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INTERVENTIONAL
RESEARCH PROTOCOL TEMPLATE

STUDY INFORMATION

- **Title of Project:**
  [redacted] Randomized Comparison of Combination Azithromycin and Hydroxychloroquine vs. Hydroxychloroquine Alone for the Treatment of Confirmed COVID-19
- **Principal Investigator Name**
  [redacted]
- **Principal Investigator Div. & Dept.**
  [redacted]
- [redacted]
- [redacted]
- **Protocol Version and Date:**
  Version 6.0: 08-May-2020

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[redacted]

1.0 Research Design

1.1 Purpose/Specific Aims

The purpose of this study is to explore the efficacy of Azithromycin and Hydroxychloroquine in patients with proven SARS-CoV-2 infection with symptoms consistent with COVID-19.

A. Objectives

Primary Objective:

Determine change in viral load at day 6 compared to baseline between two regimens to treat COVID-19 and a contemporaneous control group.

Secondary Objective:

- Time to resolution of symptoms (symptom questionnaire)
- Change in the fever curve resulting in shorter time to afebrile for 48 hours
- Normalization of vital signs
- Time to discharge (if hospitalized)
- Assessment of agent toxicity as measured by standard metrics
- Collection of throat swabs and blood for viral load, presence of IgM or IgG antibodies
- If feasible on samples collected for quantitative PCR decrease in virus shedding (in oropharyngeal secretions)
- Measures of cytokines in blood including IL6, IL-8, TNF, INF
- Routine standard of care labs obtained as part of the care of these patients such as differential white count, CRP, troponin and LFTs will be analyzed for correlative trends

B. Hypotheses / Research Question(s)

We propose performing a three-arm randomized trial comparing the efficacy of single agent hydroxychloroquine to the combination of hydroxychloroquine and azithromycin, and to a delayed hydroxychloroquine regimen, which will serve as a contemporaneous Day 1-6 placebo control, in eliminating detectable SARS-CoV-2 on day 6 following the initiation of treatment in order to determine which regimen is more effective.

1.2 Research Significance

COVID-19, a respiratory disease caused by the novel SARS-CoV-2 virus, appeared in Wuhan, China in late 2019 and has spread rapidly across the globe [1, 2]. This epidemic has rapidly progressed to a pandemic as declared by the WHO [3]. Experience with COVID-19 in China has demonstrated that approximately 80% of patients present with mild disease however, their data suggests an overall case-fatality rate of 2.3% which can be as high as 8.0% in patients aged 70 to 79 years and 14.8% in patients ≥80 years of age [4]. As of March 19, 2020, there are 229,289 confirmed cases and 9,324 deaths world-wide (*https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6*). The rate of increase in new cases outside of China is exponential, putting health systems across the world at risk for not being able to meet the demand for beds and intensive care. With no vaccine at present, and a vaccine unlikely to be available for 12-18 months, effective treatments to address symptomatic patients and serious hospitalized patients are critically needed.

Chloroquine (an antimalarial drug) has been shown to inhibit the growth of SARS-CoV-2 in vitro, [5]. A clinical trial conducted in COVID-19 patients in China, demonstrated a significant effect of chloroquine on clinical outcome and on viral clearance, compared to controls [6, 7]. Based on this work, experts in China have recommended that patients diagnosed with COVID-19 having mild, moderate and severe cases of

[redacted]

pneumonia and without contraindications to chloroquine, be treated with 500 mg chloroquine twice a day for ten days [8].

A group in France [9] has recently reported on a completed clinical study substituting hydroxychloroquine (an analogue of chloroquine), which has been shown to have an anti-SARS-CoV (agent of SARS in 2002) activity in vitro [10] a virus sharing significant homology with SARS-CoV-2. There is strong evidence that the safety profile of hydroxychloroquine is better than that of chloroquine allowing higher daily dosing [11] and fewer drug-drug interactions [12-16]. In this study, a total of 26 COVID-19 patients were included in a single arm trial receiving 600mg of hydroxychloroquine po daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin was also added to the treatment. Sixteen untreated patients from a second center and cases refusing to participate in the protocol were included as controls. Presence and absence of virus at Day 6-post inclusion was considered the end point. Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at day six-post inclusion compared to controls, and much lower average duration of viral carriage than that reported in the untreated patients. Of those receiving hydroxychloroquine alone, 8/14 had no evidence of virus at day six. Azithromycin [17-19] added to hydroxychloroquine was significantly more efficient for virus elimination with 0/6 patients with detectable virus on day six [9]. Based on these results we propose performing a three-arm randomized trial comparing the efficacy of single agent hydroxychloroquine to the combination of hydroxychloroquine and azithromycin as well as to a group receiving a placebo, where initiation of hydroxychloroquine treatment may begin after viral sampling on day 6. The primary endpoint in this study is a measure of success in eliminating detectable SARS-CoV-2 on day 6 following the initiation of treatment (or in the case of delayed hydroxychloroquine, the initiation of supportive care). Secondary endpoints will address questions surrounding clinical and biologic endpoints. This trial is needed in order to determine if the addition of azithromycin to hydroxychloroquine is superior in reducing viral load to hydroxychloroquine alone. At present, hydroxychloroquine is one of only a handful of agents that have shown some promise in treating COVID-19. Determining the activity of azithromycin in combination with hydroxychloroquine would be of benefit by either discovering there is improved activity, or by determining that there is little or no improvement in activity and therefore spare the logistics and expense of adding azithromycin to the regimen. The use of a short-term placebo arm where the initiation of hydroxychloroquine can begin following day 6 virus level sample collection will allow hydroxychloroquine treatment and a placebo treatment arm to be compared. This study will also provide a significant opportunity to learn more about COVID-19 and SARS-CoV-2 through the completion of the studies supporting the secondary endpoints.

1.3 Research Design and Methods

This is a randomized trial conducted by the Rutgers Cancer Institute of New Jersey and at NJMS/University Hospital Newark), which will prospectively enroll 160 patients with proven SARS-CoV-2 infection by qPCR assay with symptoms consistent with COVID-19 such as a fever of $\geq$ 100.6. This study will evaluate the efficacy of Azithromycin and Hydroxychloroquine in this patient population. Study participants will be randomized to 1) Azithromycin and Hydroxychloroquine; 2) Hydroxychloroquine alone; or 3) placebo for 6 days followed by hydroxychloroquine. Treatment with the investigational agents will continue for 10 days. Viral loads will be collected to monitor response to treatment at baseline and on day 3 and day 6.

[redacted]

A. Research Procedures

1. Study Procedures:

- ***Day 0 – Screening Visit:***
  - Obtain informed consent for trial enrollment
  - Demographic data
  - Medical history
  - Physical examination
  - Vital signs (blood pressure, heart rate, temperature)
  - Document disease severity (mild, moderate or severe)
    - Severity Assessment Criteria
      - Temp >100.5°F (1 point)
      - Fatigue (1 point)
      - Cough (1 point)
      - Shortness of breath (1 point)
      - Heart rate >90 BPM (2 points)
      - Respiratory rate > 14 breathes/min (2 points)
      - Pulse Ox < 94% on room air (3 points)
      - Blood pressure < 90/60 (3 points)

      Score:
      Mild/Moderate = 0-7 points
      Severe = 8-15 points
  - Document location of patient (inpatient versus outpatient)
  - Review eligibility criteria
  - Complete baseline COVID signs and symptoms questionnaire (Appendix C)
  - Electrocardiogram. The QT corrected interval may be calculated by either Bazett's, Fridericia's, or Framingham's formula.
    - Bazett's formula: $QTc = QT/\sqrt{(RR \text{ in seconds})}$
    - Fridericia's formula: $QTc = QT/RR^{0.33}$
    - Framingham's formula: $QTc = QT + 0.154 (1-RR)$
  - Labs: CBCD, Ferritin, D-Dimer, LDH, CRP and Troponin (8 mL); urine or serum pregnancy test for women of childbearing potential
  - Concomitant medications (starting from the time the patient signs the informed consent)
  - Collect research specimens: saliva, oropharynx swab and whole blood (16 mL)
  - Randomize study participant through OnCore®
  - Dispense study medication
  - Provide education to patient on how to complete pill diary and temperature log. Each subject will receive an electric thermometer for use.

- ***Treatment Period – For those study participants randomized to Arm 1 and Arm 2:***
  - Days 1 - 10
    - Study participant doses self with prescribed study medications (unless inpatient)
    - Assessment completed by Research Nurse. May be conducted by phone.
      - Complete follow-up COVID signs and symptoms questionnaire (Appendix D)
      - Review of daily temperatures
      - Review of medication compliance

[redacted]

- Adverse events
- Record standard of care treatments and/or procedures prescribed

- Day3 or 4 and Day 6
  - Repeat physical examination
  - Labs: CBCD, Ferritin, D-Dimer, LDH, CRP and Troponin (8 mL) (Day 6 only)
  - Collect research specimens: saliva, oropharynx swab and whole blood (16 mL)
- Day 10 (+/- 1 day)
  - Repeat physical examination
  - Labs: CBCD, Ferritin, D-Dimer, LDH, CRP and Troponin (8 mL)

- Day 11-20 – Daily Follow-up
  - Assessment completed by Research Nurse. May be conducted by phone.
  - Review of symptoms
  - Review of daily temperatures
  - Adverse events
  - Record standard of care treatments and/or procedures prescribed

- ***Treatment Period – For those study participants randomized to Arm 3:***
  - Days 1 - 5
    - Study participant doses self with prescribed study medications (placebo), unless inpatient.
    - Assessment completed by Research Nurse. May be conducted by phone.
    - Complete follow-up COVID signs and symptoms questionnaire (Appendix D)
    - Review of daily temperatures
    - Review of medication compliance
    - Adverse events
    - Record standard of care treatments and/or procedures prescribed

  - Day3 or 4 and Day 6
    - Repeat physical examination
    - Labs: CBCD, Ferritin, D-Dimer, LDH, CRP and Troponin (8 mL) (Day 6 only)
    - Collect research specimens: saliva, oropharynx swab and whole blood (16 mL)
    - If patient continues to have symptoms of COVID-19 on Day 6, will initiate Hydroxychloroquine sulfate for home administration.

  - Day 10
    - Repeat physical examination
    - Labs: CBCD, Ferritin, D-Dimer, LDH, CRP and Troponin (8 mL)

  - Day 11-15
    - Study participant doses self with prescribed study medications (unless inpatient)
    - Assessment completed by Research Nurse. May be conducted by phone.
      - Complete follow-up COVID signs and symptoms questionnaire (Appendix D)
      - Review of daily temperatures

[redacted]

- Review of medication compliance
- Adverse events
- Record standard of care treatments and/or procedures prescribed

- Day 15-20 – Daily Follow-up
  - Assessment completed by Research Nurse. May be conducted by phone.
  - Review of symptoms
  - Review of daily temperatures
  - Adverse events
  - Record standard of care treatments and/or procedures prescribed

- ***Follow-up Period for All Arms***
  - Weekly Follow-up for Four (4) Weeks (+/- one day) from last dose of treatment
    - Assessment completed by Research Nurse. May be conducted by phone.
    - Review of symptoms
    - Review of daily temperatures
    - Adverse events
    - Record standard of care treatments and/or procedures prescribed

  - Monthly Follow-up for Six (6) Months (+/- one week)
    - Assessment completed by Research Nurse. May be conducted by phone.
    - Review of symptoms
    - Review of daily temperatures
    - Adverse events
    - Record standard of care treatments and/or procedures prescribed

2. Treatment Plan:

- *Dosage and Administration*

  Arm 1: Hydroxychloroquine sulfate 200 mg po TID X 10 days
  Azithromycin 500 mg po on day one, followed by 250 mg po QD X 4 days

  Arm 2: Hydroxychloroquine sulfate 200 mg po TID X 10 days

  Arm 3: Placebo Days 1-6, following viral sampling on day 6
  Hydroxychloroquine sulfate 200 mg po TID x 10 days

- *Dose Modification:*
  - Hydroxychloroquine
    - For grade 1 or 2 intolerability: allow patient to hold one dose and resume as tolerated without adjustment
    - For grade 3 or 4 toxicity: hold one dose and resume at BID dosing to complete the original 10 days of dosing
    - For second episode grade 3 or 4 toxicity: hold next dose and resume at once daily dosing to complete the original 10 days of dosing.

Hydroxychloroquine sulfate
One hydroxychloroquine sulfate tablet contains 200 mg of hydroxychloroquine sulfate, which is the equivalent to 155 mg base.

[redacted]

For this study, dosing will be 200 mg TID PC x 10 days with or without azithromycin (depending on randomization).

Take hydroxychloroquine sulfate tablets with a meal or a glass of milk when permissible.

Azithromycin
For this study, dosing will be azithromycin 2 x 250 mg (500 mg) on Day 1, followed by 1 x 250 mg daily x 4 (D2 thru 5) with HCQ 200 mg TID PC x 10 days beginning on Day 1 (depending on randomization).

Placebo
Arm 3 only. For this study, participants will be provided 30 placebo tablets to maintain the blind between Arm 2 and Arm 3. Dosing will be placebo tablet x 3 daily (D1 thru 6).

Concomitant Medications & Supportive Guidelines
Study participants can receive full supportive care therapies concomitantly during the study. Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient from ≤ 7 days prior to the first dose of study drug to the end of treatment visit. All concomitant therapy, including vitamins, homeopathic/herbal remedies, nutritional supplements, must be recorded during the screening and treatment period, starting from the date of signature of informed consent, and ending at the End of Treatment (EOT) visit.

B. Subject Enrollment
Patients who are eligible for the study will be enrolled in the clinical trial after they provide informed consent for study participation. A copy of the institution's IRB approved informed consent will be on file at Rutgers Cancer Institute of New Jersey's Office of Human Research Services (OHRS) before any participating institutions may enter patients.

Sites will register and enroll patients through OnCore® the Clinical Trials Management System for this study. Contact the Rutgers Cancer Institute of New Jersey's OHRS Registration Desk (732) 235-4745 if you have any questions about the Registration/Enrollment process.

- Registration: Any subject that has signed the consent will be entered into OnCore®. A Copy of the consent will be uploaded into the Documents section.
- Enrollment: Once eligibility has been confirmed, the completed, signed and dated eligibility checklist will be uploaded into the Documents section. OnCore® will randomize the patient and a sequence number (subject study ID) will be generated at the time of enrollment, this is the point the patient is considered on study.

Patients will <u>not</u> start protocol treatment prior to registration.

C. Study Safety Assessments
The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

1. Definitions:
   - <u>Adverse Events</u>:
     An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a

[redacted]

pharmaceutical product, whether considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

- Serious Adverse Events:
  A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfills one or more of the following criteria:
  - Results in death
  - Is immediately life-threatening
  - Requires in-patient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability or incapacity
  - Is a congenital abnormality or birth defect
  - Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.
  - The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to the FDA via MedWatch form, if applicable.

2. Recording of Adverse Events
   Non-serious adverse events and SAEs will be determined from the time treatment starts and up to and including the 6-month follow-up period. All grade 3 or higher AEs will be recorded. Grade 1 AEs do not need to be recorded. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for 180 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs, they must be reported to the CINJ Data Safety Monitoring Committee (HROC) and Rutgers IRB as per SOPs.). AEs will be recorded per CINJ SOPs.

   All study-related toxicities/ SAEs must be followed until resolution, unless in the Treating Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

3. Reporting of Serious Adverse Events
   Investigators and other site personnel must inform the CINJ HROC and Rutgers IRB per the CINJ SOPs on the required forms. FDA will be informed per SOP, via a MedWatch, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32. It is the responsibility of the principal investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines.

   All SAEs meeting the criteria for expedited reporting will be reported to the Rutgers IRB within the mandated time frames. All SAEs within the safety follow-up window (e.g., within 30 days after the last dose of study medications) established in the protocol will be reported.

[redacted]

[redacted]

[redacted]

Non-serious adverse events and SAEs will be collected from the time treatment starts, throughout the treatment period and up to and including the 6-month follow-up period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for 28 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs, then they must be reported to the FDA as per their reporting criteria). All study-related toxicities/ SAEs must be followed until resolution, unless in the Treating Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

4. Clinical Safety Assessments
   - Recording of Adverse Events
     Non-serious adverse events and SAEs will be determined from the time the study drug is given, throughout the treatment period and up to and including the 6-mont follow-up period. All grade 3 or higher AEs will be recorded. Grade 1-2 AEs do not need to be recorded. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for 28 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs, they must be reported to the CINJ Data Safety Monitoring Committee (HROC) and Rutgers IRB as per SOPs.). AEs will be recorded per CINJ SOPs.

   - Adverse Events Based on Signs and Symptoms
     When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

   - Vital Signs
     Temperature will be obtained four times a day (first thing in AM, mid-day, PM, and bedtime). Significant abnormalities will be recorded as an AE. Body temperature will be measured in degrees Fahrenheit using an automated thermometer which will be provided to the patient.

5. Study Efficacy/Response Assessments
   - Quantitative PCR measurements of viral load at baseline, Day 3 and Day 6. Day 6 measurement compared to baseline will serve as the study endpoint. Other response criteria used as secondary endpoints include change in temperature curve over time, change in measured cytokines (IL6) and improvement in clinical symptoms as determined by clinician assessment and patient questionnaire.

D. Data Points

Case Report Forms

Completion of the electronic case report forms (eCRFs) will be done in accordance with the instructions outlined in the study specific data capture plan. All eCRFs are considered the primary data collection document for the study and are stored in OnCore® in a confidential format. Only key personnel who are delegated in the delegation of authority log are permitted to make entries,

[redacted]

changes, or corrections in the eCRF. All users of OnCore® will complete user training, as required or appropriate per regulations. An audit trail will be maintained automatically by the electronic CRF management system.

Data Points to be collected:

- Baseline medical history
- Treatment compliance
- Daily temperatures
- Symptoms of disease
- Adverse events
- Concomitant medications
- Any standard of care treatments or procedures to manage COVID-19

Data Submission Timeline and Forms
Completion of eCRFs will occur within 72 hours of study time point unless otherwise indicated. Baseline (pre-study) eCRFs (e.g., enrollment, medical history, concomitant medications, etc.) will be completed no later than 24 hours after the start of treatment.

E. Study Duration
Study participants will be treated for ten (10) days and will then remain on follow-up for up to 6 months after the completion of treatment. The estimated time to complete the entire study is 8 months (November 2020).

We will account for all the patients registered in the study. The number of patients who were not evaluable, who died or withdrew before treatment was completed will be specified. The distribution of follow-up time will be described and the number of patients lost to follow-up will be given.

F. Endpoints
Primary endpoint:

1. Change in viral load at day six compared to baseline between hydroxychloroquine sulfate alone and hydroxycholorquine sulfate plus azithromycin to treat COVID-19. A second concurrent comparison will evaluate change in viral load at day 6 between hydroxychloroquine sulfate alone and a placebo.

Secondary endpoints (descriptive, not driving statistics):

1. Time to resolution of symptoms (symptom questionnaire)
2. Change in the fever curve resulting in shorter time to afebrile for 48 hours
3. Improvement in vital signs
4. Time to discharge (if hospitalized)
5. Time to recovery (back to work, school etc...)
6. Assessment of agent toxicity as measured by standard metrics
7. Collection of oropharynx swab and blood for viral load and microbiome analysis
8. Decrease in virus shedding (in nasopharyngeal secretions) and serology
9. Measures of cytokines in blood including IL6, IL8, TNF and INF
10. Measures of inflammatory markers such as ferritin, D-Dimer, CRP, Troponin and LDH

1.4 Preliminary Data
There is data supporting the antiviral activity of both hydroxychloroquine and azithromycin as single agents, but not much experience with the combination. In a recently completed trial [9] patients with COVID-19 (n=14) received hydroxychloroquine alone at the same dose and frequency proposed in this

[redacted]

study. For these patients, 8/14 had no detectable virus at day 6 by PCR quantification. In a smaller group of six patients receiving the combination of hydroxychloroquine and azithromycin at the doses and frequency proposed in this study, 6/6 had no detectable virus at day 6 by PCR quantification. It is this very preliminary, pilot observation in a very small number of patients that were not stratified or randomized that will be evaluated in this larger prospective randomized study.

1.5 Sample Size Justification

Randomized clinical trial comparing hydroxychloroquine with or without azithromycin in patients with the COVID-19 disease, with the addition of a third arm with a placebo and delayed hydroxychloroquine. Here we follow Gautret et al. [9] in using, as a primary endpoint, absence of viral evidence of disease six days following start of treatment. In that study (Table 3 of ref 9), there were 14 patients treated with hydroxychloroquine alone, and 8/14 (57.1 percent) of them were virus-free at 6 days. There were six patients treated with both hydroxychloroquine plus azithromycin, and all six (100%) were virus-free at 6 days. In a third group of patients with no hydroxychloroquine, there were 16 patients, of whom 2 (12.5 percent) were virus-free at 6 days. We propose a three-arm trial as follows: Arm 1 (HCQ + AZ), Arm 2 (HCQ alone), and Arm 3 (delayed HCQ), with patients randomized 2:2:1.

The primary outcome is a comparison of Arm 1 to Arm 2, with the aim of determining if the addition of AZ is effective. Using the proportion of patients that are virus-free at 6 days as the primary endpoint of the study, and assuming that the proportion of patients in the hydroxychloroquine arm who are virus free at 6 days is 0.571, the following table shows the detectable proportion virus-free in the combination arm with 80% power. These samples sizes are with a 5% level two-sided test of proportions.

Proportion virus-free HCQ only	Proportion virus-free HCQ plus AZ	Proportion difference	Patients per rm
0.571	0.821	0.250	52
0.571	**0.805**	**0.234**	**60**
0.571	0.771	0.200	85
0.571	0.721	0.150	158

For example, if we enroll 60 patients per arm, we could detect, with 80% power, an increase in the proportion of virus-free patients from 57.1% in the hydroxychloroquine arm to 80.5% in the combination arm.

The two-sided Type I error probability associated with this test is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis.

A second, independent goal of the study is to ensure that, in fact, hydroxychloroquine is effective in reducing viral load. Thus, we plan a third, control arm, in which patients will receive a placebo for six days, at which time they will switch to receiving HCQ. We plan to compare Arms 2 and 3, with the control (Arm 3) having half the sample size of Arm 2. Based on the Gautret et al. study, we assume the baseline proportion of patients who are virus-free at six days is 0.125. The following table shows the detectable difference with a variety of baseline rates:

Proportion virus-free HCQ only	Proportion virus-free HCQ plus AZ	Proportion difference	Patients per rm

[redacted]

0.125	0.401	0.276	60
0.150	0.434	0.280	60
0.200	0.497	0.290	60
0.250	0.554	0.304	60

Thus, for a range of plausible virus-free rates for the control arm, the detectable rate for the HCQ arm is well within the range reported by Gautret et al. [9]. With this three-arm study, we will need 60 patients in each of the first two arms and 30 in the control arm, for 150 in total.

A key secondary endpoint will be the number of days from initiation of therapy to VND (virtually no disease). This can be displayed graphically using Kaplan-Meier survival curves, and formally assessed using a log-rank test. Other secondary endpoints that can be assessed in this way are (1) Time in days to being afebrile for 48 hours, (2) time in days to resolution of symptoms (as assessed by a symptom questionnaire), (3) time in days to discharge (if hospitalized), and (4) time to recovery (able to return to work or school). Other measures that will be assessed via descriptive statistics are agent toxicity and improvement over time in vital signs.

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables
The following variables will be examined for treatment outcomes of efficacy and/or predict outcomes:

- Treatment
- Baseline temperature
- Baseline viral loads
- Baseline measures of cytokines
- Baseline measure of inflammatory markers

B. Dependent Variables or Outcome Measures
The following variables will be examined for changed as result of treatment or as predictors

- Treatment Compliance
- Change in the fever curve
- Improvement in vital signs
- Time to discharge (if hospitalized)
- Adverse Events (number/percentage/grade)
- Inpatient versus Outpatient
- Mild to Moderate disease versus Severe disease
- Change from baseline viral loads
- Change from baseline inflammatory markers

1.7 Drugs/Devices/Biologics

Generic name: Azithromycin
Commercial name: Zithromax, Zmax

For complete information please refer to the package inserts at
https://dailymed.nlm.nih.gov/dailymed/azithromycin

[redacted]

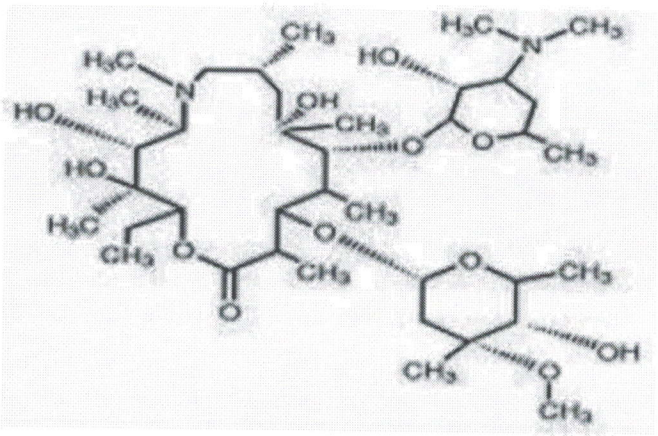
[redacted]

[redacted]

Chemical name: (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl) oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one

Azithromycin Tablets USP contain the active ingredient azithromycin, USP, a macrolide antibacterial drug, for oral administration. Azithromycin, USP is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring.

Source: Commercially available



C38H72N2O12 M.W. 749

Azithromycin, USP, as the monohydrate, is a white crystalline powder with a molecular formula of C38H72N2O12•H2O and a molecular weight of 767. Azithromycin Tablets USP are supplied for oral administration as tablets containing azithromycin monohydrate equivalent to either 250 mg or 500 mg azithromycin, USP.

Pharmacokinetics: Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were AUC0-72 = 4.3 (1.2) mcg·hr/mL; Cmax= 0.5 (0.2) mcg/mL; Tmax = 2.2 (0.9) hours. Two azithromycin 250 mg tablets are bioequivalent to a single 500 mg tablet.
Elimination: Plasma concentrations of azithromycin following single 500 mg oral and IV doses declined in a polyphasic pattern resulting in a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hr. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine. The mean Cmax and AUC0-120 increased 61% and 35%, respectively, in subjects with severe renal impairment (GFR < 10 mL/min) compared to subjects with normal renal function (GFR > 80 mL/min).

Contraindications:

[redacted]

[redacted]

[redacted]

sensitivity: Azithromycin tablets are contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.

Hepatic Dysfunction: Azithromycin tablets are contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

Warnings:

Hypersensitivity: Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in patients on azithromycin therapy. Fatalities have been reported. Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that allergic symptoms may reappear when symptomatic therapy has been discontinued.

Hepatotoxicity: Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Contact their physician if vomiting or irritability with feeding occurs.

QT Prolongation: Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during post marketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmia's or uncompensated heart failure
- patients on drugs known to prolong the QT interval
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

***Clostridium difficile*-Associated Diarrhea (CDAD)**: *Clostridium difficile*-associated diarrhea has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*.

Exacerbation of Myasthenia Gravis: Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.

Development of Drug-Resistant Bacteria: Prescribing azithromycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug interactions: Nelfinavir, Warfarin.

[redacted]

[redacted]

[redacted]

Potential Drug-Drug Interaction with Macrolides: Interactions with digoxin, colchicine or phenytoin have not been reported in clinical trials with azithromycin. No specific drug interaction studies have been performed to evaluate potential drug-drug interaction. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when digoxin, colchicine or phenytoin are used with azithromycin careful monitoring of patients is advised.

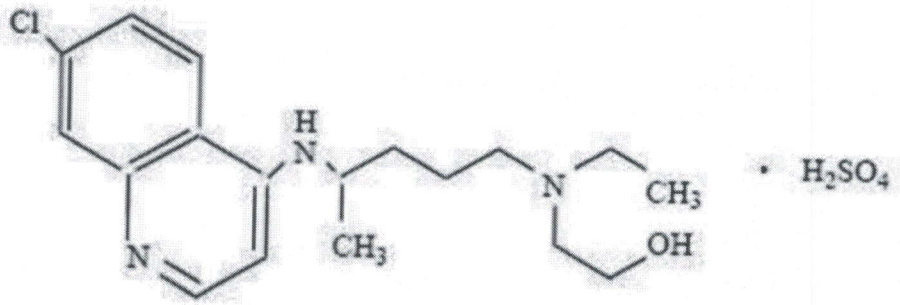
Availability: FDA approved; commercially available azithromycin will be supplied free of charge to all patients enrolled.

Generic name: Hydroxychloroquine sulfate
Commercial name: Plaquenil

For complete information please refer to the package inserts at
http://dailymed.nlm.nih.gov/dailymed/Hydroxychloroquine

Chemical name: 7-Chloro-4-[4-[ethyl-(2-hydroxyethyl)amino]-1-methylbutylamino] quinolone

Source: Commercially available



C18H26ClN3O•H2SO4 Molecular Weight: 433.95

Hydroxychloroquine sulfate tablets, USP contain 200 mg hydroxychloroquine sulfate, equivalent to 155 mg base, and are for oral administration.

Pharmacokinetics: Following a single 200 mg oral dose of hydroxychloroquine sulfate to healthy males, the mean peak blood concentration of hydroxychloroquine was 129.6 ng/mL, reached in 3.26 hours with a half-life of 537 hours (22.4 days). In the same study, the plasma peak concentration was 50.3 ng/mL reached in 3.74 hours with a half-life of 2963 hours (123.5 days). Urine hydroxychloroquine levels were still detectable after 3 months with approximately 10% of the dose excreted as the parent drug. Results following a single dose of a 200 mg tablet versus I.V. infusion (155 mg), demonstrated a half-life of about 40 days and a large volume of distribution.

Mechanism of Action: The precise mechanism by which hydroxychloroquine exhibits activity against *Plasmodium* is not known. Hydroxychloroquine, like chloroquine, is a weak base and may exert its effect by concentrating in the acid vesicles of the parasite and by inhibiting polymerization of heme. It can also inhibit certain enzymes by its interaction with DNA.

[redacted]

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[redacted]

Warnings:

Ocular: Irreversible retinal damage has been observed in some patients who had received hydroxychloroquine sulfate. Significant risk factors for retinal damage include daily doses of hydroxychloroquine sulfate greater than 6.5 mg/kg (5 mg/kg base) of actual body weight, durations of use greater than five years, subnormal glomerular filtration, use of some concomitant drug products such as tamoxifen citrate and concurrent macular disease.

Cardiac Effects, including Cardiomyopathy and QT prolongation: Post-marketing cases of life-threatening and fatal cardiomyopathy have been reported with use of hydroxychloroquine sulfate as well as with use of chloroquine. Hydroxychloroquine sulfate prolongs the QT interval. Ventricular arrhythmias and torsades de pointes have been reported in patients taking hydroxychloroquine sulfate (see OVERDOSAGE). Therefore, hydroxychloroquine sulfate should not be administered with other drugs that have the potential to prolong the QT interval.

Worsening of psoriasis and porphyria

Proximal Myopathy and Neuropathy

Neuropsychiatric events, including suicidality

Hypoglycemia: Hydroxychloroquine sulfate has been shown to cause severe hypoglycemia including loss of consciousness that could be life threatening in patients treated with or without antidiabetic medications

General precautions: General: Use with caution in patients with gastrointestinal, neurological, or blood disorders, and in those with a sensitivity to quinine.

Hepatic/Renal Disease: Antimalarial compounds should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs. A reduction in dosage may be necessary in patients with hepatic or renal disease, as well as in those taking medicines known to affect these organs.

Hematologic Effects/Laboratory Tests: Antimalarial compounds should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs. Periodic blood cell counts should be performed if patients are given prolonged therapy.

Hydroxychloroquine sulfate should be administered with caution in patients having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

Dermatologic Effects: Dermatologic reactions to hydroxychloroquine sulfate may occur and, therefore, proper care should be exercised when it is administered to any patient receiving a drug with a significant tendency to produce dermatitis.

Drug Interactions (include but not limited to): Digoxin, Insulin or antidiabetic drugs, Drugs that prolong QT interval and other arrhythmogenic drugs, Mefloquine and other drugs known to lower the convulsive threshold, Antiepileptics, Methotrexate, Cyclosporin, Praziquantel, Antacids and kaolin, Cimetidine, Ampicillin.

[redacted]

[redacted]

[redacted]

Availability: FDA approved; commercially available hydroxychloroquine sulfate will be supplied free of charge to all patients enrolled.

Generic name: Microcrystalline Cellulose
Commercial name: Placebo
Source: Commercially available

The placebo for tablet is formulated for oral administration. Placebo tablets are blue, film coated tablets with K20 debossed on one side to match the active formulation. Tablets will be provided in polyvinyl chloride (PVC) / polyethylene (PE) polychlorotrifluoroethylene (PCTFE) film blisters with a paper-backed foil and a secondary wallet for distribution to patients in clinical trials.

Composition:

Component	Standard	Strength (20 mg)	
		Quantity per Unit (mg)	% (w/w)
Intragranular			
Microcrystalline Cellulose (Avicel PH102)	NF	155.2	97.0%
Croscarmellose Sodium (Ac-Di-Sol)	NF, EP, JP	3.200	2.00%
Magnesium Stearate (non Bovine)	NF, EP	1.600	1.00%
Total	-	**160.0**	**100%**
Top-coat			
Opadry II Blue	Professed	4.800	ca. 3.0%
Purified Water[b]	USP, EP	N/A[a]	N/A
Purified Water (Packaged)[b]	USP	N/A[a]	N/A

Abbrev = ca., approximately; EP, European Pharmacopeia; NF, National Formulary; JP, Japanese Pharmacopeia

a. Removed during processing.
b. Either Purified Water (USP, EP) or Packaged Purified Water (USP) may be used during processing.

Opadry II Blue contains polyvinyl alcohol (USP, FCC, PhEur, JPE), titanium dioxide (USP, FCC, PhEur, JP), polyethylene glycol [macrogol] (NF, FCC, PhEur, JECFA, JP), talc (USP, FCC, PhEur, JP), FD&C Blue #2 (indigo carmine aluminum lake), FD&C Blue #1 (brilliant blue FCF aluminum lake), and FD&C Yellow #5 (tartrazine aluminum lake).

A. Drug/Device Accountability and Storage Methods

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

B. Treatment Compliance

The study medication will be given in accordance with the protocol and the instructions of the treating investigator. For those subjects who are treated as an outpatient, the study drugs will be provided to patients to be self-administered. Patients will be asked to bring the remaining trial medication to each visit for a compliance check. The remaining tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. A pill diary will be provided and must be completed by the patient to document treatment course.

1.8 Specimen Collection

A. Primary Specimen Collection

The research samples collected will be studied using standard laboratory assays for:

1. Viral load
2. Measurements of inflammatory cytokines in blood such as IL-6, IL-8, IL-1, TNF, INF using standard ELISA protocols.
3. Serology for presence of antibodies to SARs-CoV-2 and appropriate controls, measuring IgG and IgM. We will also assess for general antigens specific for SARS-CoV-2, as well as neutralizing epitopes.

- **Types of Specimens**:
  - Peripheral blood for whole blood, plasma, serum and buffy coat will be collected at baseline, day 3 or 4 and day 6.
  - Oropharynx swabs will be collected at baseline, day 3 or 4 and day 6.
  - Saliva will be collected at baseline, day 3 or 4 and day 6.

- **Annotation**: The specimens will be de-identified by the CINJ Biorepository and assigned a Patient ID, specimen ID, and date of collection. Assigned ID's will only be able to be associated with patient data by approved users in the OnCore® clinical trial tracking system. No other identifiers will accompany the specimens to their respective analysis laboratories.

- **Transport**: Samples will be transported to the BRS by trained personnel. Following processing, blood and samples will be stored until shipped by BRS in patches to the RUCDR Biologics, 145 Bevier Road, Piscataway, NJ 08854.

- **Processing**: Please refer to the Correlative Lab manual for sample collection, labeling, and shipping instructions.

- **Storage**: All samples will be processed by BRS and transported to RUCDR for analysis and storage.

- **Disposition**: Analysis will occur at the end of the study/accrual period. Specimens will be banked for future use as part of the analysis process for future correlative studies related to this project. Please review to Protocol **Section 7.0 Research Repository.**

B. Secondary Specimen Collection

N/A

1.9 Data Collection

A. Primary Data Collection

[redacted]

[redacted]

[redacted]

Electronic case report forms (eCRFs) have been designed to collect the data points outlined in section 1.3 (D). Completion of the electronic CRFs (eCRFs) will be done in accordance with the instructions in a study specific data capture plan. All eCRFs will be complete by the research staff of the Office of Human Research Services (OHRS) at the Cancer Institute of New Jersey. The eCRFs will be maintained in a confidential format in the OnCore® database.

B. Secondary Data Collection
N/A

1.10 Timetable/Schedule of Events
Please refer to Appendix A. All study procedures will be performed according to the schedule outlined in the Study Flow Table

2.0 Project Management

2.1 Research Staff and Qualifications
[redacted]

2.2 Research Staff Training
All research team members will complete the required Human Subject Protection training through the Collaborative Institutional Training Initiative (CITI) Program prior to being approved to take part on this study. All study will attend the site initiation visit for training about the study specific protocol.

The Principal Investigator will provide oversight and ensure that the study is conducted according to the investigational plan and applicable regulations in accordance with 21 CFR 312.

2.3 Resources Available
Azithromycin and hydroxychloroquine sulfate will be provided at no charge to the study participants.

2.4 Research Sites
[redacted]

3.0 Multi-Center Research
The Statewide Research Office oversees multi-center studies. Activation meetings are conducted prior activation of each study. These meetings are conducted on-site via Webinar to review the protocol with the local Principal Investigator and/or his/her research staff. Information reviewed includes the procedures for centralized patient registration, completion of the electronic case report forms, data submission expectations, adverse event reporting requirements, and any other study-specific issues. If investigational drugs are provided, then proper drug accountability procedures are reviewed with the pharmacist.

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[redacted]

clinical research administration and coordination to assist with IRB compliance, patient enrollment, data collection, and toxicity reporting for the sites through OnCore®.

The Quality Assurance and Data Monitoring Office of the OHRS is responsible for monitoring visits and audits of data at the system sites. Monitoring is based on level of risk but occur at a minimum of an annual basis or after enrollment of the first two patients. The monitoring visits and audits occur with the purpose of verifying that documentation in the medical and research records support data recorded in the electronic case report forms located in OnCore®. Adherence to the protocol eligibility, treatment plan, response and toxicity evaluation, and SAE reporting criteria are reviewed. The appropriate documentation of informed consent and documentation of administration of protocol therapy for all enrolled patients are reviewed.

All monitoring visit and audit findings are reviewed with the research staff and PI. Unacceptable monitoring visit findings are immediately communicated to HROC. All written reports are presented to the HROC and subsequently to the IRB.

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects

An IRB approved press release will be distributed to Rutgers physicians through the Rutgers Communications Office. The press release will include a telephone number for potential study participants to call. The potential study participants will be instructed to visit the study site closest to their home.

Potential study participants will also be identified by the treating physician-investigator from new patient referrals.

Both locations have identified a segregated location to screen potential subjects for the trial. Screening at both locations will be conducted by to be named Advanced Practice Nurse and Research Nurse. All research personnel will wear appropriate PPE as outlined

B. Recruitment Details

The subjects will be adults age 18 years and older with a diagnosis of COVID-19 and a confirmed positive test for SARS-CoV-2 my any accepted method. Potential study participants will be recruited by the treating physician-investigator and approached for study participation during consultation for treatment and management of their disease. The discussion will take place in a private room. The patient will also meet with the research team to review each page of the informed consent document.

This study will be available to all patients who meet the eligibility criteria. There will be no limitation to access with regards to race or gender. Patients will be required to sign an IRB-approved informed consent form prior to commencing any research related activity.

C. Subject Screening

Patients that lack decision-making capacity will not be approached to participate in this study. The treating investigator and research team will interview the patient and review the chart to

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[redacted]

determine if the patient is a potential candidate for the study. Screening tests to confirm whether subjects are eligible for inclusion in this study will be conducted including SARS-CoV-2 test if not already confirmed to be positive. The Principal Investigator, or designee, will be responsible for reviewing and confirming subject eligibility prior to enrollment to the study.

Subjects who do not meet all inclusion criteria will be recorded as screen failures in OnCore®.

- **Inclusion Criteria**
  1. Patients with proven SARS-CoV-2 infection by an accepted assay with symptoms consistent with COVID-19
  2. Ability to measure and quantify viral load by quantitative PCR
  3. Age 18 to 89
  4. Ability to swallow oral medications
  5. Patients must read, understand and sign IRB approved informed consent

- **Exclusion Criteria**
  1. Pregnancy or women who are breast feeding
  2. Two consecutive negative assays for SARS-CoV-2 infection
  3. Patients that lack decision-making capacity will not be approached to participate in this study
  4. Inability to tolerate oral medications
  5. Allergy or prior adverse reaction to either azithromycin or hydroxychloroquine sulfate
  6. QTc interval $\geq$ 470 Msec
  7. Conditions potentially resulting in drug-induced prolongation of the QTc intervals:
     a. Congenital or acquired long QTc syndrome
     b. Family history of sudden death
     c. History of previous drug-induced QTc prolongation
     d. Current use of medications with possibly or know risk of QTc prolongation (see Appendix B Drugs associated with a known or possible risk of QTc prolongation)
  8. History of ongoing ventricular cardiac dysrhythmias of grade 2 as described by NCI CTCAE 5.0 criteria
  9. History of serious ventricular arrhythmia (VT or VF > 3 beats in a row)

4.2 Secondary Subjects

N/A

4.3 Number of Subjects

A. Total Number of Subjects

[redacted]

B. Total Number of Subjects if Multicenter Study

N/A.

C. Feasibility

Given the current incident rate, is anticipated that enrollment will be completed within 30-40 days.

4.4 Consent Procedures

[redacted]

A. Consent Process

Provision of written or verbal Informed Consent will be obtained prior to any study-related procedures. The Investigator will ensure that the study participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Study participants will also be notified that they are free to discontinue from the study at any time. The study participant will be given the opportunity to ask questions and allowed time to consider the information provided. The original, signed written Informed Consent Form will be given to the study participant.

Current FDA, OHRP, NIH, state and institutional regulations concerning informed consent will be followed. An IRB approved written informed consent document that embodies the elements of informed consent is required 45CFR46.116.

1. The investigator shall explain participation is voluntary and all aspects of the study, purpose of the study, treatment plan, procedures, risks, benefits, alternatives, and the right to refuse and withdraw at any time without penalty in lay language.
2. The investigator will answer all the patient's questions regarding the study.
3. The investigator shall give the patient adequate opportunity to read the consent form and to discuss with family and friends.
4. If the patient decides to participate in the study, he/she will be asked to sign the Informed Consent Document. A copy of the signed Informed Consent Document will be given to the patient and this will be documented in the patient's medical record.
   - 4.1 Patients who are unable to read the consent an impartial witness who is independent of the trial will attend the informed consent process and reads the informed consent and other written information supplied to the patient. The impartial witness will sign the informed consent form. A copy of the signed Informed Consent Document will be given to the subject and this process will be documented in the patient's medical record.
5. The investigator shall inform all patients they have the right to refuse study participation and withdraw their participation at any time without penalty and will be treated without prejudice.

- **Location of Consent Process**
  The consent form will be reviewed by the investigator, or a delegated study member, in the clinic or hospital room. Study participants must sign the consent in person at the participating institution. If the patient wishes to enroll on the study, he or she will sign the informed consent in the presence of a physician or nurse on the study team.

- **Ongoing Consent**
  If there are any changes to the protocol, these changes will have to be first reviewed and approved by the Rutgers IRB via an amendment before any change is implemented. Once approved, study participants will be notified of the protocol changes and will be provided with the updated informed consent form (ICF) for their signature, if necessary. Study participants will also be provided with a copy of the updated ICF for their records whenever re-consent is required.

- **Individual Roles for Researchers Involved in Consent**
  Only a treating investigator or research nurse listed within the IRB application will consent study participants to this study.

- **Consent Discussion Duration**
  It is anticipated that the informed consent process will take 30-60 minutes.

- **Coercion or Undue Influence**

[redacted]

This study requires study participants to provide consent. Adults unable to consent or cognitively impaired adults will not be eligible for this study. The treating physician and/or research nurse will explain to the study participant that participation in this study is completely voluntary and the study participant can withdraw at any time.

- **Subject Understanding**
  The treating investigators will seek consent only under circumstances that provide the prospective study participant the opportunity to consider whether to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient will be in a language understandable to the patient. Sufficient time will be allowed for questions to be asked and answered, both by the patient and the individual obtaining consent to ensure the patient comprehends the consent information.

B. Waiver or Alteration of Consent Process
N/A

C. Documentation of Consent

- **Documenting Consent**
  Written informed consent is required. Informed consent must be obtained prior to commencing any research procedures. Informed consent will be documented in accordance with 21CFR50.27; it shall be documented by the use of a written consent form approved by the IRB and signed and dated by the study participant at the time of consent. A copy shall be given to the person signing the form.

- **Waiver of Documentation Of Consent (i.e., will not obtain subject's signature)**
  N/A

4.5 Special Consent/Populations

A. Minors-Subjects Who Are Not Yet Adults
N/A

B. Wards of the State
N/A

C. Non-English-Speaking Subjects
Both men and women and members of all ethnic groups are eligible for this trial. No special recruitment will be performed based on gender or minority status.

Where informed consent is documented in accordance with 46 CFR117 (b) (1), the written consent document should embody, in language understandable to the study participant, all the elements necessary for legally effective informed consent.

- **Process for Non-English-Speaking Subjects**
  1. An IRB approved short form written document shall be presented in a language understandable to the study participant.
  2. The IRB approved English informed consent document may serve as a summary.
  3. An interpreter fluent in English and the patient's language shall present the English IRB consent form offered, read it and orally present it to the patient.
  4. Through the interpreter, the investigator will explain participation is voluntary and all aspects of the study, the purpose of the study, treatment plan, procedures, risks,

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benefits, alternatives, and the right to refuse and withdraw at any time without penalty in lay language.

5. Through the interpreter, the investigator will answer any questions the patient may have.
6. The investigator shall give the study participant adequate opportunity to take the IRB approved English informed consent document home for review by family and/or friends who are fluent in English and the language understandable to the patient.
7. If the patient decides to participate in the study, he/she will be asked to sign the short form document.
8. The IRB approved informed consent document will be signed by the person obtaining consent for authorized under the protocol.
9. The written short form document and the English informed consent document will be signed by the witness.
10. When the person obtaining consent is assisted by a translator, the translator may serve as a witness.
11. A copy of the signed IRB approved short form document and the English informed consent document will be given to the study participant and this will be documented in the patient's medical record.
12. Through the interpreter, the investigator shall inform all patients they have the right to refuse study participation and withdraw their participation at any time without penalty and will be treated without prejudice.

- **Short Form Consent for Non-English Speakers**
  Study participants who do not speak English will be presented with a short form consent document written in a language understandable to them.

D. Adults Unable to Consent / Decisionally Impaired Adults
Patients that lack decision-making capacity will not be approached to participate in this study.
N/A

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses

[redacted]

B. Compensation/Incentives
Study participants will not receive compensation for participation.

C. Compensation Documentation
N/A

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

- **Reasonably Foreseeable Risks of Harm**

<u>Azithromycin Adverse Events</u>:

[redacted]

[redacted]

[redacted]

The incidence from three different regimens all based on the five (5) dosing regimen planned, is described in the table below (Pfizer package labeling).

Dosage Regimen	Diarrhea %	Abdominal Pain %	Vomiting %	Nausea %	Rash %
5-day	1.8%	1.2%	1.1%	0.5%	0.4%
Dosage Regimen	**Diarrhea/Loose stools %**	**Abdominal Pain %**	**Vomiting %**	**Nausea %**	**Rash %**
5-day	5.8%	1.9%	1.9%	1.9%	1.6%
Dosage Regimen	**Diarrhea %**	**Abdominal Pain %**	**Vomiting %**	**Nausea %**	**Rash %**
5-day	5.4%	3.4%	5.6%	1.8%	0.7%

- **Cardiovascular**: Palpitations, chest pain.
- **Gastrointestinal**: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.
- **Genitourinary**: Monilia, vaginitis, and nephritis.
- **Nervous System**: Dizziness, headache, vertigo, and somnolence.
- **General**: Fatigue.
- **Allergic**: Rash, pruritus, photosensitivity, and angioedema.
- **Laboratory Abnormalities:** Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, neutrophils, and

[redacted]

[redacted]

[redacted]

blood glucose; elevated serum creatinine phosphokinase, potassium, ALT, GGT, AST, BUN, creatinine, blood glucose, platelet count, lymphocytes, neutrophils, and eosinophils; with an incidence of less than 1%: leukopenia, neutropenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDH, and phosphate. Most subjects with elevated serum creatinine also had abnormal values at baseline. When follow-up was provided, changes in laboratory tests appeared to be reversible.

Hydroxychloroquine Sulfate Adverse Events:

The package labeling does not provide as clear a percent incidence as modern labels since hydroxychloroquine is an old medication. The following Council for International Organizations of Medical Sciences (CIOMS) frequency rating is used, when applicable: Very common ≥ 10 %; Common ≥ 1 and <10 %; Uncommon ≥ 0.1 and < 1 %; Rare ≥ 0.01 and <0.1 %; Very rare < 0.01 %; Not known (frequency cannot be estimated from available data).

- **Blood and lymphatic system disorders**
  Not known: Bone marrow depression, anemia, aplastic anemia, agranulocytosis, leucopenia, and thrombocytopenia (see Warnings and Precautions, Hematologic).

- **Cardiac disorders**
  Not known: Cardiomyopathy, which may result in cardiac failure and in some cases a fatal outcome. Chronic toxicity should be considered when conduction disorders (bundle branch block/ atrioventricular heart block) as well as biventricular hypertrophy are found. Drug discontinuation may lead to recovery (see Warnings and Precautions, Cardiovascular, Drug Interactions, and Symptoms and Treatment of Over dosage). Hydroxychloroquine prolongs the QT, PR and/or QRS intervals which may lead to an arrhythmia. Ventricular arrhythmias and torsade de pointes have been reported in patients taking hydroxychloroquine (see Warnings and Precautions, Cardiovascular, Drug Interactions, and Symptoms and Treatment of Over dosage).

- **Ear and labyrinth disorders**
  Uncommon: ≥ 0.1 and < 1 %: Vertigo, tinnitus.
  Not known: Hearing loss, including cases of irreversible hearing loss.

- **Eye disorders**
  Common: ≥ 1 and <10 %: Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible (see WARNINGS AND PRECAUTIONS, Ophthalmologic).
  Uncommon: ≥ 0.1 and < 1 %: Maculopathies, which may be irreversible. Retinopathy with changes in pigmentation and visual field defects (see Warnings and Precautions, Ophthalmologic). In its early form it appears reversible upon discontinuation of the drug. If allowed to develop however, there may be a risk of progression even after treatment withdrawal. Patients with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas, abnormal color visions, reduction in visual acuity, night blindness, difficulty reading and skipping words. Corneal changes including edema and opacities. They are either symptomless or may cause disturbances such as halos around lights especially at night, blurring of vision,

[redacted]

[redacted]

vision disturbances, or photophobia. They may be transient or are reversible upon discontinuation of therapy (see Warnings and Precautions, Ophthalmologic).
Not known: Macular degeneration, which may be irreversible.

- **Gastrointestinal disorders**
  Very common: ≥ *10 %*: Abdominal pain, nausea.
  Common: Diarrhea, vomiting.
  These symptoms usually resolve immediately upon reducing the dose or upon stopping the treatment.

- **Hepatobiliary disorders**
  Uncommon: ≥ 0.1 and < 1 %: Abnormal liver function tests.
  Not known: Fulminant hepatic failure (see Warnings and Precautions, Hepatic/Biliary/Pancreatic).

- **Immune system disorders**
  Not known: Urticaria, angioedema, bronchospasm.

- **Metabolism and nutrition disorders**
  Common: ≥ *1 and <10 %*: Anorexia (usually resolves immediately upon reducing the dose or upon stopping the treatment).
  Not known: hypoglycemia (see Warnings and Precautions, Endocrine and Metabolism).
  Hydroxychloroquine may exacerbate porphyria (see Warnings and Precautions, General).

- **Musculoskeletal and connective tissue disorders**
  Uncommon: ≥ 0.1 and < 1 %: Sensori motor disorders.
  Not known: Skeletal muscle palsies or skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups. Depression of tendon reflexes, abnormal results of nerve conduction tests. Myopathy may be reversible after drug discontinuation, but recovery may take many months (see Warnings and Precautions, Musculoskeletal).

- **Nervous system disorders**
  Common: ≥ *1 and <10 %*: Headache.
  Uncommon: Dizziness.
  Not known: Convulsions. Extrapyramidal reactions such as: akathisia, dystonia, dyskinesia, gait disturbance, tremor.

- **Psychiatric disorders**
  Common: ≥ *1 and <10 %*: Affect lability.
  Uncommon: ≥ 0.1 and < 1 %: Nervousness.
  Not known: Psychosis, suicidal behavior.

- **Skin and subcutaneous tissue disorders**

[redacted]

[redacted]

[redacted]

Common: ≥ *1 and <10 %*: Skin rash, pruritus.
Uncommon: ≥ 0.1 and < 1 %: Pigmentary changes in skin and mucous membranes, bleaching of hair, alopecia. These usually resolve readily upon cessation of therapy.
Not known: Bullous eruptions (including urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum), toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms (Dress syndrome), photosensitivity, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP) (see Warnings and Precautions, Skin).

- **Risk of Harm from an Intervention on a Subject with an Existing Condition**
  N/A

- **Other Foreseeable Risks of Harm**
  One potential risk is loss of confidentiality. We have taken several steps to minimize the probability of this risk.

- **Observation and Sensitive Information**
  N/A

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects
Women who are pregnant or unwilling to stop breast feeding are excluded from this trial due to the absence of data which demonstrates that this therapy changes morbidity or mortality.

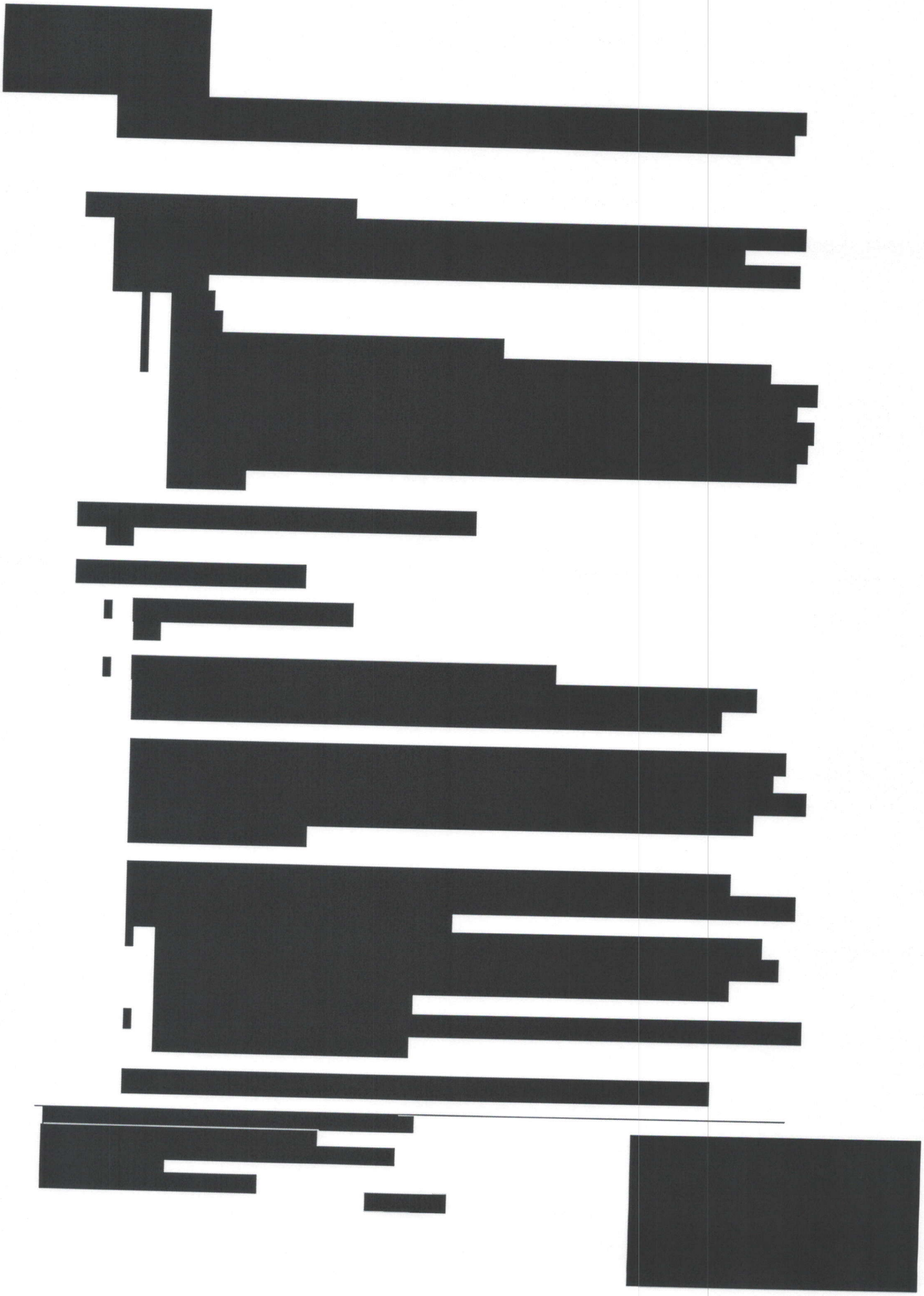
The US FDA labelling for hydroxychloroquine risk states the following:
Teratogenic Effects: Human pregnancies resulting in live births have been reported in the literature and no increase in the rate of birth defects has been demonstrated. Embryonic deaths and malformations of anophthalmia and microphthalmia in the offspring have been reported when pregnant rats received large doses of chloroquine.

Nursing Mothers: Caution should be exercised when administering PLAQUENIL to nursing women. It has been demonstrated that hydroxychloroquine administered to nursing women is excreted in human milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines."

All patients must be made fully aware of the information relating to the potential for reproductive toxicity as detailed in the Informed Consent Form. Patients of childbearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 4 weeks after last dose of study drug(s).

Women of childbearing potential
Females of childbearing potential should use reliable methods of contraception from the time of screening until 4 weeks after discontinuing study treatment. Acceptable methods of contraception include abstinence, tubal ligation, combined oral, transdermal or intra-vaginal hormonal contraceptives, medroxyprogesterone injections (e.g., Depo-Provera), copper-banded intra-uterine devices, hormone impregnated intra-uterine systems and vasectomised partners. All methods of contraception (except for total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse.

Males



[redacted]

- Protecting PHI against public viewing;
- Proper storage and disposal of documents that contain PHI;
- Safeguarding computer workstations and databases that access PHI.

F. Potential Benefits to Subjects

There may be direct benefit to the patient for participation in this study because the study participant will receive hydroxychloroquine sulfate with or without azithromycin, which are FDA approved and have been shown to have potential activity in patients with COVID-19, although this does not guarantee that each individual patient will benefit.

Data gathered from this study may allow us to identify an effective treatment for COVID-19 that could result in benefit to the patient or society as whole in the future.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

It is necessary that PHI be accessed to achieve the goals of this study. All research personnel are trained in HIPAA and routine protections of PHI will apply.

The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. In accordance with the Health Information Portability and Accountability Act (HIPAA), the written Informed Consent Form must include a subject authorization to release medical information to a regulatory authority, or Institutional Review Board (IRB), to grant access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

The core elements included in the HIPAA authorization are:

- A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion;
- The name or other specific identification of the person(s), or class of persons, authorized to make the requested use or disclosure;
- The name or other specific identification of the person(s), or class of persons, to whom the covered entity may make the requested use or disclosure;
- A description of each purpose of the requested use or disclosure;
- An expiration date or an expiration event that relates to the individual or the purpose of the use or disclosure;
- Signature of the individual and date.

5.2 Family Educational Rights and Privacy Act (FERPA)

N/A

5.3 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

N/A

5.4 General Data Protection Regulation (GDPR)

N/A

5.5 NJ Access to Medical Research Act (Surrogate Consent)

N/A