Study Protocol and Statistical Analysis Plan

Study Title: Novel Agents for Treatment of High-risk COVID-19 Positive Patients

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TITLE: Multi-arm phase II trial for initial assessment of novel agents for treatment of high-risk COVID19 positive patients

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Investigational Agent(s): Ivermectin, generic; Camostat Mesilate; Artemisia annua, Artesunate

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SUMMARY OF CHANGES
MCC-20-COVID-PMC
Protocol: Revision, v4
Version Date: 18 AUGUST 2020

#	Section	Comments
1.	Cover page	Added new agent name: Artesunate, update date of revision and version number, clarified title; revised IND status of each compound
2.	Schema	Updated figure
3.	TOC	Updated table of contents
4.	1.1	Updated primary endpoint to remove reference to hydroxychloroquine, clarified the primary purpose of this trial and clarified the change in COVID- 7-Point scale is less than a 2-point decrease in score.
5.	2.4	Removed background for hydroxychloroquine and azithromycin and updated section number for artemisia annua
6.	2.5	Added background for artesunate compound including clinical toxicology and pharmacokinetic experience
7.	2.6	Expanded rationale to include use of the pick-the-winner trial design and removed reference to hydroxychloroquine and azithromycin and added a figure for the COVID-7 point ordinal scale and primary endpoint.
8.	3.2	Removed QTc exclusion and removed references to hydroxychloroquine and azithromycin, as none of the compounds in this trial have QT prolongation. Clarified concurrent used of CYP2A6 inducers is excluded for both artemisia annua and artesunate
9.	4.9	Clarified the use of routine examination, added Day 3-4 and Day 10-11 safety assessment
10.	6.1	Removed reference to hydroxychloroquine and azithromycin throughout and regimen descriptions, and added Regimen F artesunate description. Clarified that all arms will have safety run-ins Changed the following sentence: NOTE: if a patient develops a myocardial infarction or documented QTc > 500 while on the 14 days of drug, they should be immediately taken off study medication and receive standard of care treatment per their treating physician.

#	Section	Comments
		To: NOTE: if a patient develops a myocardial infarction or grade 3 or 4 cardiac arrythmia ~~or documented QTc > 500~~ while on the 14 days of drug, they should be immediately taken off study medication and receive standard of care treatment per their treating physician.
11.	8.1	Removed reference to hydroxychloroquine and azithromycin as well as adverse events listings for these drugs and added artesunate and its adverse events listing
12.	9.1	Clarified that less than a 2 point DECREASE in COVID 7-POINT ORDINAL OUTCOMES SCALE is a positive result and clarified that comparisons between arms or with a placebo is not performed in this study design.
13.	9.2	Clarified the time from baseline to improvement is both Day 14 and Day 28
14.	9.3	Clarified the primary endpoint and goal of a decrease less than 2 points in COVID 7-POINT ORDINAL SCALE (clinical stability)
15.	9.4	Removed all references to hydroxychloroquine and azithromycin and clarified the randomization list process.
16.	9.5 and 9.6	Clarified the definition of clinical stability as a less than 2 point decrease in COVID scale.
17.	10.3	Updated expedited AE reporting guidelines
18.	11	Added phone contacts in study calendar for Day 3 or 4 and Day 10 or 11 and clarified in-person versus telehealth evaluations
19.	12.1	Clarified length of follow-up
20.	App C	Removed drug diaries for Hydroxychloroquine and Azithromycin, corrected misspellings and added Drug Diary for Artesunate

COMMON PROTOCOL ABBREVIATIONS	
Ab	Antibody
AE	Adverse event
Ag	Antigen
ALT	Alanine transaminase test; also “SGPT”
ANC	Absolute neutrophil count
ARDS	Acute respiratory distress syndrome
AST	Aspartate Aminotransferase test; also “SGOT”
AUC	Area under the curve
BID	Twice a day; also, “b.i.d.” , “bid”
BMI	Body mass index
BPTP SRF	Biospecimen Procurement and Translational Pathology Shared Resource Facility
CBC	Complete blood count; sometimes seen “with diff”, differential
CCTS	Center for Clinical and Translational Science
CDC	U.S. Centers for Disease Control and Prevention
CDMP	Clinical Data Monitoring Plan
CFR	Code of Federal Regulations
cm	Centimeter
CMP	Comprehensive metabolic panel
Co-I	Co-investigator
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRN/CRA	Clinical research nurse / clinical research associate (study staff)
CRO	Markey’s Clinical Research Organization
CRSO	Clinical Research Support Office, University of Kentucky Healthcare
CT	Computed tomography
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 isoform 3A4
DSMC	Data and Safety Monitoring Committee, Markey Cancer Center
DSMP	Data and Safety Monitoring Plan
eCRF	Electronic case report form (also CRF, case report form)
EDC	Electronic data capture system
EKG	Electrocardiogram test
FDA	U.S. Food and Drug Administration
GFR	Glomerular filtration rate
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation of Guidelines for Good Clinical Practice
IDE	Investigational Device Exemption, per the FDA
IDS	Investigational Drug Service at University of Kentucky
IHC	Immunohistochemistry

IIT	Investigator-initiated trial
IND	Investigational New Drug, per the FDA
IRB	Institutional Review Board
IV	Intravenous drug administration
kg	Kilogram
LFT	Liver function test
m^2	Square meter
MAD	Maximum administered dose
MCC	Markey Cancer Center
mcL	Microliter
mg	Milligram
mg/dL	Milligrams per deciliter
mg/kg	Milligram/ Kilogram
min	Minute; also "min."
ml	Milliliter
ml/min	Milliliter per minute
mm	Millimeter
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NSAID	Non-steroidal anti-inflammatory drug
OS	Overall survival
PI	Principal investigator
PKs	Pharmacokinetics
plts	Platelets
PO	By mouth, oral administration of drug
PRMC	Protocol Review and Monitoring Committee, Markey Cancer Center
QA	Quality assurance
QD	One a day; also "q.d." , "qd"
QTc	Corrected QT interval, in EKGs
RNA	Ribonucleic Acid
RNA-Seq	Ribonucleic Acid sequencing
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOP	Standard operating procedure
SRF	Shared resource facility
TID	Three times a day; also, "t.i.d." , "tid"
µmol/L	Micromole/liter
UK	University of Kentucky
ULN	Institutional upper limit of normal
WBC	White blood cells

SCHEMA

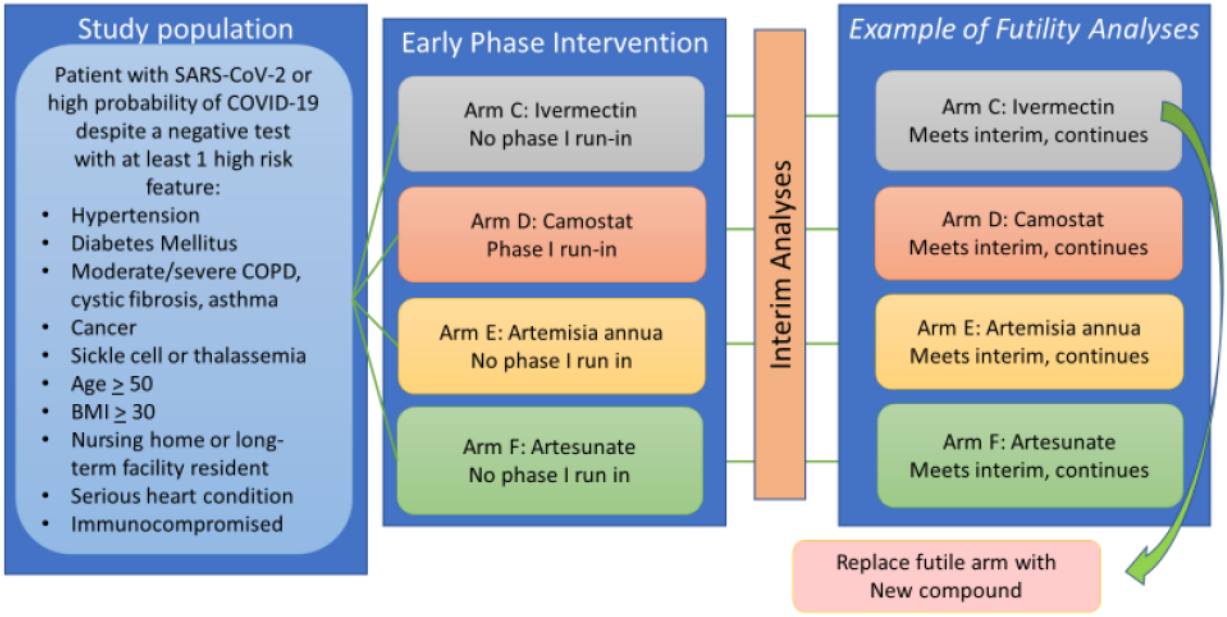

Study population
Patient with SARS-CoV-2 or high probability of COVID-19 despite a negative test with at least 1 high risk feature:
• Hypertension
• Diabetes Mellitus
• Moderate/severe COPD, cystic fibrosis, asthma
• Cancer
• Sickle cell or thalassemia
• Age ≥ 50
• BMI ≥ 30
• Nursing home or long-term facility resident
• Serious heart condition
• Immunocompromised
Early Phase Intervention
Arm C: Ivermectin
No phase I run-in
Arm D: Camostat
Phase I run-in
Arm E: Artemisia annua
No phase I run in
Arm F: Artesunate
No phase I run in
Interim Analyses
Example of Futility Analyses
Arm C: Ivermectin
Meets interim, continues
Arm D: Camostat
Meets interim, continues
Arm E: Artemisia annua
Meets interim, continues
Arm F: Artesunate
Meets interim, continues
Replace futile arm with
New compound

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objective

To rapidly evaluate initial efficacy of multiple potential inhibitors of SARS-CoV-2 viral replication in COVID19 positive patients with high-risk factors in order to decrease clinical deterioration, as defined as a less than a 2-point decrease from initial COVID 7-POINT ORDINAL OUTCOMES SCALE within 14 days from study entry.

1.2 Secondary Objectives

1.2.1 To assess the decrease in viral load at Day 14.
1.2.2 To assess the development of severe respiratory or other organ failure in the study population
1.2.3 To assess progression to ICU care or ventilation in non-critically ill hospitalized patients and overall study population
1.2.4 To assess clearance of viral RNA by PCR testing at days 1, 14, 28, and 40 days
1.2.5 To assess mortality, clinical status of subject at Day 14, using the COVID 7-point ordinal outcomes scale, and rate of severe adverse events defined as grade 3 non hematologic or greater by DMID Toxicity Scale for Determining Severity of Adverse Events
1.2.6 To assess the safety, tolerability and compliance with each regimen.

1.3 Exploratory Objectives

1.3.1 To observe and record the impact of each drug combination on inflammatory markers (procalcitonin, D-Dimer, hs-CRP) and their potential prognostic/predictive value
1.3.2 To determine the rate and timeframe of SARS-CoV-2 seroconversion as a marker of acquired immunity via the presence of COVID-19 antibodies in RNA negative patients as a marker of acquired immunity using either a rapid diagnostic test (RDT) or enzyme-linked immunosorbent assay (ELISA) assay.
1.3.3 To determine if early detection of elevated inflammatory cytokines are predictive of severe infection or severe disease.
1.3.4 To perform post-hoc covariate adjusted analysis for potential pre-treatment, outcome-prognostic covariates such as age, sex, degree of illness, clinical chemistries, and timing of onset of symptoms relative to study inclusion.
1.3.5 To evaluate the effect of COVID-19 on platelet function to assess severe coagulation complications
1.3.6 To evaluate viral clearance at Day 14, 28 and 40

2. BACKGROUND

2.1 SARS-CoV-2 Background

Coronavirus Disease 2019 (COVID-19) is a highly contagious disease, caused by a novel enveloped RNA beta-coronavirus, also known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). [1] The first case of this unprecedented outbreak “pneumonia of unknown

etiology" was reported in Wuhan City, Hubei Province, China on December 8th, 2019 and reported to the World Health Organization (WHO) on December 31st, 2019. [2] WHO declared a COVID-19 global emergency on January 30, 2020, and then categorized the outbreak as a pandemic on March 11, 2020. [3] As of April 22, 2020, more than 2,628,894 confirmed cases of COVID-19 worldwide and 182,740 people globally have died from COVID-19 since it emerged in China, according to the data from Johns Hopkins University.

While the majority of patients with COVID-19 develop mild or uncomplicated illness, approximately 20-30% of hospitalized patients have required intensive care support and 5% of those have multi-organ failure or shock. The case fatality rate ranges from 1 to 4% and it is higher among those with pre-existing comorbid conditions such as cardiovascular disease, diabetes mellitus, obesity, chronic respiratory disease, hypertension and cancer. [4] The vast majority of patients presents with fever (83-99%), cough (59-82%), fatigue (44-70%), anorexia (40-84%), shortness of breath (31-40%), sputum production (28-33%), myalgias (11-35%). [2, 5-9] Less than 10% of patients will present with headache, confusion, rhinorrhea, sore throat, hemoptysis, vomiting, or diarrhea. [2, 5, 6] Anosmia or ageusia proceeding the onset of respiratory symptoms has been anecdotally reported. [10]

The Center for Disease Control and Prevention (CDC) from China divided the clinical manifestations of the disease as below: [4]

- Mild to moderate disease (81%): non-pneumonia and mild pneumonia
- Severe disease (14%): dyspnea, respiratory frequency ≥30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio or P/F [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO2)] <300, and/or lung infiltrates >50% within 24 to 48 hours
- Critical disease (5%): respiratory failure, septic shock, and/or multiple organ dysfunction or failure

To conduct population-based surveillance for laboratory-confirmed COVID-19–associated hospitalizations in the US, the COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) was created and reported early data on hospitalization rates from March 2020. The hospitalization rate among patients during this 4-week period was 4.6 per 100,000 population. Rates were highest (13.8) among adults aged ≥65 years. Among a subset of those adults 178 (12%) with data on underlying conditions, and consistent with reports from other countries, the vast majority (89.3%) had one or more underlying conditions: hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (28.3%), and cardiovascular disease (27.8%). This early data from COVID-NET suggest that COVID-19–associated hospitalizations in the United States (US) are highest among older adults, and nearly 90% of persons hospitalized have one or more of these underlying medical conditions. [11] Given that these underlying medical conditions are rampant in the state of Kentucky, a focus on preventing progression to hospitalization amongst those who are most vulnerable to COVID 19 is warranted.

Additionally, to date, treatments for COVID-19 in high risks individuals remain experimental

and therapeutic strategies to deal with the infection are at best supportive, with prevention aimed at reducing transmission in the community as the best weapon. No proven therapies have been demonstrated to prevent progression of COVID-19 to severe illness and this is a critical unmet need for high risk individuals and warrants study. Recently, the Infectious Disease Society of America has made recommendations for the treatment of patients with COVID-19, focusing on inpatient care, and recommending randomized trials where possible as the best step to improve treatment outcomes and to increase our understanding of this coronavirus pandemic. [12] Discoveries in this area may inform clinicians on effective treatment for low risk individuals who progress to severe illness, as well.

2.2 Ivermectin

Ivermectin is an FDA approved anti-parasitic agent that also has activity against a number of RNA viruses, including influenza, equine encephalitis and West Nile. Ivermectin inhibits the interaction between the human immunodeficiency virus-1 (HIV-1) integrase protein (IN) and the importin (IMP) α/β1 heterodimer responsible for IN nuclear import. Its broad activity against RNA viruses is thought to be because of the virus's reliance on IMPα/B1 during infection. A recent publication that evaluates the antiviral activity of ivermectin towards SARS-CoV-2, *in vitro* and demonstrates a 99.8% reduction in cell-associated viral RNA after 2 hours. [13]

The IC50 for ivermectin versus Sars-CoV-2 is 2.5 uM = 2180 ug/L.[14] The AUC of the Ivermectin in humans at the approved dose in (200 mcg/kg) is 1132 ug/L. The concentrations in lung are anticipated to be 3x higher than plasma exposure. [15] Therefore we anticipate that we will achieve adequate pulmonary concentrations to have antiviral effect. Given its safety profile, we will use the FDA approved dose of ivermectin in this trial, as we are combining it with HCQ.

2.3 Camostat Mesilate

Recently, mechanistic studies have elucidated that a critical step for SARS-CoV-2 viral entry is the priming of the SARS-CoV2 spike protein, which uses the human serine protease TMPRSS2. Notably, camostat mesilate (CAM), a potent inhibitor of serine proteases, has been shown to block cellular viral entry of SARS-CoV-2 in primary human airway epithelial cells.[16]Camostat block SARS-CoV-2 replication in TMPRSS2-expressing human cells, with an apparent EC90 of 3 μM, and significantly lessens viral replication at that level.[17] Camostat has been shown to block infection with SARS-CoV-1 in human cells with roughly equivalent potency.[18] In a mouse model of SARS-CoV-1 a dose of twice daily at 30 mg/kg, equivalent to a 275 mg dose in a 70 kg human, providing a survival advantage.[19] Additionally, camostat has been shown to attenuate airway epithelial sodium channel function and enhance mucociliary clearance when nebulized into the trachea of conscious sheep. [20] This analysis was extended to cystic fibrosis patients in a small trial where is was administered via a nasal spray pump and was shown to reduce sodium transport in the airway and was well tolerated, suggesting the possibility that this might increase clearance of infectious virions. [21] Camostat is approved for remission of acute symptoms of chronic pancreatitis and post-operative esophageal reflux. Additionally, camostat was approved in the United States under IND 109035 for the relief of abdominal pain associated with chronic pancreatitis and by the FDA for use against SARS-CoV-2 in this clinical trial (IND 15103). At this time, the clinical impact of camostat on COVID-19 is not known, thus, we plan

to examine whether camostat can improve patient outcomes.

Camostat is approved for chronic pancreatitis in Japan at a daily dose of 600mg. We are using the same dose in this clinical trial. In a murine experiment, following a lethal SARS-CoV infection, the survival rate of camostat treated mice was 60%.[19] In this study, mice were treated at 30mg/kg for 9 days. A corresponding dose in a 75kg human would be 2250 mg. Camostat mesilate was well tolerated by patients when administered three times per day at a dose of 200 mg (total daily dose of 600 mg), and this is the approved dose and schedule in Japan for chronic pancreatitis.[22] Given that we are treating outpatients, for a 14-day duration, we anticipate using the approved dose in Japan is a reasonable starting point and we will consider a dose escalation if tolerable and there are hints of efficacy.

2.4 Artemisia annua

Artemisia annua, also known as sweet wormwood, is a botanical product native to Asia but grows in many countries, including the United States. Artemisia annua has been used for centuries as infusions or powders to treat malaria. Artemisinin is extracted from Artemisia annua, and artesunate is then semi-synthetically derived from artemisinin.[38]. Artesunate is a highly effective treatment for malaria but is limited by the rapid development of resistance and must be used in combination with other antimalarials.[39] Intriguingly, Artemisia annua tea, which contains a mixture of active constituents, including dihydroartemisinic acid, artemisinic acid, and artemisinin, may be more effective than artesunate in treating malaria. A randomized, placebo-controlled clinical trial enrolling 957 patients with malaria compared Artemisia annua tea to artesunate-amodiaquine therapy. Patients were randomized to receive either artesunate-amodiaquine tablets or Artemisia annua tea with 1.6g of twigs and leaves /0.33 L every 8 hours for 7 days. Tea was prepared by adding 5 g of Artemisia annua dried leaves and twigs to 1 liter of boiling water. The primary endpoint of this trial was the malaria cure rate, with the Artemisia annua cure rate of 96.4% at 28 days compared to only 34.3% in the artesunate-amodiaquine arm.[40] Artemisia annua tea was also well-tolerated, with 5% of subjects experiencing nausea or vomiting, although none severe enough to discontinue therapy and no other adverse effects reported. In contrast, 42.8% of patients in the artesunate-amodiaquine arm reported adverse effects, including nausea, asthenia, pruritus, hypoglycemia, and vertigo.

The antiviral activity of Artemisia annua and pure Artemisinin annua was tested by pretreating Vero E6 lung cells infected with SARS-CoV-2 over 120 minutes at a concentration of 130 plaque forming unites per well. Aqueous and ethanolic extracts of Artemisinin annua, and artemisinin concentrations ranging from 0-2.5 ug/mL were incubated with virus infected cells for 15, 30, 60 and 120 minutes. Both the aqueous and ethanolic extracts showed substantial activity, and were able to inhibit approximately 50% of viral replication at concentrations of 1.5 ug/mL. By comparison, pure Artemisinin was not able to inhibit the virus by 50% and no EC50 was able to be calculated. Therefore, the extracts were advanced for further clinical testing.[41]
The dose for this study is based on experience with malaria, where children as young as 5 years of age received a dose of tea (1.6g/0.33L) every 8 hours for 7 days with the only reported adverse effect to be mild nausea and vomiting. Notably, 1.6g of twigs and leaves as used in the malaria study corresponds to 221 mg of leaf alone.[42] While there is a paucity of experience with human pharmacokinetic studies in patients receiving Artemisia annua tea,[40] in rats,

receiving the same dose, the concentration of the active constituent, Artemisinin was 10 ug/mL in serum, and 5 ug/mL in the lung after a single dose[43] The Artemisia annua decaf coffee pods and tea bags used in this study are commercially available botanical products and supplied by ArtemiLife Inc. (https://artemilife.com/home). Artemisia annua decaf coffee pods contain 450 mg Artemisia annua leaf, and tea bags contain 225 mg Artemisia annua leaf. Therefore, we anticipate adequate concentrations to achieve antiviral activity while maintaining excellent tolerability. The decaf coffee pods and tea bags contain FDA food-grade quality ingredients. Artemisia annua plants for ArtemiLife coffee and tea are grown in Kentucky. ArtemiLife coffee pods and tea bags are produced and manufactured in the United States.

2.5 Artesunate

Artemisinin is extracted from Aa and artesunate is then semi-synthetically derived from artemisinin.[39] [4]. Artesunate is a highly effective treatment for malaria, but while highly effective, artesunate is limited by the rapid development of resistance and must be used in combination with other antimalarials.[40] [5]. The usual dose of artesunate in adults for malaria is 200 mg once a day for 7 days and has been used in cancer studies at a dose of 200 mg a day for up to 37 months.[42] Therefore, in this study we will administer 200mg orally daily for a total of 14 days.

In a randomized efficacy and safety trial comparing two artesunate combination therapies, artesunate + amodiaquine (ASAQ) and artemether + lumefantrine (AL), in children with uncomplicated malaria, 227 subjects with an age range of 6 months to 14 years were followed for 28 days after treatment, then monthly for a year.[44] The ASAQ group was treated once daily with 10 mg/kg body AQ and 4 mg/kg AS for 3 days. The AL group was administered a single dose of 20 mg artemether and 120 mg lumefantrine on the first day, then two doses on day 2 and 3, with dosing at one tablet/dose for body weight of 5-14 kg, two tablets/dose for body weight of 15-24 kg, three tablets/dose for body weight of 25-34 kg, or four tablets/dose with a body weight 35 kg or greater. Both ASAQ and AL were highly effective with adequate clinical and parasitological response rates of 97.1% and 98.2% at day 14 for the AL and ASAQ groups, respectively. Both artesunate combination therapies were well tolerated, with mild nausea and vomiting the most common adverse effects, with 27.5% and 12.6% of subjects reporting each, respectively.[44]

Pharmacokinetics of artesunate was completed in a multicenter trial with 472 African pediatric subjects with uncomplicated malaria. One or two fixed-dose tablets of artesunate-mefloquine (25 mg/55 mg) were consumed daily for three days. Dosing was based on age. Subjects between 6 to 11 months were administered one tablet daily, and subjects between 12 to 59 months were administered two tablets daily. Blood draws were completed on 50 subjects for PK analysis. Blood draws were performed at regular intervals, including predose to 6 hrs after first dose, predose to 6 hrs after third dose, 72 hrs after first dose, on day 7, and on one day between day 28 and day 63. For artesunate the $AUC_{0\text{-}24,\ day\ 0}$ was 0.34 ng/L/h, and the $AUC_{0\text{-}24,\ day\ 2}$ was 0.23 ng/L/h. The Cmax was 0.52 nmol/mL, and the terminal half-life was 40 min. For DHA, the $AUC_{0\text{-}24,\ day\ 0}$ was 3.30 ng/L/h, and the $AUC_{0\text{-}24,\ day\ 2}$ was 2.20 ng/L/h. The Cmax was 3.9 nmol/mL for DHA, and the terminal half-life was 40 min [45].

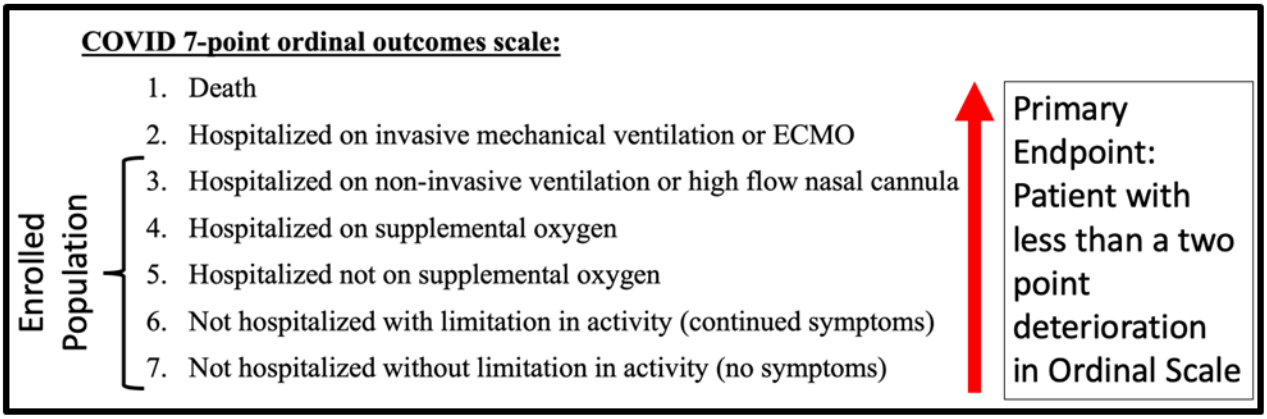
Artesunate has been reported to be well tolerated in children with malaria. A randomized efficacy

and safety trial comparing artesunate + amodiaquine and artemether + lumefantrine (AL) was conducted in 227 subjects with malaria with an age range of 6 months to 14 years. Adverse events were reported to be similar between the treatment groups. Both artesunate combination therapies were well tolerated, with mild nausea and vomiting the most common adverse effects, with 27.5% and 12.6% of subjects reporting each, respectively. However, a higher percentage of subjects reported nausea (40.5%) and vomiting (44.8%) before beginning treatment. 4.3% of subjects in ASAQ group and 3.6% of subjects in the AL group reported fatigue and excessive sleepiness. Pruritus was reported for 3 patients in the study. 12% of subjects in the ASAQ group and 8% in the AL group reported dizziness and severe anemia was reported in one subject; however, investigators determined that both symptoms were likely unrelated to treatment.[44]

Another multicenter, randomized study compared fixed dose artesunate + amodiaquine once daily (ASAQ1) or twice daily (ASAQ2) with artemether + lumefantrine (AL) in 941 patients with uncomplicated malaria. The mean age for the ASAQ1 group was 9.5 years (SD- 10.8), for the ASAQ2 group was 9.1 years (SD- 9.8), and for the AL group was 9.4 years (SD- 10.7). 29.3% of patients had at least one adverse event, 20.4% were thought to be related to treatment. Most adverse events (88.5%) were considered mild or moderate, with 24.4% experiencing insomnia or somnolence and 16.7% gastrointestinal symptoms, with 13% of subjects reported to have vomiting within 30 minutes of treatment. 7 patients were reported to have anemia, with one patient requiring hospitalization but ultimately recovered. Two subjects died during the study, but the deaths were not attributed to the treatment.[46]

2.6 Rationale

We propose the use of a multi-arm, phase II "pick-the-winner" trial design to allow initial assessment of multiple therapies in parallel and selection of promising therapies with adequate probabilities after COVID19 + testing in high risk, but non-critically ill individuals. [47] Prior to moving a promising therapeutic agent forward into large randomized trials of this therapy versus placebo, investigators need to provide substantial evidence of effectiveness and adequate characterization of safety. In addition, we incorporate rapid futility analysis where each agent is assessed independently using Bayesian posterior probability calculations. **NOTE: this is based on efficacy not toxicity assessment. The toxicity assessment will be done using run-ins for some of the arms.** This selection design approach along with interim assessments of efficacy,, used often in other disciplines such as oncology, allows for initial assessment of potential benefit using statistical probability calculations, before designing randomized comparative trials to avoid exposing large numbers of subjects to potentially futile agents. The "pick the winner" trial design and Bayesian posterior probability methods allow for an adaptive, proof-of-concept strategy which incorporates prospectively planned criteria to stop each arm independently for futility,[48] [49] with the prospect of expanding from a proof-of-concept phase to a larger confirmatory trial, typically a randomized, placebo controlled trial, if initial assessments are positive. The hypothesis of this study is that the addition of agents that inhibit viral entry or replication of SARS-CoV-2 virus, will be devoid of additional moderate to severe toxicities, will prevent clinical deterioration at 14 days, and will improve viral clearance at Day 14 in high risk individuals. Additionally, we hypothesize that clinical outcomes in COVID-19 infected patients at higher risk of poor outcomes following infection will be improved compared to the emerging standards when introduced as an early intervention after diagnosis.



COVID 7-point Ordinal Outcome Scale and Primary Endpoint

2.7 Correlative Studies Background

2.7.1 SARS-CoV-2 Viral Load

Active SARS-CoV-2 infection is diagnosed by qPCR in upper and lower respiratory specimens obtained by nasopharyngeal swabs. The initial, diagnostic test is performed at baseline in a CLIA laboratory and required for diagnostic purposes and for study entry. Subsequent samples, to avoid placing burden on clinical resources, will be research level oropharyngeal swabs or sputum samples and evaluated in the Kolesar laboratory by a validated qPCR assay. In addition, any residual specimen from nasopharyngeal swabs that are collected for routine care due to a clinical indication to retest using a CLIA laboratory assay will be collected. Correlative testing will examine the linkage of viral load with time to resolution and with clinical status, as well as correlation between viral load and seropositivity, recrudescence, of disease and clinical outcomes.

2.7.2 SARS-CoV-2 Antibody Seropositivity

Definitive methods to prove a patient had been infected with SARS-CoV-2 are currently lacking. Several groups within the UK system are developing serology tests to detect SARS-CoV-2 antibodies. Dr. Scott Berry, an Associate Professor in Engineering at the University of Kentucky and Chief Scientific Officer of Salas Discovery, is an expert the development of point of care testing for viral diagnostics. He has adapted an emerging technology in biomarker isolation/measurement, Exclusion-based Sample Preparation (ESP), for the unmet clinical need associated with point of care SARS-CoV-2 measurement. [50] This serology test combines the sensitivity and quantitative nature of an ELISA with the speed and simplicity of a lateral flow assay (i.e., a rapid test) [51-53] Briefly, ESP utilizes phase interfaces (e.g., liquid/air boundaries) to rapidly and simply manipulate analyte bound to paramagnetic particles (PMPs) within a bulk sample. ESP will be used to isolate SARS-CoV-2 antibody from a blood sample and then perform a streamlined, ESP-based immunoassay for quantitation SARS-CoV-2antibody. Importantly, ESP that has been successfully implemented as the backbone of a new HIV assay geared toward developing countries, illustrating its ability to function outside of sophisticated labs.[54, 55]

Members of the University of Kentucky CURE Alliance including Dr. Jerry Woodward has expertise in development of immune profiling and in collaboration with other members of the

Department of Microbiology, Immunology, and Molecular Genetics and other collaborators is developing an in-house serological assay to test for the presence of antibodies to SARS-CoV-2 infection in blood and saliva which will be critical to our ability to understand immunity to this virus following infection. Additionally, his group will pursue complete immune profiling of plasma based mononuclear cells (PBMCs) which is an associated and critical part of expanding our understanding of the adaptive immune response to this novel virus.

2.7.3 **Inflammatory Cytokines**

Prior studies have demonstrated that proinflammatory cytokines are associated with pulmonary infiltrates and severe infection in individuals with SARS, [56] MERS- CoV [57] and SARS-CoV-2 [2] infection. We hypothesize that inflammatory cytokines like TNF alpha, IL-1, IL-2 and IL-6 will be elevated at baseline and day 7 in individuals who go on to develop a severe infection when compared to those who do not develop a severe infection and that cytokine measurement can be an early marker of severe infection, allowing for earlier intervention in these individuals. Cytokine levels will be measures by the ELISA in the Kolesar lab, by Dr. Jill Kolesar, as previously described. [58]

2.7.4 **Coagulopathy in COVID-19 Patients**

Dr. Sidney Whiteheart (Molecular and Cellular Biochemistry) and Dr. Jeremy Wood (Medicine) have developed a collaboration to study the coagulopathies associated with COVID-19 patients. Specifically, their focus is on the dysfunction of normal hemostatic control seen in the most severe COVID-19 patients. Reports from China, Italy, and the US have shown an increase in coagulopathies in COVID-19: presenting as increased D-dimer, thrombocytopenia, and thrombotic microangiopathy. This clinical manifestation has lead ISTH and ASH to recommend low molecular weight heparin in cases where COVID-19 is severe; however, the underlying causes of this are unknown. Drs. Whiteheart and Wood will use their specific expertise and battery of functional assays to study this coagulation dysfunction at both the coagulation factor and platelet level. Whole blood is needed for some of the platelet-specific assays and plasma will be retained for analysis. The data generated will help determine what causes the increased coagulation and will guide how to better manage anticoagulant therapy in the most severely affected patients.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Age ≥18 years

3.1.2 Laboratory-confirmed SARS-CoV-2 infection within 7 days (of proposed consent) or the presence of symptoms or physical examination signs providing high probability of COVID-19 disease despite a negative COVID-19 test as determined by Infectious Disease specialist/COVID-19 Telehealth Treatment Team review

3.1.3 Subjects must have at least one of the following high-risk features for clinical

deterioration:
- Hypertension
- Diabetes Mellitus
- Moderate to severe Chronic Obstructive Pulmonary Disease, Emphysema, Cystic Fibrosis, or Asthma
- Cancer patients who have received any immunosuppressive drugs within a year from enrollment.
- Sickle cell disease or thalassemia
- Age $\geq$ 50
- BMI $\geq$ 30
- Living in a nursing home or long-term facility
- Underlying serious heart condition as determined by the treating physician
- Immunocompromised subject as defined by the treating physician or COVID-19 Telehealth Treatment Team

3.1.4 Ability to provide informed consent by the patient or healthcare proxy

3.1.5 Ability to return for repeated testing and observation to UKHC

3.1.6 Patients must have adequate organ and marrow function measured within the last 30 days as defined below:

– platelets	≥100,000/mcL
– AST(SGOT)/ALT(SGPT)	≤3 × institutional ULN
– creatinine	≤ 1.5 x institutional ULN OR
– glomerular filtration rate (GFR)	≥45 mL/min/1.73 m^2 unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73 m^2 (see Appendix B).

3.1.7 The effects of therapeutic agents used in this trial on the developing human fetus are unknown. Because therapeutic agents used in this trial may be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation.

3.2 Exclusion Criteria

3.2.1 Severe COVID-19 is defined by one or more of the following:
- blood oxygen saturation $\leq$ 90%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

3.2.2 Life-threatening COVID-19 is defined as one or more of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

3.2.3 Weight less than 45 kg.

3.2.4 Pregnant or breast-feeding females

3.2.5 Subjects on dialysis or with creatinine clearance < 45 ml/min

3.2.6 Existing DMID Toxicity Scale for Determining Severity of Adverse Events grade 3 or greater hepatic failure

3.2.7 Previously documented moderate or severe retinopathy or macular degeneration

3.2.8 Uncontrolled Seizure disorder

3.2.9 Known allergy to artemisia annua, artesunate, ivermectin, camostat mesilate, or other agents to be used in the trial.

3.2.10 Currently receiving any study medications for other indications

3.2.11 Concurrent use of medication that would cause moderate or severe due to drug-drug interactions with study medication.

Specifically:

- Patients receiving **ivermectin** may not be concurrently taking strong CYP3A4/ABCB1 inhibitors (Azole antifungals including voriconazole, ketoconazole, itraconazole and posaconazole; clarithromycin, telithromycin, nefazodone, saquinavir, darunavir, or lopinavir, etc.)
- Patients receiving **Artemisia annua tea or coffee OR artesunate** may not be currently taking strong inducers of CYP2A6, including phenobarbital and rifampin.[59]

3.2.12 Receipt in the 12 hours prior to enrollment, or planned administration during the 14-day study period that treating clinicians feel cannot be substituted for another medication, of any of the following: amiodarone; cimetidine; dofetilide; phenobarbital; phenytoin; or sotalol.

3.2.13 Cancer patients receiving active immunosuppressive treatment cannot enrolled unless they are on a treatment holiday with no antineoplastic treatment with 3 weeks of

enrollment.

Enrollment on other experimental therapies for COVID19

3.2.14 Inability to receive enteral medications

3.2.15 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.16 Any other condition that in the opinion of the treating physician justifies exclusion from the study.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. INVESTIGATOR REQUIREMENTS AND REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with MCC

All investigators must be qualified by education, training and experience to assume responsibility for the proper conduct of human subject research. Investigators are responsible for being able to provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation and training per institutional, state and federal guidelines. All investigators conducting MCC trials will complete all requisite training and registrations per MCC SOPs.

4.2 Clinical Trial Registration with clinicaltrials.gov and release of trial results

Contact the MCC-CRO Regulatory unit at mccreg@uky.edu if you need assistance in completing your clinicaltrials.gov registration. **Results will be released on clinicaltrials.gov according the data guidelines and requirements of clinicaltrials.gov.**

4.3 Enrollment Guidelines

Eligible patients will be identified by the principal investigator and co-investigators of this study. Potentially eligible patients will be screened via multiple testing sites as outlined in Appendix F. Patients will be evaluated at the University of Kentucky by the investigators and study personnel with oversight by the Principal Investigator (PI). Upon obtaining proper consent to treatment, patients will be enrolled into the study.

4.4 Delegation of Tasks Log (DTL)

All MCC studies require a Delegation Task Log which is maintained by the MCC Regulatory Unit of the Clinical Research Office.
In order to be added to the DTL for a given study, each staff member must have appropriate training to conduct assigned duties including but not limited to protocol specific training and review of the final protocol.

4.5 Informed Consent

The goal of the informed consent *process* is to provide people with sufficient information so they can make informed choices about whether to begin or continue participation in clinical research. The process involves a dynamic and continuing exchange of information between the research team and the participant throughout the research experience. It includes discussion of the study's purpose, research procedures, risks and potential benefits, and the voluntary nature of participation.

The informed consent *document* provides a summary of the clinical study and the individual's rights as a research participant. The document acts as a starting point for the necessary exchange of information between the investigator and potential research participant. Also, research participants and their families may use the consent document as an information resource and reference throughout participation in the trial. The informed consent *document* is often considered the foundation of the informed consent process; it does not, however, represent the entirety of the process. Nor is the informed consent document a risk-management tool for the investigator and/or institution.

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

4.6 Recruitment Plans:

Inpatient Recruitment
Inpatients will be screened by their treating physician team, informed of the study and if interested in participating, will be approached by study staff for review of eligibility and informed consent.

Outpatient Recruitment:
- *Initial study presentation: Appendix D, E*
  - Phone or telehealth contact to prospective outpatients who are being referred for testing at the University of Kentucky

        - Prescreening from screening lists (section 4.5.3)
        - Presentation of study to patient
        - Assessment of patient interest in participation
        - Directing interested patients to Research Designated Clinic or drive-through
    - OR, walk in patient presenting to Research Designated Clinic
    - OR to a telehealth consent conference

- *Research Designated Clinic:* University of Kentucky ambulatory care clinics that are:
    - Designated for testing and management of COVID-19 and its complications
    - Provides testing, evaluation, and treatment site adhering to current CDC and University of Kentucky COVID-19 guidelines for the provision of ambulatory care
    - Intended to enable recruitment and participation in research studies
    - Has the ability to obtain the nasopharyngeal swabs, blood samples, electrocardiograms (EKGs), and additional study related evaluations required for safety/tolerability and outcomes monitoring associated with this study

- *Study intake procedures: Appendix F*
    - Research Designated Clinic presents study and obtains either consent or decline to participate
        - Enroll consenting patients in study
        - Provide declining patients full scope of routine care for COVID-19 patients

4.7 Patient Screening Options

All individuals who are tested for COVID-19, via a drive through testing facility of the University of Kentucky, other testing sites sanctioned by the Kentucky Department of Health, any outpatient clinic associated with UKHC, or admitted to UKHC inpatient hospitals will be eligible for screening. If a screening consent is used, individuals willing to be screened will consent to the following:

1) Agree to allow study staff to review clinical COVID19 test results, baseline eligibility, labs, via medical records review
2) Agree to be re-contacted for study participation and future contact for possible plasma donor status.

Research staff will register screened patients into a password protected RedCap database.

Screening can be done via one of the following ways:

4.7.1 Face-to-face screening outside of clinic or inpatient (i.e. drive through test facility, nursing home setting, etc.). In this setting, patients will be given a screening consent.

4.7.2 Remote screening via referral from the University of Kentucky outpatient COVID-19 monitoring programs, including the GetWell Loop (an automated patient health monitoring tool, Appendix E), other testing systems or through phone or telehealth mechanisms, whether centralized or in association with specific clinics or clinical

entities, will be eligible to be asked if they are interested in enrollment in participating in research and will be electronically consented via RedCap and will be referred to research designated sites for treatment consent and evaluation as appropriate.

4.7.3 Waiver of consent for screening – The study team will be provided a list of all people testing positive for COVID-19 by the University of Kentucky outpatient COVID-19 monitoring program who have agreed to be contacted for this research study. Research staff will review this list of subjects, screen for the high risk categories which would make them eligible and contact the patient and offer participation in the trial via remote means. Those that meet entry criteria, and agree to participate will then have an informed consent conference with the PI or co-I, a CRA electronically (remotely, or in person) and e-sign the treatment consent via remote RedCap consent process. They will then be directed to the research clinic for specimen collection and clinic visit.

4.7.4 Direct screening – Patient's treating physician will be approached regarding eligibility and appropriateness for participation in this trial.

4.7.5 Face-to-face screening outside of clinic or inpatient will occur at those testing sites where people can be approached for potential participation but cannot be fully assessed for eligibility. In these cases, a screening consent will be used

4.8 Consent to Treatment

Once a patient meets eligibility, a formal consent conference will be undertaken by one of the means listed below.

4.8.1 In-person consent:

- Research staff sign their portion of the consent and the consent form is given to clinical staff who deliver the consent to the patient as part of their clinical duties.
- Research staff will contact the subject or legally authorized representatives (LAR) by telephone or videophone (method dictated by institutional policy) to have the informed consent conversation. *This step confirms subject/LAR identity*.
- If the subject or LAR consents:
    - Subject or LAR signs the consent form and this signature is witnessed by two individuals who document the signing of the consent on a paper attestation form outside the room.

  OR
    - A picture of the signed consent is made, and emailed to the study staff.
- The subject/LAR retains the consent form, and the signed attestation of consent or copy of the photograph is stored in the research staff records. No copy of the consent is stored due to the potential for transmission of COVID19 virus

4.8.2 Electronic Consenting

- Research staff email the consent to the patient or LAR. If the patient or LAR is offsite, a scan of the consent form can be emailed, faxed, or otherwise electronically transferred to the LAR (method dictated by institutional policy)
- Research staff will contact the subject or LAR by telephone or videophone (method dictated by institutional policy) to have the informed consent conversation. *This step confirms subject/LAR identity*.
    - If the subject or LAR consents a REDCAP survey link can be sent to their personal device and the e-consent RedCap signature process is completed and sent to study-specific RedCap storage where the PI will co-sign the form. This form also indicates the name of the study team member that was involved in the consent process.
    - If using a study-provided device, the subject reads the consent and follows the prompts in RedCap and the signed consent is electronically transmitted to the study-specific RedCap storage where the PI will co-sign the form. This form also indicates the name of the study team member that was involved in the consent process. The device is then disinfected according to local institutional practices.
- The subject/LAR receives an electronic copy of the consent form to the email provided, and the e-signed consent is stored in RedCap the research staff records.

4.8.3 Verbal consent

Because of the nature of this viral disease and the possibility of transmission through direct contact with the subject, verbal consent may also be given by the subject if witnessed and confirmed by two study staff. The verbal consent will be documented on the consent form and signed by the two witnesses.

If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by two people and documenting that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with the protocol at the time of IRB review.

4.9 Patient Registration to Treatment

To register a patient, the following information should be reviewed by the clinical research nurse (CRN) / clinical research associate (CRA) with the study physician per MCC SOPs to confirm eligibility:

- Copy of COVID19 testing results
- Mobile EKG tracing (outpatients) or standard EKG (inpatients) within 5 days of registration to assess QTc interval
- Eligibility labs, as well as correlative labs to be drawn
- Eligibility Checklist

Once eligibility is confirmed, the CRN/CRA will complete subject registration in the OnCore database (minimum data footprint) for randomization and complete study-required RedCap data forms. To complete the registration process, the CRN/CRA will:

- assign a patient study number
- register the patient on the study in OnCore
- receive the automated treatment arm assignment
- send an email or other communication to the study team of arm assignments.

If a patient is deemed ineligible for treatment their specimens will be retained in the COVID19 BIOBANK if the subject has indicated agreement to specimen collection and long-term storage in the consent form.

At the Day 1 visit or inpatient the following will be completed

1) Sign **treatment informed consent** (unless previously e-consented as above)
2) Undergo blood testing for eligibility (in subjects who have not had assessment of screening labs within the last 30 days will require blood draw)
3) Complete an eligibility questionnaire (age, concurrent diseases, current medications, contact information)
4) Undergo a mobile EKG or standard EKG tracing to assess QTc interval (within 5 days of registration)
5) Distribute medications, pill diary, and instructions
6) Baseline correlative blood sample
7) Sputum sample, with OP swab (alternative, if no sputum available)
8) Saliva sample
9) COVID-19 ordinal scale assessment (See Appendix B)
10) Limited visual physical exam unless a more complete exam is clinically indicated.

Day 3 or 4 phone call to assess clinical status and elicit concerns or questions.

Day 7 telehealth (+/- 4 days) is required for all patients to assess toxicity. If a subject has a standard of care telehealth visit during this period, this is also an acceptable toxicity assessment.

Day 10 or 11 phone call to assess clinical status and elicit concerns or questions

Day 14 (+/- 4 days) visit will also be completed in clinic or inpatient hospital.

1) Undergo blood testing for toxicity
2) Collection of medications, pill diary and instructions
3) Mobile EKG tracing (outpatients) or standard EKG (inpatients) to assess QTc interval
4) Correlative blood sample
5) Sputum sample, with OP swab (alternative, if no sputum available)
6) Saliva sample (optional)
7) Nasopharyngeal swab (optional and if indicated for standard of care)*
8) COVID-19 ordinal scale assessment (See Appendix B)
9) Toxicity assessment via telehealth or phone call (+/-4 days)

Day 28 (+/- 4 days) visit will also be completed in clinic or inpatient hospital.

1) Correlative blood sample
2) Sputum sample, with OP swab (alternative, if no sputum available)
3) Saliva sample (optional)
4) Nasopharyngeal swab (optional and if indicated for standard of care)*
5) Serology testing*
6) COVID-19 ordinal scale assessment (See Appendix B)
7) Toxicity assessment via telehealth or phone call (+/-4 days)

Day 40 (+/- 4 days) visit. If serology testing is negative or viral load remains positive, patients will be requested to return for a Day 40 visit (optional) will also be completed via drive through (preferred), clinic or inpatient hospital.

1) Correlative blood sample
2) Sputum sample, with OP swab (alternative, if no sputum available)
3) Saliva sample (optional)
4) Nasopharyngeal swab (optional and if indicated for standard of care)*
5) Serology testing (optional and if indicated for standard of care)*
6) COVID-19 ordinal scale assessment (See Appendix B)

*These are considered standard of care tests

4.10 General Guidelines

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the PI and the statistician must be consulted as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Archival		
	• *Discarded tissue or blood samples from original COVID19 testing* • *Residuals from any of the research samples collected below*	*Center for Clinical and Translational Science (CCTS) COVID-19 Research Registry and Specimen Bank (CRRSB)*
Baseline – Day 1		
	• *10 mL and 6 mL blood in EDTA (purple top) tubes for antibody testing, procalcitonin, CRP and cytokines* • *5 mL blood in ACD (yellow top) tube for platelet function assays (optional)* • *8mL blood in CPT tube (optional)*	*Biospecimen Procurement and Translational Pathology Shared Resource Facility (BPTP SRF) or CCTS CRRSB*

	• *Sputum sample (Mandatory) or OP swab (alternative, if sputum is unavailable)* • *1 ml of saliva (optional)*	
Day 14 (+ / - 4 day)		
	• *10 mL and 6 mL blood in EDTA (purple top) tubes for antibody testing, procalcitonin, CRP and cytokines* • *5 mL blood in ACD (yellow top) tube for platelet function assays (optional)* • *8mL blood in CPT tube (optional)* • *Sputum sample (Mandatory) or OP swab (alternative, if sputum is unavailable)* • *1 ml of saliva (optional)*	*BPTP SRF or CCTS CRRSB*
Day 28(+/- 4 days)		
	• *10 mL and 6 mL blood in EDTA (purple top) tubes for antibody testing, procalcitonin, CRP and cytokines* • *5 mL blood in ACD (yellow top) tube for platelet function assays (optional)* • *8mL blood in CPT tube (optional)* • *Sputum sample (Mandatory) or OP swab (alternative, if sputum is unavailable)* • *1 ml of saliva (optional)*	*BPTP SRF or CCTS CRRSB*
Day 40(+/- 4 days)		
	• *10 mL and 6 mL blood in EDTA (purple top) tubes for antibody testing, procalcitonin, CRP and cytokines* • *5 mL blood in ACD (yellow top) tube for platelet function assays (optional)* • *8mL blood in CPT tube (optional)* • *Sputum sample (Mandatory) or OP swab (alternative, if sputum is unavailable)* • *1 ml of saliva (optional)*	*BPTP SRF or CCTS CRRSB*

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Procurement Kits

Specimen procurement kits will be supplied by the Biospecimen Procurement and Translational Pathology Shared Resource Facility (BPTP SRF).

5.3 Specimen Collection and Processing

Residual Clinical Samples (blood, sputum, saliva, nasopharyngeal and oropharyngeal swab

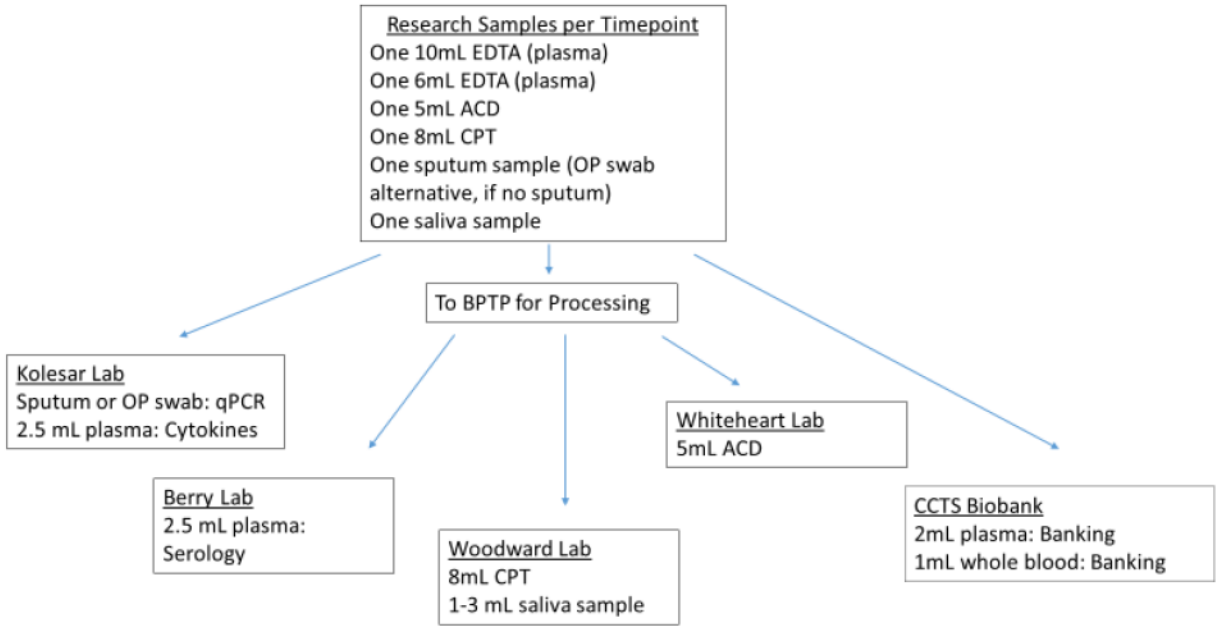
samples): Residual clinical samples will include serum and plasma originally collected in EDTA, citrated or heparinized tubes and subsequently stored at -20^{0}C in 5ml pour-off tubes. Subsequently, these samples will be transferred to the Markey Cancer Center Biospecimen Procurement and Translational Pathology Shared Resource Facility (BPTP) or the Center for Clinical and Translational Science (CCTS) COVID-19 Research Registry and Specimen Bank. BPTP or CCTS staff will log, and label and store the residual clinical plasma and serum specimens at -80^{0}C or lower. Upper respiratory tract samples will include residual nasopharyngeal and oropharyngeal swab specimens stored in viral transport media (VTM) and initially frozen at -70^{0}C. After transport to the BPTP, the staff will log, label and store the specimens at -80^{0}C or lower.

Research Peripheral Blood Samples for Procalcitonin, D-Dimer, Cytokines, Seroconversion, and Platelet Function: One10-mL and one 6-mL EDTA (purple top) tubes, one 5 mL blood in ACD (yellow top) tube and one 8mL blood in CPT tube (optional) of blood will be drawn and immediately delivered to the Markey BPTP-SRF lab or the CCTS COVID-19 Research Registry and Specimen Bank. EDTA and CPT tubes will be processed as soon as possible, but at most will occur within 24 hours of blood draw. ACD tubes will be delivered immediately to the Whiteheart lab (see below). Biobank staff will freeze a 1-mL aliquot of whole blood, then centrifuge the remainder at ~1,200 RCF for 12 minutes to separate and collect plasma and buffy coat. Samples will be logged and labeled and aliquoted and stored frozen at –80^{0}C or lower. Delivery and receipt of refrigerated blood samples will occur Monday through Friday.

Research Oropharyngeal (OP), for Viral Load: One swab sample will be collected per patient following standard procedure at each study time point, immediately placed in viral transport media and refrigerated or stored at -80^{0}C or lower. Deliveries and receipt of frozen or refrigerated samples will occur Monday through Friday.

Research Sputum Samples for Viral Load: One sputum sample per patient at each study time point will be collected following standard protocol. The specimens will be delivered immediately to the BPTP lab. Samples will be logged and labeled and stored at -80^{0}C or lower.

Research Saliva Samples: One optional saliva sample per patient at each study time point will be collected following standard protocol. The specimens will be collected in a standardized kit and held at 4^{0}C until delivery to the BPTP lab. Samples will be logged and labeled and delivered to the Woodward Lab.



Research specimen processing and delivery algorithm

5.4 Shipping/Dispensing of Specimens

Samples will be transported to the MCC BPTP SRF or the CCTS COVID-19 Research Registry and Specimen Bank for processing and transport to the appropriate labs as above.

6. TREATMENT PLAN

Subjects will be approached at the time of initial COVID-19 testing or within 7 days of a positive test. Prior to any study-required tests, subjects must first provide written informed consent to participate in this study.

6.1 Agent Administration

The CURE Alliance Drug Steering Committee will serve as the drug selection committee to identify the appropriate new drugs for each new arm of this clinical trial. Treatment will be administered on an outpatient or inpatient basis provided that entry criteria are met. If emerging data indicates futility of a medication in one or more arms of our study, and was tested in a similar patient population in a randomized clinical trial or trials, the study drug selection committee may recommend removal of that drug treatment arm for futility with approval of the study team. Once a futility endpoint is met in an arm, we will replace that arm with the next appropriate proposed arm with approval of the CURE Alliance Drug Steering Committee.
All subjects receive standard supportive treatment throughout their infection, whether outpatient or during inpatient hospitalization. Reported adverse events and potential risks are described in Section 10.

Treatment regimens will be evaluated and novel agents selected by the steering committee. Should drug supply become unavailable that arm would pause until drug supply is available.

Regimen Description- Arm C				
Agent	***Formulation Strength***	***Daily Dose***	***Route***	***Schedule***
Ivermectin	3 mg tablet	12-15 mg	Oral	Weight < 75kg: 4 tabs on Days 1 and 2, (12 mg total daily dose) Weight ≥ 75kg: 5 tabs on Days 1 and 2, (15 mg total daily dose)

Regimen Description- Arm D				
Agent	***Formulation Strength***	***Daily Dose***	***Route***	***Schedule***
Camostat Mesilate	100 mg tablet	600mg	Oral	2 tab TID after a meal (600 mg total daily dose) Days 1-14

Regimen Description- Arm E				
Agent	***Formulation Strength***	***Daily Dose***	***Route***	***Schedule***
Artemisia annua tea or coffee	Decaf coffee 450mg per pod Tea 225mg per bag	1350 mg	Oral	One 8oz brewed tea (two bags) or one coffee pod TID Days 1-14

Regimen Description- Arm F				
Agent	***Formulation Strength***	**Daily Dose**	**Route**	**Schedule**
Artesunate	*100mg*	200mg	Oral	Two tabs once day (200mg total) Days 1-14

Patients will be assigned to a treatment arm according to the randomization process described in Section 9 of this protocol

Since there are no safety data for the medications to be evaluated on all arms of this study in the mild to moderate SARS-CoV-2 infected population, the first six patients on each arm will be evaluated for any grade 3 or higher hematologic or non-hematologic toxicity for 14 days. Patients coming off study before the first 14 days for reasons other than toxicity will be replaced. If two or more of the six patients in this arm of the study develop unacceptable toxicity, the treatment for that arm would be considered unsafe and stopped. Patients exhibiting rapid progression of COVID-19 symptomatology requiring intensive care hospitalization or intubation will come off study and will be considered failures in terms as per the primary endpoints of the study but nor for safety and will be replaced if these cases occurred during the phase 1 portion of the study.

Once the phase 1 portion safety run-in has concluded, that arm will be opened for phase II accrual.

Patients will be assigned to each arm in cohorts of three at a time until accrual numbers for each arm are fulfilled or discontinued due to safety concerns occurring beyond the Phase 1 portion. Monthly phone conferences among investigators during enrollment will take place.

Patients will undergo baseline mobile EKG or standard EKG to evaluate QTc interval on Day 1 (or within 5 days of registration if inpatient) and a repeat EKG at Day 14 (+/-4 days). Any Chest X-ray or CT scan of the chest that is performed for routine care will be reviewed by the PI for eligibility and recorded on case report forms. NOTE: if a patient develops a myocardial infarction or grade 3 or 4 cardiac arrythmia while on the 14 days of drug, they should be immediately taken off study medication and receive standard of care treatment per their treating physician.

Patients will be followed for clinical outcomes by phone contact each week and hospitalizations, and all complications will be recorded on adverse event case report forms.

6.2 Definition of Dose-Limiting Toxicity (DLT) for phase I run in portions of this protocol

A DLT is defined as any of the below treatment emergent toxicities with attribution of definitely, probably or possibly related to one or more of the study drugs that occur during the first 14 days of study treatment. Toxicities that occur after the 14 day treatment period will be reported through adverse event reporting outlined in section 10.0, but will not be counted as DLTs.

- **Grade 3 or higher non-hematologic or non-hematologic toxicity at least possibly, probably or definitely related to study medication or procedures, per DMID Toxicity Scale for Determining Severity of Adverse Events**

6.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment is given until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Pregnancy
- The drug manufacturer can no longer provide the study agent
- Admission to the Intensive Care Unit and/or need for mechanical ventilation. At this

time, the treating physician will have the ability to continue study drug, discontinue therapy, place the patient on another study trial, or treat the patient with alternative therapies, per their clinical judgement. At this point, the patient will be followed by the study team to track outcomes and monitor for adverse events that might be attributable to study drug but the drug will be considered to have failed the primary endpoint

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF). For clarity, "off treatment" is the date when all medication has been completed (including the normal observation period) or discontinued due to one of the factors above, and no further treatment is planned. This is the date the patient has been officially taken off treatment. "Off study" is the date after which no further follow-up of the patient will occur

6.4 Duration of Follow-Up

Patients will be followed for up to 40 days from the beginning of therapy or until death, whichever occurs first.

7. DOSING DELAYS/DOSE MODIFICATIONS

N/A.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 10.1.

8.1 Drug Ordering and Accountability

8.1.1 Procurement of medications:
Prescriptions for medications will be written by the site PI, qualified Co-I (physician), or treating physician as outlined in Section 6.0. IDS will order and dispense ivermectin, camostat mesilate, artesunate and other investigational agents if new arms are opened during the treatment phase of this trial. Drug accountability will be maintained on a National Cancer Institute Drug Accountability Report Form (DARF). Artemisia annua, a natural product/botanical, will be ordered directly from Baesman Distributors.

8.1.2 Storage & Drug Accountability:
The University of Kentucky Investigational Drug Service pharmacist will ensure that all study drug is stored in a secured, limited access storage area, under recommended storage conditions in accordance with applicable labeling and regulatory requirements and as provided by the separate study drug accountability manual. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinics. Adequate records documenting receipts, use, return, loss, or other disposition of study provided drugs must be kept. The University of Kentucky Investigational Drug Service will supply drug accountability forms that will be used, or may approve use of standard institution forms. Drug accountability

and supply order instructions and forms will be provided in a separate study manual. The accountability ledgers will be maintained to contain current and accurate inventory records and must be readily available for inspection. Unless otherwise authorized by the sponsor, at the end of the clinical trial all drug supplies unallocated or unused by sites or patients must be returned to the University of Kentucky Investigational Drug Service (UK IDS) for final actions in accordance with sponsor instructions.

The exception to this practice will be the natural product, Artemisia annua tea or coffee which is commercially available and will be supplied by Artemilife, via its distributor, Baesman distributors (see Appendix H for instructions)

8.1.3 Ivermectin

Procurement
This medication will be dispensed by IDS service.

Formulation
3mg tablets

Preparation, Storage and Stability
Please refer to package insert for complete preparation and dispensing instructions.
Dispense eight 3mg tablets (for patients < 75 kg); ten 3 mg tablets (for patients ≥ 75 kg)

Administration
Refer to the treatment section 6.1 for specific administration instructions.

Patients should be instructed to take: 4 tabs on Days 1 and 2, (12 mg total daily dose) for weight < 75 mg; or 5 tabs on Days 1 and 2, (15 mg total daily dose) for weight ≥ 75 kg. Ivermectin should be taken on an empty stomach.

Drug Interactions
Increased Effect/Toxicity: CYP3A4 and ABCB1 inhibitors may increase therapeutic concentrations of ivermectin, avoid concurrent use of ivermectin and strong CYP3A4 or ABCB1 inhibitors
Decreased Effect: Ivermectin may decrease the therapeutic effect of BCG and live vaccines, avoid concurrent use

Herb/Nutraceutical Interactions: None

Pharmacokinetics
Absorption: Well absorbed, administer on empty stomach. High fat meal increased bioavailability 2.5 fold
Distribution: Vd: 3.1-2.5 L/kg, does not cross blood brain barrier
Metabolism: Hepatic via CYP3A4 (major)
Half-life elimination:
Terminal: 18 hours

Excretion: Less than 1% via feces and urine

Adverse Events
Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%: None

Less common known potential toxicities, 1% - 10%:
Tachycardia (4%)
Peripheral edema (3%)
Dizziness (3%)
Diarrhea (2%)
Eosinophilia (3%)
Elevations in LFTs (2%)

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Hyperbilirubinemia
Hypersensitivity

Pregnancy: The here is insufficient evidence to prove safety. Based on the animal and human data ivermectin is labeled category C in the US (animal EFD finding, but only at doses also toxic to the pregnant female). The manufacturer considers it contraindicated in pregnancy.

8.1.4 Camostat Mesilate

Procurement
This medication will be dispensed by IDS service.

Formulation
100 mg tablets

Preparation, Storage and Stability
Tablets should be stored at room temperature.

Dispense 84, 100 mg tablets

Administration
Refer to the treatment section for specific administration instructions
Patients should be instructed to take two 100 mg tablet, three times per day (after meal) Days 1-14.

Drug Interactions
Increased Effect/Toxicity: No known drug interactions

Decreased Effect: No known drug interactions

Herb/Nutraceutical Interactions: No known drug interactions

Pharmacokinetics
Absorption: well absorbed orally
Distribution: Not established
Metabolism: Metabolized to two major metabolites: the carboxylic acid derived from cleavage of the carboxamide (FOY-251); and the carboxylic acid derived from cleavage of the internal carboxyester (GBA). Both are rapidly eliminated with elimination half-lives of roughly 1 hour. FOY-251 retains activity against the protease target.
Half-life elimination: 170 minutes
Terminal: Not reported
Excretion: Most of the substance is excreted by 5 to 6 hours after dosing, through all routes including fecal, urine, bile, etc. About 20% of a 200 mg dose is excreted into the urine as GBA and about 1% is excreted as FOY-251

Adverse Events
Common known potential toxicities, > 10%:
None reported

Less common known potential toxicities, 1% - 10%:
Thrombocytopenia
Hypokalemia
Liver function abnormalities
Jaundice
Itching or skin eruption/rash
Nephrolithiasis
Diabetic ketoacidosis
Abdominal pain or bloating
Pancreatitis

Pregnancy: There is insufficient evidence to prove safety of camostat mesilate in pregnant females.

8.1.5 Artemisia annua tea and coffee

Procurement

Outpatients: Coffee and tea botanical products will be directly shipped overnight to study patients, who are outpatients by Baesman on behalf of ArtemiLife. Patients without a pod coffee maker will also receive a coffee maker.

The distributor for Artemisia annua is as follows:

Baesman Distributors
4477 Reynolds drive
Hilliard, Ohio 43026
Contact: Tbaesman@baesman.com

Subjects randomized to Arm E will have their information entered into the ordering portal of

Baesman Distributors website.

Inpatients: This botanical product will be dispensed by Artemilife to the IDS pharmacy.

Formulation
Decaf coffee: 450 mg per pod
Tea: 225 mg per bad

Preparation, Storage and Stability
Tea and coffee should be stored at room temperature.

Coffee: Dispense 42, 450 mg pods
Tea: Dispense 84, 225 mg bags

Administration
Refer to the treatment section for specific administration instructions
Patients should be instructed to brew 1 (450mg) coffee pod or 2 (225mg) tea bags in 8 oz of water three times per day Days 1-14.

Drug Interactions
Increased Effect/Toxicity: No known drug interactions

Decreased Effect: CYP2A6 strong inducers may reduce the effects of Artemisia annua

Herb/Nutraceutical Interactions: No known interactions

Pharmacokinetics
Absorption: well absorbed orally
Distribution: Not established
Metabolism: Metabolized by CYP2A6
Half-life elimination: 1hr
Terminal: Not reported
Excretion: Not known

Adverse Events
Common known potential toxicities, > 10%:
None reported

Less common known potential toxicities, 1% - 10%:
Nausea

Pregnancy: Artemisia annua tea is used for the treatment of malaria in pregnant women and is considered safe

8.1.6 Artesunate (Arm F)

Procurement

This medication will be dispensed by IDS service.

Formulation

100mg tablet

Preparation, Storage and Stability
Artesunate should be stored at room temperature.

Dispense 28, 100 mg tablets

Administration
Refer to the treatment section for specific administration instructions
Patients should be instructed to take 2 tablets once a day Days 1-14.

Drug Interactions
Increased Effect/Toxicity: No known drug interactions

Decreased Effect: CYP2A6 strong inducers may reduce the effects of Aa and artesunate

Herb/Nutraceutical Interactions: No known drug interactions

Pharmacokinetics
Absorption: well absorbed orally
Distribution: Not established
Metabolism: Metabolized by CYP2A6
Half-life elimination: 1hr
Terminal: Not reported
Excretion: Not known

Adverse Events
Common known potential toxicities, > 10%:
Neutropenia
Anemia
Nausea

Less common known potential toxicities, 1% - 10%:
Diarrhea

Pregnancy: Artesunate is used for the treatment of malaria in pregnant women and is considered safe

8.1.7 Useful Links and Contacts

- IDS website: https://idsc.sharepointsite.net.
- IDS email: IDS@uky.edu
- IDS phone and hours of service: (859) 218-5562
- IDS Fax: (859) 323-4765
- IDS hours Monday through Friday between 8:30 am and 4:30 pm (ET)

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This study is a randomized, multi-arm phase II trial. No proven effective therapies currently exist for COVID19 (Sanders J et al. JAMA April 13, 2020), thus a selection design using the frequentist pick-the-winner design will be employed as early screening for promising therapies. The primary objective is to rapidly evaluate multiple potential inhibitors of SARS-CoV-2 viral replication in COVID19 positive patients with high-risk factors in order to decrease clinical deterioration, defined as a less than 2 point decrease in initial COVID 7-POINT ORDINAL OUTCOMES SCALE within 14 days from study entry (primary). As an example, if a person enters the study at ORDINAL SCALE 6 and does not worsen to 4 or less, that is considered a success.

For each arm a phase I lead in portion, six patients per group will be followed in order to evaluate dose limiting toxicities and preliminary safety. If 2 of the first 5 patients or if ≥2 of 6 patients experience DLT, the regimen will not be considered safe for further evaluation.

The trial will be powered based on the primary endpoint of the rate of patients who will exhibit less than 2 levels of decrease in COVID 7-POINT ORDINAL SCALE from baseline to Day 14. The goal of selection designs is to select with high probability should a superior treatment exist. Note that hypothesis testing or comparisons between arms or with a placebo is not performed with this design and subsequent trials are needed for definitive hypothesis testing of the promising arm.

9.2 Secondary Endpoints

Secondary endpoints related to efficacy:

- Presence of symptoms or physical examination signs related to COVID-19 disease on Day 14 including: fever, shortness of breath, muscle aches, sore throat, loss of sense of taste or smell, etc.
- Presence of SARS-CoV-2 RNA as detected by polymerase chain reaction (PCR) in nasopharyngeal samples measured minimally on Days 1, 14 and 28
- Proportion of patients with symptoms or physical examination signs related to COVID-19 disease including shortness of breath, muscle aches, sore throat, loss of sense of taste or smell, hospital admission, length of stay, supplemental oxygen requirements, need for mechanical ventilation, intensive care unit admission, etc.

- Time to improvement and resolution of symptoms from baseline to Day 14 and 28
- Oxygen-free days to Day 28
- Ventilator-free days to Day 28
- Vasopressor-free days to Day 28
- ICU-free days to Day 28
- Hospital-free days to Day 28

Secondary endpoints related to safety and tolerability up to Day 28

- Incidence, severity, drug-relatedness, and seriousness of adverse events
- Proportion of patients meeting Hy's law criteria
- Proportion of patients with the following Liver function tests (LFT) changes:
  - Any ALT or AST ≥ 5 x ULN
  - Any AST or ALT ≥ 3 x ULN together with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophil percent or count above the ULN)
  - Persistent ALT ≥ 3 x ULN for a period of more than 4 weeks.
- Proportion of patients with significant changes in ECG findings, including heart rate, ECG intervals (PR, QTcB, QTcF), conduction changes, or abnormalities including severe QTc prolongation of > 500 ms.
- Proportion of patients with serious allergic and skin reactions
- Proportion of patients with severe hypoglycemia
- Proportion of patients with retinopathy or macular degeneration
- Proportion of patients with seizure
- Proportion of patients with acute pancreatitis
- Proportion of patients with acute kidney injury
- Proportion of patients with receipt of renal replacement therapy
- Proportion of patients with neutropenia, lymphopenia, anemia, or thrombocytopenia
- All-cause mortality rate

9.3 Sample Size/Accrual Rate

The assumption is that transition rate for deterioration in clinical scale is equal to 20% for the high-risk patients to be enrolled in this trial based on a recent MMWR report from the CDC. The goal is to determine if any of the candidate treatments will exhibit a 50% reduction in deterioration of clinical status (i.e. deterioration rate = 10%). Thus, baseline stability in clinical scale (decrease less than 2 points in COVID 7-POINT ORDINAL SCALE) is assumed to be 80% and an improvement to 90% of all patients remaining stable (decrease less than 2 points in COVID 7-POINT ORDINAL SCALE) is hypothesized. A sample of 60 patients in each arm is proposed. If there is a clear superior treatment as shown in scenarios A and B below, there is at least an 82% selection probability. If the clinical response rate across arms are not very different, the probability of selecting the superior treatment is at 70% and is much higher compared to the other treatments (scenario C); while there is an equal chance of selecting arms that have similar superior efficacy (scenario D).

Scenario A	Response Rate	n	Selection Probability
Trt 1	.80	60	.035
Trt 2	.80	60	.035
Trt 3	.80	60	.035
Trt 4	.90	60	.822

Scenario C	Response Rate	n	Selection Probability
Trt 1	.80	60	.026
Trt 2	.80	60	.026
Trt 3	.85	60	.146
Trt 4	.90	60	.700

Scenario B	Response Rate	n	Selection Probability
Trt 1	.80	60	.002
Trt 2	.80	60	.002
Trt 3	.85	60	.019
Trt 4	.95	60	.949

Scenario D	Response Rate	n	Selection Probability
Trt 1	.80	60	.011
Trt 2	.80	60	.011
Trt 3	.90	60	.421
Trt 4	.90	60	.421

Interim monitoring to assess futility or efficacy will be performed during the trial using the Bayesian posterior probability (See Section 9.6). If a total of 60 patients is enrolled in an arm, the proposed sample size will provide an estimate of clinical success rate with width of a two-sided 90% confidence interval (CI) equal to 0.143 assuming a response rate = 0.90; specifically, a 90% two-sided exact binomial CI = 0.81 – 0.95.

Based on this current design, we plan to enroll a maximum of 240 total patients.

9.4 Randomization/Stratification Factors

Blocked randomization with equal allocation will be utilized with adjustment in randomization sequence to account for the potential to drop an arm. Block size is 2 times the number of treatment arms. Randomization will be stratified by outpatient or inpatient status at time of enrollment into the trial.

Randomization lists will be generated prior to study enrollment and provided to the IDS pharmacist who will be in charge of the randomization with the randomization coordinator. All other study personnel including the PIs will be blinded to the randomization lists to prevent patient and investigator bias. Patients who are eligible for randomization will be assigned to a treatment arm according to the randomization list.

In the scenario where a treatment arm is terminated early or a new treatment is added into the study, a new randomization list may be generated to replace the existing one. The randomization list will give every patient equal probability to each study arm that is currently available.

The randomization list will be incorporated into the OnCore Clinical Trials Management System and accessible to the IDS pharmacist. This is facilitated by the OnCore CTMS which assigns different access and restriction levels depending on personnel role in the study. Treatment allocation for each patient is thus performed by the IDS pharmacist after Study Coordinator confirms patient eligibility status.

9.5 Statistical Analysis Plan

The primary analysis will include estimate of the rate of stability in clinical scale (less than 2 point decrease in COVID 7-POINT ORDINAL SCALE) for each arm along with exact binomial 90% confidence interval. This is based on the first response in clinical scale after enrollment and randomization into the trial. In addition, the Bayesian posterior probability of the response rate being greater than 90% will be calculated for each arm at the end of the trial. The rates of development of severe respiratory or organ failure, clearance of viral RNA at day 28 and mortality will be summarized in each arm. Changes in SARS-CoV-2 RNA as detected by polymerase chain reaction (PCR) over time will be summarized in each treatment arm and compared using paired tests or longitudinal linear models.

Secondary endpoints related to proportion of outcomes as indicated in Section 9.2 will be estimated along with exact confidence intervals while descriptive statistics including median, range, IQR will be calculated for the duration in days of efficacy outcomes. Survival analysis methods will be utilized to estimate time to event endpoints. The exploratory and correlative endpoints such as inflammatory markers and cytokine levels will be summarized at baseline and follow-up time points. Changes from baseline will be compared using paired test or longitudinal linear mixed models.

Secondary analyses will include estimates of rate and confidence intervals of stability in clinical scale (less than 2 point decrease in COVID 7-POINT ORDINAL SCALE) either from the outpatient or inpatient continuum using subgroup analyses or logistic regression with a variable to account for response status among outpatients for each arm.

All patients who received study drugs will be included in the safety analysis. The maximum grade of toxicity for each category of interest will be recorded for each patient and summary results will be tabulated by category and grade. We will describe all serious ($\geq$ grade 3) toxicity events. Frequency and incidence tables of toxicity and AEs will be generated in each treatment arm. Likewise, proportions of specific safety endpoints in Section 9.2 will be summarized.

m-ITT population is defined as all patients who have been randomized and received at least one dose of the study treatment. The primary analysis will be based on the m-ITT population.

Handling of missing data: The primary endpoint is based on a simple 7-scale assessment and is unlikely to be missing. Patients who are in the m-ITT population but have missing primary endpoints will be classified as non-responders to the treatment.

9.6 Interim Analysis

The timing of interim analysis will be based on rate of patient accrual. An initial interim analysis will be performed after 10 patients are randomized in each arm. Futility and efficacy will be assessed in each treatment arm by calculating Bayesian posterior probabilities. The beta distribution for the efficacy/success rate is utilized with a non-informative Jeffrey's prior equal to beta (0.5, 0.5). Specifically, a futility rate $\leq$ 80% will be assumed and the probability for stopping for futility will be set at 70%. An efficacy rate $\geq$ 90% will be assumed and a

probability for early stopping for efficacy set at 90%. Based on these assumptions, the futility stopping boundary for the first 10 patients in each arm is set at ≤ 7 patients with clinical stability (i.e. less than 2 point decrease in COVID 7-POINT ORDINAL SCALE) in a specific treatment arm.

The Bayesian methodology allows flexibility in the timing and cohort size in each arm in the conduct of each interim analysis. Thus, depending on patient enrollment and cohort size in each arm, subsequent interim analyses will be performed (e.g. after every 10 additional patients in each arm) and additional stopping bounds will be calculated. ***Real-time assessments of patient response will be critical and will be facilitated by close coordination of clinical and research teams***.

The decision making process for this trial such as dropping an arm or other changes on how to proceed with the trial will be based on clinical and safety considerations along with newly developing information on COVID19 as well as guidance by results of efficacy estimates and interim posterior probabilities.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Adverse events must be evaluated by the investigator, graded and assigned an attribution of relatedness to study treatment. The characteristics of an observed AE will determine whether the event requires expedited reporting to Overall PI, the FDA, the UK IRB, and MCC DSMC via **in addition** to routine reporting.

10.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the investigational agents described above.

10.2 Adverse Event Characteristics

Adverse events (AEs) will be summarized by presenting, for each arm, the number and percentage of patients having any AE, having an AE in each MedDRA primary system organ class (Appendix G) and having each individual AE (preferred term) including relatedness. Additionally, a summary of adverse events by preferred term and severity will be performed using the worst severity grade.

All AEs must be evaluated and commented on by the Investigator and graded according to the DMID Toxicity Scale for Determining Severity of Adverse Events (Appendix G).

All related AEs, AEs with outcome death, AEs leading to permanent discontinuation of treatment, SAEs and related SAEs will be summarized by percentages and frequencies and listed including the Investigator term, the preferred term, start and end date of AE, duration (days), severity, drug relationship, action taken and outcome.

- **Attribution** of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 MCC Expedited Adverse Event Reporting Guidelines

Investigators will report SAEs that are possibly, probably or definitely related to study drug or procedures directly to the MCC DSMC per the MCC DSMC SOP and the University of Kentucky IRB reporting policy, as specified below. Use the MCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

In addition to reporting to IRB, MCC DSMC and the PI, for agents under an IND, investigators will report all medication related (possibly, probably or definitely related) SAEs to the FDA per required reporting processes using MedWatch form 3500. In summary:

1. During phase I run in period, report grade 1-5 adverse events (AEs) that are drug-related (possibly, probably or definitely related) to PI, IRB, DSMC in an expedited fashion. Following phase I run-in period for each arm, report grade 3-5 SAEs that are drug related to PI, IRB, DSMC. After the phase I run-in period, grade 1 and 2 AEs related to FDA approved medications or botanical products are only reported if determined by the investigator to be clinically significant AEs.
2. Report any unexpected fatal or life-threatening suspected adverse reactions to the FDA no later than 7 calendar days after initial receipt of the information. Submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG).
3. Report any serious, unexpected suspected adverse reactions or a clinically important increase in the rate of a serious suspected adverse reaction to the FDA electronically in eCTD format via the ESG and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting.

Do not report COVID-19 AEs or other AEs to these entities unless they are related to study medication or procedures as listed above.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Expedited Reporting Requirements for Adverse Events that Occur on Medications in Study Arms under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report **ANY** Serious Adverse Events, as listed below(21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, nor be life-threatening, nor require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 (definite, possibly or probably related to study medication) Timeframes	Grade 3-5 (definite, possibly, or probably related to study medication Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting Section.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

Grade 1 and 2 AEs resulting in hospitalization or prolongation of hospitalization

10.4 Exceptions to AE reporting

Adverse events related to SARS-CoV-2 infection are exempt from adverse event reporting unless the investigator considers the event to be possibly, probably, or definitely related to the study drug or study procedures. Examples of COVID-19 related AEs include:

- Death not related to the study procedures
- Neurological events
    - Seizure
- Cardiovascular events
    - Atrial or ventricular arrhythmia
    - Cardiac arrest
- Respiratory events
    - Hypoxemia requiring supplemental oxygen
    - Acute respiratory distress syndrome
    - Receipt of mechanical ventilation
    - Receipt of extra-corporeal membrane oxygenation

10.5 Expedited Reporting to External Agencies

Overall PI will comply with the policies of all external funding agencies and the UK IRB regarding expedited reporting, as per the UK IRB's Mandated Reporting to External Agencies SOP C4.0150.

10.6 Expedited Reporting to the Food and Drug Administration (FDA)

Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA using the MedWatch 3500 form by one of the following means:

- To fax report: 1-800-FDA(332)-0178
- To report online: www.fda.gov/medwatch/report.htm
- To report by email: naseya.minor@fda.hhs.gov.

10.7 Expedited Reporting to Hospital Risk Management

Participating investigators will report to the UK Office of Risk Management any participant safety reports or sentinel events that require reporting according to institutional policy.

10.8 Routine Adverse Event Reporting

All Adverse Events that are definitely, probably or possibly related to study treatment **must** be reported in routine study data submissions with the exception of those listed in Section 10.4. **AEs reported expeditiously to the Overall PI and DSMC must also be reported in routine**

study data submissions.

Grade 1 and 2 adverse events related to FDA approved medications used in this trial (i.e. hydroxychloroquine, azithromycin, ivermectin, artemisia annua) are only reported if determined by the investigator to be clinically significant AEs.

10.9 Pregnancy

Pregnancy is considered an unanticipated event and pregnancy as well as its outcome must be documented and reported to overall PI and DSMC and Office of Research Integrity, as well the FDA and sponsor in according to reporting requirements. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old.

11. STUDY CALENDAR

	Pre-Study	Day 1	Day 3 or 4	Day 7 +/-2 Days	Day 10 or 11	Day 14 +/- 4 Days	Day 28 +/- 4 Days	Day 40*** +/- 4 Days
Investigational Agent (s) (section 6.0)		A						
Informed consent screening (optional)	X							
Informed consent treatment		X						
Demographics		X						
Eligibility review via medical record	X							
Medical history via medical record review		X				X	X	X
In-person evaluation		X				X		
Telehealth contact			X[a]	X[a]	X[a]			
Concurrent meds		X----------						----------X
CBC w/diff, plts*		X				X*		
Serum chemistry, (CMP)*		X				X*		
EKG for QTc		X[b]				X	X****	
Adverse Events		X----------						----------X
Standard of Care Nasopharyngeal, Swab and SARS-CoV-2 antibody testing, if clinically indicated (optional)****						X**	X**	X**
Sputum sample or OP swab (alternative)		X				X	X	X
Blood sample for Inflammatory cytokines, D-Dimer, CRP, and Procalcitonin and seroconversion (10 mL and 6 mL purple tops)		X				X	X	X
Blood sample for platelet studies (5 mL yellow top) (optional)		X**				X**	X**	X**
CPT tube (8 mL speckled top)(optional)		X**				X**	X**	X**
Saliva sample (optional)		X**				X**	X**	X**

A - based on assigned arm
*if not obtained for routine care (for screening phase, if not obtained within the previous 30 days; for treatment phase, if not obtained for routine care of COVID19)
**optional
*** Day 40 only occurs if patient's serology is negative and viral RNA is positive
****Only if indicated for routine care
[a] phone or telehealth contact if the patient is an outpatient
[b] EKG must be obtained within 5 days of registration

12. MEASUREMENT OF EFFECT

12.1 Evaluation of Response

Subjects will be assessed for incidence of change in COVID 7-POINT ORDINAL OUTCOMES SCALE from the time of diagnosis to Day 14 (primary endpoint) and Day 28 (secondary endpoint). Subject sputum samples will be assessed for viral RNA by PCR on Day 1, 14, 28 (and where indicated at Day 40) in the Kolesar lab. Viral loads will be expressed in copies per mL and the decline in viral copy number will be assessed between Day 1, 14, 28 (and where indicated at Day 40) using SAS.

12.2 Other Response Parameters

Participants' medical records will be used to assess the development of severe respiratory or other organ failure in the study population at 40 days, as well as to assess mortality and rate of severe adverse events defined as grade 3 non hematologic or greater by DMID Toxicity Scale for Determining Severity of Adverse Events.

Safety, tolerability and compliance with of each regimen will be recorded on case report forms.

13. STUDY APPROVAL, OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

13.1 Protocol Review and Monitoring Committee and Institutional Review Board Review

Before implementing this study, the protocol must be reviewed by the Markey Cancer Center's Protocol Review and Monitoring Committee and the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the University of Kentucky Institutional Review Board (IRB). A signed and dated UK IRB initial review approval memo must be maintained in the Markey Cancer Center Clinical Research Office (MCC CRO) regulatory binder. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the PRMC, study sponsor and the UK IRB.

13.2 Quality Assurance

The MCC places the highest priority on ensuring the safety of subjects participating in clinical trials and on the quality of data obtained from clinical and translation research. The MCC Quality Assurance (QA) Office oversees the maintenance of quality standards in clinical cancer research through clinical data monitoring of Investigator-Initiated Trials (IITs) and routine audits.

13.2.1 Data Monitoring

The MCC QA Office will collaborate with the PI, Biostatisticians and Data Management Specialist in creating a Clinical Data Monitoring Plan (CDMP) using a risk-based approach. The CDMP will

describe the scope, communication plan, and frequency of monitoring visits. In addition, describe query submissions and resolutions, action items and monitoring reports.

The QA monitor assigned to the trial will perform the monitoring tasks in accordance with the protocol-specific CDMP. The monitoring process will provide research staff and the PI with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of the case report forms, assure that all protocol requirements, including applicable regulations and investigator's obligations are being fulfilled, and prompt resolution of any inconsistencies in the study records.

13.2.2 Audit

To ensure compliance with the International Conference on Harmonisation of Good Clinical Practice Guidelines and all applicable regulatory requirements, the MCC Audit Committee will conduct a quality assurance audit. A minimum of *10%* of patients enrolled in the study may be selected for review. The purpose of a MCC audit is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

13.3 Data and Safety Monitoring Committee

The MCC Data and Safety Monitoring Committee (DSMC) will oversee the conduct of this trial. The MCC DSMC performs routine real-time data monitoring and safety review of all trials, with a special focus upon investigator-initiated trials (IITs). The MCC DSMC will conduct review of the trial on a schedule determined by the MCC Protocol Review & Monitoring Committee (PRMC).

The MCC DSMC will monitor the following elements of the trial: adverse event analysis, serious adverse events, protocol deviations/violations, and accrual. In addition, when applicable the DSMC will review QA audits and monitoring reports, previous reviews by the DSMC, suggested actions by other committees (such as the IRB, UK Risk Management Committee), and other parameters and outcomes as determined by the DSMC. If appropriate, the DSMC will designate and monitor corrective action(s) based on review outcome. The MCC DSMC has the authority to amend, temporarily suspend, or terminate the trial based upon patient safety or compliance matters.

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements).

13.4 Data Reporting

13.4.1 Method

This study will require minimal data set submission and reporting via the OnCore Enterprise Research Clinical Trials Management System. Case report forms will be created in a RedCap

database. Instructions for submitting data is listed in study-specific guidance documents. These guidance documents may include any of the following, as appropriate for the scope of the study: eCRF Completion Guidelines, Data Management Specifications, Subject Console Guide, and Query Resolution Guide.

13.4.2 Responsibility for Data Submission

This trial will be monitored by the MCC Data and Safety Monitoring Committee (DSMC) on a schedule determined by the Protocol Review and Monitoring Committee at the initial PRMC review. Study staff are responsible for submitting study data and/or data forms as per the Markey Cancer Center SOPs. Study staff are responsible for compiling and submitting data for all participants and for providing the data to the Principal Investigator for review.

13.5 Data Management

Data management will be performed by cross-team members at MCC. These team members will include representatives from the Biostatistics and Bioinformatics SRF, and the Quality Assurance Office. They will work closely with study staff to ensure timely and accurate data submission. A protocol-specific Data Management Plan (DMP) will be authored by the biostatistician and Principal Investigator with each expected to review and approve the finalization of the DMP. In order to maintain best clinical practices in data management, the DMP may include, but not be limited to: CRF/eCRF design, database build and design, database training, edit check/validation specifications, study database testing/release, data and paper workflow, report, metrics, query/discrepancy management, management of external (including lab) data, medical coding, SAE handling/reconciliation, data transfers and database lock. The protocol-specific DMP will additionally define the schedule at which data will be accessed by data management and study statistician to perform statistical programming for conduct of data quality, data control, data management, generation of interim reports and statistical analysis. Cross-team members will collaborate to establish procedures and timelines for quality control, audits, query resolution, annual reports, interim analysis and final data analysis.

13.6 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements. The PI or designee will be responsible for obtaining continuing and not less than annual IRB re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB and copies of the IRB continuance of approval must maintained by the MCC CRO. The PI or designee is also responsible for notifying the Data and Safety Monitoring Committee of the MCC and the UK IRB of any significant adverse events that are serious and/or unexpected, as per SOP's of those entities and compliance with protocol requirements. DSMC will review all adverse events of this IIT as per its SOP.

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APPENDIX A: OBESITY SCALE

HEIGHT	WEIGHT (lbs.)																										
	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320	330	340	350	360	370	380	390
5'0"	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59	61	62	64	66	68	70	72	74	76
5'1"	25	26	28	30	32	34	36	38	40	42	43	45	47	49	51	53	55	57	59	60	62	64	66	68	70	72	74
5'2"	24	26	27	29	31	33	35	37	38	40	42	44	46	48	49	51	53	55	57	59	60	62	64	66	68	70	71
5'3"	23	25	27	28	30	32	34	35	37	39	41	43	44	46	48	50	51	53	55	57	58	60	62	64	66	67	69
5'4"	22	24	26	27	29	31	33	34	36	38	39	41	43	45	46	48	50	51	53	55	57	58	60	62	64	65	67
5'5"	22	23	25	27	28	30	32	33	35	37	38	40	42	43	45	47	48	50	52	53	55	57	58	60	62	63	65
5'6"	21	23	24	26	27	29	31	32	34	36	37	39	40	42	44	45	47	48	50	52	53	55	56	58	60	61	63
5'7"	20	22	23	25	27	28	30	31	33	34	36	38	39	41	42	44	45	47	49	50	52	53	55	56	58	60	61
5'8"	20	21	23	24	26	27	29	30	32	33	35	36	38	40	41	43	44	46	47	49	50	52	53	55	56	58	59
5'9"	19	21	22	24	25	27	28	30	31	32	34	35	37	38	40	41	43	44	46	47	49	50	52	53	55	56	58
5'10"	19	20	22	23	24	26	27	29	30	32	33	34	36	37	39	40	42	43	44	46	47	49	50	52	53	55	56
5'11"	18	20	21	22	24	25	26	28	29	31	32	33	35	36	38	39	40	42	43	45	46	47	49	50	52	53	54
6'0"	18	19	20	22	23	24	26	27	28	30	31	33	34	35	37	38	39	41	42	43	45	46	47	49	50	52	53
6'1"	17	18	20	21	22	24	25	26	28	29	30	32	33	34	36	37	38	40	41	42	44	45	46	47	49	50	51
6'2"	17	18	19	21	22	23	24	26	27	28	30	31	32	33	35	36	37	39	40	41	42	44	45	46	48	49	50
6'3"	16	17	19	20	21	22	24	25	26	27	29	30	31	32	34	35	36	37	39	40	41	42	44	45	46	47	49
6'4"	16	17	18	19	21	22	23	24	26	27	28	29	30	32	33	34	35	37	38	39	40	41	43	44	45	46	47

BMI	
<19	Underweight
19-25	Healthy weight
26-29	Overweight
30-39	Obese
>40	Morbid Obesity

APPENDIX B: COVID 7-POINT ORDINAL OUTCOMES SCALE

http://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/

COVID 7-point ordinal outcomes scale:

1. Death
2. Hospitalized on invasive mechanical ventilation or ECMO
3. Hospitalized on non-invasive ventilation or high flow nasal cannula
4. Hospitalized on supplemental oxygen
5. Hospitalized not on supplemental oxygen
6. Not hospitalized with limitation in activity (continued symptoms)
7. Not hospitalized without limitation in activity (no symptoms)

APPENDIX C: PILL/PRODUCT DIARIES

Study Participant Self-Administration Study Drug Diary

Please record how many tablets you take, the time you take them and any comments below and bring the completed Diary as well as your study drug supply, including empty bottles, to every study visit. This will help us keep track of your study drug and how well you are tolerating it.

Arm C

Participant Identifier: **Protocol #: MCC-20-COVID-01-PMC**
Doctor: James Zachary Porterfield, MD
Doctor: Susanne Markesbery Arnold, MD
Nurse: enter name and phone number

You will take the following number of capsules/tablets each time (per dose) as listed in the table below:

Study Drug Name	# of capsules (tablets) to take per time/dose	# of times/doses each day	Approximate time to take drug
Ivermectin	**__ tablets/12mg-15mg (circle one)**	**Once a day 2 hours before or 2 hours after a meal**	**__:___ ☐ a.m.**

Day	Date	Number of Ivermectin *Tablets*	Time of Dose
1		—	____:____ □ a.m. □ Dose Not Taken Why:_____
2		—	____:____ □ a.m. □ Dose Not Taken Why:

Participant/Caregiver Signature: _____
Date:

FOR STUDY TEAM USE ONLY	
Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Study Participant Self-Administration Study Drug Diary

Please record how many tablets you take, the time you take them and any comments below and bring the completed Diary as well as your study drug supply, including empty bottles, to every study visit. This will help us keep track of your study drug and how well you are tolerating it.

Arm D

Participant Identifier: Protocol #: MCC-20-COVID-01-PMC
Doctor: James Zachary Porterfield, MD
Doctor: Susanne Markesbery Arnold, MD
Nurse: *enter name and phone number*

You will take the following number of capsules/tablets each time (per dose) as listed in the table below:

Study Drug Name	# of capsules (tablets) to take per time/dose	# of times/doses each day	Approximate time to take drug
Camostat Mesilate	2 tablets	3 times per day	__:___ ☐ a.m. __:___ ☐ p.m. : ☐ p.m.

Day	Date	Number of Camostat Mesilate 100 mg	Time of Dose	Number of Camostat Mesilate 100 mg	Time of Dose	Number of Camostat Mesilate tablets	Time of Dose
1		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
2		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
3		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
4		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
5		2	___:___ □ a.m.	2	___:___ □ p.m.	2	___:___ □ p.m.

			□ Dose not taken Why:_____		□ Dose not taken Why:_____		□ Dose not taken Why:_____
6		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
7		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
8		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
9		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
10		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
11		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
12		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
13		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____
14		2	___:___ □ a.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____	2	___:___ □ p.m. □ Dose not taken Why:_____

Participant/Caregiver Signature: _____
Date:_____

FOR STUDY TEAM USE ONLY Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Study Participant Self-Administration Study Botanical Diary

Please record the number of times you drink the Artemisia annua tea or coffee, the time you take them and any comments below and bring the completed Diary as well as your study tea or coffee supply, to your next study visit. This will help us keep track of your study product and how well you are tolerating it.

Arm E

Participant Identifier: Protocol #: MCC-20-COVID-01-PMC
Doctor: James Zachary Porterfield, MD
Doctor: Susanne Markesbery Arnold, MD
Nurse: *enter name and phone number*

You will take the following number of capsules/tablets each time (per dose) as listed in the table below:

Study Botanical Product Name	dose	# of times/doses each day	Approximate time to take tea or coffee
Artemisia annua	1 pod or 2 tea bags	3 times per day	__:___ ☐ a.m. __:___ ☐ p.m. :___ ☐ p.m.

Day	Date	Number of Artemisia annua tea bag or pod	Time of Dose	Number of Artemisia annua tea bag or pod	Time of Dose	Number of Artemisia annua tea bag or pod	Time of Dose
1		–	___:___ ☐ a.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____
2		–	___:___ ☐ a.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____
3		–	___:___ ☐ a.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____
4		–	___:___ ☐ a.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____

5		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
6		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
7		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
8		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
9		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
10		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
11		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
12		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
13		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
14		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____

Participant/Caregiver Signature: _____
Date:_____

FOR STUDY TEAM USE ONLY Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Study Participant Self-Administration Study Drug Diary

Please record the number of times you drink the Artesunate tea or coffee, the time you take them and any comments below and bring the completed Diary as well as your study tea or coffee supply, to your next study visit. This will help us keep track of your study drug and how well you are tolerating it.

Arm F

Participant Identifier: Protocol #: MCC-20-COVID-01-PMC
Doctor: James Zachary Porterfield, MD
Doctor: Susanne Markesbery Arnold, MD
Nurse: *enter name and phone number*

You will take the following number of capsules/tablets each time (per dose) as listed in the table below:

Study Drug Name	dose	# of times/doses each day	Approximate time to take drug
Artesunate	1 pod or 2 tea bags	3 times per day	__:___ ☐ a.m. __:___ ☐ p.m. : ☐ p.m.

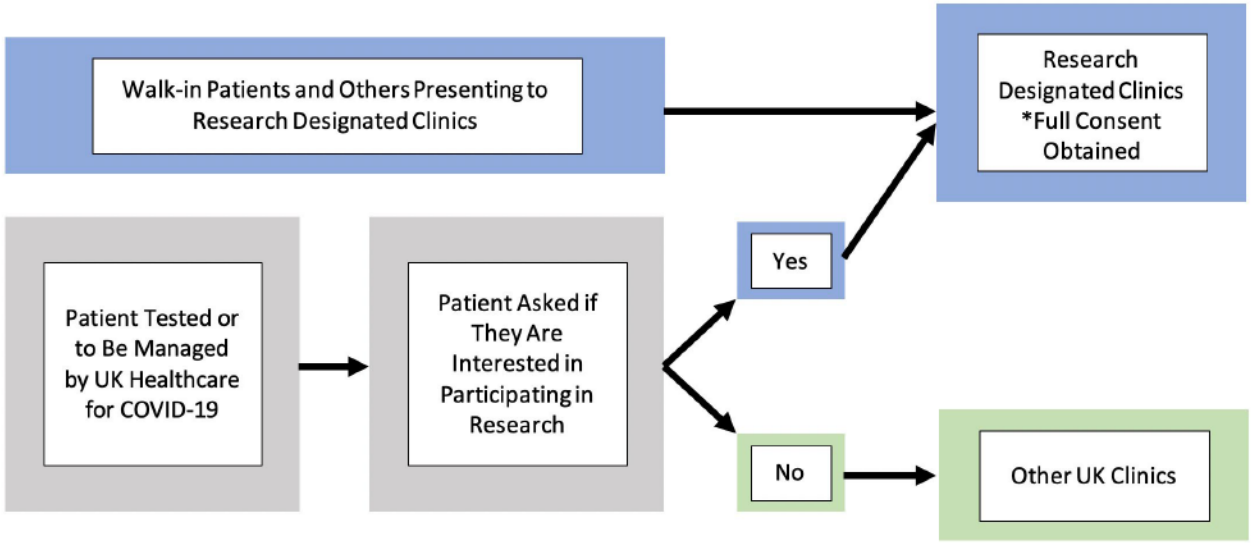
Day	Date	Number of Artesunate tea bag or pod	Time of Dose	Number of Artesunate tea bag or pod	Time of Dose	Number of Artesunate tea bag or pod	Time of Dose
1		–	___:___ ☐ a.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____
2		–	___:___ ☐ a.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____
3		–	___:___ ☐ a.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____
4		–	___:___ ☐ a.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____	–	___:___ ☐ p.m. ☐ Dose not taken Why:_____

5		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
6		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
7		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
8		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
9		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
10		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
11		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
12		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
13		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____
14		_	___:___ □ a.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____	_	___:___ □ p.m. □ Dose not taken Why:_____

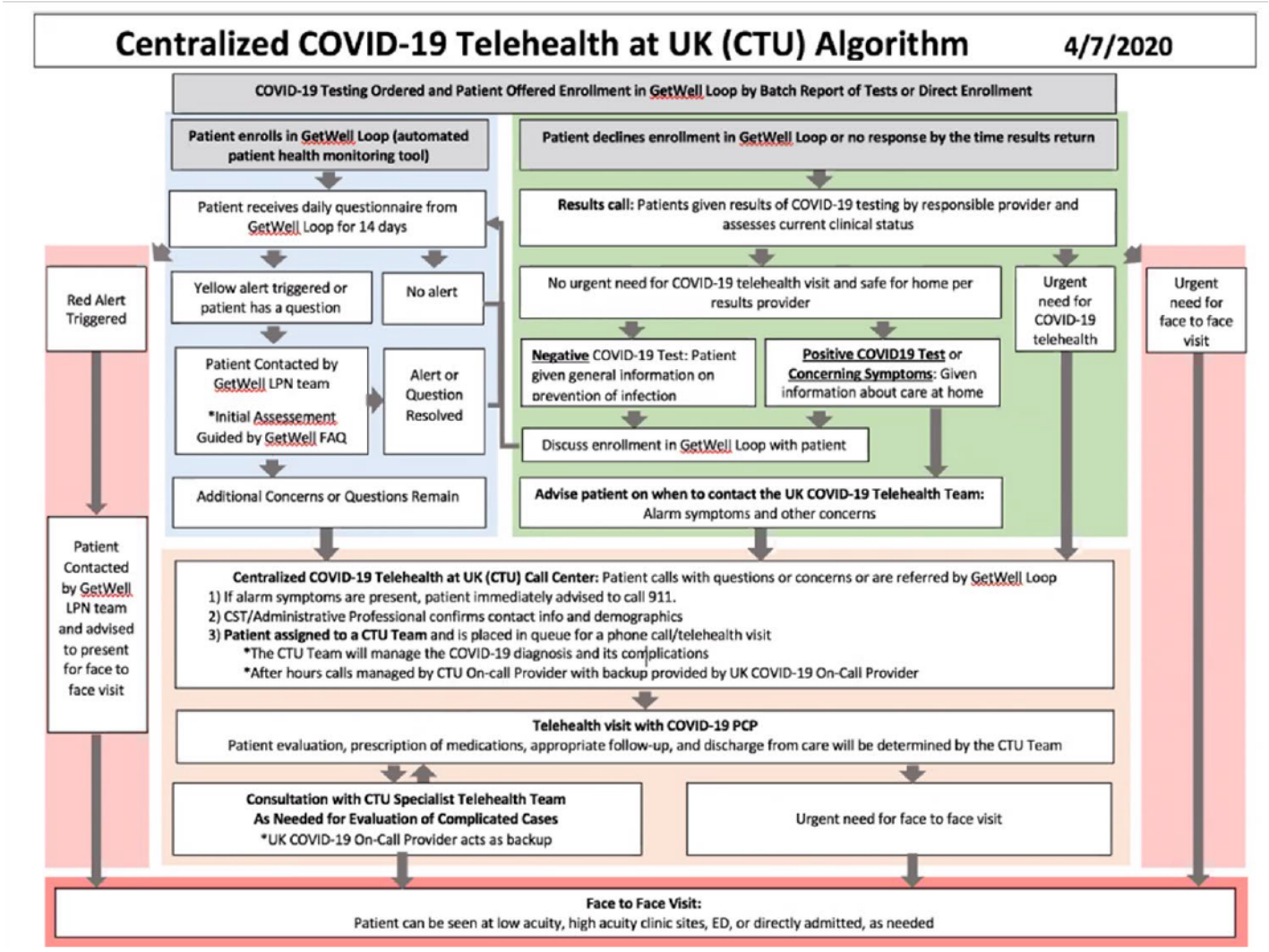
Participant/Caregiver Signature: _____
Date:_____

FOR STUDY TEAM USE ONLY Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

APPENDIX D: TELEHEALTH TRIAGE AND DRIVE/THROUGH WALK-IN ENROLLMENT



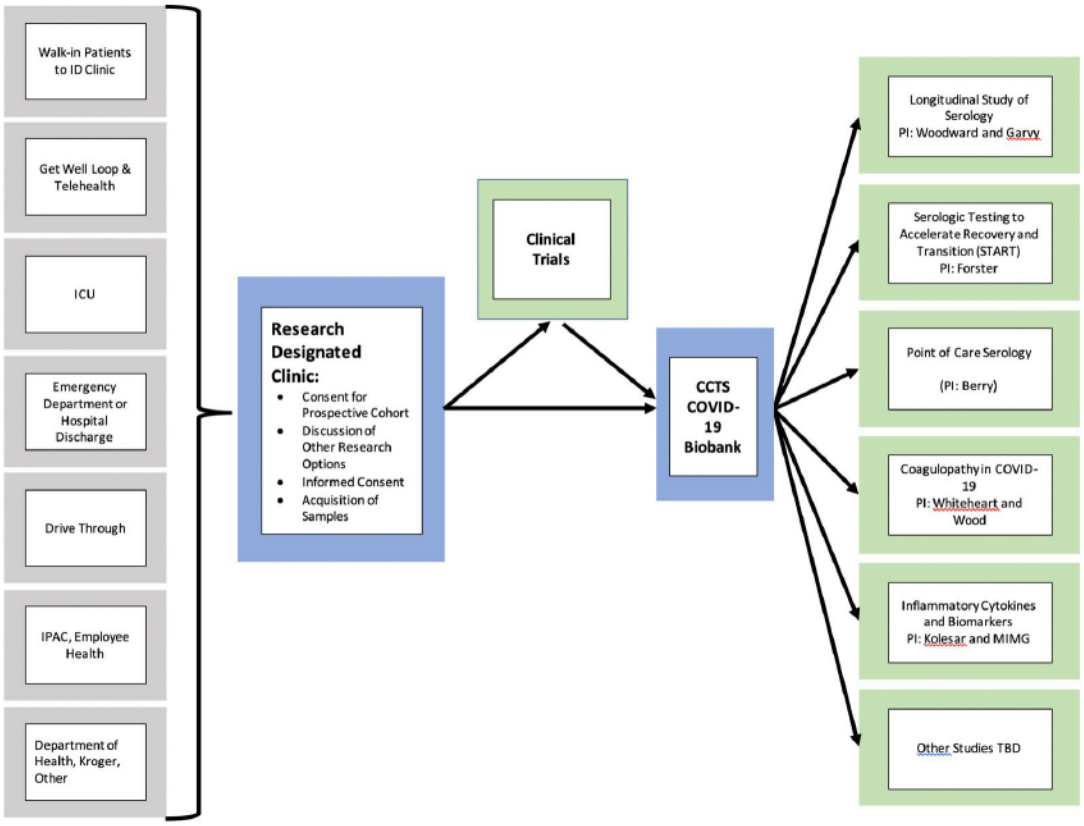
APPENDIX E: GETWELL LOOP/CENTRALIZED COVID-19 TELEHEALTH AT UK (CTU) ALGORITHM



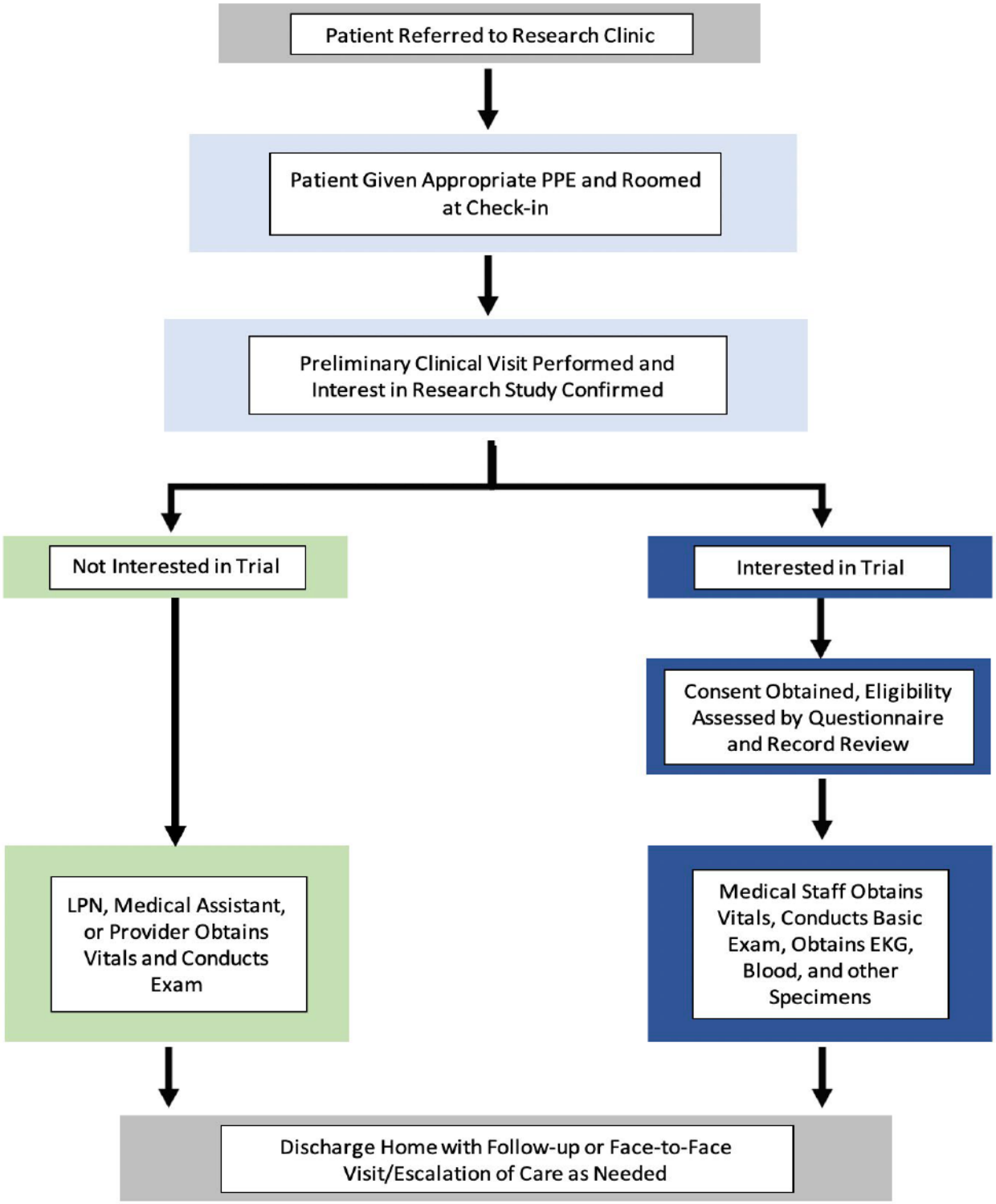
APPENDIX F: CURRENT RECRUITMENT STRATEGY AND SCHEMATIC FOR INTAKE AND CONSENT FOR RESEARCH AT RESEARCH DESIGNATED CLINIC

Proposed Patient Recruitment for COVID-19 Research:

- Multiple patient streams referred to centralized research unit
- Research unit has established COVID-19 protocols
- Creates synergy to maximize recruitment into studies – minimized competition
- Can advertise one site for research referral or to direct interested patients
- Takes advantage of existing relationship with patient referral streams and CCTS biobank to create streamlined process, avoiding duplicated efforts, and lost opportunities for recruitment



PATIENT FLOW FOR INTAKE INTO ID CLINIC



APPENDIX G: TOXICITY GRADING SCALES FOR DETERMINING SEVERITY OF ADVERSE EVENTS

https://www.niaid.nih.gov/research/dmid-safety-reporting-pharmacovigilance

ADULT TOXICITY TABLES

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal LLN = Lower Limit of Normal
R_x = Therapy Req = Required
Mod = Moderate IV = Intravenous
ADL = Activities of Daily Living Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1 Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2 Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3 Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4 Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5-10.5 g/dL	8.0-9.4 g/dL	6.5-7.9 g/dL	<6.5 g/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	>13,000/ mm^3	13,000-15,000/mm^3	15,000-30,000/mm^3	>30,000 or <1,000/mm^3
Polymorphonuclear Leucocytes + Band Cells	>80%	90-95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 µg/mL	41-50 µg/mL	51-60 µg/mL	>60 µg/mL
Prothrombin Time (PT)	1.01-1.25 × ULN	1.26-1.5 × ULN	1.51-3.0 × ULN	>3 × ULN
Activated Partial Thromboplastin (APPT)	1.01-1.66 × ULN	1.67-2.33 × ULN	2.34-3 × ULN	>3 × ULN
Methemoglobin	5.0-9.9%	10.0-14.9%	15.0-19.9%	>20.0%

CHEMISTRIES	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatraemia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium with mental status changes or seizures
Hypernatraemia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium with mental status changes or seizures
Hypokalaemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia
Hyperkalaemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium with life-threatening arrhythmia
Hypoglycaemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose with mental status changes or coma
Hyperglycaemia (non-fasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose with ketoacidosis or seizures
Hypocalcaemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium with life threatening arrhythmia or tetany
Hypercalcaemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium with life-threatening arrhythmia
Hypomagnesaemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium with life-threatening arrhythmia
Hypophosphataemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate with life-threatening arrhythmia
Hyperbilirubinaemia	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5 x ULN	> 5 x ULN
BUN	1.25 - 2.5 x	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperuricaemia (uric acid)	ULN 7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25-2.5 × ULN	2.6 -5 × ULN	5.1-10 × ULN	>10 × ULN
ALT (SGPT)	1.25-2.5 × ULN	2.6- 5 × ULN	5.1-10 × ULN	>10 × ULN
GGT	1.25-2.5 × ULN	2.6-5 × ULN	5.1-10 × ULN	>10 × ULN
Alkaline Phosphatase	1.25-2. 5 × ULN	1.6-5 × ULN	5.1-10 × ULN	>10 × ULN
Amylase	1.1-1.5 × ULN	1.6-2.0 × ULN	2.1-5.0 × ULN	>5.1 × ULN
Lipase	1.1-1.5 × ULN	1.6-2.0 × ULN	2.1-5.0 × ULN	>5.1 × ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 g loss/day	2-3+ or 1-2 g loss/day	4+ or 2-3.5 g loss/day	nephrotic syndrome or >3.5 g loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrhythmia; hospitalization and treatment required
Hypertension	transient increase >20 mm/Hg; no treatment	recurrent, chronic increase >20 mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; ECG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused
Electrocardiogram QT corrected interval prolonged		Average QTc 481 - 500 ms	Average QTc >= 501 ms; >60 ms change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia
Sinus tachycardia	Asymptomatic, intervention not	Symptomatic; non-urgent	Supraventricular tachycardia	Symptomatic, urgent intervention indicated Life

indicated	medical intervention indicated Urgent medical intervention indicated	Asymptomatic, intervention not indicated Non-urgent medical intervention indicated -threatening consequences

RESPIRATORY	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: $FEV_1 < 25\%$ of peak flow or intubation necessary
Dyspnoea	dyspnoea on exertion	dyspnoea with normal activity	dyspnoea at rest	dyspnoea requiring Oxygen therapy
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Pulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; invasive intervention not indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; intubation or urgent intervention indicated
Pneumonitis oxygen indicated	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL;	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Lung infection -		Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/ Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness / no objective symptoms/ signs	mild objective signs/symptoms/ no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15 mm	15-30 mm	>30 mm	
Erythema	< 15 mm	15-30 mm	>30 mm	
Edema	< 15 mm	15-30 mm	>30 mm	
Rash at Injection Site	< 15 mm	15-30 mm	>30 mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.5 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self
Infections and infestations - Other,	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Sepsis	-	-	Blood culture positive with signs or symptoms; treatment indicated	Life-threatening consequences; urgent intervention indicated
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related	Life-threatening consequences; urgent intervention indicated

	edema/angioedema; hypotension

APPENDIX H: ORDERING INSTRUCTIONS FOR ARM E, ARTEMILIFE TEA OR COFFEE

The information for supply of Artemisia annua is as follows:

Baesman Distributors
4477 Reynolds drive
Hilliard, Ohio 43026
Contact: Tbaesman@baesman.com

Record of Request for Arm E, MCC-COVID-01-PMC clinical trial

OVERNIGHT SHIPMENT TO:

Name:_____

Address:_____

_____

_____

Contact Phone Number:_____

Dispense:

- ☐ Coffee: Dispense 42 pods (450 mg)
- ☐ Pod coffee maker (if patient does not have a pod coffee maker)

OR

- ☐ Tea: Dispense 84 tea bags (225 mg)

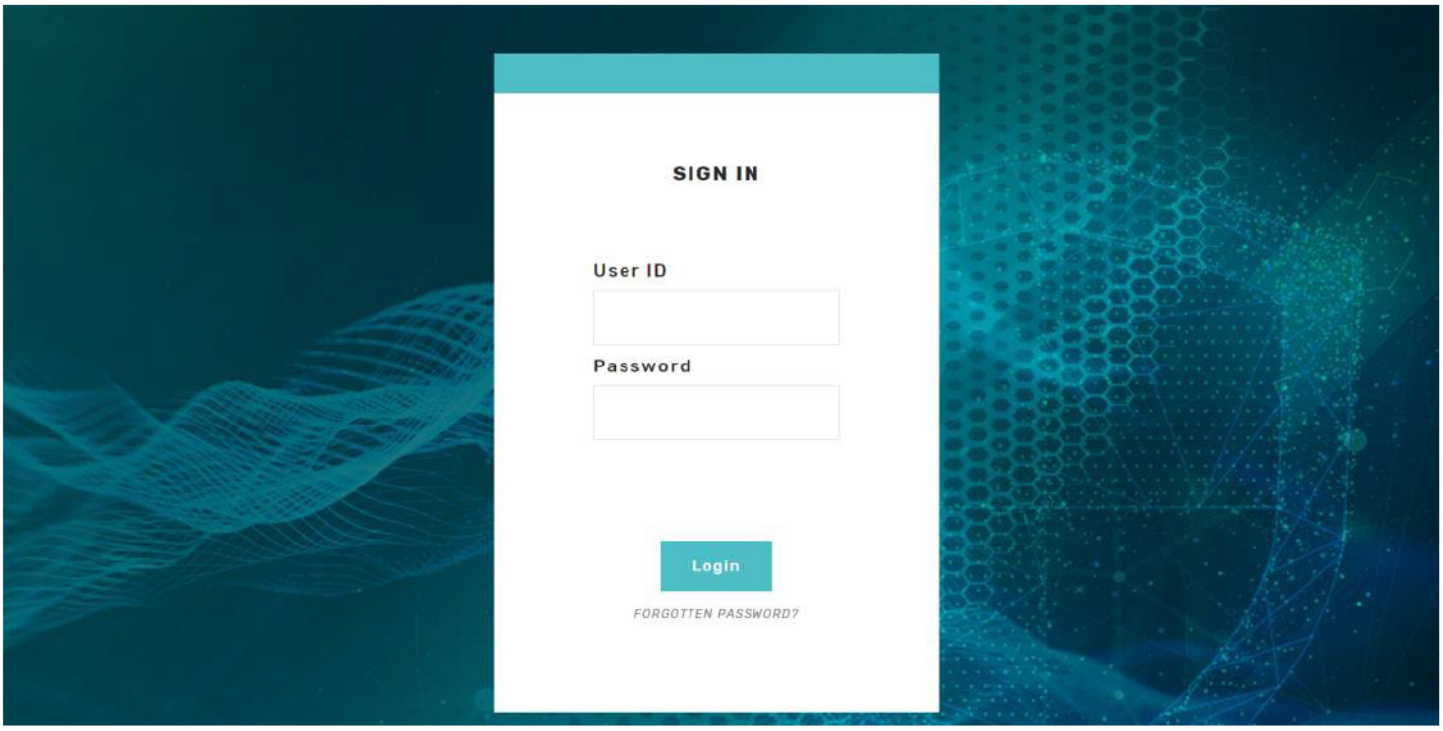
Ordered by:

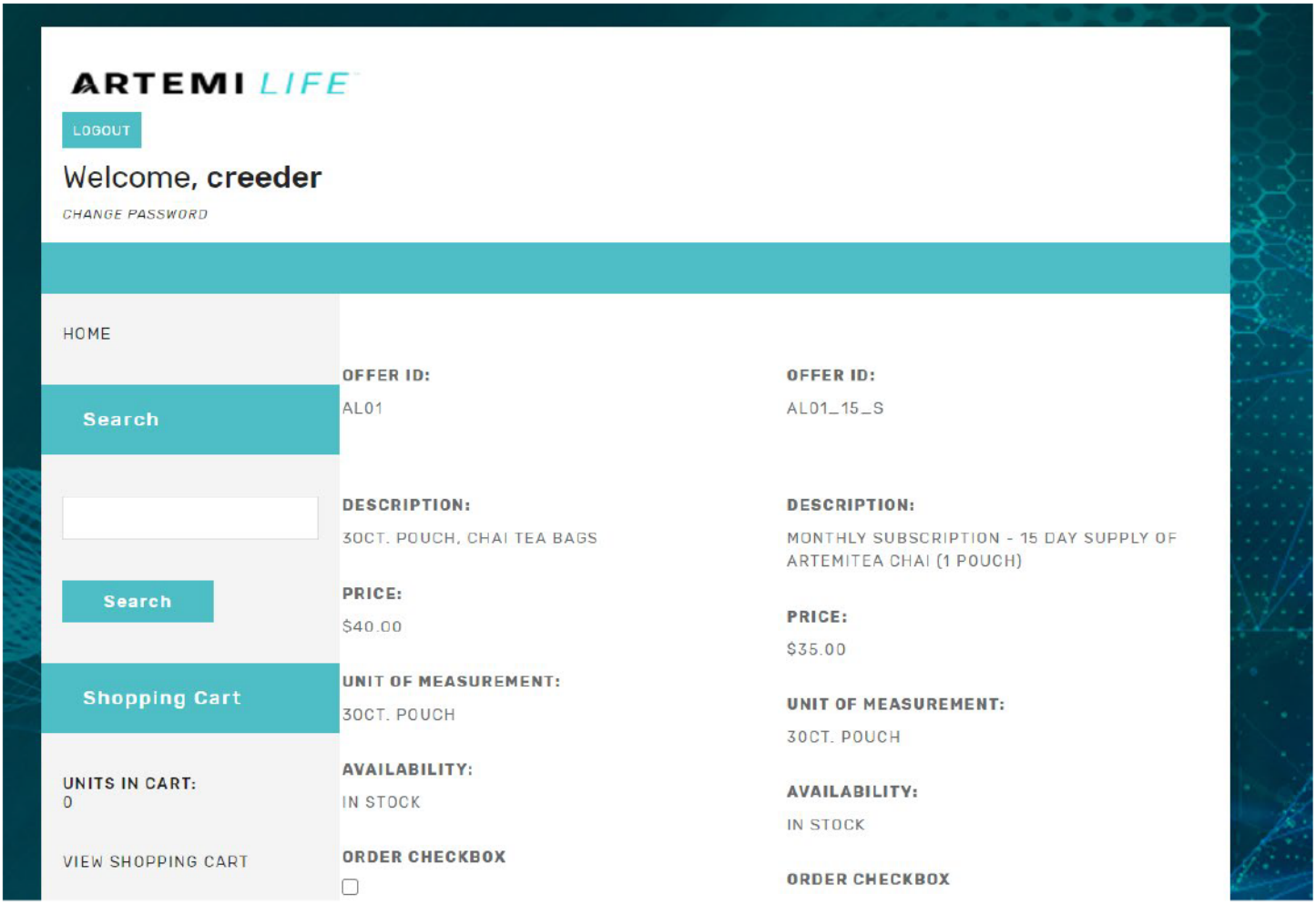
_____ _____

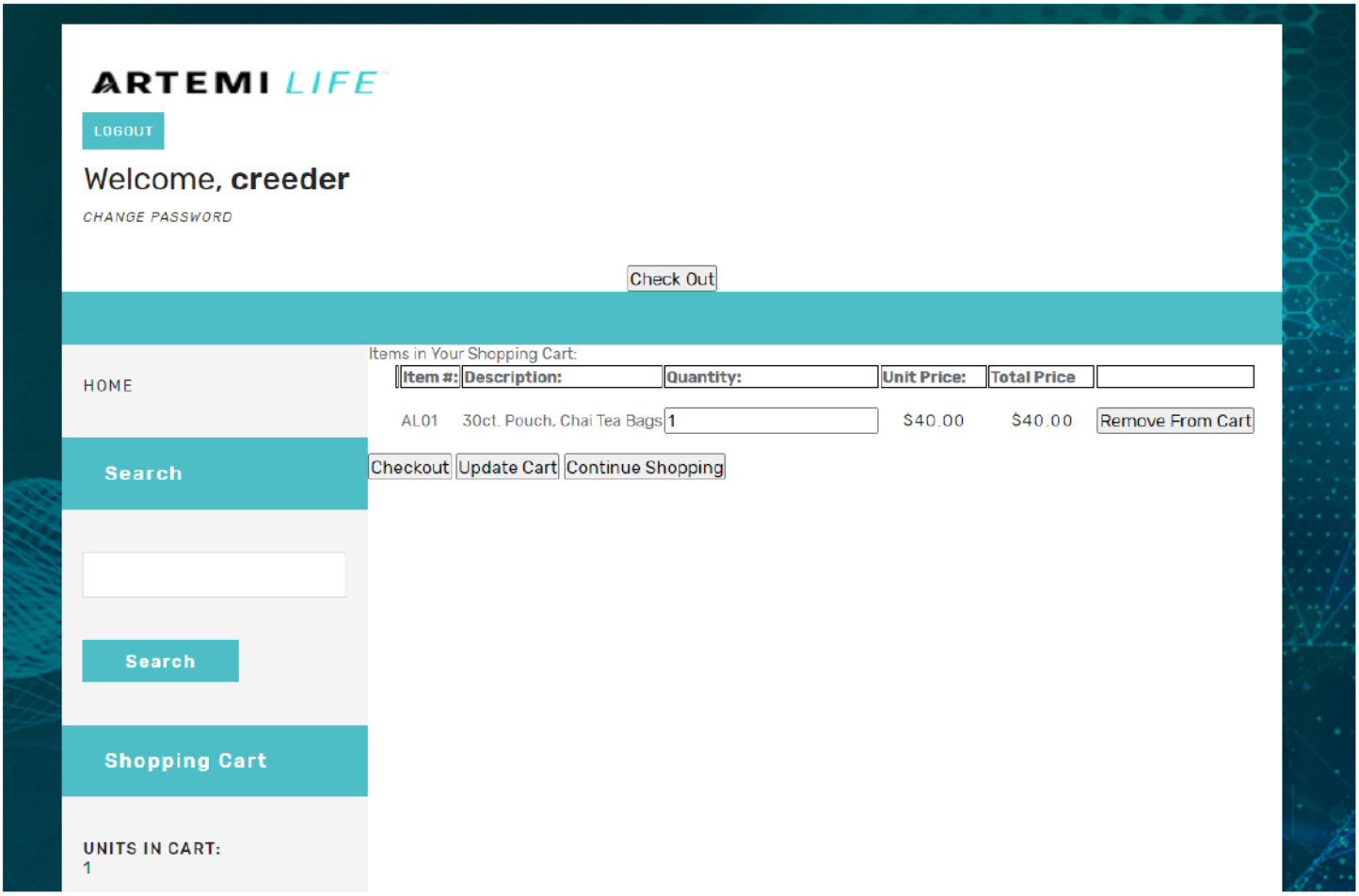
Study Coordinator Date

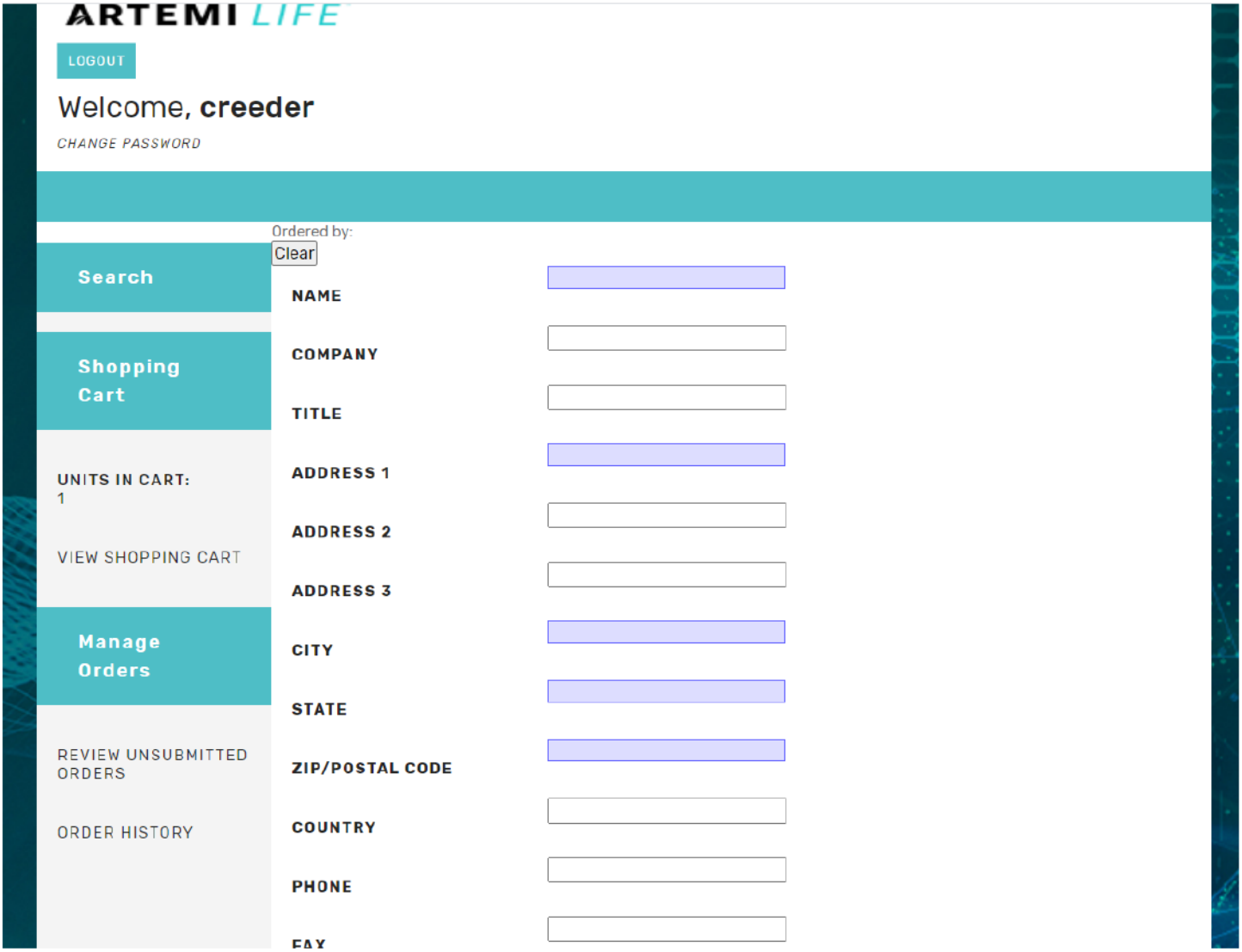
Enter data into portal as described below.

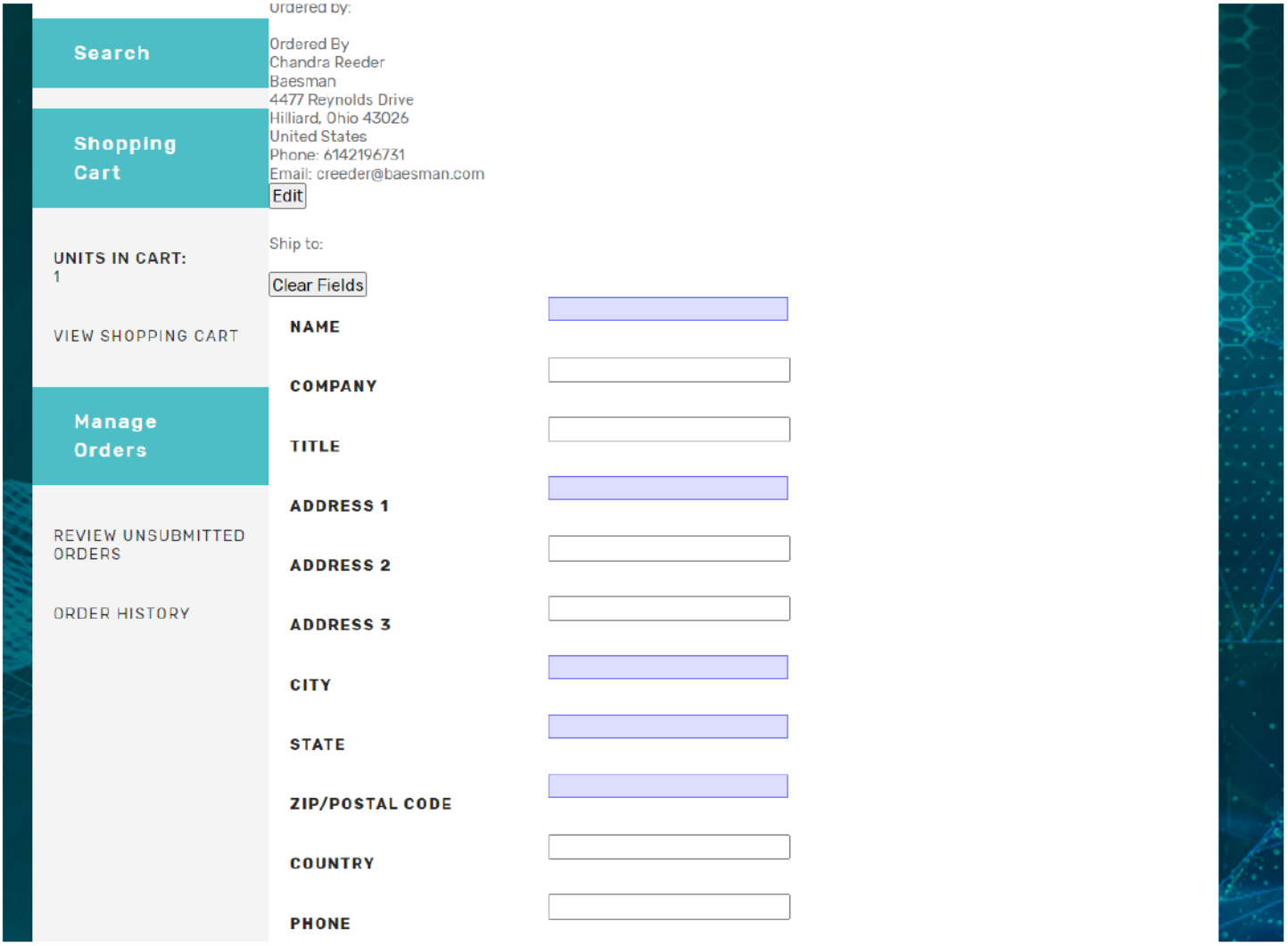
SCREEN SHOTS OF ORDERING PORTAL






ARTEMI LIFE
LOGOUT
Welcome, creeder
CHANGE PASSWORD
Check Out
HOME
Search
Search
Shopping Cart
UNITS IN CART:
1
Items in Your Shopping Cart:
Item #:
Description:
Quantity:
Unit Price:
Total Price
AL01
30ct. Pouch. Chai Tea Bags
1
$40.00
$40.00
Remove From Cart
Checkout
Update Cart
Continue Shopping


ARTEMI LIFE
LOGOUT
Welcome, creeder
CHANGE PASSWORD
Search
Shopping Cart
UNITS IN CART:
1
VIEW SHOPPING CART
Manage Orders
REVIEW UNSUBMITTED ORDERS
ORDER HISTORY
Ordered by:
Clear
NAME
COMPANY
TITLE
ADDRESS 1
ADDRESS 2
ADDRESS 3
CITY
STATE
ZIP/POSTAL CODE
COUNTRY
PHONE
FAX


Ordered by:
Search
Ordered By
Chandra Reeder
Baesman
4477 Reynolds Drive
Hilliard, Ohio 43026
United States
Phone: 6142196731
Email: creeder@baesman.com
Shopping Cart
Edit
UNITS IN CART:
1
Ship to:
VIEW SHOPPING CART
Clear Fields
NAME
COMPANY
TITLE
Manage Orders
ADDRESS 1
ADDRESS 2
REVIEW UNSUBMITTED ORDERS
ADDRESS 3
CITY
STATE
ORDER HISTORY
ZIP/POSTAL CODE
COUNTRY
PHONE