Clinical-trial of COVID-19 Convalescent Plasma in Outpatients (C3PO)

Study Protocol and Statistical Analysis Plan

NCT04355767

February 16, 2021

SIREN

STUDY PROTOCOL

Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO)

C3PO
Clinical Trial of COVID-19 Convalescent Plasma in Outpatients

A multicenter, two arm, randomized, single-blind clinical trial to determine if receiving one dose of convalescent plasma (CP) for mild COVID-19 illness prevents illness progression.

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Sponsor of FDA Investigational New Drug: Kevin Schulman, MD

Clinicaltrials.gov:

Protocol Signature Page

I have reviewed and approved this protocol. My signature assures that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

02/16/2021

Investigator-Sponsor's Signature | Date of Signature (DD MMM YYYY)

I have read this protocol and agree that it contains all the necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practices (GCP).

Site Principal Investigator's Signature | Date of Signature (DD MMM YYYY)

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For updated contact information, including the Emergency 24/7 Toll Free Contact Number, please refer to the study website or the study Manual of Procedures.

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Table of Abbreviations

AE	Adverse Event
ADE	Antibody-dependent enhancement
ARDS	Acute respiratory distress syndrome
BARDA	Biomedical Advance Research and Development Authority
C3PO	Clinical-trial of COVID-19 Convalescent Plasma in Outpatients
CCC	Clinical Coordinating Center
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CP	Convalescent Plasma
CRF	Case Report Form
DCC	Data Coordinating Center
DM	Data Manager
DNR	Do Not Resuscitate
DSMB	Data and Safety Monitoring Board
EC	Executive Committee
ED	Emergency Department
eConsent	Electronic Consent
ESC	External Steering Committee
FDA	Food and Drug Administration
FM	Financial manager
GCP	Good Clinical Practices
HIPAA	Health Information Portability and Accountability Act
IDE	Investigational device exemption
IMSM	Independent medical safety monitor
IND	Investigational new drug
IQR	Internal quality reviewer
ITT	Intention to treat
LAR	Legally authorized representative
NCATS	National Center for Advancing Translational Science
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
PI	Principal Investigator
SAE	Serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Study Coordinators
SCG	Scientific Coordinating Group
SIREN	Strategies to Innovate Emergency Care Clinical Trials Network
TACO	Transfusion Associated Circulatory Overload
TRALI	Transfusion-related acute lung injury
WHO	World Health Organization

Table of Contents

1. Protocol Summary

1.1 Brief Synopsis

Title	Clinical-trial of COVID-19 Convalescent Plasma in Outpatients (C3PO)
Protocol Number	Pro00044489
Phase	Phase III
Methodology	Multi-center, randomized, single-blind, two-arm, placebo-controlled trial with blinded outcome assessment.
Study Duration	June 2020 to July 2021
Study Center(s)	SIREN Trial Network
Objectives	**Primary**: To determine the efficacy and safety of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe COVID-19 illness. **Secondary**: Characterize the immunologic response to CP administration.
Endpoints	**Primary:** Disease progression defined as death or hospital admission or seeking emergency or urgent care within 15 days of randomization. **Secondary**: ● Worst severity rating on the WHO's COVID Ordinal Scale for Clinical Improvement during the 30 days following randomization ● Time to disease progression on the COVID Outpatient Ordinal Outcome Scale censored at 15 days after randomization. ● Hospital-free days during the 30 days following randomization ● All-cause mortality at 30 days

	• Symptom inventory measured using the CDC list of COVID-19 symptoms on days 2, 4, 6, 8, 10, 14, 15, 30 • Neutralizing antibody titers at days 0 (pre-intervention and post-intervention), 15, and 30 • Spike protein IgG antibody titers pre and post CP administration
Number of Subjects	Original planned maximum sample size: 600 (300 per arm) Revised maximum sample size based on planned re-estimation: 900 (450 per arm)
IND Sponsor	Kevin Schulman, MD, MBA
Main Inclusion Criteria	• One or more symptoms of COVID-19 illness and laboratory-confirmed SARS-CoV-2 infection. • Has at least one study defined risk factor for severe COVID-19 illness • Clinical team deems stable for outpatient management without new supplemental oxygen • CP available at the site at the time of enrollment • Duration of symptoms ≤ 7 days at ED presentation and randomization • Informed consent from subject
Major Exclusion Criteria	• Age less than 18 years • Prisoner or ward of the state • Presumed unable to complete follow-up assessments • Prior adverse reaction(s) from blood product transfusion • Receipt of any blood product within the past 120 days • Treating clinical team unwilling to administer up to 250 ml fluid • Enrollment in another interventional trial for COVID-19 illness or receipt of other active or passive immunization against SARS-CoV2.
Study Product(s), Dose, Route, Regimen	One unit (~200 ml) dose of ABO group compatible SARS-CoV-2 convalescent plasma (CP) or placebo (250 ml) of normal saline with multivitamin.
Duration of administration	One time

Statistical Methodology	Outcomes will be analyzed using the intent-to-treat principle (ITT). The primary analysis is to test the hypothesis of superiority of CP as compared to placebo. The posterior probability that the proportion of primary outcome events at 15-days post randomization is higher in the saline arm as compared to the CP arm will be calculated. The primary null hypothesis will be rejected if the posterior probability is greater than or equal to 0.975 (selected to coincide with a one-sided alpha level of 0.025 under a frequentist design). Interim monitoring for stopping early due to overwhelming efficacy or futility will be conducted. We will conduct the first interim analysis after approximately 33% of consecutively randomized ITT subjects complete the primary outcome assessment. Safety will be closely monitored and reported to the independent DSMB.

1.2 Synopsis

Overview

A multi-center randomized, single blind, two arm, placebo controlled phase III trial with blinded outcome assessment to establish the safety and efficacy of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe COVID-19 illness.

COVID-19 is a respiratory illness caused by the *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2). As of May 1, 2020, over 3 million persons worldwide have been diagnosed with COVID-19 and approximately 250,000 persons have died from this disease. The majority (80%) of cases are categorized as mild, while approximately 15-20% of cases are categorized as severe, with about 5% of all cases progressing into critical illness, characterized by hypoxemic respiratory failure, shock, and end-organ failure.[1,2] Among the 5% who develop severe disease, as many as 50% die.[3] At present there is no specific therapy for preventing the progression of COVID-19 from mild to severe disease.

Passive antibody therapy using plasma from donors who have been infected and then recovered (convalescent plasma, CP) contains neutralizing antibodies against the infectious agent. Specifically, CP has been used in different respiratory illness epidemics, including the 1918 influenza pandemic, the 2003 SARS-CoV-1 outbreak, and the 2009 H1N1 influenza pandemic. Use of CP for emerging infections has persisted because of strong mechanistic and observational data, but efficacy has yet to be well tested or demonstrated in clinical trials. At this moment, there is no high quality evidence to support the efficacy of CP for treating COVID-19 illness. Conceptually, CP has the highest chance of showing efficacy if used for early treatment of patients at the highest risk for severe disease and mortality.

Objectives

The overarching goal of this project is to confirm or refute the role of passive immunization as a safe and efficacious therapy in preventing the progression from mild to severe/critical COVID-19 illness and to understand the immunologic kinetics of anti-SARS-CoV-2 antibodies after passive immunization.

Primary Objective:

To establish the safety and efficacy of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe/critical COVID-19 illness.

Secondary Objectives:

Characterize the immunologic response to CP administration.

Study Design

This is a multi-center randomized, two-arm, single-blind placebo-controlled phase III trial with blinded outcome assessment.

Sample size: Original planned maximum sample size: 600 (300 per arm)
Revised maximum sample size based on planned re-estimation: 900 (450 per arm)
Study Duration: 12 months
Study Duration for individual subjects: 30 days
Age range: 18 years of age or greater

Primary Endpoint

Disease progression defined as hospital admission, death or seeking emergency or urgent care within 15 days of randomization

Secondary Endpoints

- Worst severity rating on the WHO's COVID Ordinal Scale for Clinical Improvement during the 30 days following randomization
    - Death
    - Hospitalized on invasive mechanical ventilation or ECMO
    - Hospitalized on non-invasive ventilation or high flow nasal cannula
    - Hospitalized on supplemental oxygen
    - Hospitalized not on supplemental oxygen
    - Not hospitalized with limitation in activity (continued symptoms)
    - Not hospitalized without limitation in activity (no symptoms)
- Time to disease progression on the COVID Outpatient Ordinal Outcome Scale censored at 15 days after randomization
    - Patient requires care in the hospital
    - Patient requires care in the ED or urgent care
    - Patient at home with symptoms rated as moderate (defined as fever, shortness of breath, abdominal pain)
    - Patient at home with symptoms rated as mild (defined as afebrile, constitutional symptoms (flu-like illness) without shortness of breath)
    - Patient in their usual state of health
- Hospital-free days during the 30 days following randomization
- All-cause mortality at 30 days

Exploratory Endpoints

- Symptom inventory measured using the CDC list of COVID-19 symptoms on days 2, 4, 6, 8, 10, 14, 15, 30
- Neutralizing antibody titers at days 0 (pre-intervention and post-intervention), 15, and 30
- Spike protein IgG antibody titers pre and post CP administration

Study Population

Adults presenting to the emergency department (ED) with their first episode of symptomatic, laboratory-confirmed COVID-19 illness, who are at high risk for progression to severe/critical illness, but who are clinically stable for outpatient management at randomization.

Inclusion Criteria

- One or more symptoms of COVID-19 illness and laboratory-confirmed SARS-CoV-2 infection
- Has at least one study defined risk factor for severe COVID-19 illness
- ED team deems stable for outpatient management without new supplemental oxygen requirement
- Informed consent from subject
- ABO-compatible CP available at the site at the time of enrollment
- Duration of symptoms ≤ 7 days at ED presentation and randomization

Exclusion Criteria

- Age < 18 years
- Prisoner or ward of the state.
- Presumed unable to complete follow-up assessments
- Prior adverse reaction(s) from blood product transfusion
- Religious, social or other contraindications to receiving blood products
- Receipt of any blood product within the past 120 days
- Inability to tolerate up to 250 ml of intravenous fluid
- Enrollment in another interventional trial for COVID-19 illness or receipt of other active or passive immunization against SARS-CoV2.

Randomization

A web-based central randomization system will assign treatment using a fixed 1:1 allocation ratio. The randomization algorithm will prevent possible selection bias by providing random treatment assignment to each subject and prevent accidental treatment imbalances in age and site.

Consent

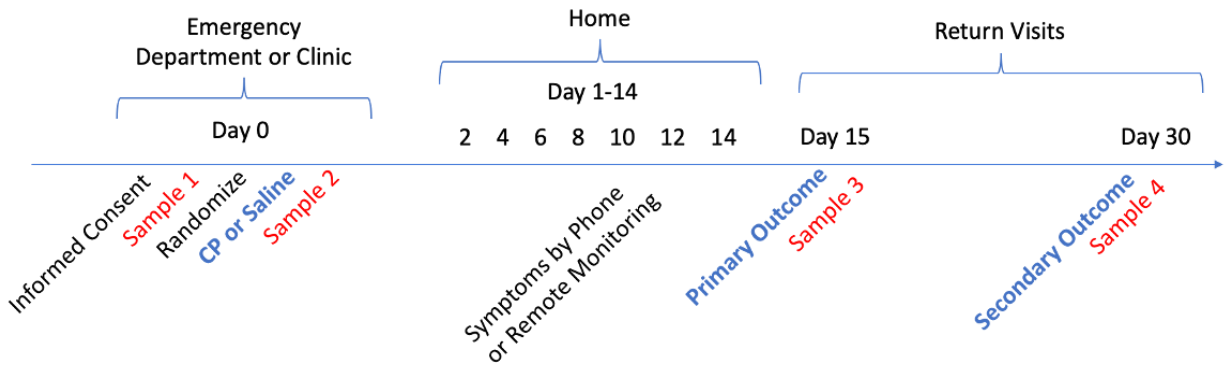
Patients who are eligible for this trial will provide written informed consent. The COVID-19 pandemic has created a need for novel consent and recruitment procedures. We have developed entirely electronic consent forms, which will be used in this trial. REDCap software can serve these forms to any internet connected device. Coordinators, working from remote locations, may communicate with potential subjects in any ED using telephone or video connection (e.g. Zoom, FaceTime, Skype or other methods). We have several years experience with electronic consent in emergency patients.

Intervention

Subjects will be randomized in a 1:1 ratio to receive either one unit (~200 ml) dose of ABO group compatible SARS-CoV-2 convalescent plasma (CP) with neutralizing SARS-CoV2 antibodies titers of ≥1:160 or placebo infusion of 250 ml of normal saline with 1-5 ml parenteral multivitamin concentrate.

1.3 Schema

Timeline for study events. Enrollment and intervention (CP or Placebo) occurs in the emergency department (or adjacent care clinic). Blood samples 1 and 2 are collected during that visit. Residual viral media samples from nasopharyngeal swabs and/or saliva samples will also be collected during the enrollment visit. Outpatient follow-up is conducted remotely by telephone or other contact. Subjects have phlebotomy on Day 15 and Day 30 for blood samples 3 and 4. In-person or remote contact on Day 15 and Day 30, and medical record review on Day 30, will confirm subject outcomes. We will collect information on participants' SARS-CoV-2 viral genotype from the enrolling institution if available.



1.4 Schedule of Activities

	Study Day									
	0	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**15**	**30**
Inclusion/Exclusion Informed Consent	X X									
Demographics Medical History Contact Information	X X X									
ABO type	X									
Randomization Pre-intervention research blood draw Administer CP or Placebo Post-intervention research blood draw	X X X X									
Research Blood Draw									X	X
Residual viral media / saliva sample	X									
Assess for Hospitalization Vital Status		X X	X X	X X	X X	X X	X X	X X	X X	X X
Symptom Inventory	X	X	X	X	X	X	X	X	X	X

Adverse Event Assessment Review Electronic Medical Record / Death Index	X X	X	X	X	X	X	X	X	X	X X X

Study Day 0 is the same as the day of randomization. Day 0 starts from the time of randomization until 23:59 of that calendar day. Day 1 begins at 00:00 on the following day.

1.5 Study Flow and Daily Data Collection

The enrollment and follow-up process will be tailored to the particulars of each site, but will generally be as follows.

- Units of SARS-CoV-2 convalescent plasma (CP) with neutralizing SARS-CoV2 antibodies titers of ≥1:160 will be sent to sites for storage.
- Site study teams will be notified whenever a COVID-19 test is ordered on an Emergency Department patient.
- The site study team will then consult with the treating team and/or the electronic health record to screen for potential eligibility.
- If the treating team anticipates discharge, the site study team will connect with the patient on the patient's mobile device, by bedside telephone in the ED room, on a study provided tablet device, or in person using all appropriate personal protective equipment. They will verbally describe the trial and participation and complete the informed consent process.
- Those wishing to participate will complete the electronic informed consent document and provide contact information.
- When all eligibility criteria have been met, the site study team will enroll and randomize the subject in the study web-based clinical trial management system (WebDCU).
- The site study team will complete Day 0 (Baseline) case report forms.
- All subjects will have a pre-infusion blood draw. Blood from consented subjects will be sent for blood type. Blood from all subjects will be processed and frozen for later analysis.
- Residual viral media samples from nasopharyngeal swabs and/or saliva samples will also be collected during the enrollment visit.
- If randomized to CP, an order will be placed by the study team to the blood bank for 1 unit of study CP.
- If randomized to placebo, an order will be placed to the pharmacy for 250 ml NS + 1-5 ml parenteral MVI (see MOP for details).
- CP or placebo will then be infused in a fashion blinded to the participant over 30 minutes (or longer depending on subject's cardiopulmonary status) with the infusion bag covered.
- The participant will be observed in the emergency department for at least 1 hour after infusion. At one hour, another blood sample will be drawn and frozen for later analysis.
- The participant will then be discharged from the emergency department.
- The central study team follow-up core will contact the participant by telephone or video

chat every other day to assess disease progression and serious adverse events for 2 weeks. They will assess blinding to treatment on day 2.

- The site study team will arrange collection of blood samples at days 15 and 30 to be frozen for later analysis. Subjects may visit a clinic, phlebotomy site, or other site-specific arrangement.
- The site study team will also collect data from any hospitalizations and ED/Urgent Care visits occurring within the study period. In addition, the study team will collect a symptom inventory on days 15 and 30 and assess blinding to treatment on day 15.
- Participation in the trial ends 30 days after enrollment.
- Blood samples from participants will be shipped to the study core lab at the University of Pittsburgh for analysis.
- Residual viral media and saliva samples will be shipped to a central lab for analysis.
- If hospitalized, participants are permitted to receive non-study CP or other emergency use or investigational treatments if available. In the event a participant is hospitalized, they may contact the study team for information regarding their study group allotment.

1.5.1 Day 0 Enrollment

1.5.1.1 Screening, Informed Consent, and Randomization

- Inclusion and Exclusion Criteria
- Informed Consent
- Random Assignment via WebDCU

1.5.1.2 Data Collection

- Demographics
- Detailed Contact Information
- Medical History
- Concurrent Medications
- Symptoms, including day of symptom onset
- SARS-CoV-2 viral genotype, if available

1.5.1.3 Intervention

- Blood type
- Blood sample for antibody titer
- Infuse CP or saline placebo
- Blood sample for antibody titer, 1 hour after infusion
- Residual viral media and/or saliva sample

1.5.2 Follow-up Assessments

1.5.2.1 Day 2 Telephone or remote assessment of

- Hospitalization, urgent medical visits, and vital status
- Symptoms
- Blinding to intervention arm

1.5.2.2 Day 4 Telephone or remote assessment of

- Hospitalization, urgent medical visits, and vital status

- Symptoms

1.5.2.3 Day 6 Telephone or remote assessment of

- Hospitalization, urgent medical visits, and vital status
- Symptoms

1.5.2.4 Day 8 Telephone or remote assessment of

- Hospitalization, urgent medical visits, and vital status
- Symptoms

1.5.2.5 Day 10 Telephone or remote assessment of

- Hospitalization, urgent medical visits, and vital status
- Symptoms

1.5.2.6 Day 12 Telephone or remote assessment of

- Hospitalization, urgent medical visits, and vital status
- Symptoms

1.5.2.7 Day 14 Telephone or remote assessment of

- Hospitalization, urgent medical visits, and vital status
- Symptoms

1.5.2.8 Day 15

- Collect blood sample for antibody testing

Telephone, remote, or in-person assessment of

- Hospitalization, urgent medical visits, and vital status
- Any adverse event
- Symptoms
- Blinding to intervention arm

1.5.2.9 Day 30

- Collect blood sample for antibody testing

Telephone, remote, or in-person assessment of

- Hospitalization, urgent medical visits, and vital status
- Any serious adverse event
- Symptoms

1.5.3 Day 30 End of Study

- Review electronic medical record for hospitalizations or serious adverse events
- Review death notifications for any subjects lost to follow-up

2. Introduction

This trial will test a therapy of strategic importance to the current and future worldwide response to COVID-19 (right therapy) in subjects most likely to benefit from the therapy (right patients) at the time during their illness when the therapy is most likely to show efficacy (right time). This trial uses clinically important, objectively measured endpoints with low risk of missingness (rigorous). The analysis of the trial data will describe the probability that the therapy has benefit in the most important manner for making decisions about further refinement or immediate adoption into clinical use (impact), including providing data on dose-effect relationship (right dose).

2.1 Study Rationale

Passive antibody therapy involves the administration of antibodies against a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent. In contrast, active vaccination requires the induction of an immune response that takes time to develop and varies depending on the vaccine recipient. Some immunocompromised patients fail to achieve an adequate immune response with active immunization, and some immunocompetent patients fail to generate protective antibodies in response to a given vaccine. Thus, passive antibody administration is the only means of providing immediate immunity to susceptible or non-immune persons and immunity of any measurable kind for highly immunocompromised patients.

The only antibody type that is currently available for immediate use is that found in human convalescent plasma (CP). As more individuals contract COVID-19 and recover, the number of potential donors will continue to increase. CP can be collected and administered anywhere in the world that is affected by COVID-19. Thus, CP represents an immediately and universally available therapeutic strategy for treating a pandemic prior to development of effective vaccines and in the absence of other pharmacological tools.

If CP is effective, it will support subsequent development of hyperimmune antibody preparations that can be immediately available for future outbreaks, prophylaxis, or individual treatment. This strategy has resulted in widely used products including hepatitis B-Ig, rabies-Ig, tetanus-Ig, and even respiratory pathogen products like respiratory syncytial virus-Ig. It is important to study CP now, because it is unknown if hyperimmune globulins (hyper-Ig) will be developed successfully, and it is also possible that hyper-Ig will be too expensive for all markets globally. However, CP can be made available even in resource-poor areas. In addition, this trial will inform decisions regarding the use of CP early on in future pandemics. The trial will also inform the design and justification for any future hyper-Ig trials.

At this moment, no high quality evidence supports the efficacy of CP for treating COVID-19 illness. Therefore, this is a pivotal trial to test the ability of passive antibody therapy to prevent progression of COVID-19 illness. This will provide an immediate treatment for the current global pandemic, a treatment for future patients who cannot benefit from active vaccination, and a scientific basis for development of strategically important hyperimmune globulins that could help mitigate future outbreaks.

2.2 Background

Importance of research question

Passive antibody therapy has been used for various illnesses for over 120 years. Plasma from donors who have been infected and then recovered (convalescent plasma, CP) from many illnesses contains neutralizing antibodies against the pathogen. Specifically, CP has been used in different respiratory illness epidemics, including the 1918 influenza pandemic, the 2003 SARS-CoV-1 outbreak, and the 2009 H1N1 influenza pandemic.[1] Use of convalescent plasma for emerging infections has persisted because of strong mechanistic and observational data, but efficacy has yet to be well tested or demonstrated in clinical trials. The challenges for CP therapy include identifying suitable donors, identifying adequately active antibodies, and learning who are the optimal patients and what is the optimal timing in the course of the disease for receiving CP. However, there is a suggestion in the SARS outbreak that the administration of CP earlier is more likely to be effective.[2] For this reason, this trial will test CP in early, mild COVID-19.

COVID-19 is a respiratory disease caused by the *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2). As of May 1st, 2020, over 3 million persons worldwide have been diagnosed with COVID-19 and approximately 250,000 persons have died from this disease. In the United States alone, as of May 1, 2020, there are approximately 1 million cases and 55,000 deaths. In the most current case series, the majority (80%) of cases were mild and were characterized by fever, myalgia, fatigue or dry cough. However, approximately 15-20% of cases were severe and were characterized by dyspnea and hypoxia, with about 5% of all cases progressing into critical illness, characterized by hypoxemic respiratory failure, shock, and end-organ failure.[1,2] Among the 5% who develop severe disease, as many as 50% die.[3] Although the time between illness onset and progression to severe disease is variable, it has been estimated to be approximately 10 days.[4] Older age and comorbidities such as hypertension, diabetes, and coronary heart disease increase the risk for developing severe COVID-19 illness and mortality.[3,4] At present there is no specific therapy for preventing the progression of COVID-19 from mild to severe disease. Hundreds of clinical trials are examining the efficacy of novel and repurposed therapeutic agents for treating patients with severe disease. In addition, efforts are currently underway to develop a vaccine for SARS-CoV-2 infection. However, only a handful of trials are exploring therapeutic agents for preventing the progression of mild to severe/critical COVID-19 illness.

Passive antibody therapy has been used since the 1890s, and it was the only means of treating certain infectious diseases prior to the development of antimicrobial therapy in the 1940s.[3,4] Experience from prior outbreaks with other coronaviruses, such as SARS-CoV-1 shows that such convalescent plasma contains neutralizing antibodies to the relevant virus.[5] In the case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy would mediate protection is viral neutralization. However, other mechanisms may be possible, such as antibody dependent cellular cytotoxicity and/or phagocytosis. Convalescent serum was also used in the 2013 African Ebola epidemic. A small non-randomized study in Sierra Leone revealed a significant increase in survival for those treated with convalescent whole blood relative to those who received standard treatment.

CP has the highest chance of showing efficacy if used for treatment of COVID-19 patients early in the course of disease. A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, passive immunization is most effective when administered shortly after the onset of symptoms. The reason for temporal variation in efficacy could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease. The benefit of CP may be greatest during the time prior to the recipient developing their own antibodies.[6] Another explanation is that antibody works by modifying the inflammatory response, which is also easier during the initial immune response, which may be

asymptomatic.[7] As an example, passive antibody therapy for pneumococcal pneumonia was most effective when administered shortly after the onset of symptoms and there was no benefit if antibody administration was delayed past the third day of disease.[8] In the SARS outbreak, administration of CP early in the disease appeared to be more effective.

For passive antibody therapy to be effective, a sufficient amount of antibody must be administered. When given to a susceptible person, this antibody will circulate in the blood, distribute into the total interstitial fluid in order to reach tissues, and provide protection against infection. As a rough estimate, one unit of donor CP (~250 ml) will be diluted into ~15 L of total extracellular fluid in an adult recipient, resulting in about 60-fold dilution of antibody concentration. For this reason, it is recommended that CP contain at least 1:80 titer and preferred 1:160 titer of antibodies against the pathogenic agent*. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin can last from weeks to months.

*https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

Supporting Evidence

Pre-clinical studies:

In the 21st century, there were two other epidemics with coronaviruses that were associated with high mortality, SARS in 2003 and MERS in 2012. In a mouse model of SARS infection, animals receiving immune serum from infected mice were protected against lower airway disease after intranasal challenge with virus.[9] Several groups have also identified monoclonal neutralizing antibodies that have shown efficacy in animal models of SARS.[10] In a mouse model of MERS infection, transfusion of sera from MERS-infected camels was efficacious for both prophylaxis and treatment.[11] Similar results for convalescent sera were obtained in a marmoset model of MERS.[12]

Clinical studies:

In both SARS and MERS outbreaks, the high mortality and absence of effective therapies led to the use of convalescent plasma in human studies. The largest study involved the treatment of 80 patients in Hong Kong with SARS.[13] Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. In addition, those who were RT-PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis. There is also some anecdotal information on the use of convalescent plasma in seriously ill individuals. Three patients with SARS in Taiwan were treated with 500 ml of convalescent plasma, resulting in a reduction in plasma virus titer and each survived.[14] Three patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients had neutralizing antibody in their plasma.[15] The latter study highlights a challenge in using convalescent plasma, namely, that some who recover from viral disease may not have high titers of neutralizing antibody.[16] Consistent with this point, an analysis of 99 samples of convalescent sera from patients with MERS showed that 87 had neutralizing antibody with a geometric mean titer of 1:61. This suggests that antibodies decline with time and/or that only some patients make high titer responses. It is also possible that other types of non-neutralizing antibodies are made that contribute to protection and recovery as described for other viral diseases.[17]

Current Trials of CP in Severe COVID-19

There are also recent reports of improvement from SARS-CoV-2 infection in hospitalized patients given convalescent plasma (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm). In another report, 5 critically ill patients with COVID-19 were given high-titer convalescent plasma.[18] All patients had improved viral loads, 4 had resolution of ARDS, and 3 were weaned from mechanical ventilation within 2 weeks of treatment. There were no reported adverse events in the treated patients. However, this study was uncontrolled and all 5 patients also received other anti-viral treatments and corticosteroids, highlighting the need for a randomized controlled trial. In another case series, 10 patients with severe COVID-19 were administered convalescent plasma, and all improved clinically without any serious adverse events. In a historical control group matched to the 10 treated patients, only 1 out 10 patients showed similar improvements.[19]

2.3 Risk/Benefit Assessment

2.3.1 Known potential risks

A theoretical risk of CP is antibody-dependent enhancement (ADE) of illness. ADE involves an enhancement of disease in the presence of cross-reacting antibodies that activate receptors that suppress immune response. For coronaviruses, there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain.[20] However, use of CP in the COVID-19 epidemic will rely on products with neutralizing antibody against the same virus, SARS2-CoV-2, which should make ADE unlikely. The available evidence from the use of CP in patients with SARS1 and MERS[21] and anecdotal evidence of its use in patients with COVID-19 (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm and,[18] suggest it is safe. Nevertheless, this trial will monitor illness severity over time for any evidence of enhanced infection.

Another theoretical risk is that antibody administration to those exposed to SARS-CoV-2 may avoid disease but modify the immune response such that those individuals mount attenuated immune responses, which would leave them vulnerable to subsequent re-infection. In this regard, passive antibody administration before vaccination with respiratory syncytial virus was reported to attenuate humoral but not cellular immunity.[22] This concern could be investigated as part of a clinical trial by measuring immune responses in those exposed and treated with convalescent plasma to prevent disease. If the concern proved real, these individuals could be vaccinated against COVID-19 when a vaccine becomes available. *These concerns seem modest compared to the possibility of limiting the duration and severity of disease, and avoiding interventions like mechanical ventilation, ARDS and sepsis.*

Finally, there are risks associated with any transfusion of plasma including transmission of transfusion transmitted viruses (e.g. HIV, HBV, HCV, etc.), allergic transfusion reactions, anaphylaxis to transfusion, febrile transfusion reaction, transfusion related acute lung injury (TRALI), transfusion associated cardiac overload (TACO), and hemolysis should ABO incompatible plasma be administered.[23] In addition, donors will fulfill donor requirements for whole blood donation and frequent apheresis plasma donation with the exception of recent illness, in this case COVID-19 infection. With current practice, transfusion transmission of infections is very rare. In addition, the risk of TRALI is also very rare because CP will be collected from populations with reduced risk for allo-antibodies such as: males, never pregnant females, and females who test negative for HLA antibodies.

Preliminary safety results from the Expanded Access Program for CP in moderate-severe COVID-19 have been posted, but not yet peer-reviewed (https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1). Among 5000 transfusions, there were 36 serious adverse events (0.7%) with 25 adjudicated as related (0.5%). Related

events included mortality (n=4, 0.08%), TACO (n=11,0.22%), TRALI (n=7,0.14%) and allergic reaction (n=3,0.06%). Another 11 deaths were reported but judged not to be related.

2.3.2 Known potential benefits

A key potential benefit is treatment for established infection. Convalescent plasma would be administered to those with clinical disease in an effort to reduce their symptoms and mortality. Based on the historical experience with antibody administration, it can be anticipated that *antibody administration relatively early in the course of disease would be more effective in preventing disease progression than in the treatment of established severe disease.*

Given that historical and current anecdotal data on use of CP suggest it is safe in coronavirus infection, the high mortality of COVID-19, particularly in elderly and vulnerable persons, suggests that the benefits of its use in those at high risk for or with early disease outweigh the risks. However, for all cases where convalescent plasma administration is considered, a risk-benefit assessment must be conducted to assess individual variables.

3. Objectives and Endpoints

Objectives	Endpoints	Justification for endpoints
Primary		
To establish the efficacy of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe COVID-19 illness.	Disease progression defined as death or hospital admission or seeking emergency or urgent care within 15 days of randomization	This will allow quantification of disease progression from mild to moderate/severe/critical.
Secondary and Exploratory		
Determine the effect of CP on COVID-19 illness severity	Worst severity rating on the WHO's COVID Ordinal Scale for Clinical Improvement during the 30 days following randomization ○ Death ○ Hospitalized, intubated, mechanically ventilated and requiring additional organ support (pressors, renal replacement therapy) ○ Hospitalized on invasive mechanical ventilation or ECMO ○ Hospitalized on non-invasive ventilation or high flow nasal cannula ○ Hospitalized on supplemental oxygen	This scale was developed by a special World Health Organization (WHO) committee for quantifying COVID-19 illness severity

	○ Hospitalized not on supplemental oxygen ○ Not hospitalized with limitation in activity (continued symptoms) ○ Not hospitalized without limitation in activity (no symptoms)	
Determine the effect of CP on COVID-19 illness severity	Time to disease progression on the COVID Outpatient Ordinal Outcome Scale censored at 15 days after randomization ● Patient requires care in the hospital ● Patient requires care in the ED or urgent care ● Patient at home with symptoms rated as moderate (defined as fever, shortness of breath, abdominal pain) ● Patient at home with symptoms rated as mild (defined as afebrile, constitutional symptoms (flu-like illness) without shortness of breath) ● Patient in their usual state of health	This scale was adapted for outpatient use from Harrell 2020 (http://hbiostat.org/proj/covid19/bayesplan.html) to provide more granular detail for outpatients than the WHO scale.
Determine the effect of CP on prevention of hospitalization	Hospital-free days during the 30 days following randomization	This is a more graded measurement of hospitalization than the binary primary outcome
Determine the effect of CP on mortality	All-cause mortality at 30 days	Critical safety outcome
Determine the effect of CP on the duration of symptoms	Symptom inventory measured using the CDC list of COVID-19 symptoms on days 2, 4, 6, 8, 10, 14, 15, 30	Patient centered outcome relevant to patient experience of illness
Characterize the immunological response to CP administration	Neutralizing antibody titers at days 0 (pre-intervention and post-intervention), 15, and 30 using different methods	Determine if CP administration increases recipient antibody titers that can inhibit virus

Measure change in spike protein IgG titers in CP recipient from pre- to post-CP	Spike protein IgG antibody titers pre and post CP administration using different methods	Determine distribution of CP antibodies into recipient

3.1 Primary Endpoint

Operational definition of Hospitalization Care in the primary endpoint:

- The endpoint is determined based on the order to admit the patient to an inpatient hospital bed (including admission to observation status). Patients may board in emergency departments or other outpatient areas awaiting inpatient beds for some time; therefore, the intent to place the patient in an inpatient bed is considered to be hospitalization. Observation in an emergency department observation unit would not count as hospitalization but only as emergency care. In the event that a patient worsens in the emergency department shortly after administration of the intervention and requires admission during that same visit, we will consider that that patient has met this primary endpoint.

Operational definition of Emergency Care in the primary endpoint:

- This endpoint is determined based on any presentation to an emergency department or urgent clinic for care. COVID-19 patients may be redirected to special areas adjacent to or outside of the usual emergency department for evaluation and treatment; therefore, the presentation for emergency or urgent care is considered the endpoint rather than physical entry into a specific area.

Operational definition of Death in the primary endpoint:

- Patients who die outside the hospital during the 15 days following randomization will meet this endpoint. Death notice or public records can confirm death.

Justification of the primary endpoint:

Hospitalization is a hard metric of meaningful worsening of disease.

- Hospitalization is a readily observable and objective outcome. It does not depend on self assessment, does not depend on return to the enrollment site, and can be verified by self-report, proxy-report, or even limited source documents from any admitting hospital or clinic. As such, it has low vulnerability to missing data or bias.
- The endpoint is a marker for worsening of disease. Hospitalization is a marker for the need of more intensive treatment that cannot be managed as an outpatient and is similar to the criteria used to characterize an adverse event as serious.
- The endpoint matters to patients. The need for hospitalization is a significant and meaningful event for patients. Hospitalization also removes patients from families and support systems further aggravating other symptoms of disease progression.
- The endpoint matters to the healthcare system. The need for hospitalization is the primary indicator of demand and capacity of the healthcare and public health systems during pandemic illness. This endpoint has direct implications for healthcare utilization in times of healthcare system stress.
- Preventing treatment imbalances within site (while maintaining randomness in treatment assignment) minimizes the effect of variations in practice or hospital capacity on the primary endpoint.

- Fifteen days is an appropriate time frame given the natural history of COVID-19. The median time to hospitalization from symptom onset is approximately 9-10 days. Longer time periods increase the risk of competing unrelated events.

Seeking Emergency Care is a hard metric of meaningful worsening of disease.

- Emergency and Urgent care is readily observable and objective. Like hospitalization, this event can be captured with limited source documents or patient report, and thus has low vulnerability to missing data or bias.
- Seeking medical care represents symptom progression that a patient cannot manage at home. Therefore, this is an event of sufficient severity to require action.
- The endpoint matters to the healthcare system. Emergency and urgent care represents health care utilization.
- This endpoint captures moderate disease progression. Patients treated in emergency departments or clinics but not admitted to the hospital have actionable disease progression that is less severe than those admitted to the hospital.

Death is a the most profound worsening of disease

- Subject death is readily ascertained and objective. Death can be confirmed by multiple data sources.

3.2 Secondary Endpoints

These endpoints explore the trajectory of illness in greater detail. These will provide additional information about CP effects on disease progression and maximal disease severity.

- WHO's COVID Ordinal Scale for Clinical Improvement
- COVID-19 Outpatient Ordinal Scale
- Hospital-free days
- All-cause mortality

3.3 Exploratory Endpoints

- Symptom inventory

These endpoints will determine the ability of CP to increase the titers of neutralizing antibodies in recipients.

- Antibody titers at pre-infusion, post-infusion and at 15 and 30 days in CP recipients and controls
- Spike protein IgG antibody titers pre and post CP administration

4. Study Design

4.1 Overall Design

This is a multi-center randomized, two-arm, single-blind, placebo-controlled phase III trial with blinded outcome assessment. We hypothesize that in patients with mild COVID-19 illness, the administration of convalescent plasma will decrease the need for hospital admission or emergency care for worsening, severe, or critical illness.

4.2 Scientific Rationale for Study Design

Rationale for using normal saline control group:

We considered comparing CP to non-immune plasma collected either prior to the spread of the SARS-CoV-2 virus or from donors with no known COVID-2 illness. Non-immune plasma would have similar appearance, volume, protein content and non-specific factors.

We believe there is some small risk to fresh frozen plasma (allergic, anaphylactic, and hemolytic reactions, and risk of transmission of infectious diseases) with no known benefit to the subject. This fact increases risk primarily in order to improve blinding. In addition, there is possible prevalence of antibodies to other coronaviruses in non-immune plasma which may in fact modulate COVID-19 illness or even cross-react with SARS-CoV-2. These antibodies, if present, might reduce the ability to detect an effect of CP. Finally, the trial must instruct future clinicians not whether to give CP versus non-immune plasma, but instead whether to give CP or not. Thus, a non-plasma control is a better placebo for a trial to guide clinical practice.

Saline as Control Group	**Plasma as Control Group**
Advantages ● No risk of reaction ● Maximizes opportunity to see effect of CP, including any non-specific effects ● Participants perceive as low-risk ● ED providers perceive as no-risk	***Advantages*** ● Preserves double-blind ● Controls for non-specific or immunomodulatory effects of plasma
Disadvantages ● Risk that subject may be unblinded ● ED staff will not be blinded ● ED staff must receive CP intervention from blood bank and placebo intervention from pharmacy	***Disadvantages*** ● 1-3% chance of mild reaction ● Blood Bank must manage randomization ● Non-specific antibodies that cross-react with SARS-CoV-2 may reduce opportunity to see effect of CP ● ED providers ambivalent about giving plasma without clear indication

Rationale for single-blind design:

We considered blinding ED providers by using fresh frozen plasma or other colloid fluid as a control. This procedure would require overcoming a number of major logistical hurdles including securing supply of sham plasma, labeling and tracking of sham plasma, and creating mechanisms to unblind providers in the event a patient seemed eligible for subsequent compassionate use CP. If a non-plasma control is used, it is unlikely that we can make it resemble plasma sufficiently to deceive experienced clinicians.

We believe that the patient can be blinded well to the intervention. Most patients do not receive blood products often or ever and will have no comparison. The bag and infusion line will be covered from patient view, removing clues from the appearance of the infusion. Adding a multivitamin to the saline will make the placebo bag color similar to plasma. Other aspects of treatment will be identical.

Because ED providers will not interact with the subject after the intervention is delivered, we believe that allowing these providers to know the intervention will not bias outcomes. Follow-up coordinators who make telephone or remote assessments usually will not be at the same site and will not look at the medical record: therefore, their outcome assessments will be blinded. Site coordinators who review the medical record may become unblinded, but these coordinators will be collecting primarily very objective data on health care visits (yes/no), vital status (live/dead), and adverse events. Those outcomes are easily audited and less prone to bias. For safety, if a patient presents to another healthcare facility during their follow-up, the single-blind design allows the subsequent clinicians to easily discover what the patient has received prior using standard medical record data.

Rationale for Dose (1 unit) of convalescent plasma

We discussed weight-based dosing of CP. However, the optimal titer of neutralizing antibodies in CP and the minimum effective dose of CP have not yet been established. Secondary analyses from this trial will provide information about dose-effect by examining the association between different titers and outcomes. In the absence of knowledge to be gained from this trial, we have no rationale to administer more than a single unit of CP. Risks of volume overload or other side-effects may increase with administration of more units.

4.3 Definitions of Enrolled, Discontinued and Completed

Enrolled

A subject will be considered enrolled at the time of randomization. Patients who provide electronic consent but are not randomized will be documented as a screen failure.

Discontinued

Subjects are considered discontinued when they meet 1 or more of the following criteria:

- Subject withdraws consent after being dosed and prior to the completion of Day 30.
- Subject is lost to follow-up.

Completed

Subjects are considered completed when they are followed through Study Day 30 and complete the final study follow-up visit scheduled for that time.

5. Study Population

5.1 Inclusion Criteria

- One or more symptoms of COVID-19 illness
- Laboratory-confirmed SARS-CoV-2 infection
- Has at least one study defined risk factor for severe COVID-19 illness:
    - Study defined risk factors initially include: age≥50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression; sickle cell disease, and obesity (body mass index [BMI]≥30) and are updated as needed in the C3PO Manual of Procedures in response to changes in CDC guidance or other information.
- Clinical team deems stable for outpatient management without new supplemental oxygen

- ABO-compatible CP available at the site at the time of enrollment
- Duration of symptoms ≤ 7 days at ED presentation and randomization.
- Signed informed consent

Criteria	Metric	Rationale
One or more symptoms of COVID-19 illness	Cough, shortness of breath or difficulty breathing, fevers, chills, repeated shaking with chills, muscle pain, headache, sore throat, new loss of taste or smell	CDC has defined a list of symptoms that include cough, shortness of breath or difficulty breathing, fevers, chills, repeated shaking with chills, muscle pain, headache, sore throat, or new loss of taste or smell. For purposes of this trial symptoms include any symptoms of COVID-19 illness listed by the CDC case definition guidance at the time of enrollment. Symptomatic COVID-19 illness justifies therapy. Asymptomatic illness is unlikely to be present in the emergency department unless it is an incidental finding.
Laboratory-confirmed SARS-CoV-2 infection	Local laboratory approved test for acute infection with SARS-CoV-2	Target illness is present. Testing for the presence of virus continues to improve at different sites over time. Tests should be specific and results available prior to enrollment. This should be their first episode of COVID-19 illness. See MOP for additional details.
Has at least one study defined risk factor for severe COVID-19 illness:	Age is biological age. Hypertension must be treated with medications. Diabetes must be treated with medications. Chronic lung disease, coronary artery disease, chronic kidney disease[23] per medical record. Immunosuppression with	Age, hypertension, diabetes, coronary heart disease, chronic lung disease and chronic kidney disease are associated with higher COVID-19 morbidity and mortality.[22,23] Hypertension and diabetes are on a continuum and sometimes controlled without

	medications. Obesity is defined as BMI≥30 Sickle cell disease is based on past medical history	medications. We will restrict to medication-treated conditions in order to clearly define comorbidities that have prompted medical treatment. Patients on immunosuppression for solid organ transplants are more often hospitalized for severe COVID-19 illness.[25] Emerging data suggests that sickle cell disease and obesity are risk factors for severe disease.
ED team deems stable for outpatient management without new supplemental oxygen requirement	Plan is to not place patient in inpatient bed, but to discharge from emergency department without supplemental oxygen (patients intended for observation for <24 hours or <2 midnights in an outpatient observation unit without oxygen supplementation would be eligible). Patients discharged from the ED may be brought back for randomization and treatment so long as they meet study inclusion criteria at the time of randomization.	Illness is mild, which allows potential to observe progression. Supplemental oxygen use would imply that the patient has little physiological reserve and already is at the verge of primary outcome.
ABO-compatible CP available at the site at the time of enrollment	Blood bank to check blood type	Must be able to deliver intervention.
Duration of symptoms ≤ 7 days at ED presentation and randomization	Subject report of symptom onset	CP therapy is most likely to have benefits early in the course of illness.
Signed informed consent	Informed consent document	Subject understands the risk and details of the trial

Immunocompromised: Any condition that causes reduced ability to fight infections. This may be caused by certain diseases (eg: cancer, diabetes); genetic disorders (eg: severe combined immune deficiency); or medications (eg: steroids, chemotherapy)

5.2 Exclusion Criteria

- Age less than 18 years
- Prisoner or ward of the state

- Presumed unable to complete follow-up assessments
- Prior adverse reaction(s) from blood product transfusion
- Receipt of any blood product within the past 120 days
- Treating clinical team unwilling to administer up to 250 ml fluid
- Enrollment in another interventional trial for COVID-19 illness or receipt of other active or passive immunization against SARS-CoV2.

Criteria	Metric	Rationale
Age less than 18 years	Biological age	Persons <18 years of age are less likely to develop severe/critical illness, and remote consent via parent or guardian will be more complex
Prisoner or ward of the state	Documentation of the same	A vulnerable population
Presumed unable to complete follow-up assessments	Multifactorial determination (clinical, psychosocial, subject self-report)	Difficulties with ascertaining outcome
Prior adverse reaction(s) from blood product transfusion	Subject self-report	Decrease the risk research presents to subjects
Receipt of any blood product within the past 120 days	Subject self-report	Minimize the risk of confounding
Treating clinical team unwilling to administer up to 250 ml fluid	Clinical team's assessment of whether patient will tolerate fluid, based on history and exam	To avoid iatrogenic fluid overload resulting from the administration of intervention
Enrollment in another interventional trial for COVID-19 illness or receipt of other active or passive immunization against SARS-CoV2.	Subject self-report	Minimize the risk of confounding

5.3 Screen Failures

We will track screen failures to characterize the population of COVID-19 patients that are not enrolled in the study at participating institutions. We will utilize total counts of all COVID-19 patients who are evaluated in the emergency department of a participating institution, and are discharged home from the emergency department, but are not enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics and reason(s) for exclusion.

5.4 Strategies for Recruitment and Retention

Target study sample size: Maximum of 900

Anticipated accrual rate: Accrual will vary by month depending on the progression or resolution of the pandemic.

Anticipated number of sites: The C3PO trial will be conducted in the Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN) network. The network is composed of the Clinical Coordinating Center (CCC) at the University of Michigan, which provides overall project management for the trial, the SIREN Data Coordinating Center (DCC) at the Medical University of South Carolina, which provides data management and statistical support, and 11 SIREN Hubs located in tertiary care facilities across the US. Subjects will be enrolled from at least 30 sites that are hub and spoke hospitals within the SIREN network who anticipate being able to enroll at least 4 cases per month.

Source of participants: Hospital emergency departments

Identifying and Recruiting Candidates. Potential subjects for this trial will be recruited from emergency department patients who have their first episode of symptomatic laboratory-confirmed SARS-CoV-2 infection and are being considered for outpatient management. All participating clinical sites are staffed by trained research personnel capable of performing careful screening of each potential subject according to the inclusion/exclusion criteria described above.

Recruitment of a diverse study population: COVID-19 disproportionately affects ethnic minorities with African-Americans accounting for up to 50% of cases and up to 70% of deaths in some cities.[25] We also believe that sex may be an important biological variable that may affect treatment outcomes for COVID-19. Therefore, we will enroll a racially diverse study population that is representative of the at-risk target population. In addition we will do our best to ensure that the proportions of males and females in the study population is balanced. Given the diversity in the geographical location, practice type (urban and non-urban academic medical centers and community hospitals) and racial composition of SIREN hub and spoke hospitals, our network is well positioned to recruit a study population that adequately represents the target population. Since 2006, we have completed 7 clinical trials in the NETT, and the enrollment of African American and Hispanic subjects reflects the disease population most affected, rather than the percentage of the US population. We accomplished this by having geographically representative sites with a good mix of large urban teaching hospitals, academic medical centers and community hospitals. Below is a table of the percentage of African-Americans and Hispanics enrolled in previously completed trials:

Study	**Synopsis**	**% African-American**	**%Hispanic**
Rampart	Treatment of status epilepticus in the prehospital setting comparing IM midazolam with IV lorazepam	51	12
ProTECT	Treatment of moderate-severe TBI with progesterone vs placebo	15	14
ESETT	Comparative effectiveness study of 3 anticonvulsants for benzodiazepine refractory status epilepticus	43	16
SHINE	Comparison of intensive treatment of blood glucose to	30	16

	usual care in Type 2 diabetic subjects with acute stroke		
POINT	Treatment with clopidogrel and aspirin vs aspirin alone after TIA or minor stroke	20	6
ALIAS2	Treatment of acute stroke with albumin vs usual care	19	6
ATACH2	Comparison of intensive blood pressure control vs usual care in acute intracerebral hemorrhage	28	15

For each DSMB report we will provide a summary table of the age, sex and racial composition of the subjects enrolled in this trial. We will monitor these distributions in real-time to ensure that the final study is representative of the target population.

How potential participants will be identified and approached: Trained research coordinators will monitor all emergency department presentations for eligible subjects. They will ask the treating team for permission and introduction to approach potentially eligible participants for informed consent. See section 10.1.1 for information on informed consent procedures.

Contact information at enrollment: Separate from the clinical data in case report forms, we will collect multiple methods of contacting subjects while they are still in the emergency department. At a minimum, this includes phone number, address and email for the subject, but also should include the phone numbers for an informant. The informant may be a family member, caregiver, or close contact who will be able to report important information on the status of the subject in the event that the subject does not respond (e.g. whether the subject is hospitalized, at an emergency visit, or deceased).

Remuneration of Subjects: Subjects may be eligible for compensation for travel/parking at any of their visits based on local institution practices.

5.5 45 CFR 46 Subpart B Determination

Pregnant women are not systematically excluded from enrollment in the C3PO clinical trial, which therefore requires a 45 CFR 46 Subpart B determination by the IRB. This research study does not, by design, target enrollment of pregnant women. In fact, the risk factors necessary for inclusion markedly reduce the likelihood of pregnancy among eligible subjects. However, the potential to enroll pregnant participants exists. Pregnant patients are not systematically excluded from eligibility because pregnancy is not a contraindication to plasma infusion in any clinical setting. Specifically, convalescent plasma is not contraindicated in pregnant patients with COVID-19 infection in clinical practice. There are neither data to indicate, nor rationale to presuppose, any increased risk to pregnant participants or their pregnancies attributable to randomization to convalescent plasma or placebo in this trial.

Not excluding pregnant women from this trial is consistent with current FDA draft guidance on the inclusion of pregnant women in clinical trials of drugs and biologics. It is also consistent with the intent of the revised common rule, in which pregnant women are no longer examples of inherently vulnerable populations.

6. Study Intervention

6.1 Study Intervention Administration

6.1.1 Study Intervention Description

Subjects will be randomized in a 1:1 ratio to receive either ABO group compatible SARS-CoV-2 convalescent plasma (CP) or normal saline with multivitamins.

6.1.2 Dosing and Administration

- Subjects will receive either one unit (~200 ml) of CP or 250 ml of normal saline with multivitamins.
    - Volume of the CP unit actually administered will be recorded to account for variable volumes of units and any instances when infusion stopped because of reaction or other event
- Study intervention will be administered after randomization and prior to discharge from the emergency department.
- Infusion rate: 500 mL/hour or slower depending on subject's cardiopulmonary status
- Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given
- If an AE develops during infusion, the infusion may be slowed or stopped as per the treating team's decision.
- Most reactions to plasma are relatively minor and the infusion can generally be continued. Infusion site burning and non-allergic systemic effects can generally be managed with slowing of the infusion. Infusion is generally stopped in cases of itching or hives. Participants may be treated and then infusion re-started.
- Allergic reactions, such as bronchospasm and hypotension, generally require discontinuation of the infusion.

6.1.3 Blinding of Subjects

To facilitate the blinding of participants to the intervention, the control arm will receive normal saline infused with 1-5 ml parenteral multivitamin. Blinding of the participant is supplemented by IV bag light shield bag covers. Placebo is intended to contribute to the single blind of the participant but not the care team.

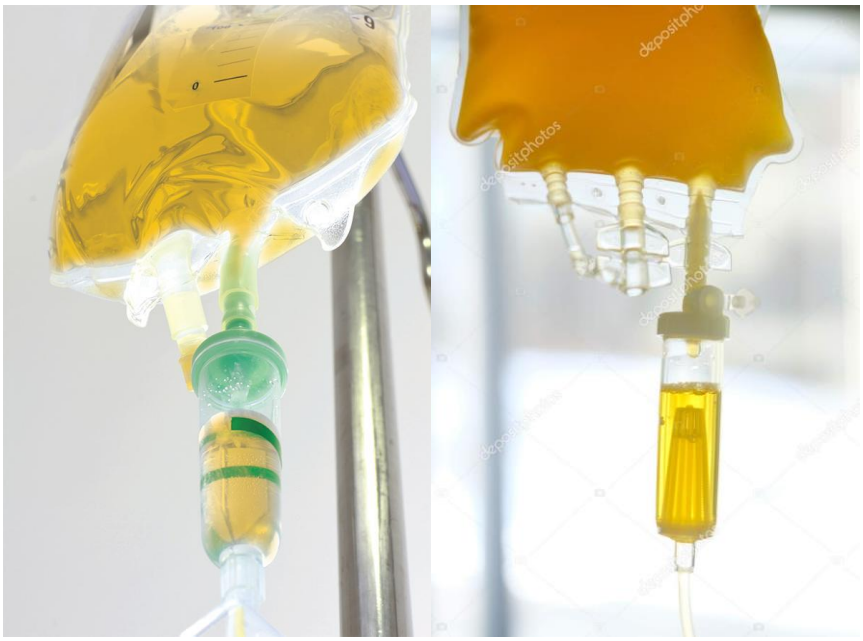


Figure: Placebo (saline with MVI) infusion on the left, Active intervention (plasma) infusion on the right. Placebo is intended to contribute to the single blind of the participant but not the care team. Blinding of the participant is supplemented by IV bag light shield bag covers.

6.2 Preparation/Handling/Storage/Accountability

NHLBI is collaborating with BARDA who will contract with Vitalant to provide up to 500 units of CP with known titers of neutralizing SARS-CoV2 antibodies of 1:160 or higher for this trial. The supplier (Vitalant) has already collected many units of CP. Donors will meet current FDA eligibility requirements for COVID-19 Convalescent Plasma (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma)

1. COVID-19 convalescent plasma will be collected from individuals who meet all donor eligibility requirements.

2. COVID-19 convalescent plasma is collected from individuals who meet all of the following qualifications:
    a. A positive serological test for SARS-CoV-2 antibodies after recovery.
    b. Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.
    c. Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.

Serologic testing will be performed using state-of-the-art research methods. Specifically, CP will be tested using a chemiluminescent test for IgG and IgM against spike protein (Ortho VITROS Anti-SARS-CoV2 Total) or equivalent assay. This assay has been granted FDA Emergency Use Authorization (EUA). If this qualitative test is positive, then the CP is also tested with the Vitalant Research Institute SARS-CoV2 Reporter Viral Particle Neutralization (RVPN) test or equivalent assay. The presence of antibodies are generally confirmed within 48 hours of donor collection. Assays will be conducted by a central laboratory and assays will also be made available to

study investigators.The CP is labeled with the titer from the RVPN test as: negative, <1:40, positive 1:40, 1:160; 1:640, 1:2560, 1:10240, >1:10240. We do not intend to use CP with 1:40 or <1:40 titer.

Plasma will be distributed from the central supplier to local blood banks at study sites and replenished as it is used. Each site will receive 4 or more units of CP at a time, and units will be replenished from the central supplier as they are used. Over the trial, each of the 30 or more SIREN sites will receive an average of 10-12 units of CP. We will ensure that, at all times, approximately half of the units of CP at each site will be of the group O-type and the remaining half will be group A units. Given the low prevalence of the AB group in the population, we expect very few CP donors will be of the AB-group. CP will be stored using usual storage for blood products, and ABO-type compatible CP dispensed to subjects, using local standard care for ABO compatibility. Vitalant will send samples from each CP unit to the study core laboratory at the University of Pittsburgh for antibody characterization.

In order to increase the rigor and reproducibility of antibody characterization in the CP units, we will determine the total titers to SARS CoV-2 S (Spike) protein (BSL-2+) using at least one other assay (e.g. EuroImmun ELISA). We will measure neutralization antibody titer in CP using a viral plaque assay at University of Pittsburgh (inhibition of SARS-CoV-2 infection of cells in vitro - the Gold Standard), thereby providing information about whether high titer CP has superior neutralization capacity for SARS-CoV-2. These data will inform large-scale screening of donors for CP in regions and settings where it is impossible to work directly with live viral inhibition assays (BSL-3).

A blood type will be performed in all potential subjects after the informed consent form is signed. If a subject is randomized to the CP arm, an order will be sent to the blood-bank for one unit of ABO-compatible CP. Upon receiving the order, the local blood bank will thaw ABO-compatible plasma at 30 - 37°C in an FDA cleared thawing device. If thawed in a water bath, a protective wrap will be used to prevent contamination of the ports on the unit. Thawed CP will be sent to the emergency department for infusion.

If a subject is randomized to the control (saline) arm, an order will be sent to the pharmacy or investigational drug service for a 250 ml bag of isotonic saline with 1-5 ml of parenteral multivitamin (to provide color similar to plasma). This bag will be sent to the emergency department for infusion. When administering the saline, nurses will place a light cover over the bag to hide its contents from the subject.

A study PI and/or study investigators who are transfusion medicine specialists will be available 24/7 to answer questions related to the study intervention in real time. Sites will be able to reach these investigators via the study hotline.

One threat to this trial is that the national demand for CP in severe COVID illness may compete with the supply of CP for this study. However, Vitalant has already secured many units of CP and anticipates no problem with supply. Vitalant also is a separate supplier from the sources being used in the expanded use authorization for severe COVID-19 (e.g. American Red Cross), and will not deplete that supply. Many of the SIREN sites who will conduct this trial are developing local plans to create a CP pool using local donors. For example, Stanford University has recruited enough donors at present that it could supply some other sites. Similarly, the University of Pittsburgh has developed its own CP inventory. In the event that the NHLBI and BARDA national suppliers cannot match demands from trial recruitment, the Transfusion Medicine core of our Scientific Core Group will work with the blood bank for each individual SIREN site to develop local CP supplies. This ability will also become important in the event that any sample size re-estimation concludes that more CP units would be desirable.

6.3 Measures to Minimize Bias: Randomization and Blinding

A web-based central randomization system will be developed by the SIREN DCC and installed on the WebDCU™ study website. Allocation will be fixed using a 1:1 allocation ratio. The objective of randomization is to prevent possible selection bias by providing random treatment assignment to each subject and to prevent accidental treatment imbalances for known prognostic variables. Variables that will be included in the randomization scheme are: age (treated as a continuous variable) and site. Site is included in the randomization scheme to avoid severe treatment imbalances within each site. Randomization will occur via the study-specific password-protected website accessed by an authorized research coordinator or investigator at the clinical site. If, in rare circumstances, the web system is not available, the coordinator or investigator will have access to emergency randomization procedures that will allow the site to randomize the subject. Subjects will be considered randomized in this trial at the time of randomization, regardless of whether or not they receive the assigned study treatment.

The primary outcome assessment in this trial will be performed by study team members who are blinded to study group allotment. To test the effectiveness of blinding procedures, subjects will be asked at the Day 2 and Day 15 follow-up assessment to which treatment arm they believe they were assigned and how confident they are in their response. If the subject becomes knowledgeable of their treatment assignment at any point during study participation, this will be documented in the study database. Regardless of unblinding, the subject will remain in the study and be part of the analysis population.

6.4 Concomitant Therapy and Hospitalization

Concomitant medications will be documented on the CRF. We will not enroll patients already in another clinical trial. Subjects should not enroll in another interventional trial as an outpatient while in this clinical trial.

In the event that a subject worsens and is admitted to a hospital, that subject will have met the primary endpoint of this trial. We will not restrict that subject from enrolling in another trial if eligible, especially because other trials may be the only access for potential COVID-19 therapies. In particular, control subjects should be eligible for compassionate use CP, though this trial cannot guarantee CP will be available at a site precisely when the subject is hospitalized. Patients in either arm who develop severe/critical disease are not precluded from receiving compassionate use CP after meeting the primary endpoint, if this therapy is available for routine clinical care at the institution where they receive care.

7. Participant Discontinuation/Withdrawal

7.1 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. The reason for participant discontinuation from the study will be recorded on the Case Report Form (CRF). Subjects who are randomized and subsequently withdraw informed consent will not be replaced.

7.2 Loss to Follow-Up

To attain a high rate of follow up (>90%), the study team will request multiple phone numbers (home, cell phones, pagers, etc) and addresses from the subject and his/her relatives, friends, primary doctor (if available), clergy and clinics. At the time of consent and enrollment, subjects

will be asked to provide the address and telephone number of the place where the subject will likely reside following discharge.

Following ED discharge, a blinded research coordinator will telephone subjects every other day for a health status inquiry and to maintain and update tracking information. During follow-up phone calls, if medical concerns are raised, subjects will be referred to their usual care provider or to emergency care if urgent. In the event that the research coordinator cannot reach a subject or an informant, the coordinator will continue to call frequently for up to 2 weeks after the last scheduled contact before considering a subject lost to follow-up. Subjects cannot be deemed "Lost to Follow-up" without the C3PO Operations Committee approval. The site PI must present a case to the C3PO Operations Committee that includes the efforts exerted to locate the study subject. The Site PI may be asked to continue their efforts prior to approval.

8. Study Assessments and Procedures

8.1 Efficacy Assessments

Trained study personnel who are blinded to study group allotment will interview participants via telephone every other day during the first 14 days of the study and on day 15 (window: days 14,15 and 16) and 30 (window: days 29, 30, 31, 32, 33) to ascertain efficacy and safety endpoints. Assessments will be performed either by study personnel at local sites or by a centralized pool of trained personnel. Data will be documented in WebDCU.

Central caller assessments completed within 1 day of the time point will be counted as qualifying and not considered missing.

On study days 15 (window: days 14, 15, 16) and 30 (window: 29, 30, 31, 32, 33), participants will be asked to return for research blood draws. If there is no follow-up due to lack of patient response, the patient will be considered lost to follow-up.

8.1.1 Primary Endpoint

These events can be ascertained from the subject or informant report during follow-up calls, electronic health record review, death notices, or direct contact with the subject during follow-up visits. Thus, we have multiple opportunities to collect and confirm the primary endpoint, minimizing risk of missing data.

Subjects will meet the primary endpoint of the study (1) if they are admitted to a hospital as an inpatient/observation status for <u>any reason</u> during the 15 days following randomization, (2) if they have an emergency department or urgent clinic visit during the 15 days following randomization, or (3) die outside the hospital during the 15 days following randomization. Scheduled medical follow-up visits or rechecks will not meet the definition of emergency care.

8.1.2 Secondary Endpoints (clinical)

These endpoints can be ascertained from the subject or informant report during follow-up calls, supplemented by review of health records. Surveys and assessments from day 0-14 that are completed within 1 day of the time point will be counted as qualifying and not considered missing (for example day 4 assessment may be done on day 4 or 5).

COVID-19 illness severity: We will quantify COVID-19 illness severity using a 8-point ordinal scale developed by a World Health Organization (WHO) committee. We will record the worst illness severity rating observed during the 30 days following randomization:

<u>WHO's COVID Ordinal Scale for Clinical Improvement</u>

- 8 = Death
- 7 = Hospitalized, intubated, mechanically ventilated and requiring additional organ support (pressors, renal replacement therapy)
- 6 = Hospitalized, intubated and mechanically ventilated
- 5 = Hospitalized on non-invasive ventilation or high flow nasal cannula
- 4 = Hospitalized on supplemental oxygen by mask or nasal prongs
- 3 = Hospitalized not on supplemental oxygen
- 2 = Not hospitalized with limitation in activity (continued symptoms)
- 1 = Not hospitalized without limitation in activity (no symptoms)

COVID-19 illness severity (outpatient): An adaptation of the WHO scale, based on the quality of symptoms reported by the subject, can quantify outpatient disease severity among patients at home (scores 1-2 on the WHO scale). This 5-point COVID Outpatient Ordinal Outcomes scale was adapted for outpatient use from Harrell 2020 (http://hbiostat.org/proj/covid19/bayesplan.html). This scale is hierarchical where 1 is the highest severity (hospitalization) and 5 is the lowest severity.

COVID Outpatient Ordinal Outcomes Scale

- 1 = patient requires care in the hospital
- 2 = patient requires care in the ED or urgent care
- 3 = patient at home with symptoms rated as moderate (defined as fever, shortness of breath, abdominal pain)
- 4 = patient at home with symptoms rated as mild (defined as afebrile, constitutional symptoms (flu-like illness) without shortness of breath)
- 5 = patient in their usual state of health

Worsening of symptoms is defined as any subject admitted to the hospital (level 1), seen in the emergency room (level 2), a patient who reports increased symptoms of 2 levels on the scale over a 24 hour period, or a patient who reports increased symptoms of 1 level observed for a 48 hour period.

Symptom inventory: On study days 2, 4, 6, 8, 10, 12, 14, 15 and 30, we will record the burden of symptoms listed by the Centers for Disease Control and Prevention (CDC) as typical of COVID-19 illness. For purposes of this trial symptoms include any symptoms of COVID-19 illness listed by the CDC case definition guidance at the time of enrollment. These include but are not limited to the following: .

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea
- Abdominal pain
- Limitations of activities because of COVID-19 symptoms

Refer to the Manual of Procedures for the latest CDC list of COVID-19 symptoms.

Hospital-free days: We will record the number of days a subject was not admitted to a hospital during the first 30 days following randomization.

All-cause mortality: We will record death from any cause that occurred during the first 30 days following randomization.

8.1.3 Secondary Endpoints (immunological):

These endpoints will be measured using 4 blood samples collected pre-intervention in the emergency department, post-intervention in the emergency department, and at days 15 and 30 (as outpatients). At days 15 and 30, subjects will return to a clinic, phlebotomy site, or have outpatient phlebotomy to measure circulating antibodies. Each site will need to determine a blood sampling site that is qualified and safe for phlebotomy in persons with recent COVID-19 illness according to current CDC guidance. While guidance continues to evolve, patients are thought to be safe to leave isolation when symptoms have resolved for 3 days or at least 10 days have passed since COVID-19 diagnosis (https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/steps-when-sick.html), which will be prior to any of the in-person evaluations.

No more than 50 mL of blood will be drawn per day: 15 ml (one tablespoon) of whole blood will be collected from subjects at the following timepoints:

- After consent but before the administration of study intervention
- 1 (+/- 30 minutes) hours following the end of the administration of study intervention, and
- During study visits occurring on study days 15 and 30.

Whole blood will be processed into serum and plasma, and stored in a -70ºC freezer or colder within 2 hours of sample collection. Samples will be shipped periodically to the study biorepository housed at the University of Pittsburgh.

Our exploratory aim is to characterize the agreement between or differences between the multiple assays for antibodies. This is important to inform future investigations about how to interpret titers reported by one platform or another. This will also inform about the development of innate immunity in control subjects. Increase in antibodies over time in CP recipients, if it occurs, will also inform about development of innate immunity after passive immunization. Therefore, we plan to perform multiple assays on any available sample from the donor unit, and also on the blood obtained from recipients of the intervention. Specifically, we plan to measure at least the following well characterized tests:

- Quantitate Anti-spike (S1) protein IgG, IgA titers (e.g. EUROIMMUN) on CP units
- Correlation of ELISA titers with Vitalant RVPN titers (neutralizing antibodies) on CP units
- Assessment of S1 titers in CP recipients and controls pre-CP, 1 hr post, 15 and 30 days post to assess the impact of CP and determine whether titers rise with time (showing endogenous response not negatively impacted by CP)
- Use Lentiviral pseudovirus reporter assay to quantitate neutralization Ab titers in recipients of CP units at pre- post-CP.
- Neutralization of SARS CoV-2 Plaque Formation (gold standard) in a subset of CP to correlate with other assays.

In addition to the blood samples collection outlined above, for subjects who consent to participating in an optional study evaluating the evolution of the adaptive immune response in CP recipients, an additional 20 ml of whole blood will be collected on the day of enrollment and

on study days 15 and 30. These samples will be shipped within 1 day of collection to a central laboratory for processing.

Residual viral media and saliva specimens collected will be analyzed for SARS-CoV-2 viral genotype

8.1.4 Blood Sample Storage, Processing and Shipping for Antibody Titer Testing

Each site will ship the 4 blood samples from each participant to the central testing laboratory (University of Pittsburgh). The site can ship all of the samples for one participant together in a single package. Labels for samples with barcodes will be provided to sites in advance in order to ensure accurate sample tracking. Labeling samples with the subject ID from WebDCU can serve as a backup procedure.

Antibody titres: To determine the immunologic response to CP administration, we will measure anti-SARS-CoV-2 IgG, IgM and neutralizing antibody titres pre-intervention, post-intervention and at days 15 and 30.

Testing will be identical to the testing performed to determine the titer of the donor CP. We will determine the IgG/IgM titers to SARS CoV-2 S (Spike) protein using enzyme linked immunoassays (BSL-2+). There are multiple assays available and in development. We will compare titres from the Vitalant (Ortho VITROS Anti-SARS-CoV2 Total) assay to titres from other assays (e.g. EuroImmun ELISA) whenever possible to determine the concordance. In a subset of these samples, we will measure antibody neutralization titers using the gold standard assay, a viral plaque assay performed in a BSL-3 facility at University of Pittsburgh. This will allow us to determine whether high titers in binding assays actually represent superior neutralization capacity for inhibiting SARS-CoV-2 infection.

8.1.5 Assessment of Blinding

As part of follow-up assessments on Days 2 and 15, investigators will ask subjects to indicate which intervention (CP or placebo) they believe that they received, and how confident they are in their response. If blinding is successful, subjects will be no more accurate than chance. We will also examine the rate of successful follow-up contacts between groups. If blinding is successful, missingness will not differ between groups. We will have local site investigators review emergency department practice and communication, potentially to create a corrective action plan, in the event we see a pattern at a site that suggests a high rate of subject unblinding.

If the subject becomes knowledgeable of their treatment assignment at any point during study participation, this will be documented in the study database. Regardless of unblinding, the subject will remain in the study and be part of the analysis population.

8.1.6 Clinical and Demographic Data

At enrollment, we will collect data from the subject and the medical record to validate eligibility for enrollment into the trial and to assess risk factors for developing severe/critical COVID-19 illness. This data includes but is not limited to: inclusion and exclusion criteria, demographic information, vital signs, medical history, and medications. We will collect time of COVID-19 symptom onset by self-report from the subject.

8.2 Safety and Other Assessments

8.2.1 Safety Assessment

All adverse events (AEs) will be recorded until ED discharge. All AEs occurring until discharge from the emergency department must be reported in WebDCU™. After discharge from the emergency department and at each follow-up contact until the end of study, only serious adverse events will be reported in WebDCU and any event that leads to hospitalization or an ED or urgent care visit even if deemed non-serious. Investigators will also review medical records on Day 30 for any serious adverse events.

Subjects will be monitored for the following plasma-specific AEs:

- Transfusion reactions: fever, rash, itching
- Serious allergic reactions (anaphylaxis or bronchospasm requiring treatment)
- Transfusion Associated Acute Lung Injury (TRALI), as defined by https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6850655/ (21). Given that these are patients with other risk factors for ARDS, a diagnosis of “possible TRALI” will require stable respiratory status in the 12 hours before transfusion. Because TRALI may mimic the natural progression of COVID-19, the demonstration of HLA antibodies in the donor product that matches the recipient’s HLA type will also be necessary to make the diagnosis of “possible TRALI”.
- Transfusion Associated Circulatory Overload (TACO)

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

8.3.2 Definition of Serious Adverse Event (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events may also be considered serious when they require medical or surgical intervention to prevent death, risk of permanent injury or disability, or prolonged hospitalization.

COVID-19 patients who require hospital admission are clinically expected to have adverse events related to their underlying condition and standard treatment, independent of any research intervention. Examples of common medical events in this population include (but are not limited to): respiratory failure requiring oxygen supplementation and/or intubation, ventilator associated pneumonia, venous thromboembolic disease, or encephalopathy, cytokine storm, shock requiring vasopressors and renal failure requiring renal replacement therapy.
Subjects may also incur AEs that could be expected to occur at higher rates because of the study intervention. These include medical events such as: serious allergic reactions (anaphylaxis or bronchospasm requiring treatment), transfusion related acute lung injury

(TRALI), transfusion associated circulatory overload (TACO) and transmission of infectious agents.[23]

Pre-existing medical conditions or unchanged, chronic medical conditions. Pre-existing medical conditions or unchanged, chronic medical conditions are NOT considered AEs and should not be recorded on the AE case report form (CRF). These medical conditions should be adequately documented on the medical history and/or other source documents. In this trial, any medical conditions not present prior to randomization but that emerge after randomization are considered AEs.

Exacerbation of Pre-existing medical conditions. A pre-existing medical condition judged by the investigator to have worsened in severity or frequency or changed in character is considered an adverse event.

8.3.3 Classification of an Adverse Event

For adverse events (AEs) not included in the protocol defined grading system, the severity of adverse events will be determined referencing the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE). The CTCAE provides a grading (severity) scale for AEs with unique clinical descriptions of severity based on this general guidance:

Grade 1: Mild AE

Grade 2: Moderate AE

Grade 3: Severe AE

Grade 4: Life-Threatening or Disabling AE

Grade 5: Death related to AE

8.3.4 Relationship to Study Intervention

Adverse reaction is different from an adverse event. Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the study intervention caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the study intervention and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means an adverse event is definitely caused by the study intervention.

Per FDA guidance a suspected adverse reaction is one that is known to be strongly associated with the study intervention, or one that is very uncommon in the study population, or one shown in aggregate analysis to occur more frequently in the treatment group. Generally anticipated adverse events are not suspected adverse reactions.

Because 'reasonable possibility' can be difficult to determine, this trial uses an algorithmic approach to describing relatedness.

Algorithm to Determine Relatedness of Adverse Event to Study Agent

Not Related	The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)
Unlikely	Must have both of the following 2 conditions, but may have reasonable or only tenuous temporal relationship to intervention.
	● Could readily have been produced by the subject's clinical state, or environmental or other interventions. ● Does not follow a known pattern of response to intervention.
Reasonable Possibility	Must have at least 2 of the following 3 conditions
	● Has a reasonable temporal relationship to intervention. ● Could not readily have been produced by the subject's clinical state or environmental or other interventions. ● Follows a known pattern of response to intervention.
Definitely	Must have all 3 of the following conditions
	● Has a reasonable temporal relationship to intervention. ● Could not possibly have been produced by the subject's clinical state or have been due to environmental or other interventions. ● Follows a known pattern of response to intervention.

8.3.5 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by an independent medical safety monitor (section 10.4).

Adverse events will be captured and reported in WebDCU™. Information to be collected includes time of onset, clinician's assessment of severity, relatedness to study intervention, and time of resolution/stabilization of the event. All SAES will also include a narrative of the event with additional testing results if conducted. All AEs occurring until discharge from the emergency department must be reported in WebDCU™. After discharge from the emergency department, only serious adverse events will be reported in WebDCU™. All AEs will be followed to adequate resolution/stabilization or subject end of study.

All non-serious AEs must be recorded on the electronic AE CRF within 5 days from the time it was discovered by the site study personnel. For SAEs, the data entry must take place within 24 hours of discovery of the event. Upon submission of an SAE, the system will trigger an automatic email notification to the Independent Medical Safety Monitor (iMSM) stating that an SAE has occurred. The iMSM will access the information via the password protected web

based system and will review the SAE data within 2 business days of being notified for completeness of reporting, and will enter their assessment of relatedness and expectedness. Expedited reporting to the DSMB and regulatory parties will occur for all potentially related unexpected SAEs. The reporting timeline will follow FDA requirements: within 7 calendar days of the sponsor's knowledge of an unexpected fatal or life-threatening event; within 15 calendar days for all other unexpected potentially related SAEs.

8.4 Unanticipated Problems

An Unanticipated Problem is any event, incident, experience, or outcome that is

- unexpected in terms of nature, severity, or frequency in relation to
    - the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents;
    - the characteristics of the subject population being studied (persons with life threatening COVID-19); and
- possibly, probably, or definitely related to participation in the research; and
- places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated Problems will be reported in WebDCU. Unanticipated problems may include problems with protocol implementation, participant safety, and/or concerns regarding informed consent. Initial reports will be submitted within 7 calendar days of site awareness of the event.

9. Statistical Considerations

This trial is designed with sample size re-estimation to adapt to the evolving landscape of COVID-19 illness. This trial design, as well as its implementation mechanics, can serve as a template for subsequent studies of how interventions delivered to patients presenting to the emergency department alter disease trajectory.

We believe that clinicians will change practice if CP can afford ~10% absolute risk reduction in disease progression, but the constrained sample size limits power to detect clinically significant changes if the control event rate for hospitalization, the most important sign of worsening, is too low.

For this reason, we will look at a composite outcome that combines hospitalization, symptom progression that results in seeking medical evaluation or treatment (ED visit or urgent clinic visit), and death outside of the hospital. The total event rate for this composite will be larger than hospitalization alone.

In addition, we have selected a population with risk factors for more severe disease, based on the case series reported to date: older age and chronic end-organ disease or comorbidities. The event rate for the primary outcome is expected to be higher in this population than in all outpatients with COVID-19. Further, this population is the one with most potential to benefit from CP therapy and is the most likely outpatient population in whom clinicians may choose to use a blood product.

We considered comparing time to event as an alternative to comparing proportions of events between the treatment arms. The gain in power from time to event analysis is offset by the concern that the time to event is affected more by the time course of the illness than by initiation of treatment, and that patient self-report of the day of symptom onset will not be sufficiently accurate to adjust. For example, a patient who presents to the ED and is enrolled on day 7 of

COVID-19 illness may progress to hospitalization more quickly than a patient who presents to the ED and is enrolled on day 2 of COVID-19 illness. In our chosen analysis, the similar worsening of illness in both patients is accurately captured by counting the presence of the primary endpoint by Day 15. Moreover, a delay in disease progression is not clinically important if the proportion of subjects who progress is not different.

9.1 Sample Size

Sample size is restricted by the availability of CP for the participating sites. Based on discussions with the NHLBI, we are assured to have sufficient CP available for roughly 300 patients at the time of study initiation.
Therefore, we provide power estimations based on our primary outcome, assuming a maximum of 600 randomizations (300 per group).

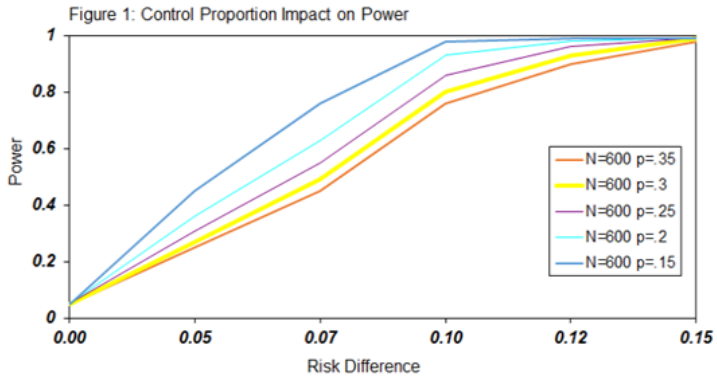


Figure 1 provides a range of risk differences (control minus treatment) based on potential event rates for our control population. For example, if the primary outcome event proportion within 15 days from randomization is 20% in the control population, then we have 85% power to detect an absolute decrease of at least 10% in this proportion for those treated with CP. If the control proportion is less than 20% then we can detect differences of roughly 8% while maintaining more than 80% power. Alternatively, if the control rate is closer to 30%, then our power begins to drop for detecting risk differences less than 10%. Based on the current information on hospitalizations in this COVID population, we do not expect the proportion in the standard of care arm to vary greatly from 20%. Clinicians are unlikely to discharge patients whose risk for the primary outcome is significantly greater than 30%..

Sample Size Re-Estimation

We recognize that sample size estimation is based on assumptions and, if our control proportion greatly varies from what we assumed, then we may begin to see a decrease in power. To reduce the likelihood of an underpowered study due to an incorrect assumption, we propose to conduct a sample size re-estimation at the time of the first interim analysis . The overall primary outcome proportion of the population will be estimated using the interim data for the sole purpose of sample size re-estimation (not for interim testing of a treatment effect). If the observed overall event rate is greater than the assumed, then we may require additional subjects to maintain adequate power. Ultimately it is the DSMB's decision to recommend an increase in the total sample size and this decision should take into account the safety profile, which will be provided to the DSMB at the time of analysis. Based upon the DSMB's recommendation, the study team in conjunction with NHLBI will need to determine the feasibility of an increase to the sample size in terms of the availability of additional units of CP and impact on funding. We do not plan to decrease the sample size based on the re-estimation plan.

9.2 Analysis Plan

9.2.1 Primary Analysis

Outcomes will be analyzed using the intent-to-treat principle (ITT). The primary analysis for this trial is to test the hypothesis of superiority of CP as compared to saline in the ITT population. To

test this hypothesis, the posterior probability that the proportion of primary outcome events at 15-days post randomization is higher in the saline arm as compared to the CP arm will be calculated. Because little is known about the impact of CP, we assume a non-informative beta distribution for the prior probability. The primary null hypothesis (that the CP proportion is greater than or equal to saline) will be rejected if the posterior probability is greater than or equal to 0.975 (selected to coincide with a one-sided alpha level of 0.025 under a frequentist design). The treatment effect and corresponding credible interval will be constructed.

If the trial fails to enroll the planned sample size due to a significant decrease in the number of COVID-19 patients, then Bayesian posterior and predictive probabilities will be used to assist in the interpretation of the observed data.

Secondary analyses of the primary outcome will explore the impact of potential prognostic variables including age, sex, onset of symptoms duration and site. A logistic regression model will be used for these additional analyses. We will also examine whether participants' pre-treatment antibody levels and/or the genotype of the SARS-CoV2 virus that they carry modify the association between CP and outcome.

The inherent variability in antibody titer among CP units will provide an important opportunity to explore the dose-effect relationship for CP. We envision performing a similar regression of the primary outcome using CP titer categories.

9.2.2 Interim Analysis Plan

The study design will include frequent monitoring of the primary outcome with planned looks for both overwhelming efficacy and futility after 33%, 50% and 75% of consecutive enrollments complete 15 day follow-up. For efficacy, we will calculate the posterior probability that the primary outcome event proportion is higher in the saline arm as compared to the CP arm. If this probability is greater than 0.999, then the trial could stop for overwhelming superiority of the CP. This threshold is based on a Haybittle-Peto type boundary, where the stopping threshold is constant across interim looks and the threshold at the final look approximates a design with no interim analyses. For futility, we will calculate a predictive probability (probability of success if the trial were to achieve the predefined maximum sample size). If the probability is less than 0.20 then the trial may stop for futility. Since several factors need to be taken into consideration before stopping a study, a complete report of overall study progress, data quality, and safety will be provided to the DSMB at each interim analysis. If a boundary is crossed, the report will also include secondary outcomes. This information will be taken into consideration by the DSMB in the decision to recommend stopping the study if an efficacy or futility boundary is crossed. The ITT population, defined as all randomized subjects, will be used for the interim analyses.

9.2.3 Missing Data

Although every attempt will be made to prevent incomplete data, a certain amount of missing data is inevitable due to losses to follow-up or withdrawn consents. For the primary outcome data, subjects who do not complete the follow up because of withdrawal of consent will be considered missing. In the case of loss to follow-up, we would expect that the sites will be able to obtain information on the event within 15 days from randomization from the medical record; if the site cannot obtain information, the outcome will be considered missing. At the time of the planned analyses, the unblinded statistician will conduct a thorough analysis of outcome variables, reasons, and patterns of missing data, and provide this information in the DSMB report. Sensitivity to missing data will be assessed. If the outcome is insensitive to missing data, defined as no change in the conclusion regardless of the set of imputed values, each missing observation will be imputed an unfavorable outcome (i.e., event occured). If the

outcome is sensitive to missing data, each observation will be imputed using a Bayesian imputation model.

9.2.4 Analysis of Secondary and Exploratory Outcomes

This study is designed to test the primary hypothesis; however, it also offers the opportunity to evaluate important additional secondary and exploratory outcomes. Continuous secondary endpoints will be summarized by the mean and standard deviation with corresponding 95% confidence intervals. Categorical endpoints will be summarized by the sample proportions with exact or asymptotic confidence intervals. For time to event analyses, we will construct Kaplan Meier curves. Our analyses will consider sex as a biological variable that may affect treatment outcomes for COVID-19.

10. Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the Central IRB (Advarra). A signed consent form will be obtained for every subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

10.1.1.1 Provision of Consent Form to Participants

A copy of the consent form will be given to the subject, and this fact will be documented in the subject's record.

10.1.1.2 Consent Procedures and Documentation

Consent is obtained by either the clinical site PI or by individuals to whom the clinical site PI has delegated authority to obtain informed consent. The delegation of authority is documented and maintained in WebDCU™. As with most clinical trial responsibilities delegated by the clinical site PI, it is his/her responsibility to ensure that the delegation is made only to those individuals who are qualified to undertake the delegated tasks, and that there is adherence to all applicable regulatory requirements and Good Clinical Practices (GCP) Guidelines. Additionally, it is the investigator's responsibility to ensure that the subject has been given an adequate explanation of the purpose, methods, risks, potential benefits and subject responsibilities of the study. The consent form must be an up-to-date document that has been approved by the Central institutional review board (CIRB). A signed and dated informed consent is required prior to randomization. We anticipate that the electronic consent platform (eConsent) will be utilized for almost all subjects in this trial.

Rationale for the use of e-consent: We have chosen this method of consent in order to minimize risk to the research team and healthcare providers and to decrease community spread of the disease. We have prior experience using telemedicine and phone consent coupled with electronic consent form review for time-sensitive clinical trials of traumatic brain injury and cardiac arrest. While the rationale for eConsent is different in this case (minimization of disease spread during a pandemic), we believe it is appropriate for the disease and intervention being studied. The low risk of adverse effects from CP, combined with the close remote follow-up methods proposed in this study make the risk: benefit ratio for the alteration of traditional

consent process acceptable for participants, providers, and the public.

10.1.2 Study Discontinuation and Closure

The study may be modified or discontinued at any time by the NHLBI, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

10.1.3 Confidentiality and Privacy

The subject's identity will be kept as confidential as possible as required by law. Upon enrollment, WebDCU™ assigns a unique subject ID to each subject. The link between the subject ID and the subject's name will be confidentially maintained at the enrolling sites. In compliance with Health Information Portability and Accountability Act (HIPAA), collection, storage, display, and transfer of study subject personal identifiers in the WebDCU™ are carefully controlled. Prior to creating the Public Use Dataset any personal identifiers, such as date of enrollment, will be de-identified.

10.2 Key Roles and Study Governance

Demonstrated ability of the group or history of the investigators in conducting clinical research: The C3PO trial will be conducted in the Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN) network. The network is composed of the Clinical Coordinating Center (CCC) at the University of Michigan, which provides overall project management for the trial, the SIREN Data Coordinating Center (DCC) at the Medical University of South Carolina, which provides data management and statistical support, and 11 SIREN Hubs located in tertiary care facilities across the US. Funded by the National Institute for Neurological Disorders and Stroke (NINDS), the National Heart Lung and Blood Institute (NHLBI) and the National Center for Advancing Translational Science (NCATS), the goal of SIREN is to improve the outcomes of patients with neurologic, cardiac, respiratory and hematologic emergencies by identifying effective treatments given in the earliest stages of care. Regional hubs, with an average of five regional spokes, were chosen through a competitive funding mechanism of the NIH and provide training and clinical infrastructure for nearby spokes, comprising both academic and community hospitals with investigators but perhaps without fewer research staff. This improves access to patients receiving advanced care capabilities at sites that might not normally compete for NIH grants.

SIREN currently provides trial management for three NIH funded clinical trials. SIREN builds upon the success of the previous Neurologic Emergency Treatment Trials (NETT) network and incorporates expertise and experiences from the Resuscitation Outcome Consortium (ROC). Our previous experience as a clinical trial network has allowed NETT/SIREN to continuously hone our ability to recruit efficiently in the Emergency Department and to retain subjects through to their planned subject end of study. Consequently we have a strong track record of recruiting ahead of projections in 4 of our previously completed 7 trials, and we were on or close to projections for the others, with only one of 7 requesting supplemental funds to assist completion. We also have very low rates of loss to follow-up and subject withdrawal.

The Clinical Coordinating Center (CCC) for the C3PO trial will be the SIREN CCC at the University of Michigan and the Data Coordinating Center (DCC) will be the SIREN DCC at the Medical University of South Carolina. The Scientific Coordinating Group includes investigators from Stanford University, University of Michigan, and University of Pittsburgh.

***Clinical Coordinating Center (CCC)*.** The CCC is responsible for coordinating the Network and C3PO enrolling site leadership and for overall organization, administration, and communication. These responsibilities include site management (regulatory management,

enrollment performance, data monitoring, etc.), trial management (coordination of trial recruitment, publications, clinical translation), and management of study operations (protection of human subjects, outcomes assessment, training and education, etc.). The SIREN CCC has a Financial Specialist who will provide management and reconciliation of the C3PO financial activities within the SIREN CCC, including review and processing of invoices for C3PO funded activity and enrollment at the clinical sites.

Data Coordinating Center (DCC). The main responsibilities of the DCC are to collaborate with the CCC on trial management/operations and to provide the clinical trials management system and statistical activities for the C3PO trial. The DCC will be responsible for development and maintenance of the study database including the central randomization module, data processing and management of data obtained at all study sites and generation and distribution of progress reports as well as reports to the Data and Safety MonitoringBoard (DSMB). The DCC will also implement any adaptive design procedures, such as sample size reestimation, interim analyses and will provide statistical support throughout the trial and participate in manuscript preparation and dissemination of study information at the end of the trial.

Scientific Coordinating Group (SCG). The SCG includes scientific experts in Transfusion Medicine, Immunology, Pulmonology and Emergency Medicine. This group is responsible for scientific integrity of the study, interpretation of data, and review of study progress. Together with the DCC and CCC, the SCG will lead preparation of publications resulting from this trial, including the primary manuscript. The SCG will review and approve requests for trial data from outside investigators, proposals for ancillary trials or secondary analyses. Unique to this trial, the SCG experts in Transfusion Medicine will lead implementation of CP acquisition, tracking, banking and release from the many blood banks across the network.

Executive Committee (EC). The EC consists of the leadership of the SCG, the CCC, the DCC, NIH Liaisons for the SIREN network, and the NHLBI program officer. The EC is a working group responsible for the development and amendment of the study documents (e.g., protocol, case report forms and manual of procedures), collection, review, and oversight of dissemination of SAEs (occurrences and other important events pertinent to the study), and communication among all components of the study participants (e.g., CCC, DCC, SCG, clinical sites, and the NHLBI).

***Independent Medical Safety Monitor (IMSM)*.** The IMSM will have expertise in evaluating transfusion-related complications. The IMSM will review all SAEs and determine whether they are serious, possibly related to CP administration, and unexpected. If all three criteria are met, expedited reporting to the FDA and cIRB will be initiated.

Data and Safety Monitoring Board (DSMB). A Data and Safety Monitoring Board (DSMB) will be appointed by NHLBI. The DCC will generate Open and Closed DSMB Reports at a frequency determined by the DSMB, but no less than semi-annually. They also will create reports for each planned interim analysis. The DSMB's overarching responsibility is the oversight of safety of the trial participants. The DSMB will review reports on safety, data quality and recruitment and retention, request additional data/information if necessary, and will be cognizant of external new information regarding the safety of CP treatment. They also will receive reports for the planned interim analyses. Upon review of the interim data reports or any ongoing reporting, they will advise the study team and the NHLBI regarding continuation of the trial.

10.3 Safety Oversight

Data and Safety Monitoring Board (DSMB). The DSMB is the COVID-19 trial board appointed by NHLBI. The DCC will generate safety and other reports as requested by this DSMB.

10.4 Site Monitoring, Quality Assurance, and Quality Control

We will perform monitoring consistent with SIREN Site Monitoring standard operating procedures.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, with applicable FDA regulations (21 CFR 312), and with the FDA's "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring." Monitoring for this study will be performed by the DCC/CCC centrally, on site, and remotely. Per the study's monitoring plan, monitoring will include a combination of on-site monitoring (to verify data entered into the WebDCU™ database against source documents and query inaccuracies between the source documents and WebDCU™ database), remote monitoring (source document verification, including verification of written consent, may be performed remotely by reviewing source documents that have been uploaded into WebDCU™ or via remote access to electronic medical records), and central monitoring (using web-based data validation rules, data manager review of entered data, statistical analysis, and on-going review of site metrics). Further details of clinical site monitoring are documented in the study's Monitoring Plan.

The EC, on a regular basis, will review a summary of the data entered in the C3PO WebDCU™ database by the participating clinical sites to identify deficiencies in data collection and/or entry. This summary will be the result of the ongoing review by the DCC Data Manager (DM) and IMSM of data entered by all participating clinical sites.

The DCC's goal is to provide high quality, efficient data management for the successful implementation of studies conducted within SIREN. Proper clinical trial oversight requires the monitoring of both study data as well as trial operations. Our clinical trials management system, WebDCU™, enables the collection and maintenance of study data as well as study operational data (e.g., regulatory documents, drug receipt/tracking, subject enrollment, randomization and retention), which has afforded the DCC and its collaborators (e.g., CCCs, Trial PIs, NIH) the opportunity to make significant advances in its procedures for clinical trial oversight and monitoring. We work closely with the CCC to provide a risk-based monitoring approach that is multifaceted, dynamic, and focused on preventing and correcting errors associated with critical data, protocol compliance, protection of subjects, and study integrity. Central monitoring is aimed at quickly and systematically identifying issues affecting subject safety, trial operation integrity and data accuracy, reducing the effort required by on-site monitors, and providing an accurate final study database.

One of the strengths of WebDCU™ is that it is an integrated clinical trials management system (CTMS), housing both the eCRF data as well as the complete trial operations data. This provides the appropriate stakeholders including DCC and CCC personnel, site monitors, protocol PIs, and cIRB with real-time, secure access to the information needed to carefully monitor the performance at each site (including central calling centers) and identify and manage critical issues. Examples of trial operation aspects to monitor quality include but are not limited to: timeliness and completeness of AE reporting, timeliness and completeness of regulatory document submission, certification/training of investigators, rate of screening, subject enrollment and subject retention, frequency of protocol violations, frequency of randomization errors, frequency of staff turn-over, timeliness and completeness of data submission and query response, and rate of data corrections.

Reports programmed in WebDCU™ or provided by the statistical team facilitate the sharing of this information within and across studies as well as by Hub/Spoke through the duration of each

trial. As errors are identified, data managers generate data clarification requests (DCRs) in WebDCU™. Site personnel receive email alerts and are required to provide a response for each DCR and correct the eCRF data, if needed. Critical and/or systemic errors identified by central monitoring are shared with all study team members via weekly team meetings so that swift and appropriate action can be taken, and consideration of a remote or on-site monitoring visit can be determined. To facilitate this review, WebDCU™ houses a SIREN Network Dashboard that provides specific trial metrics within and across trials on enrollment, retention, adherence and data quality.

10.5 Study Records Retention

In June 2005, Federal law extended the statute of limitations to six years to bring forward an allegation of research misconduct. In response to this extension, research records must be retained for a sufficient period to investigate an allegation of research misconduct and in compliance with federal law (currently a minimum of six years)or longer if local regulations require.

Records will be maintained in a secure location to ensure confidentiality.

10.6 Protocol Deviations

At regular intervals, the EC will review the material and discuss, among other items, any concerns regarding the principles and intensity of the overall care and aggregations of protocol violations/deviations at particular sites. The EC may recommend that individual sites be contacted to discuss the issues identified at those sites and potential remedial measures. As a result of these reviews, the EC may make recommendations for protocol changes if serious safety concerns arise or there is an overarching issue with implementation of the protocol.

10.7 Publication and Data Sharing Policy

Because of the ongoing pandemic, we will rapidly disseminate study findings to the medical community via high impact, peer-reviewed scientific journals within 2 months of the completion of study enrollment, via ClinicalTrials.gov, websites such as https://covid19.trialstracker.net, https://covid-19.cochrane.org, https://covid-evidence.org, and via presentations at SIREN network meetings, national and international meetings, clinical practice committees and think thanks. Publication of the results of this trial will be governed by the policies and procedures developed by the EC. The Publication Policy will be fully compliant with the voluntary NIH Public Access Policy mandated by the Consolidated Appropriations Act of 2008 (Division G, Title II, Section 218 of PL 110-161). The EC will follow NIH policies on data-sharing (as described at the site: http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm and any updates thereto).

At the completion of the study, the DCC will generate de-identified public use data files and data documentation elements that will be shared with the NHLBI data repository that is managed by the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). The investigators at University of Pittsburgh will house biological specimens, and the investigators will make those available, quantities permitting, to legitimate members of the research community with appropriate approval and agreements. Long-term, residual samples can be deposited with NHLBI in the BioLINCC.

11. Protocol Amendment History

	Version 1		Version 2	
Section	**Page**	**Previous text**	**Page**	**New text**
Table of Abbreviations	5	PROMIS® Patient-Reported Outcomes Measurement Information System (PROMIS)	5	Removed
1.1	9	Dyspnea measured by the PROMIS measure on days 4, 10, 15, and 30	9	Removed
1.1	10	Treating clinical team unwilling to administer 300 ml fluid	10	Treating clinical team unwilling to administer up to 250 ml fluid
1.1	10	One unit (~250 ml)	10	One unit (~200 ml)
1.2	12	Dyspnea measured by the PROMIS® Pool V 1.0 Dyspnea Characteristics Questionnaire measured on days 4, 10, 15 and 30		Removed
1.2	12	Age≥50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunocompromised state	12	Removed.
1.2	13	Inability to tolerate 300 ml of intravenous fluid	1	Inability to tolerate up to 250 ml of intravenous fluid
1.2	13	one unit (~250 ml)	13	one unit (~200 ml)
1.2	13	5 ml multivitamin concentrate, see MOP (MVI-Adult, Hospira).	13	1-5 ml multivitamin concentrate, see MOP (MVI-Adult).
1.4	14	Symptom Inventory	14	Symptom Inventory

		PROMIS Dyspnea Characteristic Scale		
1.5	15	250 ml NS + 5 ml MVI.		250 ml NS + 1-5 ml parenteral MVI (see MOP).
1.5.2.1	16	PROMIS® Pool V 1.0 Dyspnea Characteristics Questionnaire	16	Removed
1.5.2.2	16	PROMIS® Pool V 1.0 Dyspnea Characteristics Questionnaire	16	Removed
3	24	Determine the effect of CP on the severity of symptoms Dyspnea measured by the PROMIS® Pool V 1.0 Dyspnea Characteristics on days 4, 10, 15, and 30 Validated measures of dyspnea and function	24	Removed
3.3	26	PROMIS Dyspnea Characteristics Questionnaire		Removed
5.1	28	Has at least one study defined risk factor for severe COVID-19 illness: Age≥50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease;[24,24] immunosuppression[25];	28	Has at least one study defined risk factor for severe COVID-19 illness: Study defined risk factors initially include: age≥50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression; sickle cell disease, and obesity (body mass index [BMI]≥30) and are updated as needed in the C3PO Manual of Procedures in response to

				changes in CDC guidance or other information..
5.1	29	Has at least one study defined risk factor for severe COVID-19 illness: Age≥50 years; hypertension; diabetes; coronary artery disease; chronic lung disease chronic kidney disease; immunosuppression	29	Has at least one study defined risk factor for severe COVID-19 illness.
5.1	29	Age is biological age. Hypertension must be treated with medications. Diabetes must be treated with medications. Chronic lung disease, coronary artery disease, chronic kidney disease[23] per medical record. Immunosuppression with medications.	29	Age is biological age. Hypertension must be treated with medications. Diabetes must be treated with medications. Chronic lung disease, coronary artery disease, chronic kidney disease[23] per medical record. Immunosuppression with medications. **Obesity is defined as BMI≥30** **Sickle cell disease is based on past medical history**
5.1	29	Age, hypertension, diabetes, coronary heart disease, chronic lung disease and chronic kidney disease are associated with higher COVID-19 morbidity and mortality.[22,23] Hypertension and diabetes are on a continuum and sometimes controlled without medications. We will restrict to medication-treated conditions in order to clearly define comorbidities that have prompted medical treatment. Patients on immunosuppression for solid organ transplants are more often hospitalized for severe COVID-19 illness.[25]	29	Age, hypertension, diabetes, coronary heart disease, chronic lung disease and chronic kidney disease are associated with higher COVID-19 morbidity and mortality.[22,23] Hypertension and diabetes are on a continuum and sometimes controlled without medications. We will restrict to medication-treated conditions in order to clearly define comorbidities that have prompted medical treatment. Patients on immunosuppression for solid organ transplants are more often hospitalized for severe COVID-19 illness.[25] **Emerging data suggests that sickle cell disease and obesity are risk**

				factors for severe disease.
5.2	30	• Treating clinical team unwilling to administer 300 ml fluid	30	• Treating clinical team unwilling to administer up to 250 ml fluid
5.2	31	Treating clinical team unwilling to administer 300 ml fluid	31	Treating clinical team unwilling to administer up to 250 ml fluid
6.1.2	33	one unit (~250 ml) of CP	33	one unit (~200 ml) of CP
8.1.2	39	*Symptom inventory*: On study days 2, 4, 6, 8, 10, 12, 14, 15 and 30, we will record the burden of symptoms listed by the Centers for Disease Control and Prevention (CDC) as typical of COVID-19 illness. The presence or absence of each of the following symptoms will be ascertained. • Fever or chills • Cough • Shortness of breath or difficulty breathing • Fatigue • Muscle or body aches • Headache • New loss of taste or smell • Sore throat • Congestion or runny nose • Nausea or vomiting • Diarrhea	39	*Symptom inventory*: On study days 2, 4, 6, 8, 10, 12, 14, 15 and 30, we will record the burden of symptoms listed by the Centers for Disease Control and Prevention (CDC) as typical of COVID-19 illness. **For purposes of this trial symptoms include any symptoms of COVID-19 illness listed by the CDC case definition guidance at the time of enrollment. These include but are not limited to the following**: • Fever or chills • Cough • Shortness of breath or difficulty breathing • Fatigue • Muscle or body aches • Headache • New loss of taste or smell • Sore throat • Congestion or runny nose • Nausea or vomiting • Diarrhea **Refer to the Manual of Procedures for the latest CDC list of COVID-19 symptoms.**

	Version 2	**Version 3**

Section	Page	Previous text	Page	New text
Header	2-59	Protocol 2.0	2-59	Protocol 3.0
Protocol Signature Page	2	Date of Signature 7/2/2020	2	9/7/2020
1.0	9	(blank)	9	Pro00044489
1.1	10	We will conduct the first interim analysis after approximately 150 consecutively randomized ITT subjects complete the primary outcome assessment.	10	We will conduct the first interim analysis after approximately 200 consecutively randomized ITT subjects complete the primary outcome assessment.
1.2	12	Adults presenting to the emergency department (ED) with mild, symptomatic, laboratory-confirmed COVID-19 illness, who are at high risk for progression to severe/critical illness, but who are clinically stable for outpatient management at randomization	12	Adults presenting to the emergency department (ED) with symptomatic, laboratory-confirmed COVID-19 illness, who are at high risk for progression to severe/critical illness, but who are clinically stable for outpatient management at randomization
1.4	14	Pre-intervention Blood Sample	14	Pre-intervention research blood draw
1.4	14	Post-intervention Blood Sample	14	Post-intervention research blood draw

1.5	15	All subjects will have a pre-infusion blood draw. Blood from consented subjects will be sent for type and screen.	15	All subjects will have a pre-infusion blood draw. Blood from consented subjects will be sent for blood type.
1.5	15	A sample of the CP will be frozen for later analysis.	15	Removed
1.5	15	At one hour, another blood sample will be drawn from the existing IV access and frozen for later analysis.	15	At one hour, another blood sample will be drawn and frozen for later analysis.
1.5	15	The central study team follow-up core will contact the participant by telephone or video chat every other day to assess disease progression and serious adverse events for 2 weeks and at days 15 and 30.	15	The central study team follow-up core will contact the participant by telephone or video chat every other day to assess disease progression and serious adverse events for 2 weeks. They will assess blinding to treatment on day 2.
1.5	15	The site study team will also collect data from any hospitalizations and ED/Urgent Care visits occurring within the study period.	15	The site study team will also collect data from any hospitalizations and ED/Urgent Care visits occurring within the study period. In addition, the study team will collect a symptom inventory on days 15 and 30 and assess blinding to treatment on day 15.

1.5	16	Blood samples from participants and a sample of each CP unit administered will be shipped to the study core lab at the University of Pittsburgh for analysis.	16	Blood samples from participants will be shipped to the study core lab at the University of Pittsburgh for analysis.
1.5	16	If hospitalized, participants are permitted to receive non-study compassionate use of CP or other emergency use or investigational treatments if available.	16	If hospitalized, participants are permitted to receive non-study CP or other emergency use or investigational treatments if available.
1.5.2.1	16	Type and Screen	16	Blood type
1.5.2.1	16	Any adverse event	16	remove
1.5.2.2	16	Any adverse event	16	remove
1.5.2.3	16	Any adverse event	16	remove
1.5.2.4	17	Any adverse event	16	remove
1.5.2.5	17	Any adverse event	17	remove
1.5.2.6	17	Any adverse event	17	remove
1.5.2.7	17	Any adverse event	17	remove
5.1	28	(body mass index [BMI]>30)	28	(body mass index [BMI]≥30)
5.1	29	BMI>30	29	BMI≥30

5.1	30	Blood bank to check type and screen	30	Blood bank to check blood type
5.4	31	Average of 3 - 4 subjects per month at each study site over 6 months (~100 subjects in the study per month)	31	Average of 6 subjects per month at each study site over 2 months (~300 subjects in the study per month)
6.2	34	The supplier (Vitalant) has already collected over 1700 units of CP.	34	The supplier (Vitalant) has already collected many units of CP.
6.2	35	Specifically, CP will be tested using a chemiluminescent test for IgG and IgM against spike protein (Ortho VITROS Anti-SARS-CoV2 Total).	35	Specifically, CP will be tested using a chemiluminescent test for IgG and IgM against spike protein (Ortho VITROS Anti-SARS-CoV2 Total) or equivalent assay.
6.2	35	If this qualitative test is positive, then the CP is also tested with the Vitalant Research Institute SARS-CoV2 Reporter Viral Particle Neutralization (RVPN) test.	35	If this qualitative test is positive, then the CP is also tested with the Vitalant Research Institute SARS-CoV2 Reporter Viral Particle Neutralization (RVPN) test or equivalent assay.
6.2	35	A positive Ortho VITROS test corresponds to at least a titer of 1:160 in the RVPN test.	35	remove

6.2	35	The presence of antibodies is confirmed within 24 hours of donor collection.	35	The presence of antibodies are generally confirmed within 48 hours of donor collection.
6.2	35	Each site will receive 4 units of CP at a time, and units will be replenished from the central supplier as they are used.	35	Each site will receive 4 or more units of CP at a time, and units will be replenished from the central supplier as they are used.
6.2	35	Over the trial, each of the 30 SIREN sites will receive an average of 10-12 units of CP.	35	Over the trial, each of the 30 or more SIREN sites will receive an average of 10-12 units of CP.
6.2	35	Samples from each CP unit will be sent to the study core laboratory at the University of Pittsburgh for antibody characterization.	35	Vitalant will send samples from each CP unit to the study core laboratory at the University of Pittsburgh for antibody characterization.
6.2	35	A type and screen will be performed in all potential subjects after the informed consent form is signed.	35	A blood type will be performed in all potential subjects after the informed consent form is signed.

6.2	36	If a subject is randomized to the control (saline) arm, an order will be sent to the pharmacy or investigational drug service for a 250 ml bag of isotonic saline with an added ampule of multivitamin (to provide color similar to plasma).	36	If a subject is randomized to the control (saline) arm, an order will be sent to the pharmacy or investigational drug service for a 250 ml bag of isotonic saline with 1-5 of parenteral multivitamin (to provide color similar to plasma).
6.2	36	Vitalant has already secured over 1700 units of CP and anticipates no problem with supply.	36	Vitalant has already secured many units of CP and anticipates no problem with supply.
8.1	38	Surveys and assessments completed within 2 days of the time point will be counted as qualifying and not considered missing.	38	Central caller assessments completed within 1 day of the time point will be counted as qualifying and not considered missing.
8.1.2	38	Surveys and assessments from day 0-14 that are completed within 1 days of the time point	38	Surveys and assessments from day 0-14 that are completed within 1 day of the time point

8.1.2	39	· Fever or chills · Cough · Shortness of breath or difficulty breathing · Fatigue · Muscle or body aches · Headache · New loss of taste or smell · Sore throat · Congestion or runny nose · Nausea or vomiting · Diarrhea	39	· Fever or chills · Cough · Shortness of breath or difficulty breathing · Fatigue · Muscle or body aches · Headache · New loss of taste or smell · Sore throat · Congestion or runny nose · Nausea or vomiting · Diarrhea · Abdominal pain · Limitations of activities because of COVID-19 symptoms
8.1.3	40	Whole blood will be processed into serum and plasma, and stored in a -80ºC freezer within 2 hours of sample collection.	40	Whole blood will be processed into serum and plasma, and stored in a -70ºC freezer or colder within 2 hours of sample collection.
8.1.5	41	As part of follow-up assessments on Day 15,	41	As part of follow-up assessments on Days 2 and 15,

8.2.1	41	After discharge from the emergency department and at each follow-up contact, only serious adverse events will be reported in WebDCU.	41-42	After discharge from the emergency department and at each follow-up contact until the end of study, only serious adverse events will be reported in WebDCU and any event that leads to hospitalization or an ED or urgent care visit even if deemed non-serious.
8.2.1	42	All serious adverse events (SAEs) will be recorded until the end of the study.	42	remove
9.1	46	The DSMB will be closely monitoring this assumed control rate in order to adjust sample size prior to the first official interim analysis as needed.	46	remove

9.2.3	48	A Bayesian imputation model will be used to impute the primary outcome using information from previous time periods.	48	Sensitivity to missing data will be assessed. If the outcome is insensitive to missing data, defined as no change in the conclusion regardless of the set of imputed values, each missing observation will be imputed an unfavorable outcome (i.e., event occurred). If the outcome is sensitive to missing data, each observation will be imputed using a Bayesian imputation model.
10.1.1.2	49	(in those studies, eConsent is used for consent via legally authorized representatives (LAR)	49	remove

		Version 3		**Version 4**
1.2	12	Adults presenting to the emergency department (ED) with symptomatic, laboratory-confirmed COVID-19 illness	12	Adults presenting to the emergency department (ED) with *their first episode of* symptomatic, laboratory-confirmed COVID-19 illness
5.1	29		29	This should be their first episode of COVID-19 illness. See MOP for additional details
5.4	31	Potential subjects for this trial will be recruited from emergency department patients who have	31	Potential subjects for this trial will be recruited from emergency department

		laboratory-confirmed SARS-CoV-2 infection		patients who have their first episode of symptomatic laboratory-confirmed SARS-CoV-2 infection
5.4	33	Subjects may be eligible for compensation for the Day 15 and Day 30 blood draws based on local institution practices.	33	Subjects may be eligible for compensation for travel/parking at any of their visits based on local institution practices.
8.1.3	40	No more than 30 mL of blood	40	No more than 50 mL of blood
8.1.3	40	Shortly after randomization but before the administration of study intervention	40	After consent but before the administration of study intervention
8.1.3	40		40	In addition to the blood samples collection outlined above, for subjects who consent to participating in an optional study evaluating the evolution of the adaptive immune response in CP recipients, an additional 20 ml of whole blood will be collected on the day of enrollment and on study days 15 and 30. These samples will be shipped within 1 day of collection to a central laboratory for processing.

	Version 4		**Version 5**	
Section	**Page**	**Previous text**	**Page**	**New text**
Header	2-68	Protocol 4.0	2-73	Protocol 5.0
Protocol Signature Page	2	Date of Signature 11/3/2020	2	Date of Signature 2/16/2021

1.1 Study Duration	9	June 2020 to May 2021	9	June 2020 to July 2021
1.1 Number of Subjects	9	600 (300 per arm)	9-10	Original planned maximum sample size: 600 (300 per arm) Revised maximum sample size based on planned re-estimation: 900 (450 per arm)
1.1 Main Inclusion Criteria	10	Clinical team deems stable for outpatient management without supplemental oxygen	10	Clinical team deems stable for outpatient management without new supplemental oxygen
1.1 Main Inclusion Criteria	10	Duration of symptoms ≤ 7 days at ED presentation	10	Duration of symptoms ≤ 7 days at ED presentation and randomization
1.1 Major Inclusion Criteria	10	Enrollment in another interventional trial for COVID-19 illness	10	Enrollment in another interventional trial for COVID-19 illness or receipt of other active or passive immunization against SARS-CoV2.
1.1 Statistical Methodology	10	We will conduct the first interim analysis after approximately 200 consecutively randomized ITT subjects complete the primary outcome assessment.	10	We will conduct the first interim analysis after approximately 33% of consecutively randomized ITT subjects complete the primary outcome assessment.
1.2 Study Design	11	Sample size: 600 subjects	11	Original planned maximum sample size: 600 (300 per arm) Revised maximum sample size based on planned re-estimation: 900 (450 per arm)
1.2 Study Design	11	Study Duration: 6-9 months	11	Study Duration: 12 months
1.2 Inclusion Criteria	12	Duration of symptoms ≤ 7 days at ED presentation	12	Duration of symptoms ≤ 7 days at ED presentation and randomization
1.2 Exclusion Criteria	13	Enrollment in another interventional trial for COVID-19 illness	13	Enrollment in another interventional trial for COVID-19 illness or receipt of other active or passive immunization against SARS-CoV2.

1.3 Schema	13	Timeline for study events. Enrollment and intervention (CP or Placebo) occurs in the emergency department (or adjacent care clinic). Blood samples 1 and 2 are collected during that visit. Outpatient follow-up is conducted remotely by telephone or other contact. Subjects have phlebotomy on Day 15 and Day 30 for blood samples 3 and 4. In-person or remote contact on Day 15 and Day 30, and medical record review on Day 30, will confirm subject outcomes.	13	Timeline for study events. Enrollment and intervention (CP or Placebo) occurs in the emergency department (or adjacent care clinic). Blood samples 1 and 2 are collected during that visit. Residual viral media samples from nasopharyngeal swabs and/or saliva samples will also be collected during the enrollment visit. Outpatient follow-up is conducted remotely by telephone or other contact. Subjects have phlebotomy on Day 15 and Day 30 for blood samples 3 and 4. In-person or remote contact on Day 15 and Day 30, and medical record review on Day 30, will confirm subject outcomes. We will collect information on participants' SARS-CoV-2 viral genotype from the enrolling institution if available.
1.4 Schedule of Activities	14	(No text)	14	Residual viral media / saliva sample Study Day 0
1.5 Study Flow and Daily Data Collection	15	(No text)	15	Residual viral media samples from nasopharyngeal swabs and/or saliva samples will also be collected during the enrollment visit.
1.5 Study Flow and Daily Data Collection	16	(No text)	16	Residual viral media and saliva samples will be shipped to a central lab for analysis.
1.5.2.1 Data Collection	16	1.5.2.1 Data Collection	16	1.5.1.2 Data Collection

1.5.2.1 Data Collection	16	(No text)	16	SARS-CoV-2 viral genotype, if available
1.5.2.1 Intervention	16	1.5.2.1 Intervention	16	1.5.1.3 Intervention
1.5.2.1 Intervention	16	(No text)	16	Residual viral media and/or saliva sample
5.1 Inclusion Criteria	28	Clinical team deems stable for outpatient management without supplemental oxygen	28	Clinical team deems stable for outpatient management without new supplemental oxygen
5.1 Inclusion Criteria	28	Duration of symptoms ≤ 7 days at ED presentation	28	Duration of symptoms ≤ 7 days at ED presentation and randomization.
5.1 Inclusion Criteria Metric	29	observation unit without oxygen supplementation would be eligible)	30	observation unit without oxygen supplementation would be eligible). Patients discharged from the ED may be brought back for randomization and treatment so long as they meet study inclusion criteria at the time of randomization.
5.1 Inclusion Criteria Criteria	30	Duration of symptoms ≤ 7 days at ED presentation	30	Duration of symptoms ≤ 7 days at ED presentation and randomization
5.2 Exclusion Criteria	30	Enrollment in another interventional trial for COVID-19 illness	30	Enrollment in another interventional trial for COVID-19 illness or receipt of other active or passive immunization against SARS-CoV2.
5.2 Exclusion Criteria	31	Enrollment in another interventional trial for COVID-19 illness	31	Enrollment in another interventional trial for COVID-19 illness or receipt of other active or passive immunization against SARS-CoV2.

5.4 Strategies for Recruitment and Retention	31	**Target study sample size:** 600	31	**Target study sample size:** 900
5.4 Strategies for Recruitment and Retention	31	**Anticipated accrual rate**: Average of 3 - 4 subjects per month at each study site over 6 months (~100 subjects in the study per month), with the expectation that accrual will vary by month depending on the progression or resolution of the pandemic. It is expected that accrual will be higher at the onset of the trial and will slow with decreasing numbers of new cases.	31	**Anticipated accrual rate**: Accrual will vary by month depending on the progression or resolution of the pandemic.
8.1.3 Secondary Endpoints (immunological)	40	(No text)	41	Residual viral media and saliva specimens collected will be analyzed for SARS-CoV-2 viral genotype
9. Statistical Considerations	45	Design of this trial is initially constrained by the supply of CP to 300 total subjects.	45	(Previous text removed)
9.2.1 Primary Analysis	47	Secondary analyses of the primary outcome will explore the impact of potential prognostic variables including age, sex, onset of symptoms duration and site. A logistic regression model will be used for these additional analyses.	47	Secondary analyses of the primary outcome will explore the impact of potential prognostic variables including age, sex, onset of symptoms duration and site. A logistic regression model will be used for these additional analyses. We will also examine whether participants' pre-treatment antibody levels and/or the genotype of the SARS-CoV2 virus that they carry modify the association between CP and outcome.

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