IGHID 12021 - A RANDOMIZED, PHASE II STUDY COMPARING THE EFFICACY AND SAFETY OF STANDARD VERSUS HIGH-TITER ANTI-SARS-COV-2 NEUTRALIZING ANTIBODY PLASMA IN HOSPITALIZED PATIENTS WITH COVID-19

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SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Investigator of Record: _____

Print/Type

Signed: _____ Date: _____

Title: _____

Table of Contents

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug sponsor, funding agency, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

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

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: **A Randomized, Phase II Study Comparing the Efficacy and Safety of Standard versus High-Titer Anti-SarS-CoV-2 Neutralizing Antibody Plasma in Hospitalized Patients with COVID-19**

Study Description: This randomized, double-blinded, phase 2 trial will assess the efficacy and safety of anti-SARS-CoV-2 convalescent plasma in hospitalized patients with less than 8 days of symptoms. Eligible participants will receive institutional-guided standard-of-care (SOC) and ABO-compatible convalescent COVID-19 plasma (CCP). The CCP units will be tested for the presence of anti-SARS-CoV-2 antibodies and pre-assigned as high-titer (CCP1) or standard-titer (CCP2) in a 1:1 randomization. Participants and clinical investigators will be blinded to the CCP titer group identities.

Participants will be randomized within 48 hours of admission to a COVID service and will receive convalescent plasma within 24 hours of randomization. At least two units of CCP will be transfused 4-24 hours apart on study Day 0. If available, a third unit may be administered. All participants will undergo a series of safety and efficacy assessments pre-, during, and post-transfusion. Samples for research will be collected on Day 0 through Day 28, unless previously discharged. Additionally, after discharge, participants can provide longitudinal samples collected at 1, 3, and 6-month timepoints after the infusion.

Objectives:

Primary Objectives

Evaluate the safety of high neutralization titer anti-SARS-CoV2 plasma in patients hospitalized due to COVID-19, compared to standard neutralization titer anti-SARS-CoV2 plasma.

Evaluate the efficacy of high versus standard neutralization titer anti-SARS-CoV2 plasma to decrease length of hospitalization stay among patients hospitalized due to COVID-19.

Exploratory Objectives

Evaluate the efficacy of high versus standard neutralization titer anti-SARS-CoV2 plasma to improve clinical outcomes and mortality among patients hospitalized due to COVID-19.

Evaluate the safety and efficacy of high vs. standard total antibody titer anti-SARS-CoV-2 plasma to increase survival and speed of hospital discharge in patients hospitalized due to COVID-19.

Evaluate the safety and efficacy of high vs. standard antigen-specific titers of anti-SARS-CoV2 plasma to increase survival and speed of hospital discharge in patients hospitalized due to COVID-19.

Compare length of hospitalization, clinical outcomes, and mortality among patients hospitalized due to COVID-19, who consented to concurrent UNC IRB approved observational studies but did not receive anti-SARS-CoV2 plasma.

Compare SARS-CoV2 viral recovery from anatomic sites in patients hospitalized due to COVID-19, who received high vs. low neutralization titer anti-SARS-CoV2 plasma.

Compare anti-SARS-CoV2 total antibody, antigen-specific antibody, and neutralizing antibody titers at 28 days, 3 months, and 6 months in participants who received high vs. low neutralization titer anti-SARS-CoV2 plasma.

Compare biomarkers obtained for clinical care in patients hospitalized due to COVID-19, who received high vs. standard neutralization titer anti-SARS-CoV2 plasma.

Primary endpoint: The primary safety endpoint will be assessed by the cumulative incidence of serious adverse events (SAEs) at study Day 14.

The primary efficacy endpoint will be assessed by days to hospital discharge (or discharge equivalent) following first dose of CCP.

Exploratory endpoints:

- Change in World Health Organization (WHO) ordinal clinical status scale while hospitalized and at Days 14 and 28
- Change in National Early Warning Score (NEWS) while hospitalized and at Days 14 and 28
- Days of supplemental oxygen or greater, days of NIV/high-flow oxygen or greater, days mechanical ventilation/ECMO while hospitalized and respiratory support at Days 14 and 28
- In-hospital mortality
- 28-day mortality
- Change in SARS-CoV-2 RT-PCR Day 0, 3 (+/-1), 7 (+/-1) (and/or discharge date), 21, and 28 (if still hospitalized) from nasopharyngeal, endotracheal, fecal, and blood specimens
- Change in anti-SARS-CoV-2 total antibody, antigen-specific antibody, and neutralizing antibody titers on Day 28, 3 months, and 6 months

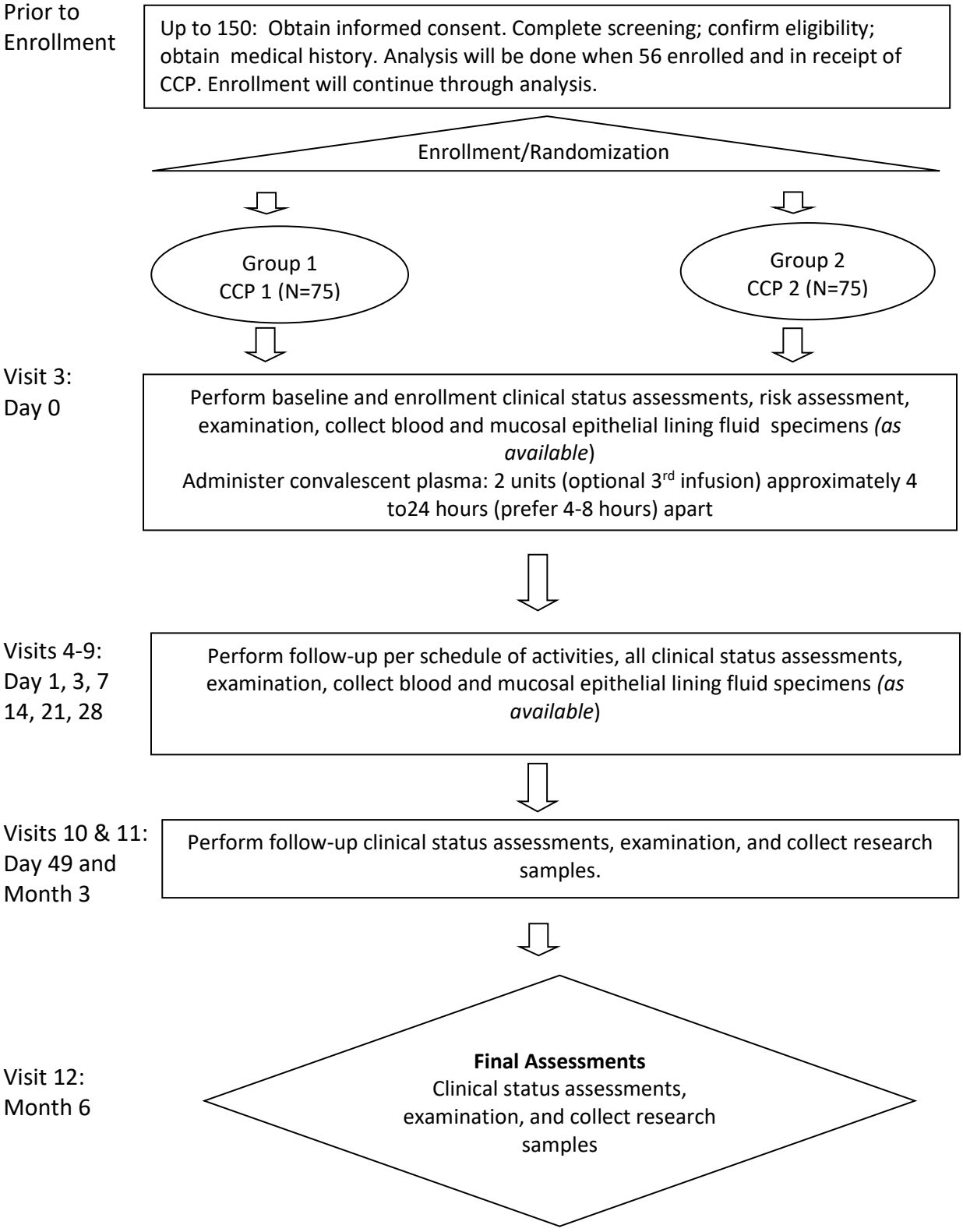
Study Population: This study will enroll up to 150 men and women, aged ≥ 18 years of age, hospitalized with COVID-19 infection, and reporting less than 8 days of symptoms prior to admission to a COVID service.

For the purpose of this study we define symptoms as self-reported fever or documented fever ≥ 38.0 °C (100.4 °F).

Phase: Phase II

Description of Sites/Facilities Enrolling Participants:	UNC Medical Center
Description of Study Intervention:	This randomized phase II study will assess the administration of at least 2 units of CCP. Participants will be randomized 1:1 to the blinded receipt of high or standard neutralizing SARS-CoV2 antibody on study Day 0. Clinical investigators will also be blinded to the CCP titer group identities. Standard of care will be defined as current standard treatment for hospitalized patients.
Study Duration:	Up to 12 months
Participant Duration:	An individual participant may be in this study for up to 6 months. The study participant will complete the study at Day 28, but we would like to follow the participant if participant is able for up to 6 months following the transfusions for observation of immune response over time.

1.2 SCHEMA


Prior to Enrollment
Up to 150: Obtain informed consent. Complete screening; confirm eligibility; obtain medical history. Analysis will be done when 56 enrolled and in receipt of CCP. Enrollment will continue through analysis.
Enrollment/Randomization
Group 1
CCP 1 (N=75)
Group 2
CCP 2 (N=75)
Visit 3:
Day 0
Perform baseline and enrollment clinical status assessments, risk assessment, examination, collect blood and mucosal epithelial lining fluid specimens (as available)
Administer convalescent plasma: 2 units (optional 3rd infusion) approximately 4 to24 hours (prefer 4-8 hours) apart
Visits 4-9:
Day 1, 3, 7
14, 21, 28
Perform follow-up per schedule of activities, all clinical status assessments, examination, collect blood and mucosal epithelial lining fluid specimens (as available)
Visits 10 & 11:
Day 49 and
Month 3
Perform follow-up clinical status assessments, examination, and collect research samples.
Visit 12:
Month 6
Final Assessments
Clinical status assessments, examination, and collect research samples

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Visit 1	Baseline, Enrollment Randomization	Study Visit 3 (CCP Transfusion)	Study Visit 4	Study Visit 5	Study Visit 6	Study Visit 7 (*if hospitalized*)	Study Visit 8 (*if hospitalized*)	Study Visit 9 End of Study (EOS)	Visit 10 Outpatient Longitudinal Visit	Study Visit 11 Outpatient Longitudinal Visit	Final Study Visit 12 Outpatient Longitudinal Visit
Visit Day #	-2	-2 to 0	0	1	3	7	14	21	28	49	90	180
Visit Window in days					+/- 1	+/- 2	+/- 2	+/- 2	+/- 7	+/- 10	+/- 14	+/- 14
Clinical Assessments												
Informed consent	X											
Demographics[1]	X											
Medical history[1]	X											
ABO typing ◊	X											
Record Admission ECG[1]		X										
Confirmed SARS-CoV-2 infection	X											
Randomization		X										
Assign Partcipant ID (PID)	X											
Assign Randomization ID (RID)		X										
Administer CCP◊			X									
Concomitant medication review		X[1]		X[1]	X [1,8]	X [1,8]	X [1,8]	X [1,8]	X[1,9]	X[9]	X[9]	X[9]
Physical exam	X[1]	X[1]	X[1]	X[1]	X [1,8]	X [1,8]	X [1,8]	X [1,8]	X[1,9]			
Height		X[1]										
Risk Assessment		X[1]										
Vital signs	X	X[1]	X[1]	X[1]	X [1,8]	X [1,8]	X [1,8]	X [1,8]	X [1,9]	X[9]	X[9]	X[9]
SOFA score		X[1]	X[1]	X[1]	X [1,8]	X [1,8]	X [1,8]	X [1,8]	X [1,9]			
NEWS score		X[1]	X[1]	X[1]	X [1,8]	X [1,8]	X [1,8]	X [1,8]	X [1,9]	X[9]	X[9]	
WHO Ordinal status		X[1]	X[1]	X[1]	X [1,8]	X [1,8]	X [1,8]	X [1,8]	X [1,9]	X[9]	X[9]	X[9]
Adverse event assessment			X[1]	X[1]	X [1,8]	X [1,8]	X [1,8]	X [1,8]	X [1,9]	X[9]	X[9]	X[9]
Laboratory Procedures⏚												
Hematology[1,2]		X	X	X	X[8]	X[8]	X[8]	X[8]	X[8]		X	
Coagulation[1,2]		X	X	X	X[8]	X[8]	X[8]	X[8]	X[8]			
Serum chemistry[1,2]		X	X	X	X[8]	X[8]	X[8]	X[8]	X[8]			
Pregnancy test [1,3]	X											
Mucosal Lining Fluids [4, 5]			X[6,10]		X[6 8]	X[6,8,10]	X[6,8]	X[6,8]	X[6,9]	X[9,10]	X[9,10]	X[9,10]
Record Radiologic/Imaging assessment [1,7]		X	X	X	X[8]	X[8]						
Blood for Immunology & virologic assays [6]			X		X[8]	X[8]	X[8]	X[8]	X[9]			
Blood for Immunology & virologic assay (optional study component) [5,10]			X			X[8]			X	X	X	X

[#] Identify the day of discharge day as # of days from Day 0. Complete a chart note based on the events required (and obtainable) per the next scheduled study visit. Collect remnant samples and data as available from this day. The collection of optional samples may or may not occur due to unknown nature of date and time of discharge.

◊ Per Hospital policy and guidelines.

⏚ Please reference the study-specific laboratory schedule of sample collections to verify all collections and amounts.

[1] Information abstracted from medical record, as necessary and if available.

[2] CBC, differential, PT/INR, PTT, d-dimer, fibrinogen, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium, C-reactive protein, IL-6. Collect if testing results available through routine clinical care.

[3] Serum pregnancy test on all women less than 60 years of age.

[4] Mucosal Lining Fluids include: Nasal fluids (NP swab, and/or nasal epithelial lining strips (NELFS), Oral fluids (saliva), Intestinal (stool) and Respiratory (endotracheal secretions on intubated inpatient as available).

[5] Collections will be deferred if the participant refuses or is too clinically unstable to undergo sample collection.

[6] Collect remnant samples acquired for clinical care. Collect remnant NP swab if obtained within 48 hours prior to CCP transfusion, if available in McLendon Lab.

[7] Chest x-ray and/or CAT scan (CT) chest if performed as part of routine clinical care.
[8] These samples and data will not be collected on participants once discharged from hospital.
[9] These data and samples will be collected from participants returning for outpatient visits.
[10] Collect samples for optional immunology research (page 23).

2 INTRODUCTION

2.1 STUDY RATIONALE

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. [1,2] Preliminary evidence indicates that CCP may possibly be of benefit for some patients with COVID-19, leading to improvement. [3,4]

2.2 BACKGROUND

The current outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel virus that causes the clinically variable but often severe viral respiratory syndrome now known as COVID-19, is now a global pandemic that threatens the lives of millions of people across the world. As of April 16th, 2020, there have been 632,548 confirmed cases and 31,071 deaths due to COVID-19 in the United States alone, with the former likely being a gross underestimate of the actual incidence and prevalence (U.S. Centers for Disease Control and Prevention [CDC] 2020). Reported mortality rates have demonstrated some variability between countries; however, all data to date indicate that SARS-CoV-2 is a highly infectious and lethal virus in the elderly population, as well as in patients with comorbidities that are exceedingly common in the U.S., and can in fact be fatal in patients of any age.

Compounding the formidable natural course of SARS-CoV-2 is the absence of any pre-existing immunity to it in the human population and the resulting exponential growth of clinically severe infections.

Current options for treatment
Currently, the treatment of patients hospitalized with COVID-19 is supportive, ranging from supplemental oxygen to invasive ventilation in nearly 75% of those admitted to the ICU. [5] Multiple investigational therapies are currently under study in clinical trials; however, no therapy has been proven. Importantly, many of these therapies, including the RNA-dependent RNA polymerase inhibitor, remdesivir, that is effective in pre-clinical animal models [6], were not specifically developed to target SARS-CoV-2. Similarly, although hydroxycholoroquine might inhibit endosomal-mediated viral cellular injury, this agent is not specifically active against SARS-CoV-2. In addition, while anti-IL-6, anti-IL1β, and other monoclonal antibodies might attenuate disease severity by modulating cytokine release syndrome, the mechanisms of these agents are not expected to enhance innate or adaptive immune responses to promote viral clearance. Lastly, even if these agents are effective, the ability to mass-produce on a scale necessary to address this global pandemic is limited. SARS-CoV-2 is highly transmissible and is likely to spread in regions that may lack access to novel pharmaceuticals, but have existing blood donation and re-infusion capacity.

Rationale for the use of CCP for the treatment of severe COVID-19
COVID-19 convalescent plasma (CCP) represents the only current therapeutic option against SARS-CoV-2 that has the potential to augment virus-specific immune responses and is also scalable to deploy rapidly. The *hypothesis* for the efficacy of CCP is that plasma from COVID-19-recovered patients contains antibodies that are directed against, and could neutralize, SARS-CoV-2. This concept of passive antibody therapy is established in clinical practice through the use of intravenous immune globulin (IVIg). [7-9] IVIg provides concentrated passive antibody to augment humoral immunity and therefore can prevent and have therapeutic activity against some viral and

bacterial infections. Historically, plasma from recovered patients has been used to treat other viral respiratory infection outbreaks including SARS-CoV-1 and Influenza. [1, 10]

Experience from SARS-CoV-1 shows that such convalescent plasma (CP) contains neutralizing antibodies to the relevant virus. [11] During 2009 H1N1, there was an 80% reduction in risk of death in severely ill patients who received CP versus controls who declined it (OR: 0.2, 95% CI: 0.06-0.69, *P*=0.011). [1] 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. [12] A systematic review of CP use in severe acute respiratory infections identified 32 studies between 1919 and 2011 that collectively suggested a similar reduction in risk of death with this approach (OR: 0.25, 95% CI: 0.14-0.45, I^2=0%). [13] Although this historical using CP for viral outbreaks, CCP as a plausible intervention for COVID-19, randomized controlled trials are needed to establish the efficacy of CCP.

Two uncontrolled case series encompassing 15 CCP-treated patients in China have been published. [3, 4] Both of these studies reported signs of clinical improvement days after receiving CCP in doses of either 1 unit (200 mL) or 2 units (400 mL). There were no reports of harm. CCP-treated patients in one study were found to have lower levels of IL-6, IL-10, and TNFα compared to controls at corresponding timepoints, suggesting that CCP could potentially exert a dampening effect on the cytokine release syndrome (CRS) suspected to be involved in the pathogenesis of severe COVID-19. [3, 14] In another pilot study in Wuhan, China CCP collected from SARS-CoV-2 positive patients 3 weeks following the onset of illness was used to treat patients diagnosed with 'severe COVID-19' as defined by WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 National Health Commission of China. [4] Ten patients were treated with one dose of CCP (200ml, >1:640 titer by neutralization assay) at a median of 16.5 days (11-19.3 days) post-onset of symptoms. A COVID-19 positive control cohort was retrospectively identified and matched by demographics, comorbidities, and severity of illness. There were no serious adverse reactions or safety events recorded with convalescent plasma, including no reported transfusion-related reactions, transfusion-related acute lung injury, or antibody-mediated enhancement of infection. In the treatment group, there were 0 deaths, 3 discharges, and 7 patients improved, whereas there were 3 deaths and 7 patients who improved in the control group ($p < 0.001$). [4] In addition, 2 of 3 patients in the treatment on mechanical ventilation were weaned to high flow nasal canula, which was discontinued in one patient. There was a reduction in blood RNA viral load in 7 of 10 patients on day 6 post-convalescent plasma therapy as well as improvement in laboratory markers. There were also varying degrees of improvement in pulmonary lesions on chest CT after convalescent plasma therapy. In another case series from China, five severely ill patients with COVID-19, all on mechanical ventilation received convalescent plasma within 22 days of admission. [3] Temperatures normalized in 4 of 5 patients within 3 days, NEWS scores decreased, and there was improvement in oxygenation and Acute Respiratory Distress Syndrome (ARDS) resolution. All survived, with 3 discharged home and 2 in stable condition. These reports suggest convalescent plasma may hold promise for ameliorating the severity of COVID-19 and deserves immediate investigation for this indication.

Justification for a randomized FDA-standard versus high-anti anti-SARS-CoV-2 neutralizing antibody titer plasma design

The therapeutic benefit of CCP is hypothesized to be due to the presence of high concentrations of antibodies that neutralize the virus. When present in high concentrations, these neutralizing antibodies interrupt viral replication and halt disease progression. [15] Data from China suggests that by 14 days after onset of symptoms from SARS-CoV-2, most patients have developed evidence of antibody responses. [16] Although this humoral immune response appears nearly universal, there is variability in the neutralizing properties of the serum of these individuals. In a study comparing total antibody to neutralizing antibody using serum neutralization assays, the presence of co-morbidities was associated with lower titers of neutralizing antibody at similar timepoints of the disease process. [17] Co-morbidities also associate with more severe COVID-19 outcomes and more prolonged viral shedding. [18]. This suggests that the 'quality' and/or quantity of neutralizing antibodies varies between

individuals. In addition, data from humoral responses in SARS-1 also demonstrates that specific antibodies persist for >3 months. [19]

When used for therapy, the optimal dose of neutralizing antibody in plasma has not been well defined. Either under-dosing by using plasma with inadequate neutralizing antibody titer, or over-dosing could alter the safety and efficacy profile. A theoretical, but unproven complication of administering CCP is the phenomenon of antibody-dependent enhancement of infection (ADE). ADE occurs when cross-reacting antibodies and/or low levels of neutralizing antibody against a viral pathogen can paradoxically worsen the viral syndrome. Although the ADE phenomenon has not been described for COVID-19, this risk needs to be considered. [20] The clinical relevance of ADE has been best elucidated in dengue disease, wherein secondary infection by the dengue flavivirus can be considerably more severe than primary infection due to the enabling of viral entry into FcγR-expressing cells by antibodies generated against the initial viral serotype. A recent study of a long-term pediatric cohort in Nicaragua suggests that this process occurs within a narrow window of pre-existing antibody levels, above which the patient is protected from clinically significant ADE. [21] Human coronavirus infection is not known to be clinically exacerbated by ADE, although ADE has been demonstrated to occur in a feline coronavirus model. [22] ADE has been demonstrated to occur in both SARS-CoV-1 and MERS-CoV infection *in vitro* via conformational change of the spike protein induced by neutralizing antibody ligation that triggers antibody-dependent and non- endosomal viral entry into FcγR-expressing cells. In this model, enhanced viral entry can be overcome by higher antibody levels that saturate the FcγRs. [23] Although the historical data on CP use during past viral outbreaks do not suggest that ADE-mediated worsening of COVID-19 severity is likely to occur, these data nevertheless suggest that it remains a possibility, which adds further justification for an randomized control trial (RCT) design.

Publications to date have infused CCP with neutralizing antibody titers ranging from ≥1:40 [3] to ≥1:640 [4] to treat COVID-19. The FDA has authorized the use of CCP on a compassionate use basis with a recommended minimum neutralizing antibody titer of ≥1:160 or ≥1:80 if rare ABO-type matching is required. While there is little evidence to establish a minimum effective neutralizing antibody titer for SARS-2, in a prospective cohort of patients with H1N1 who consented to CP with neutralizing antibody titer of ≥1:160, there was a significant reduction in mortality (20.0% vs 54.8%; P=0.01) and more rapid decline in respiratory tract viral loads when compared with patients who declined plasma. [1] In a Phase II study, a greater proportion of patients receiving CP with neutralizing antibody titer ≥1:80 in addition to standard of care, compared with standard of care alone, improved clinical status by day 7 (20% vs 38%; p=0.041). [2] A phase III, blinded randomized study compared CP with anti-influenza neutralizing antibody titer ≥1:80 given early after symptom onset, compared with low-titre CP (≤ 1:10), failed to show any significant benefit. [24] All patients also received anti-viral therapy with oseltamivir, a drug with proven anti-influenza activity.

A large number of patients with COVID-19 will receive CCP through the FDA authorized compassionate use mechanism. This registry should provide important safety data, and will be informative regarding efficacy; however, the level of evidence will not achieve that of a randomized control trial. Several have proposed to use fresh-frozen plasma (FFP) as a placebo. FFP as a placebo has the benefit of blinding, and addresses the possibility that components of CCP other than the neutralizing antibodies themselves could exert a therapeutic effect, which could favorably impact clinical outcomes. However, absent a standard of care arm, an FFP compared with CPP design will not allow for recognition of possible benefits from FFP. We therefore propose an alternative trial design that compares the FDA-recommended minimum titer of ≥1:160 with CCP containing very high titer neutralizing antibody ≥1:640. This allows all participants to receive potential benefit, while intentionally evaluating the paradigm the most beneficial component of CCP is neutralizing. Our study will also centralize the neutralizing antibody assay, which can be difficult to interpret across various assay methods. If high-titer-CCP rather than FDA-standard-titer CCP ultimately proves to improve clinical outcomes in the study population, it would provide support that clinical benefit would be attributable to the antibody present in the convalescent donor source, and not to components common to all donor plasma. A dose-dependent clinical benefit would

inform screening criteria for possible CCP donors, including inter-individual factors that might be identified as predicting high-neutralizing titer plasma as well as intra-individual factors such as time since viral diagnosis and/or viral clearance. Knowing how donor factors predict neutralizing antibody titer could help focus CCP collections to increase the likelihood of banking CCP with the maximum therapeutic potential.

Given that the expected role of CCP is to leverage passive immunity to accelerate viral clearance, CCP would best be given early in the disease course. 50% of patients develop a humoral response within the first 7 days of symptoms. [16] It is therefore optimal to intervene with CCP at this earlier timepoint if possible. One potential side effect of passive antibody therapy, however, is interference in the development of humoral immunity in the host. This phenomenon is well-described in the setting of Measles vaccine responses in infants where-in the presence of maternal anti-measles antibodies attenuate post-vaccine seroconversion. [25] Thus, CCP at different titer ranges might not only have different dose-dependent effects during acute infection, but could differentially alter natural immune development during the convalescent period. It is not yet known whether natural immunity to SARS-2 is sustained. In the absence of an available vaccine, it is important to evaluate not only the effect of CCP during acute severe illness, but the potential resulting modulation in host-derived humoral immunity, and therefore risk of re-infection.

There are limited data on use of convalescent plasma in pregnancy. A non-randomized comparative study that evaluated use of convalescent plasma for Ebola Virus Disease reported that eight out of 84 participants were pregnant and that mortality was 25% among pregnant women and 32% among non-pregnant individuals after receiving plasma treatment. [26] A case series of 4 Chinese patients, among whom one was pregnant, received convalescent plasma and had recovered from SARS-CoV-2 infection. [27] We do not have robust data of using convalescent plasma in pregnancy as most trials have excluded pregnant patients. IVIg therapy, however, is safe to give during pregnancy and is often used in those with inflammatory disorder and/or autoimmune conditions. Given the limited experimental treatment options for women with SARS-CoV2, we will not exclude pregnant women from this trial. We will document the presence or absence of pregnancy prior to administering study product, and ensure that participants are informed if they are pregnant prior to receipt of CCP.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

1. Risks of receiving CCP:
   Convalescent plasma represents a licensed blood product, for which the risks are well described. In a safety analysis of 5,000 patients treated with CCP, the risk of a severe transfusion reaction (c or d below) was less than 1% and no fatalities were attributed to CCP. The risks associated with the administration of plasma include but are not limited to the following transfusion reactions:
   a. allergic transfusion reactions (1- 3%),
   b. anaphylactic reactions (<0.01%),
   c. transfusionassociated circulatory overload (TACO) (1%),
   d. transfusion-related acute lung injury (TRALI) (<0.1%),
   e. hemolytic transfusion reactions (<1% or very rare),
   f. viral and bacterial infections (very rare or <1%), and
   g. febrile non-hemolytic transfusion reactions (<1%)

   Plasma is collected per FDA Guidelines. [28] There are additional FDA requirements for COVID-19 plasma donations which include:
   a. Evidence of COVID-19 documented by a laboratory test either by:
      i. A diagnostic test (e.g., nasopharyngeal swab) at the time of illness

OR

ii. A positive serological test for SARS-CoV-2 antibodies after recovery, if prior diagnostic testing was not performed at the time COVID-19 was suspected.

b. Complete resolution of symptoms at least 14 days prior to donation.

CCP units collected at the University of North Carolina's (UNC) Blood Donation Center (BDC) will be tested for the presence of anti-SARS-CoV-2 antibodies prior to transfusion or units.

There are several theoretical risks associated with the administration of convalescent plasma:

a. Antibody-mediated enhancement of infection (ADE). ADE can occur in viral diseases, such as dengue and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms of ADE have been described, including the theoretical concern that antibodies to one type of coronavirus could enhance infection to another strain. [23] It may be possible to predict the risk of ADE in SARS-CoV-2 experimentally, as proposed for MERS. [23] Preliminary studies in the Baric and De Silva laboratories at UNC (unpublished) suggest minimal or no cross-reactivity between SARS-CoV-2 antibodies and other coronaviruses known to circulate in our community. Since the proposed use of convalescent plasma in the COVID-19 epidemic would rely on preparations with high titers of antibody against the same virus, SARS2-CoV-2, ADE may be unlikely. Available evidence from the use of convalescent plasma in patients with SARS-1 and MERS demonstrated it is safe [13] and there were no adverse effects in a pilot study of patients with COVID-19. [4] Nevertheless, caution and vigilance will be exercised to use clinical and laboratory measures to detect evidence of enhanced infection.

b. Risk is that antibody administration to those exposed to SARS-CoV-2 may prevent disease but modify the immune response such that those who are treated may mount attenuated immune responses. This may leave them vulnerable to subsequent re-infection. Passive antibody administration before vaccination with respiratory syncytial virus attenuated humoral but not cellular immunity. [27] This will be investigated as part of this clinical trial by comparing early (first month) and late (up to 6 months) immune responses in those who receive standard of care and those who additionally received convalescent plasma. If responses differ, those with attenuated levels could be vaccinated against COVID-19 when a vaccine becomes available.

There is also the risk that convalescent plasma may be ineffective.

2. Risk of Blood Draw (<1%)

Blood drawing may cause pain, bruising, and may infrequently cause a feeling of lightheadedness or fainting. Rarely, it may cause infection, vein irritation (called phlebitis) or blood clot at the site where the blood is taken. We will minimize risk by using aseptic technique and universal precautions.

The risks to participants entailed by this study are minimal as research labs will be collected as part of the clinical care and other research studies, eliminating a separate collection and phlebotomy for these blood samples. This will also decrease the burden of large amount of extra blood collected on participants acutely ill.

3. Risks of Intravenous (IV) Infusion

Problems from use of an IV are generally mild and may include pain, bruising, minor swelling or bleeding at the IV site, and rarely, infection, vein irritation (called phlebitis), or blood clot. Risk will be minimized by using sterile technique and universal precautions.

The placement of an intravenous catheter can allow for the development of bacteremia because of the contact between the catheter and unsterile skin when it is inserted. This will be prevented through careful decontamination of local skin prior to catheter placement and through the use of infection control practices during infusion. Product contamination will be prevented by the use of aseptic technique in the pharmacy and universal precautions during product administration.

4. Risk of Nasopharyngeal (NP) Swab, Oropharyngeal (OP) Swab, Nasal Swab, Nasal Strips and other body fluid collections
   Collecting a respiratory swab may cause transient discomfort. Collection of the nasal epithelial lining fluid via nasal swab or strips may cause transient discomfort or the very rare risk (<1%) of aspiration of the filter paper. Discomfort and risk will be minimized by using experienced clinical staff at each site, and samples will be taken at the same time as clinical samples in order to minimize these risks. Nasal strips and/or nasal swabs will be self-collected when possible by the participants.

   Collection of stool, endotracheal and saliva secretions is not expected to cause any excessive discomfort. Stool and saliva will be self-collected when possible by the participants.

5. Unknown Risks
   New therapies can lead to unexpected, incidental findings that could have a potential effect on the participant's health. Upon confirmation of a potential health or reproductive effect, the study team will notify participants impacted by the new information and will advise proper medical follow-up when indicated. If findings require more immediate medical attention, the study PI in conjunction with the study coordinator will assist participants in getting an appropriate medical care appointment.

6. Risk of breach of confidentiality:
   Data gathered on study participants will include but not be limited to the following: their age, gender, race, laboratory-confirmed COVID-19 infection, and COVID-19 specific symptoms history. In the early phase of the epidemic, a COVID-19 diagnosis may carry significant stigma. Standard measures will ensure confidentiality of participants and data generated, as described later in the protocol.

2.3.2 KNOWN POTENTIAL BENEFITS

The most important potential benefit is that CCP may reduce progression to respiratory failure in patients with COVID-19 and early respiratory symptoms, such as shortness of breath, cough, chest pain, and pulmonary infiltrates. The benefit of plasma is expected to result in improvements in symptoms, oxygenation, and preventing the need for mechanical ventilation and possibly reduced mortality, earlier hospital discharge, and better clinical outcomes. Based on historical experience with antibody administration, it is expected to be effective if administered relatively early in the disease course. [15] CCP was safe, appeared to reduce symptoms, and improved oxygenation in a non-randomized open label study of patients with more advanced COVID-19 disease in Wuhan, China. [3, 4]

There may be no potential benefit of collection of samples other than the knowledge that one is helping advance science that may lead to understand ways to promote improved treatment.

The experimental agent remdesivir may soon be available to some patients with COVID-19 via an expanded access program. While the clinical criteria to allow expanded access to remdesivir are not currently known, it is likely that many COVID-19 patients eligible for CCP may not be eligible for remdesivir. However, if patients are eligible for remdesivir and desire to receive CCP, to avoid

depriving them of a possible benefit, we will allow co-enrollment (if allowed by the remdesivir program).

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Given historical data showing convalescent plasma was safe and possibly effective in patients with SARS-1, [10, 13] and emerging data from China suggest it is safe and possibly effective in patients with severe COVID-19 along with the relative lack of other readily available therapeutic options for severe or life-threatening disease, the benefits of its use in those at high risk for severe disease outweigh the risks.

However, for all patients in whom CCP administration is considered, a risk-benefit assessment will be conducted to assess all individual variables. This protocol proposes a randomized controlled trial to assess the efficacy of CCP in preventing respiratory progression in patients with COVID-19. A recent JAMA editorial by experts note the importance of randomized clinical trials to demonstrate efficacy of this approach and to change the course of the epidemic. [3]

There are limited data on potential risks and/or benefits for pregnant women and possible effects on the fetus. Pregnancy can cause changes in the coagulation and fibrinolytic systems and CCP may potentially benefit individuals by providing the coagulation factors.

There is sufficient expectation that the proposed NP swabs, OP swabs, nasal swab, nasal strips,plasma, stool, endotracheal, saliva, and blood collections will be safe and well tolerated.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
Evaluate the safety of high neutralization titer anti-SARS-CoV2 plasma in patients hospitalized due to COVID-19, compared to standard neutralization titer anti-SARS-CoV2 plasma. Evaluate the efficacy of high versus standard neutralization titer anti-SARS-CoV2 plasma to decrease length of hospitalization stay among patients hospitalized due to COVID-19.	The primary safety objective will be assessed by the cumulative incidence of serious adverse events (SAEs) at study Day 14. The primary efficacy endpoint will be assessed by days to hospital discharge (or discharge equivalent) following CPP first dose.
Exploratory	
1. Evaluate the efficacy of high versus standard neutralization titer anti-SARS-CoV2 plasma to improve clinical outcomes and mortality among patients hospitalized due to COVID-19.	1. Change in WHO ordinal clinical status scale while hospitalized and at Day 28 Change in National Early Warning Score (NEWS) while hospitalized and at Day 14 and Day 28 Days of supplemental oxygen (if applicable) while hospitalized at Day 14 and Day 28

OBJECTIVES	ENDPOINTS
	Days of NIV/high-flow oxygen (if applicable) while hospitalized and at Day 14 and Day 28 Days of Invasive ventilation/ECMO (if applicable) while hospitalized and at Day 14 and Day 28 In-hospital mortality 28-day mortality
2. Evaluate the safety and efficacy of high vs. standard <u>total antibody</u> titer anti-SARS-CoV2 plasma to increase survival and speed of hospital discharge in patients hospitalized due to COVID-19.	2. Same as above
3. Evaluate the safety and efficacy of high vs. standard <u>antigen-specific</u> titers of anti-SARS-CoV2 plasma to increase survival and speed of hospital discharge in patients hospitalized due to COVID-19.	3. Same as above
4. Compare length of hospitalization, clinical outcomes, and mortality among patients hospitalized due to COVID-19, who consented to concurrent UNC IRB approved observational studies but did not receive anti-SARS-CoV2 plasma.	4. Same as above
5. Compare SARS-CoV2 viral recovery from anatomic sites in patients hospitalized due to COVID-19, who received high vs. standard neutralization titer anti-SARS-CoV2 plasma.	5. SARS-CoV-2 RT-PCR on Day 0, 3 (+/-1), 7 (+/-1) (and/or discharge date), 21, and 28 (if still hospitalized) from nasopharyngeal, endotracheal, fecal, and blood specimens
6. Compare anti-SARS-CoV-2 total antibody, antigen-specific antibody, and neutralizing antibody titers at 28 days, 3 months, and 6 months in participants who received high vs. low neutralization titer anti-SARS-CoV2 plasma.	6. Serum anti-SARS-CoV-2 total antibody, antigen-specific antibody, and neutralizing antibody titers on Day 28, 3 months, and 6 months
7. Compare biomarkers obtained for clinical care in patients hospitalized due to COVID-19, who received high vs. standard neutralization titer anti-SARS-CoV2 plasma.	7. Lymphocyte and neutrophil counts, hematological and coagulation measurements (D-dimer, fibrinogen, PT), renal and liver function, and inflammatory markers (ferritin, CRP, and IL-6 if available) during hospitalization on Days 0, 1, 3, 7 (and/or day of discharge), 14, 21, and 28.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This randomized, double-blinded, phase 2 trial will assess the efficacy and safety of anti-SARS-CoV-2 convalescent plasma in hospitalized patients with less than 8 days of symptoms. Symptoms for this study are defined as self-reported fever or documented fever ≥ 38.0°C.

We plan to enroll up to 150 participants and all will receive CCP. Participants will be randomized in a 1:1 ratio to receive institution-guided standard-of-care together with CCP of either high or standard titer of SARS-CoV2 neutralizing antibodies. Information collected following plasma administration will include adverse events, participant, demographics, clinical status and laboratory and radiographic data collected for routine clinical care, acute care resource utilization, and characteristics of the CCP administered. The study will undergo primary analysis when 56 participants are enrolled and received CCP. Enrollment will continue during the analysis period to provide potential for benefit to hospitalized persons as well as to increase enrollment number for additional analysis. Following primary analysis we will close the study if a conclusion can be made, or propose an additional analysis plan for additional enrollees.

The study will also create a biobank of blood and mucosal lining fluids inclusive of nasal fluids (NP swab, and/or nasal epithelial lining strips (NELFS), oral fluids (saliva), intestinal (stool), and respiratory (endotracheal secretions) from hospitalized participants who received CCP early in the disease process. The study will collect samples prior to the first administration of CCP through 28 days following this transfusion participation through 6 months is optional. The study will primarily collect remnant blood and tissue samples on all participants during their hospitalization. We will collect real time samples on a subset of participants who agree to provide optional samples.

Biospecimens will also be obtained at timepoints per SOA, section 1.3. The study will attempt to collect as many specimens as possible, understanding that many collections will not be possible due to COVID-19 restrictions, access, and participant's clinical condition. The purpose of these biospecimens will be to measure the relationship between administration of CCP and viral load dynamics (from blood, nasal/respiratory fluids, saliva, and stool), immune responses, and biological indicators of COVID-19 disease severity. Biospecimens will be used to study and develop research assays to understand the antibody and cellular responses to SARS-CoV-2 coronavirus after human infection.

The study will collect data from hospitalized patients, who opted not to be on this study and whose data is captured in the UNC IRB Study #: 20-1095 entitled: IGHID 12018 - UNC COVID Cohort (UCC).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Convalescent plasma collected from individuals who have recovered from a prior viral infection for the passive transfer of antibodies has been used at various times over the past century. There has been some evidence for benefit against hepatitis B, polio, measles, influenza, Ebola, and other pathogens. [12] Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course. Additionally, there is preliminary clinical evidence that suggests that convalescent plasma might provide benefit to individuals with SARS-CoV-2 infection and manifestations of COVID-19. [3, 4] Patients with COVID-19 who have received convalescent plasma in these reports also received various other therapies, including anti-virals, anti-bacterial, and immune modulators. The use of such empiric therapies is currently a common practice in medical centers

treating hospitalized patients with COVID-19. As such, the additional benefit and/or safety of convalescent plasma to local standard of care practices is unknown. Several current randomized control trials in hospitalized patients with moderate and/or severe disease are designed to compare the effect of convalescent plasma to non-convalescent FFP. However, such a trial design cannot account for the effect of non-antibody components plasma that could modify the disease course. Based on the preliminary evidence of possible efficacy of convalescent plasma, and an expected evolution in local standard of care practices, this protocol is designed to ascertain the dose-dependent safety and efficacy of convalescent plasma with neutralizing antibody in standard compared with high titer range. In addition to standard of care in individuals with documented SARS-CoV-2 disease at acute care facilities who are within 8 days of onset of symptoms, defined as self-reported fever or fever ≥38.0 °C.

The study design allows for the collection of blood and tissue samples for research to expand our ability to understand SARs-CoV-2 and the efficacy of CCP through the analysis of convalescent blood derived from different de-identified donors and the clinical and biological outcomes of patients treated with CCP.

4.3 JUSTIFICATION FOR DOSE

Two units of plasma (approximately 200-250 mL each) containing anti-SARS2-CoV-19 antibodies at a minimum titer of 1:160 per May 1, 2020 FDA guidelines (*https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma*) will be infused. Functional neutralization assays are performed at UNC-CH. Should functional neutralization assays not be available, an ELISA targeting SARS-2-specific IgG will be used as a surrogate to determine titer. ELISA is a widely available methodology and the de Silva and Baric laboratories at UNC-CH are cross-validating these two methods. For standard titer units, the neutralization assay titers will range from ≥1:160 ≤1:640 and for the high-titer units the neutralization assay titers will exceed 1:640.

Dosing is based on experience with previous use of convalescent plasma therapy in SARS-1 where 5 mL/kg of plasma at titer ≥ 1:160 was utilized. [10] For a 70 kg person, plasma volume is estimated at 2800 mL (40 mL/kg x70 kg) with baseline anti-SARS-CoV-2 titer of 0. For example, if protective titer was 1:25 and each unit had titer of 1:160, ~250 mL can achieve this ([250/(2800)] x 1:160>1:25).

4.4 END OF STUDY DEFINITION

The end of study is defined as participants completing study follow-up through Day 28, or had an adverse event ≥ Grade 3 related to study product or death occurring prior to Day 28. Optional outpatient follow-up visits extend through month 6 for observation of immune response over time.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age at least 18 years

2. Ability and willingness of participant or Legally Authorized Representative (LAR) to give written informed consent.

3. Laboratory confirmed diagnosis of infection with SARS-CoV-2 by PCR

4. Hospitalized for COVID-19 with one or more respiratory or gastrointestinal (GI) symptoms:

- COVID-19 associated respiratory symptoms include but are not limited to: cough, shortness of breath, difficulty breathing, or sore throat
- COVID-19 associated GI symptoms include but are not limited to: loss of taste, loss of sense of smell, diarrhea, nausea, or vomiting,

Note: Respiratory and GI symptoms other than those listed above, must be noted as acceptable and signed by study PI or designee.

5.2 EXCLUSION CRITERIA

1. Receipt of pooled immunoglobulin in past 30 days
2. Current or prior enrollment in a SARS-CoV-2 antibody or T- cell therapeutic study.

   Note: Patients enrolled on other randomized controlled trials of pharmaceutical and/or non-pharmaceutical interventions for COVID-and meeting eligibility criteria will not be excluded, as determined by study PI (or designee) on a case-by-case basis and as allowed by eligibility criteria of the other trials.
3. Contraindication to transfusion or history of prior reactions to transfusion blood products. This may include religious or cultural objections to receiving blood products and transfusions.
4. ABO-compatible titered plasma is not available
5. > 10 days from noted COVID-related subjective or objective fever at randomization. Patients without subjective or objective fever, > 10 days from symptom onset as determined by study PI.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients eligible for this trial will be identified by their treating providers. Study coordinators will follow up with participants during their hospitalization and after discharge.

6 STUDY INTERVENTION

Participants will be randomized in a 1:1 ratio to receive standard of care and study product (CCP) of high or standard titer. Standard of care will be defined as current standard treatment for hospitalized patients at respective study site. It is expected that standard of care may vary as advances are made in therapeutic options and data from ongoing trials becomes available.

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

ABO compatible CCP will be obtained from the Institution's Transfusion Medicine Service. CCP will be administered according to standard hospital procedures per May 1, 2020 guidelines (*https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma*). Plasma units will be labeled with an International Society of Blood Transfusion (ISBT) label.

6.1.2 DOSING AND ADMINISTRATION

Two units (a total of ~ 400-500 mL) of plasma with antibodies to SARS-CoV-2 measuring a minimum neutralization titer of 1:160 as per May 1, 2020 FDA guidelines will be administered. The standard titer group will receive units ranging from ≥ 1:160 ≤ 1:640 and high-titer group will receive units exceeding 1:640. Whenever possible, both units will be derived from the same donor. The 2 units will be administered between 4-24 hours apart, and preferentially between 4-8 hours apart when feasible. If available, a third unit from a matched donor may be infused. At the discretion of the treating physician, one unit may be administered if the patient experiences an adverse reaction after the first transfusion and/or is deemed to be at high risk of circulatory overload.

1. CCP will be administered within 24 hours of randomization.

2. CCP will be infused at rate per institutional guidelines/SOPs for the administration of plasma.

3. Premedications may be given per institutional guidelines/SOPs for the administration of plasma. Pretreatment will be administered to minimize transfusion reactions (e.g., acetaminophen, diphenhydramine).

4. If an AE develops during infusion, the infusion may be slowed or stopped per the treating provider's decision per institutional guidelines/SOPs for the administration of plasma.. Most reactions to plasma transfusions are relatively minor and the infusions are generally continued.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

All convalescent plasma units will be prepared and stored per instiutitional SOPs as governed by the the FDA CFR Title 21.

6.3 MEASURES TO MINIMIZE BIAS

Randomization

Participants will be randomized 1:1 to one of two treatment arms:

CCP1: SOC and high titer anti-SARS-CoV-2 antibody plasma
CCP2: SOC and standard titer anti-SARS-CoV-2 antibody plasma

Enrolled patients will be assigned to an arm using a permuted block randomization, with block size randomly varied between 2, 4, or 6. We will generate a list of random numbers using the SAS procedure PLAN.

Blinding

Study personnel, participants, providers and investigators will be blinded to treatment arm assignment.

Clinical investigators will be blinded to identity of the group assignment (CCP1 or CCP2) that includes plasma with the higher neutralizing antibody end-point titer.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY

Discontinuation of the study: The study sponsor, FDA, and IRB all have the right to terminate this study at any time.

7.2 PARTICIPATION TERMINATION

Participants will be considered terminated if:

- consent was withdrawn by the participant,
- the study Principal Investigator discontinues the participant from study for severe lack of compliance,
- or the participant is lost to follow-up.

7.3 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

1. Participants can terminate study participation and/or withdraw consent at any time without prejudice.
2. Randomized participants who withdraw from the study will not be replaced. If participant withdrawal occurs prior to plasma transfusion, the participant will have inadequate data, and therefore "new" replacement participants can be enrolled.
3. The investigator may withdraw participants if the investigator determines that continued participation in the study would be harmful to the participant.
4. Under certain circumstances, an individual participant's receipt of CCP will be prematurely or permanently discontinued. Specific events that will result in stopping a participant's infusions in this study include:
    a. Failure to meet requirements established for safety
    b. Withdrawal from study
    c. Adverse event related to plasma administration
    d. Intercurrent illness that is not expected to resolve prior to the next scheduled transfusion which is assessed by the study PI or designee to require withdrawal of 2nd transfusion.
    e. Clinically significant reaction associated to plasma transfusion.
    f. Death

If the study PI (or designee) decides that a participant should be withdrawn from further plasma transfusions, the protocol team must be alerted within 24 hours. All participants who discontinue treatments should comply with protocol-specified visits and follow-up as required by the protocol and evaluation by the study PI (or designee). The only exception to this requirement is when a participant withdraws consent for all study procedures. If a participant is withdrawn before completing the study, the reason for withdrawal must be documented appropriately in the study documents.

Premature Discontinuation of Evaluations
For participants who begin but do not complete both plasma infusions, the continued collection of virologic, immunologic, and other samples will be determined on a case-by-case basis in discussion with the protocol team. The ability to complete virologic and immunologic endpoint analysis will be determined on a case-by-case basis in discussion with the protocol team.

7.4 LOST TO FOLLOW-UP

Participants classified as lost to follow-up (LTFU) need to meet both of the following criteria:

- Failure to respond or reply to 3 documented phone contact attempts by the study staff, followed by
- Failure to respond to a certified letter sent to the address provided by the participant.

Only after documentation of these failed attempts to connect with the participant, will they be determined to be LTFU.

8 STUDY ASSESSMENTS AND PROCEDURES

SAFETY AND OTHER ASSESSMENTS

8.1 EFFICACY ASSESSMENTS

This section provides a general description of the procedures and assessments associated with this study.

Informed Consent

Prior to performing any study-related procedures or assessments, the investigator or study coordinator discusses the study with the potential participant (or their legally authorized representative) and obtains signed informed consent. This communication will be documented.

Screening

Screening for participant eligibility will be performed within 24 hours of hospital admission to a COVID service and within 24 hours of enrollment. Only those participants who meet all eligibility criteria specified in Section 5.1 Inclusion Criteria and Section 5.2 Exclusion Criteria will be enrolled. A unique PID will be assigned during the screening visit.

Baseline and Enrollment

Assign risk assessment (refer to page 33) and complete clinical status assessments using the WHO ordinal scale*, National Early Warning Score (NEWS)* [24], and SOFA* [29] at enrollment. Clinical status assessments will include calculations done at enrollment (within 24 hours prior to plasma infusion). Screening, enrollment, and randomization can occur on the same day provided eligibility criteria is met.

As feasible, enrollment assessments will be performed by study coordinators or investigators. Given the nature of the COVID-19 pandemic, if hospital policies and/or PPE shortages prohibit in-person independent investigator physical exams and clinical status assessments, these parameters will be obtained by review of the electronic medical record (EMR).

**These illness severity assessment scales and scoring tools are described and available in the study-specific procedures.*

Randomization

Participants will be randomized to CCP1 or CCP2 at enrollment.

CCP Transfusion

Participants will be assessed on study Day 0 (pre-dose), and following transfusions per SOA (Section 1.3) while hospitalized and after discharge.

Other Assessments

- **Physical Examination (PE)**. Will be recorded as documented in the EMR by clinical care team during hospitalization. The PE at the Day 28 timepoint will be completed by PI, co-investigator, primary care provider, or appropriately licensed study staff, when possible.
    - Complete PE will include examination of skin, head, eyes, ears, nose, throat, lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic system.
    - The PE information obtained from the EMR (due to limitations imposed by COVID-19 restrictions) will be inclusive of system assessments as documented in the EMR and may not include all the information listed above.

- **Medical History**
  Significant medical history in most cases will be obtained by the admitting physician upon hospital admission. All concurrent medical conditions in the last 30 days and any significant medical conditions (e.g., hospitalizations, surgeries, prior medical history) should be collected as available in the participant's medical record. Medical history obtained will include demographic information (e.g., date of birth, gender, race, and ethnicity, etc.), participant's medical history, and medication history. This information can be obtained from the EMR as necessary.

  Participants will be asked if they have any cultural or religious objections to receiving CCP during this assessment.

- **Concomitant Medications**
  At enrollment, document concomitant medications taken by participant prior to hospitalization through EOS. These medications can be recorded from the EMR and will include the following:
    1. Prescription medications
    2. Over-the-counter medications
    3. Herbal treatments/nutritional supplements
    4. Blood products
    5. Prior and current receipt of medications used as therapies for COVID-19

- **Signs and Symptoms Assessments**
  At entry, all signs and symptoms, regardless of grade, that occurred within the 2 weeks before entry will be recorded as medical history. Assessment of adverse events (AEs) will be done at every study visit after the first unit of CCP is transfused. Post-transfusion signs and symptoms, Grade ≥ 2, will be recorded. All signs or symptoms, definitely, possibly, or probably related to study interventions, will be recorded, regardless of grade. Information will be obtained from EMR$.

- **Treatment Emergent Adverse Events**
  An event that first appears during treatment, which was absent before or which worsens relative to the pre-treatment state.

- **Vital Signs**
  Vital signs (weight (as available), body temperature, pulse or heart rate, respiratory rate, and blood pressure) will be recorded according to the SOA and as recorded in the EMR. Repeat vital signs (EMR documented) may also be captured as necessary to elucidate the course of any untoward event or AE.

- **Electrocardiogram (ECG or EKG)** – Collect from EMR, if available and completed as part of hospital admission.

- **Routine Clinical Procedures**
  The study will collect the following information per SOA (Section 1.3) when done as part of clinical care (and documented in EMR). The study will collect these results as available in the medical record.
    - **Radiographic or other imaging assessments.** As performed for routine clinical care.
    - **Clinical laboratory evaluations for safety evaluation***.* Laboratory evaluations performed for routine clinical care (reference SOA for laboratory values to be assessed). Safety and clinically relevant labs will be performed at UNC McLendon Laboratories.

- **Special Assays or Procedures***.*
  Neutralization assays, antibody titer by ELISA and SARS-CoV-2 PCR will be performed at participating research laboratories at UNC-Chapel Hill.

- **Optional Outpatient Longitudinal Visits and Immunology Research Specimens**
  Participants will be informed of the opportunity to provide optional immunology samples and/or remain on the study through 6 months.

  Participant options include the following:
  1. Agree to the collection of optional samples during hospitalization and Day 28 only.
  2. Agree to optional outpatient visits on Days 49, 90, and 180 with the collection of optional samples.
  3. Refuse optional outpatient visits and sample collections.

  This option will collect samples at 5 timepoints (Reference Study-Specific Laboratory Manual).
  The samples to be collected include:
    1. Blood samples
        a. The blood samples obtained will be used for measuring primary and memory B-cell responses to SARS-CoV-2 and the trafficking and longevity of antibodies after CCP infusion.
        b. Collect these samples at Days 0, 7, 28, 49, 90, and 180.
            i. Persons agreeing to optional sample collection, will have extra blood collected (up to 37 mL) at the Day 28 visit.
    2. Mucosal lining fluid samples which include but are not limited to: nasal fluids (NP swab, and/or nasal epithelial lining strips (NELFS), oral fluids (saliva), intestinal (stool) and/or respiratory (endotracheal secretions).
        a. The NELF collection involves the use of two absorbent filter paper strips placed into the nares and held there for 2 minutes. The mucosal samples will be used to study the trafficking of antibodies in CCP to primary site of SARS-CoV-2 infection.
            i. Collect at Days 0, 7, 49, 90, and 180.
        b. The NP swab – collect only if participant agrees to the collection. Participant can refuse this sample and still be part of optional collections.
            i. Collect at Days 0 and 7.
        c. Saliva
            i. Collect at Days 0, 7, 49, 90, and 180.
        d. Stool
            i. Collect if participant is able to provide sample or sample available at inpatient visits (Days 0 and 7).
            ii. Collect at outpatient visits – provide participant with kit and directions for collection and storage of specimen prior to visits (Days 49, 90, and 180).

All participants are required to complete the Day 28 visit (inpatient or outpatient) and all samples will be collected at this visit (reference SOA). If unable to collect sample, document reason. Inability to collect sample or participant refusal to provide sample is allowed.

There are optional sample collections during the Day 0 and 7 inpatient visits; the optional outpatient visits and sample collections include Days 49, 90 (3 month), and 180 (6 month). The Day 28 collections are part of the main study and are not optional; however, those participants providing consent for optional samples, will have extra blood collected at Day 28.

Specimens generated from these optional immunology samples will be analyzed in collaboration with other investigators.

- **End of Study Visit**
  An End of Study (EOS) visit for the primary part of the study will occur at Day 28. Participants will complete the EOS visit per the SOA but will be followed as necessary for acceptable resolution of clinical events related to the study product.

- **Final or Last Study Visit**
  The Final Study Visit may occur approximately 6 months after the CCP infusion, depending on the participant consent to the optional outpatient visit as well as and can be based on the duration and severity of any ongoing, treatment related AEs. An individual participant will be considered to have completed the study if the participant was followed through their last protocol-specified visit/assessment. Participants who have a new clinical event related to the CCP will be followed on study until the clinical event is resolved or deemed stable and irreversible.

- **Biospecimens**
  Biospecimens will be those obtained by the study for research purposes in addition to those collected as part of routine clinical care. All biospecimens will be used to address the aims of the study. The research assays will be collected from admission (when available) and at the research visits (per SOA, section 1.3). Research assays will be processed and stored in associated research laboratories. Additional details on collection, processing, storage, and shipping of laboratory samples will be provided in the Study Specific Manual. Appropriate selection and timely collection of high-quality specimens, proper storage procedures, and comprehensive diagnostic testing will ensure the quality of data. Appropriate selection and timely collection of high-quality specimens, proper storage procedures, and comprehensive diagnostic testing will ensure the quality of data. Biosafety procedures will be as per local policy/guidance, in keeping with national and/or international regulations, and will be applied to the collection, storage, transfer, and laboratory handling of research samples.

8.2 SAFETY AND OTHER ASSESSMENTS

All clinical and laboratory information required by this protocol will be obtained from clinical testing done as part of routine clinical care. Some protocol indicated evaluations, not assessed as part of clinical care will be added on the labs drawn, when possible and requested by the PI. Otherwise, these labs will be documented as unobtained. We will not list these as protocol deviations as the severity of illness and SOC restrictions/isolation procedures resulting from COVID-19 infection prohibits additional PPE and possibly additional blood draws. All protocol required procedures will be in the source documents.

Clinical Procedures for Safety

- Plasma Administration
  Plasma will be obtained and administered per Institutional standard operational policies and procedures.

- Post Infusion Management
  Participant will be managed per Institutional standard operational policies and procedures.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Common Terminology Criteria for Adverse Events (CTCAE) Terms
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. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term)..

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Any adverse event that results in any of the following outcomes:
1. Death
2. Life-threatening (immediate risk of death)
3. Prolongation of existing hospitalization
4. Persistent or significant disability or incapacity
5. Important medical events that may not result in death, be life threatening, or require intervention or escalation of care may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

Grading of study adverse events will be assessed using CTCAE grading scale developed by National Cancer Institute (NCI), National Institutes of Health (NIH), *https://evs.nci.nih.gov/ftp1/CTCAE/About.html*

8.3.3.1 SEVERITY OF EVENT

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose adverse event information, provide a medical evaluation of adverse events, and classify adverse events based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners. All AEs will be assessed by the study clinician using a CTCAE grading system.

1. **Grade 1 or Mild**: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. **Grade 2 or Moderate**: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3. **Grade 3 or Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self care ADL**
4. **Grade 4 or Life-threatening**; urgent intervention indicated.
5. **Grade 5 or Death related to AE**

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

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

8.3.3.3 EXPECTEDNESS

The investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 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 a study monitor.

Any medical condition that is present at the time that the participant is screened and prior to the CCP transfusion will be considered baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time after receipt of the study product, it will be recorded as an AE.

Given the nature of severity of the underlying illness, participants will have many symptoms and abnormalities in vital signs and laboratory values. AEs and SAEs will be documented following the first administration of CCP. All Grade 3 and 4 AEs will be recorded in the database in this trial. In addition, the following AEs will be reported:

1. All AEs (≥ Grade 2) and SAEs resulting from study product administration will be documented and followed until resolution even if AEs extend beyond the study-reporting period.
2. All AEs including local and systemic reactions related to the CCP transfusion but not meeting the criteria for SAEs will be documented.
3. Any AEs leading to dose modification.

Intermittent abnormal laboratory values or vital sign measurements common in the severely ill populations (such as electrolyte abnormalities, low blood pressure, hyperglycemia, etc.) that are part of the same clinical diagnosis (e.g., uncontrolled diabetic) can be recorded once with the worst grade for each adverse event, with the start and stops dates of the intermittent syndrome. If there is clear resolution of the event, and then recurrence, it should be treated as a separate adverse event.

Resolution of an adverse event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic. At any time after completion of the study, if the investigator becomes aware of a SAE that is suspected to be related to study product, incident will be investigated and reported as required.

IInformation to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All CCP-related AEs will be followed to adequate resolution.

AE assessment during the optional outpatient visits will be documented only as they relate to the outpatient study procedures and events. All other medical events related to medical history will be recorded as medical history and not as an adverse event.

8.3.5 ADVERSE EVENT REPORTING

Reporting will only be required for adverse events judged to be potentially or definitely related to the administration of the CCP.

Events will be reported starting with the start date of the first transfusion through Day 21 while hospitalized. No AE assessment will be required after participant discharge, unless previously reported and being followed through resolution.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Reporting will only be required for serious adverse events judged to be potentially or definitely related to the administration of the CCP.

All SAEs will be documented from the first administration of study product through Day 21. (Reference section 8.3.5)

The PI (or designee) will immediately report to the sponsor any serious adverse event, considered to be potentially related to the study intervention, and will include an assessment indicating a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All study-related serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the US Food and Drug Administration (FDA) or study sponsor and should be provided as soon as possible.

The study PI sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction potentially related to the study product as soon as possible, but in no case later than 7 calendar days after the PI initial receipt of the information. In addition, the study PI must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

We would inform all study participants by letter or electronic messaging of any AEs determined by the Safety Monitoirng Committee to merit such notice.

8.4 NEW SAFETY INFORMATION

8.4.1 DEFINITION OF NEW SAFETY INFORMATION (NSI)

The Office for Human Research Protections (OHRP) considers NSI involving risks to participants to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 NEW SAFETY INFORMATION REPORTING

The investigator will report any unanticipated NSIs related to the study product to the UNC Institutional Review Board (IRB) and the North Carolina Translational and Clinical Sciennces Institute (NC TraCS) Data and Safety Monitoring Board (DSMB). The NSI report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB study number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an NSI;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the NSI.

NSI will be reported per the UNC IRB SOP for NSI reporting.

8.4.3 REPORTING NEW SAFETY INFORMATION TO PARTICIPANTS

We would inform all study participants by letter or electronic messaging of any new safety information if it is determined by the UNC IRB to merit such notice.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

For the primary aim of assessing safety we will not perform any statistical testing. Analysis of adverse event data will primarily be descriptive. We anticipate that high and standard titer anti-SARS-CoV-2 convalescent plasma will be well tolerated.

For the primary aim of assessing efficacy of high versus low titer anti-SARS-CoV-2 convalescent plasma, our primary hypothesis is that by providing high-titer anti-SARS-CoV-2 plasma, the duration of hospitalization will decrease as compared to the group receiving standard-titer plasma.

9.2 SAMPLE SIZE DETERMINATION

The primary analysis will be done on a planned sample size of 56 participants, randomized in a 1:1 ratio to receive high-titer anti-SARS-CoV-2 convalescent plasma versus standard-titer CCP. Sample size estimation was based on having sufficient power to detect a clinically meaningful difference in time to hospital discharge comparing patients randomized to high versus low titer anti-SARS-CoV-2 convalescent plasma.

For estimating sample size we tested the null hypothesis that a hazard ratio of high versus standard titer CPP was equal to 1, versus the alternative hypothesis that the hazard ratio of high versus standard titer CPP was not equal to 1. We assumed a median time to discharge of 14 days for the low titer group, a 0.01 probability of death during hospitalization and a pre-specified two-sided significance level of 0.05. With an anticipated enrollment for initial analysis of N=28 in each arm, N=56 total enrollment, we will have 80% power to detect a hazard ratio of 2.25 for time to discharge, corresponding to a probability of remaining hospitalized at Day 14 post-infusion of 0.50 for the low titer CPP group, and 0.21 for the high titer CPP group. Our power increases to 0.92 with increasing difference in probability of remaining hospitalized at Day 14 post-infusion of 0.35. Given uncertainty of hospitalization length of stay, inpatient mortality, and expected efficacy of high versus low titer CPP, we will actively monitor outcomes with ongoing accrual.

9.3 POPULATIONS FOR ANALYSES

- Primary analysis: Intention-to-Treat (ITT) with 2 units of CCP
- Exploratory analyses: Per-protocol analysis of CCP who received both doses prior to admission to ICU

9.4 STATISTICAL ANALYSES

9.4.1 SAFETY ANALYSES

Analysis of AE data will primarily be descriptive based on MedDRA coding of events. AE data will be compared between randomized arms using Fisher's Exact Test.

For the safety endpoint, we will describe all study treatment-related AEs through the end of study approximately 24 weeks after getting their first infusion at Day 0. AEs will be coded to the Medical Dictionary for Regulatory Activities (MedDRA). Events prior to treatment (e.g., due to study-related procedures) will be listed separately in an appendix to the final clinical study report. The following tables of AE data will be created to summarize the number and percent of participants who experience at least one event of each of the following types:

- All AEs
- CCP-related AEs by severity grade
- AEs by severity grade
- All SAEs (this may be a listing if there are few events)
- CCP-related SAEs
- Fatal AEs (this may be a listing if there are few events)
- AEs that result in study discontinuation
- AEs that lead to withdrawal of study product
- AEs with severity grade 3 or greater
- CCP-related AEs with severity grade 3 or greater

All of these tables will display the number and percent of participants that experience the given event and will display events by System Organ Class (SOC) and Preferred Term (PT). Events will be displayed alphabetically for SOC and in descending order of overall PT incidence within each SOC.

9.4.2 GENERAL APPROACH

Statistical Analysis: Exploratory analyses are planned to evaluate pre-specified factors relevant to CPP administration, clinical course, and outcomes. Analyses will be intention-to-treat (ITT), with patients analyzed in their assigned arms regardless of compliance with the interventions. In addition to primary ITT analysis, we will conduct analyses that explore corrections for compliance with the interventions such as dose reduction (receiving only 1 unit instead of 2 due to a transfusion reaction after the first dose) in both arms to supplement ITT analyses with information on the actual intervention exposure while retaining the validity of the randomization-based inference. Categorical data will be presented in the form of frequencies and percentages. Continuous data will be provided with descriptive statistics, including mean, standard deviation, median, interquartile range, and full range. Ordinal data will be presented in the form of frequencies, median, and percentiles. We will use SAS version 9.4 or R version 4.0.0 for all analyses.

Tests of Hypotheses: Analyses of dichotomous outcomes by arm will be tested using a Chi-square test for proportions. As indicated, we will use nonparametric statistics including Fisher's exact test to test for differences in proportions. Analyses of continuous outcomes by arm will be tested using t-tests, with the nonparametric alternative of Mann-Whitney U test used as indicated. For continuous outcomes we will assess normality, and as indicated rely on nonparametric tests. Additionally, we will consider re-parametization and transformation based on the underlying distribution. Analyses of ordinal outcomes by arm will be tested using the Wilcoxon test.

The difference in proportions will also be calculated as a measure of effect for dichotomous outcomes. For continuous outcomes, the difference in means or a nonparametric equivalent will be calculated as a measure of effect. The summary measure of effect for ordinal outcomes will be an odds ratio estimated using an ordinal logistic model. For all measures of effect we will calculate 95% confidence limits as measures of precision. For time to event analyses we will plot Kaplan-Meier curves and use the log-rank test to test for differences in time to event. Kaplan-Meier event rates at various time points with 2-sided

confidence intervals will be summarized. In addition, Kaplan-Meier estimates of quartiles (median, 25th and 75th percentiles) with 2-sided 95% confidence intervals will be calculated if applicable. All tests will be 2-sided with a pre-specified alpha of 0.05.

Given the rapidly evolving COVID-19 pandemic, we are prepared to accommodate new knowledge and information and modify our proposed approach and analyses as indicated.

9.4.3 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Event times for discharge from the hospital will be obtained in continuous time (days) from time 0 (day of infusion) until the first of date of hospital discharge or date when the patient was last at risk (right censoring time, including date of death). Our primary analysis will use the standard Kaplan-Meier estimate of the survival or cumulative incidence function. An unadjusted log-rank test will be used to test for differences between treatment groups. The proportional hazards regression model will be used to adjust for risk (high versus average risk), age (in years), sex, ABO type, levels 2-5 on the WHO ordinal outcome scale, and time from symptom onset in days, all measured at time 0. Cox proportional hazards regression models will be used to estimate unadjusted and adjusted hazard ratios as measures of effect, and 95% confidence intervals as measures of precision. We will assess model fit of the Cox model using log likelihood statistics and the proportionality assumption will be assessed relying on graphical analyses and statistical testing. If tests of the proportional hazards assumption do not apply, inferences will be obtained using robust sandwich estimators of standard error. Additionally, we may use alternate models, such as the proportional odds model, transformations of covariates may be considered or time effects may be included in the model.

A Cox proportional hazards model with right censoring on death has a valid interpretation as the effect of the treatment assignment on the cause-specific hazard function for the event discharge from hospital. However, death prior to hospital discharge may be considered a competing risk, and treating deaths as right censoring may not be appropriate. In this case we will estimate the cumulative incidence of hospital discharge adjusting for the incidence of mortality. We anticipate a high level of completeness of data; however, in the event of missing data we will rely on stochastic multiple-imputation to account for missingness. Multiple-imputation provides unbiased estimates of the treatment effect and yields appropriate precision if data are missing completely at random, or under the weaker assumption that data are missing at random conditional on measured variables.

9.4.4 SUB-GROUP ANALYSES

At the time of randomization, participants will be assigned to a clinical severity as floor status versus ICU status as determined by the treating physician. The primary analysis will include all participants. In the sub-group analysis, floor status participants will be analyzed separately from ICU status participants.

9.4.5 EXPLORATORY ANALYSES

For exploratory analyses, logistic regression will be used to model dichotomous outcomes. For continuous outcomes we will use ordinary least squares regression and non-linear mixed models for modeling outcomes that are rare as indicated. For time to event analyses we will use proportional hazards models. All models will be adjusted for risk (high versus average risk as indicated below), age (in years), sex, levels 2-5 on the WHO ordinal outcome scale, and time from symptom onset in days, all measured at time 0. Adjusted measures of effect will be used as indicators of effect size and 95% confidence intervals as indicators of precision.

- Change in WHO ordinal clinical status scale while hospitalized and at Day 28: For the efficacy endpoint of the WHO COVID scale on each day of hospitalization beginning on day 0 (pre-infusion) and through Day 28, we will compute probabilities related to the comparison of high versus standard titer CPP. The summary efficacy parameter will be an odds ratio (OR) from an ordinal logistic model, with OR>1 being favorable to high titer versus low titer when the ordinal WHO scale ranges from 1=death to 8=no evidence of infection. For the ordinal outcome scale, the proportional odds (PO) ordinal logistic semiparametric model is an ideal approach as it allows the distribution across the levels to be arbitrary. In addition to the dichotomous treatment assignment variable, the PO model will be adjusted for baseline risk factors (high versus average risk as indicated below), age (in years), sex, levels 2-5 on the WHO ordinal outcome scale, and time from symptom onset in days, all measured at time 0.

    - Change in National Early Warning Score (NEWS) while hospitalized and at Day 28 (linear regression)

    - Days of supplemental oxygen, NIV/high-flow oxygen, mechanical ventilation/ECMO while hospitalized and at Day 28 (linear regression)

    - Mortality at Day 28: (logistic regression)

  <u>High risk:</u>
  - WHO ordinal clinical status >4 *or*
  - ordinal scale ≤ 4 with any one of the following
      - ≥60 years or age
      - immunocompromise (immunosuppressive drugs, solid tumor, solid organ transplant, hematologic malignancies, hematologic stem cell transplantation, rheumatological disease on immunosuppressants, inflammatory bowel disease on immunosuppressants, asthma or COPD on chronic steroid therapy, HIV+ with CD4 count <200 cells/µl)
      - diabetes mellitus
      - obesity
      - uncontrolled hypertension
      - cardiovascular disease
      - chronic pulmonary disease

  <u>Average risk</u>: <60 years of age AND absence any of the above high-risk factors

- <u>Analysis of the anti-SARS-CoV-2 titers</u>
  Analysis of titers will primarily be descriptive, comparing the geometric mean titers (total antibody, antigen-specific, and neutralizing antibody) at Days 0, 3 (+/-1 day), 7 (+/-1 day or at discharge), 21, 28, and at months 3 and 6 between the randomized arms. It is also of interest to describe the entire distributions of anti-SARS-CoV-2 titers by randomized arms and contrast these distributions. Therefore, we will use quantile regression to describe whether there is a shift or change in the titer distribution between randomized arms. Given that repeated measures of titers will be obtained, we will account for the correlation in measures within individuals using a cluster bootstrap in order to properly estimate the p-value and 95% confidence intervals.

- <u>Analysis of the rates, levels, and duration of SARS-CoV-2 RNA in NP swabs and other body fluids</u>
  This exploratory analysis will be primarily descriptive. The proportion positive at Days 0, 3, 7, 21, and 28 days and whether individuals lose positive status at a subsequent time. To determine the proportion that are positive, we will do a pooled complementary log-log model in order to describe the cumulative incidence of SARS-CoV-2 positivity over time. The pooled complementary log-log model is a discrete time-to-event-analysis that estimates the log hazard rate at each discrete time point. Like the analysis of anti-SARS-CoV-2 titers, the

goal of this secondary aim is to describe the distribution of SARS-CoV-2 RNA between randomized arms. Therefore, we will use the same approach as for the anti-SARS-CoV-2 titers. Because the exact day that an individual becomes negative is not known, a minimum and maximum amount of positive time will be used to describe the positive duration of each individual. If the sample is adequate, we will describe the duration of positivity using a non-parametric approach for time-to-event analysis.

- Other biomarkers
  Testing results available through routine clinical care: CBC, differential, PT/INR, PTT, d-dimer, fibrinogen, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium, C-reactive protein, and IL-6 on Days 0, 1, 3 (+/-1 day), 6 (+/-1 day), 7 (or day of discharge), 14, 21, and 28. We will use the same approach as above.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant (and/or legally authorized representative) and written documentation of informed consent is required prior to starting any study procedures and study intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

All participants will be consented, either in person or using virtual options per UNC-CH IGHID Regulatory Standard Operating Procedure (SOP). The study can use Adobe Sign for consenting remotely and securely. The study team member will review the consent(s) with the potential participant over the phone after emailing them the password protected consent(s). Potential participants meeting eligibility criteria will be invited by the study team member to participate in the study. If participants express an interest in the study, the study will be explained in detail by a study team member during a telephone meeting or in person. If the participant agrees to participate in the study, they will electronically sign the study consent form(s) if done remotely or sign in writing if done in person.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigational New Drug (IND sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and funding sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance by participant to protocol requirements

- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

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

Halting Criteria for the Study: The study enrollment and study treatment will be stopped and an ad hoc review will be performed if any of the specific following events occur or, if in the judgment of the study physician, participant safety is at risk of being compromised:

1. Death within one hour of plasma infusion

2. Occurrence of a life-threatening allergic/hypersensitivity reaction (anaphylaxis), manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation, TRALI, TACO

3. One participant with a study product-related SAE.

4. Two participants with a Grade 3 or higher lab toxicity for the same parameter associated with study product. (Grading will be assessed using Common Terminology Criteria for Adverse Events (CTCAE) grading scale developed by NCI, NIH , *https://evs.nci.nih.gov/ftp1/CTCAE/About.html*)

5. An overall pattern of symptomatic, clinical, or laboratory events that the Safety Monitoring Committee considers associated with study product and that may appear minor in terms of individual events but that collectively may represent a serious potential concern for safety.

6. Any other event(s) which is considered to be a serious adverse event in the good clinical judgment of the responsible physician. This will be appropriately documented.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly upheld. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the IND sponsor.

All research activities will be conducted in as private a setting as possible.

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

The study participant's contact information will be securely stored at the clinical study site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the UNC School of Medicine secure server. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the Shannon Wallet and Aravinda de Silva Laboratories for up to 5 years. These samples could be used to research the effectiveness of neutralizing antibodies against SARS-2, antibody-dependent enhancement of COVID-19 and its complications and other conditions for which individuals with COVID-19 are at increased risk, and to improve treatment. The Shannon Wallet and Aravinda de Silva Laboratories will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Principal Investigator.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator

Principal Investigator	**Co-Principal Investigator**
Luther Bartelt, MD	David Margolis, MD
University of North Carolina at Chapel Hill	UNC-Chapel Hill School of Medicine
7314A Medical Biomedical Research Building *120 Mason Farm Rd., CB 7032* *University of North Carolina at Chapel Hill* *Chapel Hill, NC 27599-7032*	2016 Genetic Medicine Building 120 Mason Farm Rd., CB 7042 University of North Carolina at Chapel Hill Chapel Hill, NC 27599-7042
919-966-6152	*919-966-6388*
luther_bartelt@med.unc.edu	*dmargo@med.unc.edu*

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the NC TraCS DSMB. The NC TraCS DSMB will serve as the Independent Safety Monitoring Committee, composed of ndividuals with the appropriate expertise, including infectious diseases and pulmonary specialists, without conflict of interests, will be established. Members should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least every 6 months to assess safety and efficacy data on each arm of the study. In addition, should any grade 3 or higher AEs,

SAEs, or deaths occur, these will be reported to the DSMB immediately. Reports from DSMB meetings and recommendations by the DSMB will be provided by the study team to the FDA and the IRB.

10.1.7 CLINICAL MONITORING

To ensure the safety of participants in the study, compliance with applicable regulations, and to ensure accurate, complete, and reliable data, the study PI will keep records of laboratory tests, clinical notes, and participant medical records in the participant files as source documents for the study.

An independent study monitor will monitor the study on a regular basis throughout the study period according to the study monitoring plan. The study monitor periodically will conduct a review of a sample of the participant data recorded on source documents at the study site. The study PI and site study personnel must address all queries in a timely manner.

Participation as an Investigator in this study implies acceptance of the potential for inspection by the study Sponsor/Funder and its Representatives, US or non-US government regulatory authorities, IRB, and applicable compliance and quality assurance offices. The study PI (or designee) will permit study-related audits and inspections and will provide access to all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The study PI will ensure the capability for inspections of applicable study-related facilities (e.g., IDS pharmacy, CTRC, etc.).

Minimizing risk to participants

Procedures to minimize risk to participants in the conduct of this study include: 1) informing participants about risks so they can recognize and report harms in partnership with the study team; 2) respecting local/national blood draw limits; 3) direct observation of participants after study treatment administration with CCP and collection of information regarding side effects for several days post product administration; 4) having study staff properly trained in administering study procedures that may cause physical harm or psychologic distress, such as blood draws and infusions; and 5) providing study monitoring as applicable.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical study site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. The site will have a quality management plan describing their quality management.

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

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The clinical research staff is responsible for data collection under the supervision of the site PI (or designee). The study PI (or designee) is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hard copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a UNC School of Medicine Database, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and external quality checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

It is the responsibility of the site principal investigator to use continuous vigilance to identify, document, and report protocol deviations. All protocol deviations must be addressed in study source documents and reported to UNC IRB per their reporting requirements. The site principal investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- NIH Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.
- NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov, if required.
- NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The University of North Carolina at Chapel Hill recognizes that conflicts of interest will arise from the research enterprise, from technology transfer activities, and from the many facets of our investigators' professional activities. UNC seeks to identify and manage these conflicting relationships, restricting activities where necessary, to preserve transparency, independent decision-making, protection of research participants, and integrity of the educational experience. UNC's Conflict of Interest Office will have oversight over this study.

10.2 ABBREVIATIONS

ADE	Antibody Mediated Enhancement of Infection
AE	Adverse Event
ANCOVA	Analysis of Covariance
ARDS	Acute Respiratory Disease Syndrome
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
BDC	Blood Donation Center
BUN	Blood Urea Nitrogen
CB	Campus Box
CBC	Complete Blood Count
CCP	Convalescent COVID-19 Plasma
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	SARS-CoV-2
CRF	Case Report Form
CT	CAT scan
CTCAE	Common Terminology Criteria for Adverse Events

CTRC	Clinical and Translational Research Center
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DRE	Disease-Related Event
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG/EKG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Forms
EMR	Electronic Medical Record
EOS	End of Study
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFP	Fresh Frozen Plasma
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGHID	Institute for Global Health and Infectious Diseases
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
ISBT	International Society of Blood Transfusions
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IV	Intravenous
IVIg	Intravenous Immune Globulin
LDH	Lactate Dehydrogenase
LSMEANS	Least-Squares Means
LTFU	Lost to Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCI	National Cancer Institute
NCT	National Clinical Trial
NC TraCS	North Carolina Translational and Clinical Sciences Institute
NEWS	National Early Warning Score
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NIV	Non-Invasive Ventilation
NSI	New Safety Information

OHRP	Office for Human Research Protections
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PID	Participant Identification
PO	Proportional Odds
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SNP	Single Nucleotide Polymorphisms
SOA	Schedule of Activities
SOC	Standard of Care
SOFA	Sequential Organ Failure Assessment Score
SOP	Standard Operating Procedure
TACO	Transfusion Associated Circulatory Overload
TRALI	Transfusion-Related Acute Lung Injury
UNC	University of North Carolina
US	United States
WHO	World Health Organization

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2.0	24 Aug 2020	Modification to reflect changes in knowledge about disease entity and changes in care.	
2.0	24 Aug 2020	Modification to Schedule of Activities (SOA)	Removed procedures and clinical assessments from screening visit to reduce unnecessary procedures until study eligibility confirmed
2.0	24 Aug 2020	Modified text in protocol to clarify procedures related to sample collections and clinical assessments for study participation.	Simplified and clarifiedprotocol procedures to: - identify hospital SOC procedures as separate from study procedures - clarify processes to allow modified participant contact and reduce unnecessary procedures

2.0	24 Aug 2020	Modification to the inclusion and exclusion criteria (sections 5.1 and 5.2) to clearly define exclusionary criteria, especially with the initiating of other therapeutics for COVID-19	To account for the development of new monoclonal antibody and T cells therapeutics since protocol inception. To define what numbers of days that are relevant for study exclusion.
3.0	30 Oct 2020	Section 1.3 Schedule of Activities (SOA) and Section 8.1 Efficacy Assessments: Clarified text and collection time points related to samples. More clearly defined and identified study-required visits and samples from those that are optional.	The former protocol version 2.0 did not accurately identify the optional visits and samples, leading to a lot of confusion on which samples to collect and when.
3.0	30 Oct 2020	Sections 1.3 and 8.1: Removal of Targeted Physical Exams	The longitudinal visits are for sample testing. No clinical data required for study analysis.
3.0	30 Oct 2020	Section 1.3 SOA: Removed urine from sample collections.	Testing of these samples determined to be less important than the other epithelial lining samples.
3.0	30 Oct 2020	Section 1.3 SOA: Changed pregnancy testing to include all women who are less than 60 years of age	Since many participants are not clinically stable or able to answer questions, and medical records may not be available to support child bearing potential, pregnancy testing on all women < 60 years of age eliminated the need to ask family members personal health information on the participant.
3.0	30 Oct 2020	Section 8.1 Efficacy Assessments: Broadened terms to avoid requiring testing (NP swab) that many participants do not want to have again.	Many participants uninterested in having any additional NP swab samples taken if unnecessary.
3.0	30 Oct 2020	Section 8.3 Adverse Events and Serious Adverse Events: Clarification of AE reporting	Although intent of protocol remains unchanged, the language for grading was clarified due to the many confounding AEs that occur solely due to the severity of the illness and not related or associated with the CCP transfusions.

3.1	18 Nov 2020	Allow for continued enrollment up to 150 participants. Primary analysis will start when 56 participants are enrolled with receipt of CCP.	While the initial analysis of n=56 is ongoing, we will continue to enroll given the potential for benefit, and for expanded analysis. Following initial analysis we will make a conclusion and close the study, or offer an analysis plan for additional enrollees up to 150.

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