Official Title:	Randomized Comparison of Combination Azithromycin and Hydroxychloroquine vs. Hydroxychloroquine Alone for the Treatment of Confirmed COVID-19
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[redacted]

6.0 Data Management Plan

6.1 Data Analysis

Statistical considerations

We follow Gautret et al. (2020) in using, as a primary endpoint, absence of viral evidence of disease six days following start of treatment. In that study (Table 3), 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. Arm 1 will be compared to Arm 2, and Arm 2 to Arm 3. A total of 160 patients will be accrued, with 60 patients in Arms 1 and 2 and 30 patients in Arm 3. The additional 10 patients accrued are to account for potential drop out of subjects. An interim analysis for futility will be carried out at the 50% target accrual point, which is after 75 patients have been enrolled. Randomization will be stratified on (A) in-patient vs out-patient, and (B) severe vs not severe, as defined in Section 1.3 to ensure that these factors are balanced among all three arms.

HCQ + AZ versus HCQ alone

The primary outcome is a comparison of Arm 1 to Arm 2, with the aim of determining if the addition of AZ to HCQ is effective. The primary endpoint is the proportion of patients that are virus-free at 6 days. We assume that the proportion of patients in the hydroxychloroquine arm who are virus-free at 6 days is 0.571, and that the trial is stopped for futility at the 50% accrual point if the conditional power at that time is below 0.15. The following table shows the power of detecting an improvement in the outcome for a range of proportions virus-free in the combination arm.

Proportion virus-free (HCQ only)	Proportion virus-free HCQ plus	Proportion difference	Power no futility stopping	Loss of power with futility stopping (simulation)
0.571	0.805	0.234	0.800	0.0019
0.571	0.820	0.249	0.851	0.0016
0.571	0.820	0.349	0.882	0.0013

For example, with 60 patients per arm, we could detect, with 80 percent power, an increase in the proportion of virus-free patients from 57.1 percent in the hydroxychloroquine arm to 80.5 percent in the combination arm. The loss of power associated with using futility stopping is only 0.19 percent.

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.

HCQ versus placebo and delayed HCQ

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

[redacted]) having 30 patients and the HCQ arm having 60 patients, as above. Based on the Gautret et al. study [9], 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 Control (delayed HCQ)	Proportion virus-free HCQ	Proportion difference	Power no futility stopping	Loss of power with futility stopping (simulation)
0.125	0.401	0.276	0.800	0.0005
0.125	0.420	0.249	0.848	0.0003
0.125	0.430	0.349	0.870	0.0005

Thus, for a range of plausible virus-free rates for the HCQ arm, the detectable rate for the HCQ arm is well within the range reported by Gautret et al [9]. The futility analysis has a negligible effect on power.

Futility stopping rule

This clinical trial will use a non-binding futility stopping rule based on conditional power [20]. At the 50% accrual point (75 patients), an interim analysis will be carried out and the conditional power of the primary (Arm 1 vs Arm 2) and secondary (Arm 2 vs Arm 3) calculated. A data monitoring committee will review the analysis to determine if accrual to any of the arms should be stopped for futility.

Other analyses

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), (4) time to recovery (able to return to work or school), and (5) time to death from COVID-19. Other measures that will be assessed via descriptive statistics are agent toxicity, adverse events, and improvement over time in vital signs.

The effects of additional clinical variables on the primary outcome and other binary outcomes will be assessed via logistic regression. The effects of these variables on survival endpoints will be assessed via the Cox proportional hazards model. Numbers of patient deaths due to COVID-19 in the three arms will be compared using tests of proportions, and via log-rank test comparison of Kaplan-Meier survival curves.

Power calculation methods

Power calculations were carried out using the PS sample size program [21]. Conditional power at the interim analysis was computed using the method described in Jitlal et al. [20]. Estimates of loss of power due to the use of a non-binding conditional power futility boundary were computed via a simulation of 10,000 replications of a clinical trial with the null and alternative hypotheses as specified in the above power tables. For the simulated power calculations we assume an interim analysis at the 50% accrual time, and stopping if the probability of a statistically significant result (two-sided p-value < 0.05) is below 15%, based on a conditional power calculation [20].

6.2 Data Security

[redacted]

Data will be entered into electronic case report forms (eCRFs) through OnCore® which is the Cancer Institute's clinical trials management system. These eCRFs are used to record subject data generated by subject events: typically labs, study medication administration or procedures of the protocol. Each user accesses the software using his/her Rutgers Net ID and password. Users are given access or permission to various areas of OnCore® based on their role within the Cancer Institute (I.e., data entry, regulatory, study coordination). Audit trails are built into the software to track when data entry was started, when the form was declared complete, when the form was monitored/queried, amended, and then finalized. OnCore® also functions as an honest broker and has the capability to provide de-identified data reports to the principal investigator or designee for analysis.

6.3 Data and Safety Monitoring

A. Data/Safety Monitoring Plan

The Principal Investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of once a month (including when re-approval of the protocol is sought). The Rutgers Cancer Institute of New Jersey's Human Research Oversight Committee (HROC) will be the DSMB of record. During the review process, the principal investigators (serving as monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either principal investigator, IRB or either Data or Safety Monitoring Committee have the authority to stop or suspend the study or require modifications at each institution. The PIs will be responsible for sharing this information in a timely fashion and coordinating appropriate parallel actions at the other institution.

An audit will be conducted following enrollment of the first two (2) or three (3) patients. Subsequent audits will occur dependent on the rate of enrollment by each participating site. More frequent audits of patient data and study conduct will occur if necessary. Prior audit findings and/or situations that may arise during the study will determine the need for more frequent auditing. All audit findings will be discussed with the principal investigator and report the HROC and the Rutgers University IRB.

B. Data/Safety Monitoring Board Details

[redacted]

6.4 Reporting Results

A. Individual Subjects' Results

[redacted]

[redacted]

[redacted]

Results of individual patient assessments will be shared with the individual patient as these are part of the medical record and impact medical care. These results are part of routine care (safety labs, routine radiology procedures, and physical examinations).

B. Aggregate Results

Aggregate research results will not be shared with the study participants.

C. Professional Reporting

[redacted]

D. Clinical Trials Registration, Results Reporting and Consent Posting

ClinicalTrials.Gov Registration and Data Reporting: Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

This is a research study which prospectively assigns human participants to health related interventions. The study will be registered on clinicaltrials.gov per FDA Regulations within 21 days of enrollment of the first participant and updated at least every 6 month.

6.5 Secondary Use of the Data

N/A

7.0 Research Repositories – Specimens and/or Data

[redacted]

8.0 Approvals/Authorizations

- [redacted]

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Appendix A – Study Flow Table

Procedures	Screening Day 0[4]	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11-D20	Weekly FUP x 4[2]	Monthly FUP x 6[3]
Informed consent	X													
Baseline Medical History	X													
Physical assessment	X			X			x				x			
Demographics	X													
Electrocardiogram	X													
CBCD, CRP, Ferritin, D-Dimer, LDH and Troponin	X						x				x			
Serum pregnancy (if applicable)	X													
Eligibility Review	X													
Randomization	X													
Study Drug Dispensing	X						X[1]							
Azithromycin (Arm 1)		X	X	X	X	X								
Hydroxychloroquine sulfate (Arm 1 & 2)		X	X	X	X	X	X	X	X	X	X			
Placebo/ Hydroxychloroquine sulfate (Arm 3)[1]		X	X	X	X	X	X	X	X	X	X	X		
Research Blood draw	X			X			X							
Saliva, Oropharynx swabs	X			X			X							
Pill Diary Review	X	X	X	X	X	X	X	X	X	X	X	X		
Daily Temperature Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Review		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X		
COVID-19 Symptom Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record other SOC Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Treatment will be administered Day 6 to D15 for Arm 3.
2. Phone assessments - weekly x 4 weeks (+/- one day).
3. Phone assessments – monthly x 6 months (+/- one week).
4. Screening and Day 1 visits may be combined. All procedures may be completed within 24 hours of screening visit.

[redacted]

[redacted]

[redacted]

Appendix B

Drugs associated with a known or possible risk of QT prolongation

Drug class	Known risk	Possible risk
ADHD		Atomoxetine
Alpha-blocker		Alfuzosin
Analgesic		Hydrocodone-ER Tramadol
Anesthetic, general	Propofol Sevoflurane	
Anti-androgen		Degarelix Leuprolide
Antianginal	Bepridil	
Antiarrhythmic	Amiodarone Disopyramide Dofetilide Dronedarone Flecainide Ibutilide Procainamide Quinidine Sotalol	
Antibiotic	Azithromycin Clarithromycin Erythromycin Ciprofloxacin Levofloxacin Moxifloxacin	Bedaquiline Gemifloxacin Norfloxacin Ofloxacin Telavancin Telithromycin Lefamulin
Anticancer	Arsenic trioxide Vandetanib Cesium Chloride	Encorafenib Toremifene Dpirubicin Fluorouracil (5-FU) Oxaliplatin Inotuzumab ozogamicin Glasdegib Midostaurin Ribociclib Tamoxifen Eribulin mesylate Lapatinib Osimertinib Capecitabine Sunitinib Bosutinib Dasatinib Nilotinib Bendamustine

[redacted]

[redacted]

[redacted]

Drug class	Known risk	Possible risk
		Sorafenib Ceritinib Entrectinib Necitumumab Cobimetinib Dabrafenib Vemurafenib Tipiracil/Trifluridine Crizotinib Cabozantinib Pazopanib Lenvatinib Vorinostat Tazemetostat Romidepsin Vorinostat Panobinostat Ivosidenib Apalutamide Bortezomib
Anticoagulant		Betrixaban
Anticonvulsant		Ezogabine Felbamate
Antidepressant, SNRI		Venlafaxine
Antidepressant, SSRI	Citalopram Escitalopram	Clomipramine Lithium
Antidepressant, Tetracyclic		Meprotiline Mirtazapine Desipramine Imipramine Nortriptyline Trimipramine
Antiemetic	Ondansetron Droperidol Chlorpromazine	Dolasetron Granisteron Palonosetron Promethazine
Antifungal	Fluconazole Pentamidine	
Antihypertensive		Isradipine Moexipril/hydrochlorothiazide Nicardipine
Antimalarial	Chloroquine Hydroxycholorquine	Artenimol/piperaquine Artemether/Lumefantrine
Antimanic		Lithium

[redacted]

[redacted]

[redacted]

Drug class	Known risk	Possible risk
Antineoplastic		Giltertinib
Antipsychotics	Droperidol Chlorpromazine Haloperidol Pimozide Thioridazine	Perphenazine Promethazine Pimavanserin Asenapine Clozapine Iloperidone Lumateperone Paliperidone Lurasidone Aripiprazole
Antisense oligonucleotide		Nusinersen
Antitubercular		Pretomanid
Antiviral		Efavirenz Lopinavir/Ritonavir Rilpivirine Saquinavir
Antispasmodic		Mirabegron
Cholinesterase inhibitor	Donepezil	
Dopamine agonist		Apomorphine
Estrogen agonist/antagonist		Toremifene
Glucosylceramide synthase inhibitor		Eliglustat
Gonadotropin receptor agonist/antagonist		Leuprolide
Gonadotropin-releasing hormone agonist/antagonist		Degarelix
Histamine H_2 receptor antagonist		Famotidine
Histamine 3 antagonist/inverse		Pitolisant (Tiprolisant)
Immunosuppressant		Tacrolimus
Imaging contrast agent		Perflutren lipid microspheres
Illicit drugs	Cocaine	
Muscle relaxants		Tizanidine Tolterodine
NMDA receptor antagonist		Memantine
CNS Stimulant		Atomoxetine
Oxytocic		Oxytocin
Opiates	Methadone	Buprenorphine
Phosphodiesterase 3 inhibitors	Anagrelide Cilostazol	

[redacted]

[redacted]

[redacted]

Drug class	Known risk	Possible risk
Phosphodiesterase 5 inhibitors		Vardenafil
Progesterone antagonist		Mifepristone
Sedative		Dexmedetomidine
Somatostatin analog		Pasireotide
Sphingosine phosphate receptor modulator		Fingolimod
Unknown		Dextromethorphan/Quinidine
Vasodilator, Coronary	Papaverine HCL (Intracoronary)	
Vesicular monamine transporter 2 inhibitor		Deutetrabenazine
Vesicular monamine transporter 2 inhibitor		Valbenazine
Vesicular monamine transporter 2 inhibitor		Tetrabenazine

[redacted]

[redacted]

[redacted]

Appendix C

CINJ 002011 COVID-19 Baseline Questionnaire

Your Medical History

Are you completing this Baseline Questionnaire online or in person at a study site?

- ☐ Online
- ☐ In person at study site

Please indicate if you have been diagnosed with or treated for one or more of the following conditions:

- ☐ Diabetes mellitus
- ☐ High blood pressure or hypertension
- ☐ Asthma
- ☐ Chronic bronchitis, emphysema, or chronic obstructive pulmonary disease (COPD)
- ☐ Another chronic lung disease (specify): _____
- ☐ Coronary artery disease, peripheral artery disease, angina, or heart attack (myocardial infarction)
- ☐ Congestive heart failure
- ☐ Stroke or transient ischemic attack (TIA)
- ☐ Atrial fibrillation
- ☐ Cancer other than non-melanoma skin cancer
- ☐ Chronic kidney disease (CKD)
- ☐ Crohn's disease, ulcerative colitis, or inflammatory bowel disease (IBD)
- ☐ Rheumatoid arthritis (RA), psoriasis, systemic lupus, multiple sclerosis, or another disorder for which you take medicine to lower your immune system (immunosuppressant)

Please write the names of all the medicines you have taken in the last week, including over-the-counter medicines, supplements, probiotics:

Medicine 1	_____	Medicine 8	_____
Medicine 2	_____	Medicine 9	_____
Medicine 3	_____	Medicine 10	_____
Medicine 4	_____	Medicine 11	_____
Medicine 5	_____	Medicine 12	_____
Medicine 6	_____	Medicine 13	_____
Medicine 7	_____	Medicine 14	_____

List any other medicines you take here, separated by commas.

_____

[redacted]

Do you ever take a probiotic?

- ☐ 0, Never
- ☐ 1, Occasionally, such as when I take antibiotics or have diarrhea
- ☐ 2, Yes, regularly

Have you ever received pneumococcal vaccines (Prevnar-13 or Pneumovax-23)?

- ☐ 0, No
- ☐ 1, Yes
- ☐ 2, I don't know

Did you receive the influenza vaccine this past season?

- ☐ 0, No
- ☐ 1, Yes
- ☐ 2, I don't know

In the last week, have you had a new fever > 100° F?

- ☐ 0, No
- ☐ 1, Yes
- ☐ 1, I felt feverish but did not take my temperature.

In the last week, have you had a new cough?

- ☐ 0, No
- ☐ 1, Yes

In the last week, have you felt new shortness of breath or had new difficulty breathing?

- ☐ 0, No
- ☐ 1, Yes

In the last week, have you had new vomiting?

- ☐ 0, No
- ☐ 1, Yes

In the last week, have you had new diarrhea (multiple watery stools)?

- ☐ 0, No
- ☐ 1, Yes

In the last week, have you had a new loss of smell or taste?

- ☐ 0, No
- ☐ 1, Yes

Indicate when you have lost your sense of smell, taste, or both.

- ☐ 0, Smell
- ☐ 1, Taste
- ☐ 2, Both smell and taste

In the last week, have you received care or been tested for coronavirus in an office or clinic?

- ☐ 0, No
- ☐ 1, Yes, for one or more of the above symptoms
- ☐ 2, Yes, for another reason

What diagnosis (or diagnoses) were you given? _____

[redacted]

Name of emergency contact: _____

Relationship of emergency contact:

- ☐ 0, Spouse/Partner
- ☐ 1, Child
- ☐ 2, Parent
- ☐ 3, Sibling
- ☐ 4, Grandparent
- ☐ 5, Aunt
- ☐ 6, Uncle
- ☐ 7, Cousin
- ☐ 8, Unrelated Adult/Roommate
- ☐ 9, Friend
- ☐ 10, Neighbor
- ☐ 11, Other (specify below)

Mobile phone number of emergency contact: _____

Name of second emergency contact:

Relationship of second emergency contact:

- ☐ 0, Spouse/Partner
- ☐ 1, Child
- ☐ 2, Parent
- ☐ 3, Sibling
- ☐ 4, Grandparent
- ☐ 5, Aunt
- ☐ 6, Uncle
- ☐ 7, Cousin
- ☐ 8, Unrelated Adult/Roommate
- ☐ 9, Friend
- ☐ 10, Neighbor
- ☐ 11, Other (specify below)

[redacted]

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quine for Treatment of

[redacted]

[redacted]

Mobile phone number of second emergency contact:

How would you describe your ethnicity?

- ☐ 1, Hispanic, Latino, Latina, or Latinx
- ☐ 2, Middle Eastern or North African descent
- ☐ 0, None of the above
- ☐ 3, Prefer not to report

How would you describe your race?

- ☐ 1, American Indian or Alaskan Native
- ☐ 2, Asian
- ☐ 3, Black or African American
- ☐ 4, First Nations, Inuit, or Métis
- ☐ 5, Native Hawaiian or other Pacific Islander
- ☐ 0, White
- ☐ 6, Other
- ☐ 7, Prefer not to report

[redacted]

Appendix D

CINJ 002011 COVID-19 Follow-up Questionnaire

Day: _____ **Patient:** _____

Update on how you are feeling

In the last day, have you had a new fever > 100° F?

- ☐ 0, No
- ☐ 1, Yes
- ☐ 1, I felt feverish but did not take my temperature.

In the last day, have you had a new cough?

- ☐ 0, No
- ☐ 1, Yes

In the last day, have you felt new shortness of breath or had new difficulty breathing?

- ☐ 0, No
- ☐ 1, Yes

In the last day, have you had new vomiting?

- ☐ 0, No
- ☐ 1, Yes

In the last day, have you had new diarrhea (multiple watery stools)?

- ☐ 0, No
- ☐ 1, Yes

In the last day, have you had a new loss of smell or taste?

- ☐ 0, No
- ☐ 1, Yes

Indicate when you have lost your sense of smell, taste, or both.

- ☐ 0, Smell
- ☐ 1, Taste
- ☐ 2, Both smell and taste

In the last day, have you had any additional symptoms?

- ☐ 0, No
- ☐ 1, Yes

In the last day, have you taken any new medications?

- ☐ 0, No
- ☐ 1, Yes

If so please list below

_____

_____

_____

[redacted]

[redacted]

[redacted]

In the last day, have you receive care or had tests in an office or clinic?

☐ 0, No

☐ 1, Yes

Document test or procedures

Please provide all temperatures recorded on your log in the last 24 hours.

AM: _____

Mid-day: _____

Afternoon: _____

Night: _____

In the last day, have you taken your study medication as prescribed?

☐ 0, No

☐ 1, Yes

[redacted]

[redacted]