consent signed by patient (if ≥18 years old) or parent (if <18 years old). Additionally, assent will be obtained from children ages 7 and older who are capable of providing assent. Adults who are unable to provide informed consent may be consented by legally authorized representative (see 13.3.3).
3. Positive SARS-CoV-2 PCR testing (nasopharyngeal, oropharyngeal, sputum and/or bronchoalveolar lavage) within 7 days prior to randomization
   - If testing was obtained 5-7 days prior to randomization, the patient must have progressive disease suggestive of ongoing SARS-CoV-2 infection at randomization

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Presence of the primary endpoint (ICU admission, mechanical ventilation, ECMO, and/or vasopressor requirement) at time of randomization.
2. Treatment with CQ or HCQ within the 30 days prior to the start of the study drug treatment.
3. Unable to take oral medications.
4. History of allergic reaction or intolerance to CQ or HCQ.
5. Baseline corrected qT interval (>500 milliseconds, gender neutral) history of congenital qT prolongation, and/or history of cardiac arrest.

6. Concomitant therapy with flecainide, amiodarone, digoxin, procainamide, propafenone, thioridazine, or pimozide
7. History of retinal disease including a documented history of diabetic retinopathy.
8. Known history of G6PD deficiency.

5.3 Pediatric Inclusion/Exclusion Criteria

Inclusion Criteria:

- Inclusion of patients < 18 years of age, otherwise identical to adult criteria

Pediatric Exclusion Criteria:

- Baseline QTc >470 ms in males, >480 ms in females (post puberty) or QTc >460 ms in males, >470 ms in females (pre puberty)
- History of congenital QT prolongation (LQTS) and/or history of cardiac arrest.
- Family history of LQTS
- Presence of Concomitant therapy QT prolongation: Medications will be checked against a list on www.CredibleMeds.com and those on concomitant medications with significant QT-prolonging potential will be excluded
- Basic metabolic panel (BMP) not performed within 72 hours of enrollment
- Presence of uncorrected hypokalemia (<3.4 mmol/L), hypocalcemia (<9.0 mg/dL, and/or hypomagnesemia (<1.7 mg/dL) on most recent BMP (within 72 hours of enrollment).

5.4 Vulnerable Subjects

Given the ongoing outbreak of COVID-19 and lack of data on disease outcomes in pregnant and breastfeeding women, research on this disease is relevant to these vulnerable populations. These populations may benefit from knowledge gained from this study. Individuals in these populations may enroll in this study if they are interested in study participation provided they meet eligibility requirements.

For pregnant women enrolling in this study, there is minimal risk and no direct benefit to the fetus [26-28]. Pregnant subjects will provide verbal consent and authorization once they have been fully informed of the study, including the reasonably foreseeable impact of the study on the fetus. No inducements, monetary or otherwise, will be offered to terminate a pregnancy; Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and Individuals engaged in the research will have no part in determining the viability of a neonate.

The amount of HCQ secreted into breast milk (2%) is below the threshold generally acceptable as safe during breastfeeding (<10%) [29] and is accepted by rheumatologists' professional groups [30].

The study population will include children of all ages. Hydroxychloroquine is FDA-approved for use in infants, children, and adolescents for chemoprophylaxis and/or treatment of malaria as well as for rheumatological disorders. Hydroxychloroquine dosing of children is based on weight and when dosed appropriately, the use of hydroxychloroquine in pediatric populations does not pose any additional risks exceeding those described in adults. Children have been affected by COVID-19 and while the majority of pediatric patients appear to have mild disease, severe cases have been reported in children. Over a two-week period at the NYU Langone Manhattan campus alone, 15 children were hospitalized due to COVID-19. Given that New York represents the epicenter of the COVID-19 outbreak in the United States and the population density of our area, New York City represents the optimal location to perform pediatric COVID-19 treatment trials. New York City is one of the few locations where the burden of pediatric patients requiring hospitalization will be high enough in the United States to enroll sufficient pediatric patients in COVID-19 treatment trials to provide meaningful results. No data on the effects of hydroxychloroquine in pediatric patients has been published to date. Given the lack of pediatric data on the effect of hydroxychloroquine treatment for preventing severe outcomes and the pandemic nature of COVID-19, the research objectives of this study are relevant to pediatric populations worldwide and children will be included in the study population.

5.4.1 Pediatric Safety Considerations – Cardiac

Background considerations
We know less about pediatric than adult COVID-19, but serious illness can still occur [34][38]. This is particularly true in the very young, such as infants < 1 year of age. Therefore, effective therapies directed against pediatric COVID-19 are also sorely needed. The pediatric population with COVID-19 span a broad age range and in our anecdotal experience here at Hassenfeld Children's Hospital at NYU Langone, frequently exhibit co-morbidities different from adult patients. The known risks of cardiac complications from hydroxychloroquine [36] may therefore be different or even increased in the pediatric population. Therefore, enhanced safety monitoring will need to be tailored to the infants and children who will be enrolled in this trial of hydroxychloroquine.

QT prolongation
The major concern of hydroxychloquine centers around QT prolongation, which is associated with Torsades de Pointes (TdP) [37][39] as well as atrioventricular block [35]. Very little is known about hydroxychloroquine and QT prolongation in the pediatric population, but the available scant data suggest hydroxychloroquine is safe when used for rheumatological and autoimmune diseases in children [27][33].

QT prolongation may be exacerbated by modifiable risk factors such as medications (a comprehensive list is available on CredibleMeds.com) and serum electrolyte derangements, chiefly hypokalemia, hypocalcemia, and hypomagnesemia. Serum electrolyte derangements are common in pediatric (and adult) patients with co-morbidities such as cancer and heart disease. Non-modifiable risk factors include a personal or family history of long QT syndrome (LQTS) and significant bradyarrhythmia (<45 bpm) [37].

Cardiomyopathy
Cardiomyopathy has been associated with long-term hydroxychloroquine use [36], but has not been reported in children. Because the treatment duration is short (5 days) in this trial, a routine echocardiogram will therefore not be necessary. However, should the EKG show abnormalities that may suggest myocardial abnormalities that cannot be explained otherwise (e.g., serum electrolyte abnormalities), then an echocardiogram will be performed as part of routine clinical care.

5.5 Strategies for Recruitment and Retention

We will educate treating physicians about our study using email and printed material. Additionally, an informational phone number will be provided in the electronic medical record ("COVID order set") for questions and to alert study team members of potential enrollees. We will pre-screen based off system generated lists on the electronic medical record filtered for an inpatient laboratory confirmed diagnosis of COVID-19. Additional possible recruitment strategies may include referral via word of mouth and use email listservs, the NYU Langone Medical Center website and presentations in the NYU health care community. Any recruitment materials will be submitted to the IRB for approval prior to posting.

We will use our inclusion and exclusion criteria to screen these lists and will enroll women and minorities with no exclusion. Consent will be obtained both remotely (to protect patients, providers and preserve personal protective equipment) or at the bedside (see 13.3). The majority of our study will occur during the inpatient hospitalization, so retention in the study cohort should be adequate. We will assure correct documentation of the study participant phone number and back-up phone number in the demographics eCRF to assure retention during the PTE and end-of-study (D30) phone follow-up.

5.5.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will utilize one of two methods for generating an initial patient list:

- EPIC list of hospitalized patients generated by study site PI with COVID-19 positive PCR testing on a daily basis (this will be utilized prior to Data Core capability).
- Once it is available, we will use NYU Data Core generated list of patients meeting inclusion criteria who have agreed to be approached for clinical research.

These patients will be pre-screened for eligibility using information in the electronic medical record to identify potential subjects. This information will be made available to individual site study leads.

Once potential subjects have been identified, the study team will notify the treating physician (TP) that they have patients eligible to participate as follow:

- TP will be contacted by secure messaging through EPIC, by phone, or in person and agrees to permit study team to directly contact potential subjects.
- TP may also contact study team for direct patient referrals.

Once contact is made, approved recruitment language (see remote recruitment script attached) will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

5.6 Duration of Study Participation

30 days

5.7 Total Number of Participants and Sites

We expect 200 patients to be enrolled at NYU Main Campus (Tisch/Kimmel Pavilion), 100 patients at NYU Brooklyn, 100 patients at NYU Winthrop, 150 patients to be enrolled at Bellevue Hospital Center, and 100 patients at SUNY Downstate. This number may be adjusted if additional sites agree to participate.

Recruitment will end when approximately 650 participants are enrolled. It is expected that approximately 650 participants will be enrolled in order to produce 626 evaluable participants.

5.8 Participant Withdrawal or Termination

5.8.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.8.2 Handling of Participant Withdrawals or Termination

After unblinding (see 10.6.3), withdrawal or termination from the study, we will continue to follow clinical outcomes and proposed laboratories in the electronic medical record. PTE and 30-day phone follow-up will still occur, if possible. However, if a subject voluntarily withdraws participation in the study, PTE and 30-day phone follow-up will not occur. At the conclusion of the study, we will evaluate the data for the primary and secondary endpoints with intention to treat (ITT) analysis, in which participants are analyzed according to their assigned treatment, regardless of compliance or crossover. Exploratory analyses will investigate the per protocol effect using approaches informed by causal inference.

- If a participant voluntarily withdraws, or is terminated by an investigator, specimens previously collected will continue to be used for study purposes, but no further specimens will be collected.

5.9 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to funding agency. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and IRB.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

- **Study Agent:** Hydroxychloroquine sulfate
- **Control:** Calcium citrate

Acquisition

- HCQ will be provided by the NYS Department of Health.
- Placebo will be purchased by NYU Langone pharmacy (over the counter supplement).

6.1.1 Formulation, Appearance, Packaging, and Labeling

- **Study agent:**
  - **Adults and children ≥50kg:** Hydroxychloroquine sulfate 200mg tablets
    - Each hydroxychloroquine sulfate tablet contain 200 mg hydroxychloroquine sulfate, equivalent to 155 mg base, and are for oral administration.
    - *Inactive Ingredients:* Dibasic calcium phosphate USP, hypromellose USP, magnesium stearate NF, polyethylene glycol 400 NF, polysorbate 80 NF, corn starch, titanium dioxide USP, carnauba wax NF, shellac NF, black iron oxide NF.
    - Appearance: white, oval, 1.4cm
  - **Children <50kg:** compounded hydroxychloroquine prepared as described in 6.1.3 and weight based dosing as described in 6.1.4
- **Placebo**:
  - **Adults and children ≥50kg:** Calcium citrate 200mg tablets
    - Brand: Major
    - Appearance: white, oval, 2.0cm
  - **Children <50kg:** Compounded cholcalciferol (vitamin D) 25units/mL
    - 5mL dose (125 units total)
    - Compounded by NYU pharmacy

6.1.2 Product Storage and Stability

HCQ and placebo tablets will be stored at room temperature in the NYU Langone research pharmacy.

Compounded liquid products will be stored at 4C in a refrigeration in the research pharmacy.

- Expiration date is 30 days after compounding

6.1.3 Preparation

No preparation is needed for patients ≥50kg, as they will receive oral tablets.

- For **pediatric patients <50kg randomized to HCQ**, compounding will follow the recipe:

Ingredients

Hydroxychloroquine 200mg tab	# 15
Ora-Plus	60 mL
Sterile Water	**qs** 120 mL

Directions

1) Crush tablets in a mortar and reduce to a fine powder
   a. If Brand name/ tablets are coated - With a towel moistened with alcohol, remove the coating from fifteen 200 mg hydroxychloroquine sulfate tablets.
   b. Tip - Place tablets in a small dosing cup and add isopropyl 70% alcohol to just cover tablets. Let soak 10 seconds (no longer!) then place tablets on paper towel. Gently rub each tablet to remove coating.
2) Wet powder with a small amount of Ora-Plus and mix to form a viscous, smooth paste
3) Slowly add remaining Ora-Plus, mixing well after each addition and pour into graduated cylinder
4) Rinse mortar with water, adding rinse to graduate.
5) QS with Sterile Water to make 120 ml volume

Reference [31-32]

- **For Pediatric patients <50kg randomized to placebo**, compounding with the following recipe:

Ingredients

Cholecalciferol 400 units tab	# 10
Ora-Plus	60 mL
Sterile Water	**qs** 160 mL

Directions

1) Crush 10 cholecalciferol 400 units tablets in a mortar and reduce to a fine powder
2) Wet powder with a small amount of Ora-Plus and mix to form a viscous, smooth paste
3) Slowly add remaining Ora-Plus, mixing well after each addition and pour into graduated cylinder
4) Rinse mortar with water, adding rinse to graduate.
5) QS with Sterile Water to make 160 ml volume

Bottle Labeling

Shake well. Refrigerated.

Bottle Expiration

30 days (refrigerated or room temperature)

Final concentration 25 units/mL

6.1.4 Dosing and Administration

- **Study drug:** HCQ 400mg (2 tab) by mouth BID (day 1) and 200mg (1 tab) by mouth BID (days 2-5). For pediatric patients, we will administer compounded HCQ per weight-based dosing guidelines shown in **Table 1**.

Table 1. Pediatric HCQ Dosing

Weight (kg)	Maintenance dose (mg/kg)	Loading dose (mg/kg)	Frequency of administration (h)
<5	3	6	12
5 to 15	5	6	12
15 to 35	4	6	12
35 to 50	3	6	12
>50*	200	400	12
*Absolute doses; *the efficacy, PK, and safety of HCQ has not been demonstrated in children with SARS-CoV-2 infection therefore these guidelines are designed to help clinicians who are planning to prescribe the drug for clinical care.*			

- **Placebo:** Calcium citrate 2 tablets (400mg) BID on day 1 and 1 tablet (200mg) on days 2-5.
    - For pediatric patients <50kg, we will administer compounded vitamin D (cholcalciferol) placebo 10mL (250 units) BID on day 1, 5mL BID (125 units) day 2-5.

6.1.5 Route of Administration

Oral

6.1.6 Duration of Therapy

5 days

6.1.7 Tracking of Dose

Most doses of study medication will be administered while hospitalized, allowing for close monitoring of adherence in the electronic medical record. If patients are discharged prior to finishing the study drug course, they will be provided with the remaining doses to complete after discharge. In this setting, adherence will be measured during the PTE phone follow up at D14, by patient report.

6.2 Study Agent Accountability Procedures

All study drug will be dispensed by the NYU research pharmacy. Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

Study drug is provided by the New York State department of health. At the conclusion of our study, any additional study drug can be used by our pharmacy for FDA-approved indications.

6.2.1 Administration of Intervention

Study drug will be delivered from the NYU Langone research pharmacy to the research pharmacy sites in an amount proportional to projected enrollment. The respective research pharmacies will dispense the drug to the treating teams. If the patient is going to be discharged, the remaining doses will be delivered to the patient in an unlabeled bottle and instructions will be provided to the patient for post-discharge self-administration.

6.2.2 Assessment of Subject Compliance with Study Intervention

Compliance while inpatient will be determined by medication administration record in the electronic health record. If the participant is discharged prior to EOT, compliance of remaining doses will be quantified during the PTE follow-up phone visit at D14.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

≤72 hours prior to randomization but after informed consent and screening

- Medical history: obtained on enrollment during face-to-face interview by study team on standardized form including the following prompts:
    - History of present illness: presenting COVID-19 symptoms, date of onset
    - Past medical history: with a special focus on chronic comorbidities most pertinent to COVID-19 such as lung disease, hypertension, and diabetes.
    - Past surgical history: with a focus on lung surgery.
    - Allergies
    - Social history: with a focus on smoking, use of vaporizers, occupational history, and recent travel.
    - Family history: with a focus on lung disease
        - History of LQTS or sudden death
    - Review of Systems
- Medication history: prescription and over-the-counter medications taken over the last 30 days will be reviewed. This will include a review of prohibited medications in exclusion criteria.
    - PEDIATRIC MEDICATION HISTORY: check reconciled medications against list on www.CredibleMeds.com
- Vital signs throughout the study period will be obtained from electronic medical record review.
- Radiographic assessment: Chest X-ray and CT-scan (if available) reads will be annotated for the following findings:
    - Ground glass opacities
    - Laterality (unilateral, bilateral)
    - Consolidations
- Recording of subject Cytokine Release Syndrome score [1].
- Recording of subject COVID-19 severity score (8-point ordinal scale):
    - The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or ECMO; 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities.
- Recording of qTC (Bazett) from a 12 lead EKG.

Active Treatment (D1-D5)

- Electronic medical record review to:

  - Monitor study drug administration.
  - Record presence of primary composite outcome endpoint (death, mechanical ventilation, ICU admission, ECMO and/or hypotension requiring vasopressors).
    - If endpoint reached, immediately unblind as outlined in 10.6.3.
  - Classification of Cytokine Release Syndrome score [1] on Day 3.
  - Record standard of care labs (CBC, CMP, CRP) for a trend at D3.
  - Record Vital signs daily.
  - Monitor for unsolicited adverse events.
- Daily EKG's for pediatric participants (<18 yo) while the participant remains hospitalized.
  - Discontinue HCQ if QTc ≥ 500 ms or ΔQTc (change from baseline QTc) ≥ 60 ms.

End-of-treatment (EOT – D6)

- Record presence of primary composite outcome endpoint (death, mechanical ventilation, ICU admission, ECMO and/or hypotension requiring vasopressors).
- Classification of Cytokine Release Syndrome score [1]
- Classify subjects based on COVID-19 severity score (8-point ordinal scale), defined above.
- 12 lead EKG, record if patient increased to prolonged qTC. Because this is not a standard of care procedure, member of the research team will order this EKG as research procedure. The EKG can be performed by clinical team (fee-for-service). This is to minimize exposure for the study team, while obtaining necessary research data.
- If pediatric participants remain hospitalized at D6, a 12 lead EKG will be performed, record if patient increased to prolonged qTC. Because this is not a standard of care procedure, member of the research team will order this EKG as research procedure. The EKG can be performed by clinical team (fee-for-service). This is to minimize exposure for the study team, while obtaining necessary research data.
- Record solicited adverse events

Post-treatment Evaluation (PTE, day 14)

- Phone follow-up to assure patient has not met any of the primary outcomes (death, mechanical ventilation, ICU admission, ECMO and/or hypotension requiring vasopressors).
- Record solicited adverse events.

End-of-Study Evaluation (day 30)

- Phone follow-up to assure patient has not met any of the primary outcomes (death, mechanical ventilation, ICU admission, ECMO and/or hypotension requiring vasopressors).
- Documentation of total hospital length of stay (days).
- Record solicited adverse events.

7.1.2 Standard of Care Study Procedures

Standard of care for COVID-19 includes supportive care such as supplemental oxygen therapy and IV fluids while admitted as inpatient. NSAIDs are discouraged during COVID-19. All other medical therapies during the study period are at the discretion of the treating provider.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

≤72 hours prior to randomization

- **Hematology (if not obtained as part of routine clinical care, research team will order for clinical lab to add onto remnant specimens, if available):** hemoglobin, hematocrit, white blood cells (WBC) with automated or manual differential, platelet count, ferritin, D-Dimer.
- **Biochemistry (if not obtained as part of routine clinical care, research team will order for clinical lab to add onto remnant specimens, if available):** creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, glucose, hemoglobin A1C, CRP, IL-6, troponin, LDH

  - PEDIATRIC PATIENTS: BMP (with calcium), Mg. (if not obtained as part of routine clinical care, research team will order for clinical lab to add onto remnant specimens, if available)
- **Pregnancy test**: Urine or serum beta HCG.

Day 3 of Treatment

- **Hematology (if available as part of routine clinical care):** hemoglobin, hematocrit, white blood cells (WBC) with automated or manual differential, platelet count, ferritin
- **Biochemistry (if available as part of routine clinical care):** creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, glucose, CRP, LDH
  - PEDIATRIC PATIENTS (if not obtained as part of routine clinical care, research team will order for clinical lab to add onto remnant specimens, if available): BMP (with calcium), Mg.

End-of-treatment (EOT)

- **Hematology (if not obtained as part of routine clinical care, research team will order for clinical lab to add onto remnant specimens, if available):** hemoglobin, hematocrit, white blood cells (WBC) with automated or manual differential, platelet count, ferritin, D-dimer
- **Biochemistry (if not obtained as part of routine clinical care, research team will order for clinical lab to add onto remnant specimens, if available):** creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, glucose, CRP, IL-6, LDH.
  - PEDIATRIC PATIENTS (if not obtained as part of routine clinical care, research team will order for clinical lab to add onto remnant specimens, if available): BMP (with calcium), Mg.
- **SARS-CoV-2 nasopharyngeal PCR:** to determine viral eradication

7.2.2 Other Assays or Procedures

We will collect whole blood on a subset of adult subjects (25% at NYU Main Campus, N ~50) for immunological assays including flow cytometry, microarray, detection of anti-SARS-CoV-2 antibody titers, RNA-studies, B-cell and T-cell antigen responses. We will ask each participant at NYU Tisch Hospital or Kimmel Pavilion with a hemoglobin ≥10g/dl upon enrollment if they agree to study team phlebotomy until we collect specimens on 50 adult patients. As an optional portion of this study we plan to collect about 5-6 tablespoons of blood for each research blood draw. Some subjects in this subset of 50 may also be asked to provide a stool specimen (for microbiome analysis).

7.2.3 Specimen Preparation, Handling, and Storage

The baseline labs and EOT (D6) labs will be performed as part of routine clinical care or obtained from remnant specimens obtained during routine clinical care when available. These specimens will be in the sites' core clinical labs and prepared, stored and handled according to the clinical lab SOP.

For the exploratory subset of patients (25% of adults at NYU Main Campus, N ~50) in which the study team is drawing labs outlined in 7.2.2, these will be transferred in a closed plastic container that is decontaminated prior to exiting the room. The decontaminated container, once out of the patient room, is placed into a padded cardboard box.

7.2.4 Specimen Shipment

All hematology and biochemistry labs will be performed in the core facilities at study sites. SARS-CoV-2 PCR will be performed in the clinical laboratory at NYU Langone and Bellevue Hospital. Bellevue Hospital center may send their SARS-CoV-2 PCR to BioReference laboratories. All exploratory endpoint research labs, outlined in 7.2.2, will be shipped at room temperature to the NYU Langone Vaccine Center research laboratory at Alexandria Tower for Life Sciences (West) immediately after phlebotomy by the study team.

7.3 Study Schedule

7.3.1 Screening

The study team enrollment managers will receive a list each morning from NYU Data Core of admitted patients with new positive SARS-CoV-2 PCR, or generate a list of this diagnosis in EPIC if a list from Data Core is not available. Enrollment managers will use this list to pre-screen the electronic medical record for prior HCQ administration and other inclusion/exclusion criteria to generate a list of potential subjects. Prescreening will use data obtained as a part of the individual's regular medical care.

Using this list, the study team will contact the treating provider through a secure messaging system or by phone to grant permission for an enrollment visit.

7.3.2 Enrollment/Baseline Visit (Day 1)

- Obtain consent of potential participant using study eICF (see 13.3).
- Verify inclusion/exclusion criteria.
- Obtain pregnancy test (females aged 12-50) if prior results during the hospitalization are not available.
- If baseline laboratory values of interest were not completed during routine clinical care, complete baseline laboratory studies by adding on these tests to remnant clinical samples, if available.
- Obtain demographic information and medical history as described in 7.1.1.
- Collect blood for the exploratory subset of adult patients (25% of adults at NYU Main Campus, N ~50) as outlined in 7.2.2.
- Record baseline adverse event eCRF
- Randomize subject
- Order the study treatment to be dispensed by pharmacy.

7.3.3 Intermediate Visits

7.3.3.1 End-of-Therapy (EOT) visit (D6, or day of discharge if <D6)

- Record adverse events as reported by participant or observed by investigator.
- Obtain nasopharyngeal swab for SARS-CoV-2 PCR
- Collect blood for subset of patients (25% of adults at NYU Main Campus, N ~50) as outlined in 7.2.2.
- Provide final instructions prior to discharge, including anticipatory guidance about phone follow-up.

7.3.3.2 Post-treatment Phone follow-up (Day 14 ±2)

- Record if patient has not met any of the primary outcomes (death, mechanical ventilation, ICU admission, ECMO, and/or hypotension requiring vasopressors).
- Record adverse events as reported by participant.

7.3.4 Final Study Visit (Phone Follow-up, D30 ±3)

- Record if patient has not met any of the primary outcomes (death, mechanical ventilation, ICU admission, ECMO, and/or hypotension requiring vasopressors).
- Record adverse events as reported by participant.
- Obtain date of discharge to calculate hospital length of stay.

7.3.5 Withdrawal/Early Termination Visit

If the subject or TP requests withdrawal or early termination from the study, a visit (in person if admitted; phone visit if discharged) will occur, if the participant is willing, to document the patient or TP reason for withdrawal. Adverse events will be recorded.

7.3.6 Unscheduled Visit

Unscheduled visits will occur after any related AE during the study period. These will be documented in the AE reporting form.

7.4 Concomitant Medications, Treatments, and Procedures

If the patient is on concomitant azithromycin, we will strongly recommend TP stop this medication due to risk profile outlined in 7.5.1. If azithromycin is continued, we will request TP get daily ECG for qTC monitoring (see 7.5.1)

Other than those medications explicitly prohibited (see 7.6), concomitant medication decisions will be left to the TP. Medication reconciliation will occur during the enrollment visit at the bedside, and the medication list will be reviewed on D3 and D5 while on study medication.

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5 Justification for Sensitive Procedures

Use of placebo is justified as:

- HCQ has no proven benefit in SARS-CoV-2 or other viral diseases
    - Clinical equipoise
- Providers may enact different levels of supportive care and other off-label SARS-CoV-2 therapies if they do not see the patient receiving medication, creating bias.

7.5.1 Precautionary Medications, Treatments, and Procedures

TP may have patients on Azithromycin for bacterial pneumonia or prevention of bacterial pneumonia. Due to the potential for increase in qTC prolongation with this combination, we will:

- Recommend stopping azithromycin if clinical suspicion for bacterial pneumonia is low
- Alert TP of potential for qTC prolongation and recommend daily ECG monitoring with discontinuation and alert study team if qTC becomes prolonged (>500 milliseconds, gender neutral)

7.6 Prohibited Medications, Treatments, and Procedures

Due to qTC prolongation concerns, subjects on flecainide, amiodarone, digoxin, procainamide, propafenone, thioridazine, and/or pimozide will be excluded during screening or withdrawn if these are started during the study duration.

7.7 Prophylactic Medications, Treatments, and Procedures

No prophylactic medication, treatments, or procedures will be administered during the study period.

7.8 Rescue Medications, Treatments, and Procedures

In the event of an unexpected anaphylactic allergic reaction, subcutaneous epinephrine will be available. For mild allergic reactions, glucocorticoids and antihistamines may be administered.

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, or the investigators brochure)
- Related or possibly related to participation in the research (i.e., 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 greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

For all collected AEs, the clinician who evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

The study site PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent. Furthermore, we will be regularly assessing safety for critical toxicity as described in 10.4.4.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit or phone follow-up, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

Information on all AEs should be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

8.4.2 Serious Adverse Event Reporting

Any AE that meets a protocol-defined criterion as a SAE in section 8.1.2. must be submitted immediately (within 24 hours of site awareness) on an SAE form to the IRB and the medical monitor. All SAE forms must be signed off by study PI (Dr. Mulligan).

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB, the study PI, and the medical monitor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB, study PI, and medical monitor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported IRB, the study PI, and the medical monitor within 48 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 48 hours of the IR's receipt of the report of the problem from the investigator.

8.4.4 Reporting of Pregnancy

If a patient has a positive pregnancy test on study enrollment or becomes pregnant during the study period, they will be removed from study treatment. We will report this event to the IRB and follow the patient throughout the term of the pregnancy. We will also follow-up with a phone visit after birth to evaluate for any birth defects.

8.5 Reporting Procedures

The study clinician will complete an SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the medical monitor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the medical monitor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the IRB or NYS DOH and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Study Halting Rules

Administration of study agent will be halted when certain criteria are met, or the DSMB instructs, during routine safety analysis (defined in 10.4.4). The safety analysis team will notify the study PI immediately and enrollment screens will stop accepting new study participants.

- The PI will inform the DSMB members of SAEs on a biweekly basis (summarized once every two weeks) so that they may review and determine if any study action is needed.
- Deaths will be reported to the DSMB promptly.
- SAEs of special interest (identified in 10.4.4), particularly the occurrence of ventricular arrhythmias, specifically torsades des pointes, should be monitored and enrollment halted if incidence of this event exceeds 5%.
- Other AEs of special interest (identified in 10.4.4) occurring in 3 or more subjects will trigger a report to the DSMB and a review.
- The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the study PI.

8.7 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including infectious diseases, rheumatology, and biostatistics. The DSMB will meet at 4 weeks and 8 weeks to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study PI.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Clinical monitoring will occur at enrollment visit and D6 (EOT) visit, at D14 and D30 phone visit. Additionally, the medical record will be reviewed daily by a remote central study safety coordinator while the patient is on therapy (D1-D5) to evaluate for:
    - The primary composite outcome
    - Documentation that may suggest AE (and trigger an unscheduled visit).
- Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

A formal statistical analysis plan (SAP) will be created prior to the completion of the study and before database lock. The SAP will include additional details about the statistical analyses, including specified analysis populations, plans for addressing missing data, and planned sensitivity analyses.

10.2 Statistical Hypotheses

The primary null hypothesis is that the rate of occurrence by 14 days of the primary composite outcome will be the same in the two treatment groups. The alternative hypothesis is that the rate of the outcome will differ in the two groups. We anticipate that the rate of the primary outcome may be lower in the group receiving HCQ.

10.3 Analysis Datasets

The intention-to-treat (ITT) analysis dataset will be the source of data for primary analyses. This will include all randomized patients regardless of actual receipt or compliance with therapy. The safety analysis set will consist of all patients who received at least one dose of study drug (HCQ or placebo). The per-protocol analysis set will consist of all patients who received at least 80% of study drug; this dataset will support sensitivity analyses to complement the primary ITT analyses.

10.4 Description of Statistical Methods

10.4.1 General Approach

Our simple design includes comparison of the treatment and placebo arms with respect to our pre-defined primary and secondary endpoints.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary analysis will be a comparison between the two arms (hydroxychloroquine and placebo) of the primary endpoint rate. The primary outcome will be analyzed using a generalized linear model with binomial

link function, with a binary indicator for treatment and adjustment for hospital and age group (the stratification factors). Randomization should obviate the need for additional adjustment factors but if demographic or clinical characteristics are unbalanced with respect to treatment group, we will consider adjustment. These pre-specified characteristics include age, sex, race, ethnicity, baseline COVID severity. Additionally, the PI will adjust the analyses to accommodate the information on any co-enrollments that occur. Since the study is randomized, the PI does not expect differential co-enrollment between the study arms, and thus the comparison of outcomes in patients receiving HCQ versus those receiving placebo will still be a valid test of the effect of HCQ. That is, the effect of any of the other therapies will "wash out" in the comparison of patients on HCQ and placebo in the current study.

The hypothesis will be tested using a Wald test for the statistical significance of the coefficient of the treatment indicator. We will estimate the probability of the primary endpoint for patients in the placebo and hydroxychloroquine groups, derive a relative risk ratio, and present this with its associated 95% confidence interval.

10.4.3 Analysis of the Secondary Endpoint(s)

Secondary outcomes will be analyzed with similar approaches; the link function used in the generalized linear model will be dictated by the outcome. Binary outcomes such as 30-day all-cause mortality will use the binomial link function as described above. Total hospital length of stay (LOS) will be analyzed using an identity link function (note that LOS will likely be log-transformed to address its skewed distribution). Continuous measures such as FiO2 and cytokine levels will also be analyzed using the identity link. Missing data, for example from patients discharged prior to EOT, will be imputed using multiple imputation.

10.4.4 Safety Analyses

We will conduct continuous monitoring for safety. We define the following as AEs or SAEs of special interest:

- qTC ≥500 milliseconds on any ECG during treatment or at EOT,
- any documented sustained ventricular arrhythmias,
- any complaints of decreased vision during the study period, or
- objective evidence of hemolytic anemia (acute drop in hemoglobin >2 grams with decreased haptoglobin and increased indirect bilirubin).

We will use a Bayesian monitoring rule to address the degree of evidence about differences in risk of unacceptable toxicity in patients treated with HCQ or placebo. The rate of unacceptable toxicity will be estimated with accruing data, and with every 50 additional patients, we will evaluate the rate. Considering reports of qTC prolongation, HCQ retinopathy, and hemolytic anemia have been shown primarily during chronic therapy, we estimate the event rate to be very low. If the posterior probability that the unacceptable toxicity rate is 5% higher in the HCQ group exceeds a pre-specified threshold (e.g., 80%), that will be considered sufficient evidence of a safety problem. We will assume a Beta(1,2) prior distribution, which is prior information equivalent to one unacceptable toxicity among three treated patients. This minimally informative prior is justified by preliminary clinical experience.

The DSMB will be provided data on which subjects are co-enrolled on other clinical trials. Although we project minimal additional risk to subjects in addition to the risks of each individual therapy (see 2.4.1), analysis will be performed on co-enrolled patients for increased AE or SAE in this group.

A summary of SAEs and AEs experienced by subject co-enrolled in multiple clinical trials will be reported to the IRB on a monthly basis. The report should include a statement from the PI regarding whether or not there are any safety concerns to the co-enrolled group as compared to the not co-enrolled group. The report will be submitted to the IRB via Reportable New Information (RNI) submission.

SAE leading to premature discontinuation from the study drug and serious treatment-emergent AEs will be recorded in an AE table.

10.4.5 Adherence and Retention Analyses

Receipt of medication on days 1-5 will be recorded on case report forms. Subjects who receive at least 80% of planned doses (i.e., 4 of 5 days) will be considered compliant with medication, and will constitute the per-protocol analysis set as defined above. The proportion of patients evaluated at day 15 (the primary outcome assessment time), day x (via phone) and day 30 (via phone) will be tabulated. Every effort will be made to re-contact patients who are unreachable. Due to the short timeline of trial participation we anticipate excellent patient retention.

10.4.6 Baseline Descriptive Statistics

All variables will be summarized using mean, median, standard deviation, and range (for continuous variables) and frequency (for categorical variables). Treatment groups will be compared with respect to baseline characteristics and co-enrollment in other investigational trials to verify randomization balance.

10.4.7 Planned Interim Analysis

10.4.7.1 Safety Review

See section 10.4.4.

10.4.7.2 Efficacy Review

We plan one formal interim analysis for efficacy when approximately 50% of the trial information has accrued, which will correspond to two weeks following the enrollment of 50% of subjects (i.e., approximately 313 participants). This formal interim hypothesis test will use an O'Brien-Fleming boundary with a two-sided significance level of 0.003. If the interim stopping boundary is met, the trial will be terminated and HCQ will immediately be administered to all enrolled patients. If the interim stopping boundary is not met, the trial will continue to fully enroll the planned 626 participants, and the final analysis will use a two-sided significance level of 0.049, thus maintaining the overall Type I error at the nominal level of 0.05. We do not plan any formal interim analyses for futility. An independent data safety and monitoring board (DSMB) will assist with interim analysis.

Reject Null Hypothesis			
Analysis	**% Information**	**Critical Value Z**	**p-value**
Formal Interim Look	50	+/-2.96	0.003
Formal Final Look	100	+/-1.97	0.049

10.4.8 Additional Sub-Group Analyses

We will explore differences in treatment effect by age group, sex, and race. We acknowledge that statistical power to detect interactions is low, but these descriptive analyses will provide important signals for potential evaluation in future research.

10.4.9 Multiple Comparison/Multiplicity

The single primary hypothesis will be evaluated with a two-sided Type I error rate of 0.05.

10.4.10 Tabulation of Individual Response Data

The composite outcome evaluated at 14 days will be tabulated, and broken down by component (e.g., ICU admission, mechanical ventilation, etc.). Note that some patients may experience more than one component of the primary endpoint.

10.4.11 Exploratory Analyses

We will conduct exploratory analyses in a subset of patients on whom additional basic science assays are performed. These will be descriptive and hypothesis-generating.

10.5 Sample Size

We plan to enroll 626 patients, evenly randomized between hydroxychloroquine and placebo (313 per arm). Based on preliminary data from Tisch, Bellevue, and NYU Winthrop Hospitals, we anticipate occurrence of the primary endpoint (any of ICU admission, mechanical ventilation, hypotension with vasopressor need, or death by the 14-days post-treatment evaluation) of approximately 30%. We wish to be able to detect a reduction the endpoint rate of approximately 10 percentage points, to 20% in the hydroxychloroquine arm. Using a two-sided Type I error rate of 0.05, 626 patients provide 80% power to detect this difference. Randomization will be stratified by hospital site and age >60 years. Randomization will use permuted blocks with variable block sizes of 4 and 6 to maintain balance in treatment assignment over time. The table below provides the sample size required for a range of other scenarios:

Sample sizes were calculated using a two-sided alpha = 0.05 and requiring 80% power, based on a 2-look O'Brien-Fleming interim analysis plan implemented in EAST 6.5 (Cytel, Inc). Details of the interim monitoring plan are provided above (see 10.4.7.2).

		Detectable percentage point reduction in HCQ group				
		5%	7.5%	10%	12.5%	15%
Outcome rate in placebo group	0.2	1892	810	438	268	176
	0.3	2582	1132	626	394	268
	0.4	3022	1342	752	480	330
	0.5	3210	1440	816	524	366
	0.6	3148	1426	816	530	372

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

Patients will be evenly randomized to the two study arms, HCQ and placebo. Randomization will use permuted blocks with variable block sizes of 4 and 6 to maintain balance in treatment assignment over time. Patients and providers will be blinded to treatment status. A remote study coordinators randomizing the patients may be unblinded to treatment assignment. The randomization sequence will be generated in advance and accessed electronically through the data capture system. Once the assignment is received the remote randomization study coordinator will communicate with the NYU research pharmacy to dispense the medication.

10.6.2 Breaking the Study Blind/Participant Code

If the TP requests unblinding during the study period, we will unblind the subject and all remaining treatment decisions, including decisions on prescribing HCQ, will be at the provider's discretion. If a patient reaches the composite primary endpoint (ICU admission, ventilation, ECMO and/or hypotension requiring vasopressors) during administration of the study drug (D1-D5) s/he will be immediately unblinded and all future treatment decisions, including HCQ administration or enrollment in additional clinical trials against SARS-CoV-2, will be at the discretion of the treating providers.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at

medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) or electronic case report form (eCRF) is the primary data collection instrument for the study. We will use paper CRF in the setting that eCRF are unavailable. All data requested on the eCRF or CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, NYS DOH, other government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The guiding ethical principles of study include beneficence, nonmaleficence, autonomy and justice. We believe that our placebo arm is ethical as there is current clinical equipoise. The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

After screening, the patient will be contacted from a remote study coordinator or site investigator for enrollment in the study. Coordinators will explain the study and, if patient is agreeable, send the patient an ICF as an attachment to the patient's email for them to read thoroughly and review. Consent forms will describe in detail the study agent, study procedures, and risks and written documentation of informed consent is required prior to starting intervention/administering study product. Assent materials will be used for pediatric (7 to <18 years old) participants. Consent forms will be available in English, Spanish and Russian. The ICF and assent forms are submitted with this protocol as attachments. Of note, although the majority of enrollment and consenting will be done remotely using an electronic ICF (to protect patients, staff, and preserve personal protective equipment during the COVID-19 pandemic), the study team can enroll and consent patients during a face-to-face visit using paper ICF if needed.

In addition to the informed consent form that is signed by the potential subject or potential subject's parent/guardian, persons 7 years to < 18 years of age will be asked to review and sign an age-appropriate assent form at the time of study enrollment. Both the informed consent form and assent form (if applicable) will be signed and dated by the study team member obtaining consent and assent (if applicable) and retained in the study record. Copies of the signed, dated consent and assent forms will be provided to the subject and/or their parent/guardian.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. All participants will receive a verbal explanation during the enrollment call in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign (either print and sign or electronically sign) the informed consent document prior to any procedures being done specifically for the study. A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g., use of a translator) and the justification for such alteration will likewise be documented. The participants may withdraw consent at any time throughout the course of the trial. The investigator will explain the research study to the participant and answer any questions that may arise.

The remote coordinator will contact potential subjects (identified in EPIC or lists generated via Data Core) for screening using the phone script. If the subject qualifies and they are interested (at the end of the phone script), they will be emailed a link to the REDCap ICF. They will be asked to open the consent on their phone or computer and can read it with the coordinator. The coordinator will answer any questions the subject may have. If the subject agrees to participate, they will electronically sign and submit the consent REDCap and will have an option to download the consent form as a PDF for their records.

If the subject is interested in participating but does not have a phone or computer, or would rather perform the consent in person, the research coordinator will contact the study team to perform an in-person consent.

If the consent is obtained in-person by the study team, photos of the signed ICF will be taken using an institution-provided encrypted camera phone, and the original ICF will be provided to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.3.3 Using Legally Authorized Representative

Upon clinical assessment if patient cannot fully understand the nature and purpose of the study, the risks and benefits, and/or make a rational participation about participation, enrollment study team member will pursue Legal Authorized Representative (LAR) for consent. LAR consent will be obtained prior to enrolling patient into study.

13.4 Posting of Clinical Trial Consent Form

We will register our trial with clinicaltrials.gov. The ICF will be posted on the Federal website after the clinical trial is closed to recruitment, **and no later than 60 days after the last study visit by any subject**, as required by the protocol.

13.5 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

A minimal amount of the study participant's contact information will be stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in REDCap, a HIPAA compliant database out of NYU Langone Grossman School of Medicine. This will include a minimal amount of identifying information (MRN) to allow for data entry by study team members. No third parties will have access to this data during the entire study period. Individual participants and their research data will be identified by a unique study identification number as the primary identification. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured, encrypted, and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Grossman School of Medicine.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Most source documents will be collected in electronic form. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap, a 21 CFR Part 11-compliant data capture system provided by the NYU Division of Biostatistics. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out or 5 years after final reporting/publication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 1 working days of identification of the protocol deviation, or within 2 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. We will enroll our trial on clinicaltrials.gov.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

15 Study Finances

15.1 Funding Source

The study is funded through institutional sources. Study drug is provided by NYS Department of Health.

15.2 Costs to the Participant

There are no direct costs to the participant. Any labs drawn for research purposes will be paid for by the research study through institutional support.

15.3 Participant Reimbursements or Payments

Participants will not be reimbursed for their participation.

16 Study Administration

16.1 Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the Study Chairman, the PI of the Coordinating Center, representatives of NYS DOH, the PI of the clinical sites, and the chairperson of the Study Coordinators subcommittee. The Steering Committee will meet in person at least at the interim analysis point of the study.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NYU School of Medicine has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Informed consent form
- Assent forms
- Appendix: IND exemption form
- Appendix: Pregnant women, fetuses and neonates
- Appendix: Children
- Remote recruitment script

20 Schedule of Events

	≤72h before randomization	Active Treatment (D1-D5)	EOT (D6)[1]	PTE (D14)	End of study (D30)
STUDY TEAM EFFORT					
Study team inpatient visit	X[2]		X		
Phone follow-up				X	x
Electronic Medical Record (EMR) review	X	X	X		
ACTIVITIES					
Informed Consent[2]	X				
History taking	X				
Vital signs, including pulse oximetry	X	X	X		
12 lead ECG	X	X[5]	X		
Pregnancy test (≥12 years old, female)	X				
Safety and Inflammatory labs (CBC, CMP, CRP, Ferritin, LDH, D-Dimer, IL-6)[3]	X		X		
SARS-CoV-2 nasopharyngeal PCR	X		X		
Exploratory analysis labs (flow cytometry, antigen response, anti-SARS-CoV-2 titers, stool microbiome)[4]	X		X		
Study Drug Administration		X			
Concomitant medication monitoring	X	X (D3, D5)			
Ventilator status	X	X	X		
Cytokine release syndrome score		X (D3, D5)			
Severity score calculation	X	X (D3, D5)			
Length of stay (days)					X
Adverse Event Monitoring		X	X	X	X

[1] If patient is discharged prior to D6, the EOT visit and activities may occur on day of discharge

[2] The majority of informed consents and initial visits will be performed remotely to protect patients, staff, and preserve personal protective equipment.

[3] As part of routine clinical care or added onto remnant samples, if available

[4] Study team blood draw and stool collection on a subset (25%, N~50) of adult (≥18 years old) subjects at NYU Tisch/Kimmel

[5] Daily ECG from Day 1 to Day 5 for pediatric participants (<18 yo) while the participant remains hospitalized. Discontinue HCQ if QTc ≥ 500 ms or ΔQTc (change from baseline QTc) ≥ 60 ms.