Convalescent Plasma to Stem Coronavirus: A Randomized Controlled Double Blinded Phase 2 Study Comparing the Efficacy and Safety of Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 non-immune plasma) among Adults Exposed to COVID-19

NCT 04323800

Protocol

Version December 23, 2020

1. PROTOCOL SUMMARY:

Long title: Convalescent Plasma to Stem Coronavirus: A Randomized Controlled Double Blinded Phase 2 Study Comparing the Efficacy and Safety of Human Coronavirus Immune Plasma (HCIP) vs. control (SARS-CoV-2 non-immune plasma) among Adults Exposed to COVID-19

Short title: CSSC-001

Clinical Phase: 2

IND Sponsor: Johns Hopkins University

Conducted by: Johns Hopkins University as lead institution for a consortium of sites

Sample Size: 500

Study Population: High-risk subjects aged 18 years of age and older who have experienced a close contact exposure to a person with COVID-19 in the past 120 hours AND have not yet themselves developed symptoms of COVID-19

Study Duration: April 1, 2020 to December 31, 2022

Study Design: This randomized, controlled, double-blinded phase 2 trial will assess the efficacy and safety of Anti- SARS-CoV-2 convalescent plasma as prophylaxis following exposure to COVID-19 (as defined in the inclusion criteria). Adults 18 years of age and older with high risk exposure as defined by CDC may participate. A total of 500 eligible subjects will be randomized in a 1:1 ratio to receive either high titer anti-SARS-CoV-2 plasma or control (SARS-CoV-2 non-immune plasma).

The following will be assessed in all subjects:

- Safety and efficacy: Day 0 (baseline), 1, 3, 7, 14, 28, 60 and 90. May be performed by telemedicine on days when laboratory testing not scheduled.
- Blood antibody titer[1] to SARS-CoV-2s: Day -1 to 0, 1, 7, 14 and 90
- SARS-CoV-2 molecular testing from nasopharyngeal swab, throat samples: Day -1 to 0, 1,7, 14 and 28 and at any time when there is clinical suspicion for COVID-19

Study Agent:

- SARS-CoV-2 convalescent plasma (1 unit; minimum of 175 mL collected by pheresis from a volunteer who recovered from COVID-19 disease and has SARS-CoV-2 antibody titers ≥ 1:320
- Control plasma: Plasma collected from a volunteer donor prior to January 1, 2020 will not be tested for SARS-CoV-2 antibodies. Plasma collected after December 31, 2019 will be confirmed as SARS-CoV-2 seronegative.

Primary Efficacy Objective: Evaluate the efficacy of treatment at Day 28 following high-titer Anti- SARS-CoV-2 plasma versus control (SARS-CoV-2 non-immune plasma) in subjects exposed to COVID-19 at day 28.

Primary Endpoint: Cumulative incidence of development of COVID-19 disease (symptoms compatible with infection and/or + molecular testing) regardless of disease severity.

Primary Safety Objective: Evaluate the safety of treatment with high-titer Anti- SARS-CoV-2 plasma versus control (SARS-CoV-2 non-immune plasma) in subjects exposed to COVID-19

Primary Safety Endpoints:

1. Cumulative incidence of serious adverse events categorized separately as either severe infusion reactions and ARDS during the study period
2. Cumulative incidence of grade 3 and 4 adverse events during the study period

Secondary Objectives:

1. Cumulative incidence of disease severity between the anti-SARS-CoV-2 convalescent plasma and control groups after individuals develop SARS-CoV-2 infection. Severity of disease will be measured using a clinical event scale of disease severity (evaluated up to Day 28):

    1. Death
    2. Requiring mechanical ventilation and/or in ICU
    3. non-ICU hospitalization, requiring supplemental oxygen;
    4. non-ICU hospitalization, not requiring supplemental oxygen;
    5. a stay of >24 hours for observation in an ED, field hospital, or other healthcare unit*
    6. any receipt of O2 for >24 hours, outside of hospital*
    7. Not hospitalized, but with clinical and laboratory evidence[2] of COVID-19 infection

[2] Positive molecular testing for SARS-CoV-2
*with surge of infections in December 2020 and hospitals becoming more full, these two were put into the clinical events scale as hospitalization equivalents

Other Objectives:

1. Compare the anti-SARS-CoV-2 convalescent plasma and control (SARS-CoV-2 non-immune plasma) groups' anti-SARS-CoV-2 titers at days -1 to 0, 1, 7, 14 and 90.
2. Compare the rates and duration of SARS-CoV-2 molecular testing positivity amongst the anti-SARS-CoV-2 convalescent plasma and control (SARS-CoV-2 non-immune plasma) groups at days 1, 7, 14 and 28
3. Compare the levels of SARS-CoV-2 RNA amongst the anti-SARS-CoV-2 convalescent plasma and control (SARS-CoV-2 non-immune plasma) groups at days -1 to 0, 1, 7, 14 and 28

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1.1. STUDY POPULATION

1.1.1. Inclusion Criteria for Enrollment

1. Subjects must be 18 years of age or older
2. Close contact exposure (as defined by CDC guidelines) to person with COVID-19 within 96 hours of randomization (and 120 hours of receipt of plasma)

1.1.2. Exclusion Criteria

1. Medical, psychiatric, or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect subject safety and/or compliance
2. Symptoms consistent with COVID-19 infection at time of screening (sudden onset of at least one of the following: fever, cough, shortness of breath)
3. Laboratory evidence of COVID-19 infection at time of screening
4. History or known laboratory evidence of previous COVID-19 infection
5. History of or known prior allergic reaction to transfusion blood product
6. Receipt of SARS-CoV-2 Vaccine

2. LIST OF ABBREVIATIONS

AABB: American Association of Blood Banks
AAMC: Anne Arundel Medical Center
ADR: Adverse Drug Reaction
ADE: Antibody-mediated enhancement of infection
AE: Adverse Event/Adverse Experience
ARDS: Acute Respiratory Distress Syndrome
CCC: Clinical Coordinating Center
DCC: Data Coordinating Center
CDC: United States Centers for Disease Control and Prevention
CFR: Code of Federal Regulations
CLIA: Clinical Laboratory Improvement Amendment of 1988
COI: Conflict of Interest
COVID-19: Coronavirus Disease
C-RAC: Community Research Advisory Council
CRMS: Clinical Research Management System
CRF: Case Report Form
DMC: Data Management Center
DMID: NIH Division of Microbiology and Infectious Diseases
DSMB: Data and Safety Monitoring Board
EHR: Electronic Health Record
EUA: Emergency Use Authorization
FDA: Food and Drug Administration

GCP: Good Clinical Practice
HBV: Hepatitis B virus
HCIP: Human Coronavirus Immune Plasma
HCP: Health care personnel
HCV: Hepatitis C virus
HEIC: Johns Hopkins Medicine Healthcare Epidemiology and Infection Control
HIV: Human immunodeficiency virus
HTLV: Human T-cell lymphotropic virus
IB: Investigator's Brochure
ICF: Informed Consent (Informed Consent Form)
ICH: International Conference on Harmonization
ICTR: Institute for Clinical and Translational Research
ICU: Intensive Care Unit
IEC: Independent ethics committee
IND: Investigational New Drug Application
IRB: Institutional review board
ISBT: International Society of Blood Transfusion
ISM: Independent Safety Monitor
IWRS: Interactive web response system
MERS: Middle East Respiratory Syndrome
NYBC: New York Blood Center
OP: Oropharyngeal
RT-PCR: Reverse Transcriptase Polymerase chain reaction
PER: Protocol Event Report
PK: Pharmacokinetic
PPE: Personal Protective Equipment
SAE: Serious adverse event
SARS: Severe Acute Respiratory Syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
SMC: Safety Monitoring Committee
TACO: Transfusion-associated circulatory overload
T. cruzi: *Trypanosoma cruzi*
TRALI: Transfusion-related acute lung injury
UP: Unanticipated Problem
UPnonAE: Unanticipated Problem that is not an Adverse Event
ZIKV: Zika virus

3. BACKGROUND AND SCIENTIFIC RATIONALE

There are currently no proven treatment or prophylaxis options for coronavirus disease (COVID-19), which is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Human convalescent plasma has been successfully used for other infection prevention and treatment and thus may provide an option for prevention and treatment of COVID-19 and

could be rapidly available from people who have recovered from disease and can donate plasma.

Passive antibody therapy involves the administration of antibodies against a given infectious agent to a susceptible or ill individual for the purpose of preventing or treating an infectious disease caused by that agent. In contrast, active vaccination requires the induction of an immune response that takes time to develop and varies depending on the vaccine recipient. Some immunocompromised patients fail to achieve an adequate immune response. Thus, passive antibody administration, in some instances, represents the only means of providing immediate immunity to susceptible persons and more predicable immunity for highly immunocompromised patients.

Passive antibody therapy has a storied history going back to the 1890s. It was the inaugural form of antimicrobial therapy and the only way to treat certain infectious diseases prior to the development of antimicrobial therapy in the 1940s [Casadevall A, and Scharff MD. Return to the past: the case for antibody-based therapies in infectious diseases. *Clin Infect Dis.* 1995;21(150-61) and Casadevall A, Dadachova E, and Pirofski L. Passive antibody therapy for infectious diseases. *Nature Microbiol Rev.* 2004;2(695-703.)]. Experience from prior outbreaks with other coronaviruses, such as SARS-CoV-1 shows that convalescent plasma contains neutralizing antibodies to the relevant virus [Zhang JS, Chen JT, Liu YX, Zhang ZS, Gao H, Liu Y, Wang X, Ning Y, Liu YF, Gao Q, et al. A serological survey on neutralizing antibody titer of SARS convalescent sera. *Journal of medical virology.* 2005;77(2):147-50]. In the case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy would mediate protection is viral neutralization. However, other mechanisms may be possible, such as antibody dependent cellular cytotoxicity and/or phagocytosis. Convalescent serum was also used in the 2013 African Ebola epidemic. A small non-randomized study in Sierra Leone revealed a significant increase in survival for those treated with convalescent whole blood relative to those who received standard treatment [Sahr F, Ansumana R, Massaquoi TA, Idriss BR, Sesay FR, Lamin JM, Baker S, Nicol S, Conton B, 256 Johnson W, et al. Evaluation of convalescent whole blood for treating Ebola Virus Disease in 257 Freetown, Sierra Leone. *The Journal of infection.* 2017;74(3):302-9.].

The only antibody type that is currently available for immediate use is that found in human convalescent plasma. As more individuals contract COVID-19 and recover, the number of potential donors will continue to increase.

A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease. Another explanation is that antibody works by modifying the inflammatory response, which is also easier during the initial immune response, which may be asymptomatic [Casadevall A, and Pirofski LA. Antibody-mediated regulation of cellular immunity and the inflammatory response. *Trends Immunol.* 2003;24(9):474-8]. As an example, passive antibody therapy for pneumococcal

pneumonia was most effective when administered shortly after the onset of symptoms and there was no benefit if antibody administration was delayed past the third day of disease [Casadevall A, and Scharff MD. "Serum Therapy" revisited: Animal models of infection and the development of passive antibody therapy. *Antimicrob Agents Chemotherap.* 1994;38(1695-702)].

For passive antibody therapy to be effective, a sufficient amount of antibody must be administered. When given to a susceptible person, this antibody will circulate in the blood, reach tissues and provide protection against infection. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin can last from weeks to months.

3.1. Experience with the use of convalescent plasma against coronavirus diseases

In the 21st century, there were two other epidemics with coronaviruses that were associated with high mortality, SARS1 in 2003 and MERS in 2012. In both outbreaks, the high mortality and absence of effective therapies led to the use of convalescent plasma. The largest study involved the treatment of 80 patients in Hong Kong with SARS [Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, Chan P, Wong KC, Leung CB, and Cheng G. Use of convalescent plasma therapy in SARS patients in Hong Kong. *European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology.* 2005; 24(1):44-6.]. Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. In addition, those who were PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis. There is also some anecdotal information on the use of convalescent plasma in seriously ill individuals. Three patients with SARS in Taiwan were treated with 500 ml of convalescent plasma, resulting in a reduction in plasma virus titer and each survived [Yeh KM, Chiueh TS, Siu LK, Lin JC, Chan PK, Peng MY, Wan HL, Chen JH, Hu BS, Perng CL, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. *The Journal of antimicrobial chemotherapy.* 2005; 56(5):919-22.]. Three patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients had neutralizing antibody in their plasma [Ko JH, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, Kim YJ, Park JK, Chung CR, Kang ES, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. *Antiviral therapy.* 2018; 23(7):617-22.]. The latter study highlights a challenge in using convalescent plasma, namely, that some who recover from viral disease may not have high titers of neutralizing antibody [Arabi YM, Hajeer AH, Luke T, Raviprakash K, Balkhy H, Johani S, Al-Dawood A, Al-Qahtani S, Al- Omari A, Al-Hameed F, et al. Feasibility of Using Convalescent Plasma Immunotherapy for MERS-283 CoV Infection, Saudi Arabia. *Emerging infectious diseases.* 2016; 22(9):1554-61.]. Consistent with this point, an analysis of 99 samples of convalescent sera from patients with MERS showed that 87 had neutralizing

antibody with a geometric mean titer of 1:61. This suggests that antibody declines with time and/or that few patients make high titer responses.

It is also possible that other types of non-neutralizing antibodies are made that contribute to protection and recovery as described for other viral diseases [van Erp EA, Luytjes W, Ferwerda G, and van Kasteren PB. Fc-Mediated Antibody Effector Functions During Respiratory Syncytial Virus Infection and Disease. *Frontiers in immunology.* 2019;10(548), Gunn BM, Yu WH, Karim MM, Brannan JM, Herbert AS, Wec AZ, Halfmann PJ, Fusco ML, Schendel SL, Gangavarapu K, et al. A Role for Fc Function in Therapeutic Monoclonal Antibody-Mediated Protection against Ebola Virus. *Cell host & microbe.* 2018; 24(2):221-33. e5.]. There are reports that convalescent plasma was used for therapy of patients with COVID-19 in China during the current outbreak (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm). Although few details are available from the Chinese experience and published studies involved small numbers of patients, the available information suggests that convalescent plasma administration reduces viral load and was safe.

3.2. Overview of known potential risks

Historical and current anecdotal data on use of convalescent plasma suggest it is safe in coronavirus infection. Therefore, the large number of exposed healthcare workers, public servants and first responders, in combination with the high mortality of COVID-19, particularly in elderly and vulnerable persons, strongly argue that the benefits of convalescent serum outweigh its possible risks in high risk exposed individuals and/or those with early disease. However, for all cases where convalescent plasma administration is considered, a risk-benefit assessment must be conducted to assess individual variables.

The theoretical risk involves the phenomenon of antibody-mediated enhancement of infection (ADE). ADE can occur for several viral diseases and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms for ADE have been described and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain [Wan Y, Shang J, Sun S, Tai W, Chen J, Geng Q, He L, Chen Y, Wu J, and Shi Z. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *Journal of Virology.* 2020; 94(5)]. It may be possible to predict the risk of ADE of SARS-CoV-2 experimentally, as proposed for MERS. Since the proposed use of convalescent plasma in the COVID-19 epidemic would rely on preparations with high titers of neutralizing antibody against the same virus, SARS2-CoV-2, ADE may be unlikely. The available evidence from the use of convalescent plasma in patients with SARS1 and MERS [Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, Makki S, Rooney KD, Nguyen-Van-Tam JS, and Beck CR. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *The Journal of infectious diseases.* 2015; 211(1):80-90.)], and anecdotal evidence of its use in patients with COVID-19

(http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm), suggest it is safe. Nevertheless, caution and vigilance will be required in for any evidence of enhanced infection.

Another theoretical risk is that antibody administration to those exposed to SARS-CoV-2 may avoid disease but modify the immune response such that those individuals mount attenuated immune responses, which would leave them vulnerable to subsequent re-infection. In this regard, passive antibody administration before vaccination with respiratory syncytial virus was reported to attenuate humoral but not cellular immunity [Crowe JE, Firestone C-Y, and Murphy BR. Passively acquired antibodies suppress humoral but not cell-mediated immunity in mice immunized with live attenuated respiratory syncytial virus vaccines. *The Journal of Immunology.* 2001; 167(7):3910-8.]. This concern will be investigated as part of this clinical trial by measuring immune responses in those exposed and treated with convalescent plasma to prevent disease. If the concern proved real these individuals could be vaccinated against COVID-19 when a vaccine becomes available.

Passive antibodies are derived from human plasma. The antibodies used in this study will be derived from plasma obtained from convalescent patients, and will be subjected to testing protocols that are similar to those used by blood banks and transfusion services. However, as is the case with any biological product, there is a very small risk of allergy/anaphylaxis, transfusion related acute lung injury (TRALI), and transfusion associated circulatory overload (TACO) or passive transfer of potential unknown infectious agents or infections. Most adverse effects are mild and transient including headaches, flushing, fever, chills, fatigue, nausea, diarrhea, blood pressure changes and tachycardia. Late adverse events are rare and include acute renal failure and thromboembolic events.

3.3. Known potential benefits

A benefit of convalescent plasma administration is that it can prevent infection and subsequent disease in those who are at high risk for disease following close contacts of patients with COVID-19. This is especially so for those with underlying medical conditions. Many who will qualify for prophylaxis are health care workers and first responders who are critical to maintenance of stability of the healthcare system. Passive antibody administration to prevent disease is already used in clinical practice. For example, patients exposed to hepatitis B and rabies viruses are treated with hepatitis B immune globulin (HBIG) and human rabies immune globulin (RIG), respectively. Botulism Immune Globulin Intravenous (Human) (BIG-IV) is an intravenous preparation for infant botulism. In addition, passive antibody is used for the prevention of severe respiratory syncytial virus (RSV) disease in high-risk infants. Until recently, polyclonal hyperimmune globulin (RSV-IG) prepared from donors selected for having high plasma titers of RSV neutralizing antibody, was used but these preparations have now been replaced by palivizumab, a humanized murine monoclonal antibody.

Another potential benefit is societal: If the frequency with which exposed persons become infected decreases, the risk of further transmission (R naught might be reduced and the

epidemic slowed. Another avenue (not pursued in this protocol) is as a treatment for established infection. Convalescent plasma would be administered to those with clinical disease in an effort to reduce their symptoms and mortality. Based on the historical experience with antibody administration, it can be anticipated that antibody administration would be more effective in preventing disease than in the treatment of established disease.

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

4. INVESTIGATIONAL PLAN

4.1. Study Objectives

4.1.1. Primary Efficacy Objective: Evaluate at day 28, the efficacy of treatment with high-titer Anti- SARS-CoV-2 plasma versus control (SARS-CoV-2 non-immune plasma) in subjects exposed to COVID-19

4.1.2. Primary Safety Objective: Evaluate the safety of treatment with high-titer Anti-SARS-CoV-2 plasma versus control (SARS-CoV-2 non-immune plasma) in subjects exposed to COVID-19

4.1.3. Secondary Objectives:

I. Cumulative incidence of disease severity between the anti-SARS-CoV-2 convalescent plasma and control groups after individuals develop SARS-CoV-2 infection. Severity of disease will be measured using a clinical event scale of disease severity (evaluated up to Day 28):
   1. Death
   2. Requiring mechanical ventilation and/or in ICU
   3. non-ICU hospitalization, requiring supplemental oxygen;
   4. non-ICU hospitalization, not requiring supplemental oxygen;
   5. Not hospitalized, but with clinical and laboratory evidence[3] of COVID-19 infection

4.1.4. Other Objectives:

[3] Validated test for presence of SARS-CoV-2

I. Compare the anti-SARS-CoV-2 convalescent plasma and control (SARS-CoV-2 non-immune plasma) groups for anti-SARS-CoV-2 titers at days -1 to 0, 1, 7, 14 and 90

II. Compare the rates and duration of SARS-CoV-2 molecular testing positivity amongst the anti-SARS-CoV-2 convalescent plasma and control (SARS-CoV-2 non-immune plasma) groups at days 1, 7, 14 and 28

III. Compare the levels of SARS-CoV-2 RNA amongst the anti-SARS-CoV-2 convalescent plasma and control (SARS-CoV-2 non-immune plasma) groups at days -1 to 0, 1, 7, 14 and 28

IV. Understand how the immune system responds to COVID-19 infections and try to understand why some people have mild symptoms and other people have life-threatening disease.

4.2. Definitions

I. Enrolled: From time consented to participate until designated as a screen failure or have either been discontinued from the study or completed it.
II. Randomized: when a randomization number is assigned
III. Screen Failures: signed informed consent, but then determined to be ineligible or withdraws before being randomized
IV. Discontinued: randomized, but then withdrawn by investigator or withdraws consent
V. Completed: Subjects are considered completed when they are followed through to day 28 or died before that.

4.3. Study population

4.3.1. Inclusion Criteria for Enrollment

1. Subjects must be 18 years of age or older
2. Close contact exposure (as defined by CDC guidelines)to person with COVID-19 within 96 hours of randomization (and 120 hours of receipt of plasma)

4.3.2. Exclusion Criteria for Enrollment

1. Medical, psychiatric, or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect subject safety and/or compliance
2. Symptoms consistent with COVID-19 infection at time of screening (sudden onset of at least one of the following: fever, cough, shortness of breath)
3. Laboratory evidence of COVID-19 infection at time of screening
4. History or known laboratory evidence of previous COVID-19 infection
5. A history of or known prior allergic reaction to transfusion blood product
6. Receipt of SARS-CoV-2 Vaccine

Table: Schedule of Events

Study period	Screen	Baseline	Transfusion	Follow up						
Day	-1 to 0	0	0	1	3	7	14	28	60	90
Window				+/- 1 day	+/- 1 day	+/- 1 day	+/- 3 days	+/- 3 days	+/- 3 days	+/- 8 days
Eligibility										
Informed consent	x									
Demographic and Medical history	x									
COVID-19 symptom survey	x									
SARS-CoV-2 molecular testing for eligibility	x									
Pregnancy test [4]	x									
ABO[5]	x									
Study Drug Administration										
Randomization		x								
Drug infusion			x							
Study Procedures										
Vital signs	x	x	xxxx[6]	x		x	x			
Physical examination			x							
COVID-19 symptom screen	x	x	x	x	x	x	x	x	x	
Concomitant medications	x	x	x							
Assessment of clinical event scale of disease severity[7]		x		x	x	x	x	x	x	
Adverse event monitoring		x	x	x	x	x	x	x	x	

[4] Result of urine or serum pregnancy test for women of childbearing potential must be documented prior to transfusion

[5] Assessment of ABO type on file or determination of ABO type if not on file

[6] Vital sign testing: Immediately prior to infusion, 10-20 minutes after start of infusion, at completion of infusion and 30-60 minutes after the end of the infusion

[7] Assessment evaluates whether subject has shifted from "no clinical or laboratory evidence of COVID-19 infection to any of the clinical event scale of disease severity

Laboratory testing										
CBC and CMP	x			x		x	x			
SARS-CoV-2 molecular testing[8]	x			x		x	x	x		
Blood for future testing[9]	x			x		x	x			x

4.3.3. Subject Withdrawal

I. Subjects can terminate study participation and/or withdraw consent at any time without prejudice.
II. Randomized subjects who withdraw from the study will not be replaced.
III. The investigator may withdraw subjects if they are lost to follow up, non-compliant with study procedures or if the investigator determines that continued participation in the study would be harmful to the subject or the integrity of the study data
IV. Discontinuation of the study: The study sponsor, FDA and IRB all have the right to terminate this study at any time

4.3.4. Intervention

I. Subjects will be randomized in a 1:1 ratio to receive treatment vs SARS-CoV-2 non-immune plasma
II. Study drug: The investigational product is anti-SARS-CoV-2 convalescent plasma. Patients identified as having recovered from COVID-19 will serve as potential donors. Donors with SARS-CoV-2 antibody titers ≥ 1:320 by validated ELISA will be used for the trial. The ELISA testing will be performed in a CLIA certified laboratory. Potential donors and samples will be screened for transfusion-transmitted infections (e.g. HIV, HBV, HCV, WNV, HTLV-I/II, *T. cruzi*, ZIKV) and plasma will be collected using apheresis technology. This is similar to standard blood bank protocols.
III. Samples of convalescent plasma will be reserved by the blood bank for further testing
IV. Active arm will receive 1 unit of anti-SARS-CoV-2 plasma with titers ≥ 1:320)
V. Control arm will receive 1 unit of SARS-CoV-2 non-immune plasma
VI. Both active and control drugs will be in standard plasma unit bags, with a study-specific ISBT label.
VII. For blood that will be collected locally (Johns Hopkins) the source of donor plasma will be as detailed in protocol JHM IRB00248402.
VIII. all subjects must be negative for active SARS-CoV-2 via a validated molecular test within 24 hours preceding the plasma infusion.

[8] Sites could include nasopharyngeal, throat
[9] Includes anti-SARS CoV-2 titers.

4.3.5. Randomization

I. Subjects enrolled in the study will be randomized using an interactive web response system (IWRS) to receive study drug vs control at a 1:1 ratio.
II. Randomization will occur after the result of the initial coronvirus testing is known to be negative.

4.4. Rationale for dosing

Dose calculation is based on 1 unit (minimum of 175 mL) of plasma with anti-SARS-CoV-19 titers of >1:320 and 1 unit of standard plasma. For the purposes of the proposed trial, we will require titers ≥1:320. The current FDA recommendations target titers that are optimally greater than 1: 320 in the event that testing is available. We have favored a more conservative ≥1: 320 given findings from a pilot study in China that showed most (39/40) convalescent donors had titers ≥1:160 (Duan K, et al.medRxiv. 2020:2020.03.16.20036145). We intend to infuse a minimum of 175 ml (1 unit) of plasma to all individuals.

4.5. Study drug administration

- Drug will be administered within 24 hours of randomization
- Transfusions for Johns Hopkins site participants will be performed at HEIC and Blood Bank approved JHM locations such as: 1) The Adult Clinical Research Unit (CRU) on Blalock 3 at Johns Hopkins Hospital and 2) the Neurosciences Consultation and Infusion Center at Green Spring Station, Pavilion 2, Suite 115, room #5.
- If infusion takes place at the Adult CRU, Adult CRU registered nurses (RN's) will administer the infusion per JH policy. They will attend to the participant throughout the infusion and post infusion observation period. For infusion at any HEIC approved JHM location, registered nurses (RN's) from Johns Hopkins will administer the infusion per JH policy. They will attend to the participant throughout the infusion and post infusion observation period. All RNs are BLS trained. A study physician or advanced practice clinician with clinical privileges at JH will be available by phone and within 5 minutes physical response time to respond to any emerging event during the infusion.
- For non-Johns Hopkins sites, infusion will take place in the area designated for this research project. All infusions will be performed and monitored by appropriate personnel as defined by institutional policy for blood product transfusion.
- Infusion rate $\leq$ 500 mL/hour
- Vital signs will be taken immediately prior to infusion, 10-20 minutes after start of infusion, at completion of infusion, and 30-60 minutes after the end of the infusion.

- Medicines for transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given.
- If an AE develops during infusion, the infusion may be slowed or stopped as per investigator or infusion monitor decision.
    - Management of transfusion-associated AE will follow AABB guidelines; Outside of a simple allergic transfusion reaction, the transfusion will be discontinued and investigated appropriately (i.e. per standard practice guidelines).

- Following completion of the infusion, the participant will remain in the infusion area under observation for 30-60 minutes. If after that time the participant is not experiencing any adverse events, they may be discharged home. A written post-infusion information sheet will be given to the participant prior to discharge. The sheet will list risk and possible complications of blood transfusion. Depending on the severity and nature of the complication, the participant is advised to contact their healthcare provider or call 911.

4.5.1. Concomitant medications will be documented on the CRF

- Prescription medications
- Blood products

4.5.2. Prohibited Medications: Any approved or investigational drug with established activity against SARS-CoV-2 (Unless subject becomes ill with COVID-19 and qualifies for treatment)

5. STATISTICAL CONSIDERATIONS

5.1. Sample Size and Power Considerations

The planned sample size for the trial is 500 subjects, randomized in a 1:1 ratio to convalescent titer anti-SARS CoV-2 plasma vs SARS-CoV-2 non-immune plasma.

To evaluate the power of the study, the following assumptions were made:

a. The primary analysis will compare efficacy/prevention in the convalescent titer and SARS-CoV-2 non-immune plasmas groups using proportional odds model and a one-sided Type I error rate (alpha) of 0.05 (i.e., for superiority) and Type II error rate (beta) of 0.2

b. It is anticipated that very few of these subjects will be randomized and not start study plasma infusion (and so be excluded from the primary analysis) or be lost to follow-up prior to Day 28 (and so have missing data for the primary endpoint).

c. 13% incidence of symptomatic disease in exposed individuals treated with SARS-CoV-2 non-immune plasma
d. 6.5% incidence of symptomatic disease in exposed individuals treated with anti-SARS CoV-2 plasma

We estimate a sample size of 488 patients (244 in each arm) would be sufficient to detect a difference in outcomes between those two arms with a power of 0.8. To allow for some loss-to-followup, we have rounded our target sample to 500 patients.

5.2. Statistical Analysis

Primary endpoint:

Our primary hypothesis is that by providing anti-SARS-CoV-2 plasma, the cumulative incidence of the development of COVID-19 will be lower among the individuals receiving HCIP as compared to those receiving control plasma over the course of follow-up. Therefore, our primary endpoint is the development of COVID-19 regardless of severity.

Our analysis will be a time to event analysis examining the effect of anti-SARS-CoV-2 plasma. We will estimate the survival function for each treatment arm in order to estimate the risk difference over time as well as the restricted mean survival time which is the area under the survival function and provides the expected mean time to hospitalization or death up to time t[22]. Our approach will be to estimate the cumulative incidence using the doubly robust estimator based upon targeted minimum loss based estimator as described by Diaz et al [Díaz, I., Colantuoni, E., Hanley, D.F. *et al.* Improved precision in the analysis of randomized trials with survival outcomes, without assuming proportional hazards.*Lifetime Data Anal* **25,** 439–468 (2019)]. By adjusting for baseline covariates that are related to the outcome, we increase precision. The TMLE based approach was shown to increase precision by around 10% to 20% over an inverse probability weighted or augmented inverse probability weighted estimator. As stated above, we will use a hybrid approach of adjusting for pre-specified variables (age) and an algorithmic approach to identify additional variables related to the outcome. Specifically, a random survival forest will be used to identify variables that are related to the outcome in order to increase precision. We will use a random survival forest blinded to the treatment arm allocation and *not* including an indicator variable for treatment. The following pre-randomization variables will be considered: clinical site, race, ethnicity, sex, category of exposure, hematology factors and other laboratory markers (i.e., CBC and metabolic panels), body mass index, ABO blood group, targeted physical exam, and prior comorbidities that have specifically been associated with worse COVID-19 outcomes including: asthma, chronic kidney disease, chronic lung disease (COPD, idiopathic pulmonary fibrosis, cystic fibrosis), diabetes, hemoglobin disorders (thalassemia, sickle cell disease), immunocompromised (cancer, HIV, organ transplantation, prolonged use of corticosteroids), chronic liver disease,

hypertension, and serious heart conditions (hear failure, coronary artery disease, cardiomyopathies, pulmonary hypertension) [Guan W-j, Liang W-h, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020; 55: 2000547, https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html].

The primary outcome analysis will be the adjusted comparison of proportions of cumulative incidence of SARS-CoV-2 infection (symptoms compatable with infection and RT-PCR positive) at day 28 comparing the risk-difference and restricted mean survival time between treatment groups with a significance threshold of p=0.047 (p-value adjusted for interim analysis) for a one-sided test.

Finally, statistical inference will use a one-sided Type 1 error rate of 0.05 for superiority and 95% confidence intervals (note: interim analyses are based upon O'Brian-Flemming spending function see below under section 8.3 Halting Criteria for Study).

5.2.1. Analysis of AE data

Analysis of AE data will primarily be descriptive based on MedDRA coding of events. The proportion of subjects experiencing an SAE and the proportion experiencing a Grade 3 or higher. AE will be compared between randomized arms using Fisher's Exact Test.

5.2.2. Analysis of disease severity

A secondary hypothesis is that individuals receiving anti-SARS-CoV-2 convalescent plasma are likely to have less disease severity than control. Therefore, this analysis is restricted to individuals who have developed a SARS-CoV-2 infection. We have devised a clinical event scale for disease severity based on the COVID clinical severity scale which is composed of clinical events that range from being symptomatic and not hospitalized, to being hospitalized, to mechanical ventilation/ICU, to death.

We will separately analyze each of the clinical events by determining the cumulative incidence from time from randomization. Similarly to the primary analysis, we will utilize the TMLE based estimator and adjust for age and any pre-specified candidate variables selected via the algorithm as described above. If individuals jump in severity (e.g., progress from symptomatic not hospitalized to ICU without being hospitalized in non-ICU) then we will interval censor the lower events between the two time points prior to more severe and time of severe clinical event. This will allow individuals to contribute to the progression through the clinical events.

5.2.3. Analysis of anti-SARS-CoV-2 titers

Analysis of titers will also primarily be descriptive, comparing the geometric mean titers at days 0, 1, ,7, 14, and 90 between the randomized arms. Furthermore, it is 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 in order to describe whether

there is a shift or change in the titer distribution between randomized arms [Roger Koenker, Quantile Regression. Cambridge University Press, May 5, 2005]. Quantile regression does not require the assumption of a parametric or any other type of distribution as it identifies the titer at each percentile (e.g., what is the 10^{th}, the 15^{th}, …, 50^{th} [the median], …, 90^{th} percentiles of anti-SARS-CoV-2 titers). Given that this is a repeated measurement at days 0, 1, 7, 14, and 90 we will account for the correlation within individuals using a cluster bootstrap in order to properly estimate the p-value and 95% confidence intervals.

5.2.4. Analysis of rates and duration of SARS-CoV-2 molecular testing positivity

Analysis of the rate and duration of SARS-CoV-2 molecular testing positivity between the randomized arms will primarily be descriptive examining proportion positive at days 0, 1, 7, 14, and 28 and then among those who are positive whether individuals lose positivity status at a subsequent visit. To determine the proportion that are positive at each visit, we will do a pooled complementary log-log model in order to describe the cumulative incidence of SARS-CoV-2 molecular testing 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. From this a cumulative incidence of positivity can be estimated. To determine the duration of positivity, the analysis is complicated by the exact day that an individual becomes positive and the exact day that an individual becomes negative is not known since SARS-CoV-2 molecular testing positivity will only be acquired at days 0, 1, 7, 14, and 28. However, we can estimate a minimum and maximum amount of time that an individual was positive. For instance if an individual first positive visit is at day 1 and then is positive at day 7 but negative at day 14, then we know that this individual became positive between day 0 and 1 and negative between day 7 and 14. Therefore, the minimum amount of time positive is 7 days (day 8 – day 1) and the maximum is 14 days (day 14 – day 0). Therefore, we can interval censor these individuals. That is we know that the duration is between 7 and 14 days for this example individual. Across all individuals we can describe the duration of positivity either using a non-parametric approach for time-to-event analysis, but more likely given the sample size a parametric model. We will assess several parametric distributions aiming for parsimony in the number of parameters being estimated due to the interval censored data which results in increased uncertainty in the model. To determine the best model, we will use Akaike's Information Criterion (AIC) to choose the best model fit. However, if the sample that becomes positive is really small, then we will only be able to describe the observations without a formal statistical model.

5.2.5. Analysis of SARS-CoV-2 RNA

Similar to the secondary aim of comparing the 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 above of applying quantile regression.

5.3. Endpoints

Primary Efficacy Endpoint:
28 day incidence of COVID-19 infection with both clinical and laboratory evidence.

Primary Safety Endpoints:
1. Cumulative incidence of serious adverse events categorized separately as either severe infusion reactions and ARDS during the study period
2. Cumulative incidence of grade 3 and 4 adverse events during the study period

Secondary Endpoints
1. 28 day incidence of severe COVID-19 infection defined by death or initiation of mechanical ventilation.
2. Anti-SARS-CoV-2 titers at days -1 to 0, 1, 7, 14, and 90.
3. Rates and duration of SARS-CoV-2 molecular testing positivity at days 1, 7, 14, and 28.

6. STUDY PROCEDURES

Day -1 to 0

In-person visit

A. Screening (must be completed before randomization)
B. Informed consent (may be obtained prior to Day-1and before performing study related activities)
C. Baseline Evaluation (at screening)

1. Demographics (Age, sex ethnicity, race, number of people in household)
2. Medical history (timing of exposure to COVID-19 source patient, acute and chronic medical condition, medications, allergies. Any medical condition arising after consent should be recorded as AE
3. COVID-19 symptom screen (fevers, cough, shortness of breath)
4. Vital signs
6. COVID-19 molecular testing prior to infusion, from nasopharyngeal, throat samples (may be omitted if test already performed on same day as part of usual care)
7. Draw and result ABO and Rh if no documented ABO typing within the past year.
8. CBC, comprehensive metabolic panel
9. Stored samples for future studies

10. Urine or serum pregnancy test for females of childbearing potential. Results from laboratory tests obtained up to 7 days before randomization may be used for the pregnancy test.
11. Determination of eligibility as per inclusion/exclusion criteria
12. Confirmation of emergency contact information in EMR.

To the extent possible and with goal of minimizing exposure of health care workers and study team members to risk, there will be a pre-visit explanation and consent done using a video platform at sites that permit video platform use.

Day 0

In-person visit

1. Randomization of eligible subject in IWRS
2. Study Plasma Administration: A single unit of plasma will be transfused. Time at start and end of infusion will be recorded and Vital signs will be measured immediately prior to infusion, 10-20 minutes after start of infusion, at completion of infusion and 30-60 minutes after the end of the infusion.
3. COVID-19 symptom screen (fevers, cough, shortness of breath). Done by telephone before they come in for transfusion.
4. Assessment of clinical status (composite outcome of disease severity)
5. New medical conditions, concomitant medication, AE evaluation
6. Physical examination

Day 1, (+/-) 1 day

In-person visit

1. Vital signs
2. COVID-19 symptom screen (fevers, cough, shortness of breath
3. Assessment of clinical status (clinical event scale of disease severity)
4. New medical conditions, AE evaluation
5. CBC, comprehensive metabolic panel
6. COVID-19 molecular testing from nasopharyngeal, throat samples
7. Stored samples for future studies

Day 3, (+/-) 1 day

Phone Call

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (clinical event scale of disease severity)
3. New medical conditions, AE evaluation

Day 7, (+/-) 1 day

In-person visit

1. Vital signs
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (clinical event scale of disease severity)
4. New medical conditions, AE evaluation
5. CBC, comprehensive metabolic panel
6. COVID-19 molecular testing from nasopharyngeal, throat samples
7. Stored samples for future studies

Day 14, (+/-) 3 days

In-person visit

1. Vital signs
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (clinical event scale of disease severity)
4. New medical conditions, AE evaluation
5. CBC, comprehensive metabolic panel
6. COVID-19 molecular testingfrom nasopharyngeal, throat samples
7. Stored samples for future studies

Day 28, (+/-) 3 days

In-person visit

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (clinical event scale of disease severity)
3. New medical conditions, AE evaluation
4. COVID-19 molecular testing from nasopharyngeal, throat samples

Day 60, (+/-) 3 days

Phone Call

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (clinical event scale of disease severity)
3. New medical conditions, AE evaluation

Day 90, (+/-) 8 days

In-person visit

1. Stored samples for future studies

Clinical research sites for infusion and follow-up

Infusion of plasma will occur after subjects have been determined to be at extremely low risk for having an active COVID-19 infection. Specifically, these subjects will be asymptomatic AND have had a negative validated test for coronavirus in the preceding 24 hours. This plan has been discussed and approved by Johns Hopkins Medicine Health Care Epidemiology and Infection Control (HEIC). Local sites will follow their institutional guidelines regarding location and infection control for COVID-19 related research.

Study staff will wear adequate PPE according to local infection control practices. Local sites will follow their institutional guidelines regarding location and infection control for COVID-19 related research. Samples that require transport will be delivered by courier or a member of the research team and triple packaged for travel (e.g. specimen container, leakproof ziplock bag or other container, outer rigid container with marking such as biohazard symbol, medical specimen or diagnostic specimen).

These tests will be processed at a central investigational laboratory and the results of these tests will not be provided to subjects or their treating physicians in real time. Patients who develop signs and symptoms suggestive of COVID-19 will be referred to standard of care coronavirus testing.

The research team may use remote data collection, which may include use of telemedicine in accordance with the Guidance for Incorporation of Telemedicine into Research with Human Participants to interview and view the participant. (Relying sites may adhere to their own local policies and guidelines for this remote data collection). For residents at nursing facilities, data that is being routinely collected (e.g. vital signs if being done for clinical care purposes or other clinical or medical record information that is collected for clinical care purposes) may be obtained from the nursing facility with appropriate authorization for release.

The testing and specimen collection will be conducted in accordance with the Johns Hopkins HEIC policies for managing patients and with recent COVID exposure, and protection for study staff (mask, PPE when required) as appropriate. The HEIC protocols are:

https://intranet.insidehopkinsmedicine.org/heic/novel_coronavirus/clinical_resources

https://intranet.insidehopkinsmedicine.org/heic/_docs/2019-nCoV_outpatient_guidelines.pdf

https://intranet.insidehopkinsmedicine.org/heic/_docs/2019-nCoV_patient_discharge_protocol.pdf

Local sites will follow their institutional guidelines regarding infection control and PPE for COVID-19 related research.

6.1. EFFICACY, VIROLOGIC AND PK MEASURES

Clinical Efficacy (clinical event scale of disease severity)

1 Death
2 Requiring mechanical ventilation and/or in ICU
3 Non-ICU hospitalization, requiring supplemental oxygen;
4 Non-ICU hospitalization, not requiring supplemental oxygen;
5 Not hospitalized, but with clinical and laboratory evidence[10] of COVID-19 infection

Virologic measures

1. Rates and duration of SARS-CoV-2 molecular testing positivity at days 1, 7, 14, and 28
2. virlogical studies of SARS-CoV-2 RNA at days -1 to 0, 1, 7 , 14, and 28

Pharmacokinetic (PK) measures: Anti-SARS-CoV-2 titers at days -1 to 0, 1, 7, 14 and 90.

Using samples from 20 donors, we will measure the viral growth inhibition titers of SARS-CoV-2 neutralizing antibodies compared to the current FDA benchmark neutralizing titer of 1:320. However, the ability to detect neutralizing antibodies for SARS-CoV-2 through true viral neutralization in culture is time consuming. Other approaches include in-house ELISA tests for the receptor binding subdomain on the external spike glycoprotein trimer, which correlate with viral culture neutralization in previous coronavirus work. Finally, there are an increasing number of non-FDA validated, commercial ELISA tests with the entire spike

[10] Positive molecular test for SARS-CoV-2

glycoprotein trimer or nucleocapsid as capture proteins. The viral specificity of these commercial ELISA assays for antibodies to the more frequent common cold beta coronavirus like OC43 or the rare SARS-CoV-1 as well as sensitivity for SARS-CoV-2 antibodies is evolving in the ongoing pandemic. Therefore, we will compare the SARS-CoV-2 donor plasma neutralizing titer levels to the whole protein commercial ELISAs being adopted by hospitals versus the receptor binding domain ELISAs. The goal will be to accurately determine the correlation of serum antibody titers measured by the two ELISA assays to virus neutralization titers determined with SARS-CoV-2 live virus.

7. RISKS AND BENEFITS

Potential Benefits of treatment

The potential benefits of antiviral treatment with anti-SARS CoV-2 plasma in patients at high risk for developing COVID-19 due to a close contact with another individual with COVID-19 are unknown. However, it is anticipated that treatment will decrease the risk of developing symptomatic disease and decrease the severity of illness should it develop.

Potential benefits of clinical monitoring and virologic testing

Subjects enrolled in the study will undergo close clinical and virologic monitoring that could facilitate earlier diagnosis of development of COVID-19 with associated benefit to the individual, their family and the community at large.

Potential risks

1. Risks of plasma: Fever, chills, rash, headache, serious allergic reactions, TRALI, TACO, transmission of infectious agents
2. Risks of phlebotomy: local discomfort, bruising, hematoma, bleeding, fainting,
3. Total blood draws will not exceed 500 mL
4. Risks of oropharyngeal and throat swab: local discomfort, vomiting

Alternatives

The alternative to participation in this study is routine care and monitoring following close contact with an individual with COVID-19

Safety measures

1. Safety Evaluations will assess for the safety of high titer anti-SARS-CoV-2 plasma and determine if it is higher, lower or the same as SARS-CoV-2 non-immune plasma
2. Clinical evaluations: In-person vital signs and symptom screen on days 0,1,7,14 and remote (phone call) symptom screens on days ,3 and 60
3. Laboratory evaluations

4. Safety laboratory tests (ABO typing, pregnancy testing, CBC and comprehensive metabolic panel) will be performed at the local CLIA-certified clinical laboratory on days -1 to 0,1, 7 and 14

Event (AE)

Any untoward medical occurrence in a clinical investigation subject who has received a study intervention and that does not necessarily have to have a causal relationship with the study product. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the study product, whether or not considered related to the study product.

Serious Adverse Event (SAE)

An SAE is any adverse event that results in any of the following outcomes:

1. Death;
2. Life-threatening (immediate risk of death);
3. Inpatient hospitalization or prolongation of existing hospitalization;
4. Persistent or significant disability or incapacity;
5. Congenital anomaly/birth defect;
6. Important medical events that may not result in death, be life threatening, or require hospitalization 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, or the development of drug dependency or drug abuse.

Unexpected Adverse event: (UAE): An adverse reaction, the nature or severity of which is not consistent with the investigator's brochure.

Serious and Unexpected Suspected Adverse Reaction (SUSAR)

Investigators should report SUSARs to Johns Hopkins University within 5 calendar days of awareness. Johns Hopkins will submit the SUSARs to the FDA within 15 calendar days. Fatal or life-threatening SUSARs should be reported to Johns Hopkins as soon as possible and no later than 3 calendar days of awareness. Fatal or life-threatening SUSARs will be reported to the FDA within 7 calendar days.

Unanticipated Problem (UP)

Unanticipated Problem that is not an Adverse Event (e.g. breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

Protocol Deviation

Deviation from the IRB-approved study procedures. Designated major and minor:

1. Major Protocol Deviation: Protocol deviation that compromises trial integrity and/or the safety, welfare or rights of subjects or others
2. Minor Protocol Deviation: Other protocol deviation

Sites should follow their IRB guidelines for reporting.

7.1. Reporting Interval

All AEs and SAEs will be documented from the first administration of study product All AEs and SAEs will be followed until resolution even if this extends beyond the study-reporting period. 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.

Reporting should also occur 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

Investigator's Assessment of Adverse Events

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.

Laboratory abnormalities will be reported as AEs if they are considered clinically significant by the investigator.

Assessment of Seriousness

I. Event seriousness will be determined according to the protocol definition of an SAE
II. Assessment of Severity

Event severity will be assigned according to the MedDRA parameters in the EDC, which correspond to the following definitions:

1 = Mild: Transient or mild discomfort (<48 hours); no medical intervention/therapy required.)

2 = Moderate: Mild to moderate limitation in activity-some assistance may be needed; no or minimal medical intervention/therapy required)

3 = Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

4 = Life-threatening: Extreme limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization or hospice care probable

5= Death

Assessment of Association

The association assessment categories that will be used for this study are:

- Associated – The event is temporally related to the administration of the study product and no other etiology explains the event.
- Not Associated – The event is temporally independent of the study product and/or the event appears to be explained by another etiology.

The investigator must provide an assessment of association or relationship of AEs to the study product based on:

- Temporal relationship of the event to the administration of study product;
- Whether an alternative etiology has been identified;
- Biological plausibility;
- Existing therapy and/or concomitant medications.

8. SAFETY OVERSIGHT

8.1. Monitoring Plan

1. All AE and SAE will be reviewed by protocol team twice monthly, or more if needed.
2. A medical monitor has been appointed for safety oversight of the clinical study. The independent medical monitor, mutually agreed upon with the DoD sponsor, will have the authority to A.) stop a research study in progress; B.) remove individual from a study; and C.) take any steps to protect the safety and well-being of participants until the IRB can assess the problem or event:

Ronald Rodriguez, MD., PhD
Henry B. and Edna Smith Dielmann Memorial Professor of Urologic Science
Doctor's Hospital Renaissance Distinguished University Chair of Urology
University of Texas Health Science Center at San Antonio

Pia Mikkelsen Lynch, M.D.
President & Managing Director
PML Medical Consulting, Aps.
Denmark

3. A data safety monitoring board (DSMB), composed of independent experts without conflict of interests will be established. The Board will review the study before initiation and quarterly thereafter. The Board will review study data to evaluate the safety, efficacy, study progress, and conduct of the study

    - The following have accepted and will serve on DSMB (and are working with on their contracts):
        - Pablo Tebas from University of Pennsylvania (as DSMB Chair)
        - Roy F. Chemaly, MD Anderson Cancer Center
        - Joe Massaro, Boston University School of Public Health
        - Keith Kaye, University of Michigan

    DSMB Charter –This document will be drafted using the DCRI DSMB charter template and will be developed in collaboration with the statistical help of Bryan Lau at JHBSPH and a comprehensive SAP (statistical analysis plan).

    An organizational meeting was held April 27, 2020

    Maya McKean-Peraza
    Project Leader for the DSMB for CSSC001
    Government Trials & Networks
    Duke Clinical Research Institute
    300 W. Morgan Street, Office 425
    Durham, NC 27701
    Office: 919.668.4044 | Mobile 919.316.8281
    maya.mckean.peraza@duke.edu | trialinnovationnetwork.org | dcri.org

8.2. Study monitoring

As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. Research monitors will be managed by:

Emissary International LLC
CEO: Steven W. Mayo, PD, CCRA, PMP
10900 Research BLVD, Suite 160C-1020
Austin, TX 78732

Research monitors will verify that

(1) There is documentation of the informed consent process and signed informed consent documents for each subject

(2) There is compliance with recording requirements for data points

(3) All SAEs are reported as required

(4) Individual subjects' study records and source documents align

(5) Investigators are in compliance with the protocol.

(6) Regulatory requirements as per Office for Human Research Protections-OHRP), FDA, and applicable guidelines (ICH-GCP) are being followed.

8.3. Halting Criteria for the Study

The study enrollment and dosing 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, subject safety is at risk of being compromised:

I. Unexpected death of a dosed subject in relation to infusion

II. 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.

III. One subject with an unexpected SAE associated with study product.

IV. Two subjects with a Grade 3 or higher toxicity for the same parameter associated with study product.

V. An overall pattern of symptomatic, clinical, or laboratory events that the medical monitor, ISM, or SMC consider 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.

VI. 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.

Interim Analyses for efficacy: There will be two formal review of interim results. The first will occur after 15 infections which is expected to occur near 150 participants reaching day 28 and the second after 50% of the total recruitment (n=500) has been achieved and these individuals followed to at least day 28. Interim analyses will only be adjusted for age. Stopping guidelines will be based on O'Brien-Flemming boundary. The interim analysis Z-value boundary of 3.03 (nominal p-value of 0.0011, spent alpha 0.0011), 2.38 (0.0087, 0.008), and 1.68 (0.464, 0.408) for a one-sided test with Type 1 of 0.05.

Special considerations for death:

Furthermore, given that ADE may be an issue with convalescent antibody treatment, out of an abundance of caution we will monitor the number of subjects in each trial arm that progresses to death. Given that we plan to recruit 75 participants in each arm and with the following assumptions 1) 20% of those in standard arm progress to symptomatic infection, 2) 5% in the anti-SARS-CoV-2 treatment arm are expected to progress to symptomatic infection, and 3) 1.4% of those with symptomatic infection progress to death, the probability of observing one death in either arm is unlikely (Table 1). Even with a higher symptomatic case fatality rate of 2.7% that has been estimated for those >64 years in Wuhan, China (Table 1) [Wu JT, LeungK, Bushman M, et al. Estimating Clinical Severity of COVID-19 from the transmission dynamics in Wuhan, China. *Nature Med*] . However, it is possible that more than one death may be seen by random chance in the sample that we accrue. Therefore, we will monitor the number of subjects that die and thoroughly evaluate whether each death is likely due to anti-SARS-CoV-2 plasma (definite, probable, possible, or unlikely). The DSMB will be unmasked for all interim analyses and reviews for safety. It is likely if 2 deaths occur in intervention arm that the DSMB would need to consider stopping due to safety concerns as two deaths would be highly unlikely (Table 2). After at least 50% of trial participants have accumulated follow-up, the number of subjects that progress to this stage will be presented to the masked DSMB and formally asked whether they see a clinically meaningful difference between trial arms that trigger an unmasking of the DSMB. This interim safety analysis will adjust for factors related to mortality including age and presence of cardiopulmonary comorbidities.

Table 1: Binomial probability of at least one death among each treatment arm by overall symptomatic case fatality rate and for those >64 years of age as estimated in Wuhan, China

Symptomatic Case Fatality Rate	Standard Plasma arm Expected Symptomatic N=15 participants	Anti-SARS-CoV-2 Plasma arm Expected Symptomatic N=4 participants
1.4%	0.191	0.055
2.7%	0.337	0.10

Table 2: For 1, 2, or 3 deaths observed among the expected number of symptomatic cases, the event probability of death (95% CI) and the probability that this would be observed under the overall symptomatic case fatality rate of 1.4% from Wuhan, China

	Standard Plasma Arm			Anti-SARS-CoV-2 Plasma arm		
# of deaths	Point Estimate of Mortality	95% Confidence Interval	Probability of occurring under true symptomatic case fatality rate of 0.014	Point Estimate of Mortality	95% Confidence Interval	Probability of occurring under true symptomatic case fatality rate of 0.014
1	0.07	(0.002, 0.319)	0.19	0.25	(0.006, 0.806)	0.05
2	0.13	(0.017, 0.405)	0.018	0.50	(0.068, 0.932)	0.001
3	0.20	(0.043, 0.481)	0.001	0.75	(0.194, 0.993)	<0.0001

Special considerations for ARDS: Given that ARDS is a significant potential consequence of COVID-19 and potentially a sign of ADE, we will monitor participants for development of ARDS as a medical consequence of concern by monitoring differences between participants receiving control plasma and anti-SARS-CoV-2 plasma. Given that we plan to recruit 75 participants in each arm and with the following assumptions 1) 20% of those in standard arm progress to symptomatic infection, 2) 5% in the anti-SARS-CoV-2 treatment arm are expected to progress to symptomatic infection, and 3) in an abundance of caution *as a worst case scenario* we will assume that 40% will progress to ARDS (in Wuhan the reported frequency of ARDS was 3.4% for all subjects and 40% among the group reaching the composite endpoint of ICU admission, ventilation or death). Under this scenario of assumed maximum severity, we are likely to see at least one case in both treatment arms (Table 1). Specifically, we would expect *six* participants in the control and *two* participants in the treatment arm to develop ARDS (table 4). After at least 50% of trial participants have accumulated follow-up, the number of subjects that progress to this stage will be presented to the masked DSMB and formally asked whether they see a clinically meaningful difference between trial arms. This interim analysis will adjust for factors related to worsening of COVID-19 such as age, prior lung disease, and presence of cardiopulmonary comorbidities.

Table 3: Binomial Probability of at least one ARDS case among each treatment arm for a worse case scenario of 40 and 50% of those developing symptoms progressing to ARDS

Proportion Developing ARDS	Standard Plasma arm Expected Symptomatic N=15 participants	Anti-SARS-CoV-2 Plasma arm Expected Symptomatic N=4 participants
40%	>0.999	0.870
50%	>0.999	0.938

Table 4: For a given number of observed ARDS cases among the control plasma and anti-SARS-CoV-2 plasma treatment arms, the point estimate, 95% confidence interval, and probability of ARDS occurring under an assumed true rate of 0.4 among those who become symptomatic

	Standard Plasma Arm			Anti-SARS-CoV-2 Plasma arm		

# of ARDS	Point Estimate of ARDS	95% Confidence Interval	Probability of occurring under true ARDS rate of 0.40	Point Estimate of ARDS	95% Confidence Interval	Probability of occurring under true ARDS of 0.40
1	0.07	(0.002, 0.319)	0.007	0.25	(0.006, 0.806)	>0.99
2	0.13	(0.017, 0.405)	0.036	0.50	(0.068, 0.932)	>0.99
3	0.20	(0.043, 0.481)	0.186	0.75	(0.194, 0.994)	0.309
4	0.27	(0.078, 0.551)	0.430	1.00	(0.398, 1.00)	0.026
6	0.40	(0.163, 0.677)	>0.99			
9	0.60	(0.323, 0.837)	0.122			
10	0.67	(0.384, 0.882)	0.061			

Upon completion of this review and receipt of the advice of the ISM or SMC, it will be determined if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol.

Halting Criteria/Rules for Subject Infusion

Infusion of study drug will be halted if any of the following manifestations of anaphylaxis develop and will not be restarted:

- Skin or mucous membrane manifestations: hives, pruritus, flushing, swollen lips, tongue or uvula
- Respiratory compromise: dyspnea, wheezing, stridor, hypoxemia
- A decrease in systolic blood pressure to < 90 mmHg or >30% decrease from baseline or a diastolic drop of >30% from baseline.
- Tachycardia with an increase in resting heart rate to > 130bpm; or bradycardia <40 that is associated with dizziness, nausea or feeling faint.
- Syncope
- Confusion
- Any other symptom or sign which in the good clinical judgment of the study clinician or supervising physician warrants halting the infusion. For example, the rapid onset of gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and cramps, for instance, may be manifestations of anaphylaxis and may warrant an immediate halt prior to meeting full SAE criteria

9. ETHICS/PROTECTION OF HUMAN SUBJECTS

9.1. Ethical Standard

The JHU is committed to the integrity and quality of the clinical studies it coordinates and implements. JHU will ensure that the legal and ethical obligations associated with the conduct

of clinical research involving human subjects are met. The information provided in this section relates to all JHU sites participating in this research study

As the Department of Health and Human Services continues to strengthen procedures for human subjects' protections via new regulations, JHU will review these evolving standards in relation to the proposed activities and will advise the investigators on those that may apply.

In addition, JHU has a Federal wide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP). The FWA number for JHU is FWA00005752.

This assurance commits a research facility to conduct all human subjects' research in accordance with the ethical principles in The Belmont Report and any other ethical standards recognized by OHRP. Finally, per OHRP regulations, the research facility will ensure that the mandatory renewal of this assurance occurs at the times specified in the regulations.

9.2. Institutional Review Board

The JHU IRB will review this protocol and all protocol-related documents and procedures as required by OHRP and local requirements before subject enrollment. The JHU IRB currently holds and will maintain a US FWA issued by OHRP for the entirety of this study.

9.3. Informed Consent Process

The informed consent process will be initiated before a volunteer agrees to participate in the study and should continue throughout the individual's study participation. The consent will explain that subjects may withdraw consent at any time throughout the course of the trial. Extensive explanation and discussion of risks and possible benefits of this investigation will be provided to the subjects in understandable language. Adequate time will be provided to ensure that the subject has time to consider and discuss participation in the protocol.

The consent will describe in detail the study interventions/products/procedures and risks/benefits associated with participation in the study. The rights and welfare of the subjects will be protected by emphasizing that their access to and the quality of medical care will not be adversely affected if they decline to participate in this study.

Johns Hopkins Remote Consent
If preferred, participants will be offered the option of reviewing and signing the consent in person during the first in person visit. However, participants in this trial are initially under investigation for SARS-CoV-2 infection, which may necessitate remote consent. At the Johns Hopkins site, when remote consent is preferred, we will follow the IRB's guidance as issued in the document "Informed Consent for Human Subjects Research at Johns Hopkins during the

COVID-19 Emergency." Following administration of the Telephone Pre-Screening Script and determination that the caller is a study participant, the research coordinator will send the written consent form to the participant via email or text for their review. Participants without email or text capabilities will be sent a hard copy of the written consent form via US Postal Service.

After the participant has had a chance to review the written informed consent, the IRB-approved consent designee and the participant will participate in the consent process remotely via phone or other video communication platform. A witness from the JH Witness Pool will be used to witness the entire consent process. When available, both the consent designee and the witness will receive remote consent training provided through the OHSR Compliance Monitoring Program.

With the permission of the participant, the proceedings will be recorded, if this option is available on the video communication platform. All parties will introduce themselves and their role in the consenting process. The consent form is reviewed in detail. The participant is next invited to ask any questions and to have them addressed by the study team. If appropriate, the physician/MLP discusses the studies risks and alternatives per the physician/mid-level provider consent policy. The consent will explain that subjects may withdraw consent at any time throughout the course of the trial. Adequate time will be provided to ensure that the subject has time to consider and discuss participation in the protocol.

If the participant is interested in joining the research study, the participant will be asked to sign the consent document. The signature may occur by signing the physical document or if the consent is delivered electronically by the participant clicking "I agree" to participate. The consent designee and witness must verify the participant physically signed the consent document by one of the following methods: by viewing via video conference; or obtaining a photo of the signed consent document; or obtaining verbal confirmation from the participant that he/she signed the consent form or agreed to participate electronically.

To reduce the risk of transmission, the hard-copy consent by the isolated participant will not be removed from the participant's space. A separate copy of the informed consent form will be used to secure the following: the signature and date of the consent designee, the signature and date of physician/MLP ("mid-level provider") on the appropriate signature page and the signature and date of the witness on the COVID-19 witness attestation page. The consent designee will return all signed components as one combined document to a study team member with EPIC access.

A study team member with EPIC access completes the documentation in EPIC, by opening an encounter for the participant, and entering a note in the Progress Note/NoteWriter section. For COVID-19 Greater Than Minimal Risk patients, the study team member will enter ".COVID19RCHGREATERRISK" for the "COVID-19 Research Consent: Greater Than Minimal Risk" statement and hit "Enter." The study team member will fax the signed completed consent form to EPIC for upload (410-367-7382). The study team must retain the completed consent

document in its entirety (i.e., all pages of the consent form) in the study record or participant binder.

Consenting a LAR for decisionally impaired participants

It is presumed that in most cases, due to visitor restrictions or the potential for the LAR to be in self-quarantine, the LAR will not be physically present to participate in the consent process and this process will occur remotely. As with participants, the LAR must be provided with a copy of the IRB-approved consent document before the consent process begins. An electronic copy of the consent should be provided where possible. In the event that this is not possible, the study team must mail a copy of the consent form by US Postal Service.

After the LAR has had a chance to review the written informed consent, the IRB-approved consent designee and the LAR will participate in the consent process remotely via phone or other video communication platform. A witness from the JH Witness Pool will be used to witness the entire consent process. When available, both the consent designee and the witness will receive remote consent training provided through the OHSR Compliance Monitoring Program.

With the permission of the LAR, the proceedings will be recorded, if this option is available on the video communication platform. All parties will introduce themselves and their role in the consenting process. The consent form is reviewed in detail. The LAR is next invited to ask any questions and to have them addressed by the study team. If appropriate, the physician/MLP discusses the studies risks and alternatives per the physician/mid-level provider consent policy. The consent will explain that the LAR may withdraw consent at any time throughout the course of the trial. Adequate time will be provided to ensure that the LAR has time to consider and discuss participation on behalf of the participant in the protocol.

If the LAR affirms, acting on the prospective participant's behalf, agrees to join the study, the LAR will be asked to sign the consent document by signing the physical document; or if the consent is delivered electronically by the participant clicking "I agree" to participate. If the consent document has been provided to the LAR by mail or email prior to the consent conversation, the full signed and dated consent form can be returned to the study team by mail, fax, email or by a photo of the entire signed consent document. If emailed, the document or photo should be returned electronically to the study team through secure electronic means. If the LAR is not able to deliver the signed document electronically, research procedures may be initiated based on the verbal attestation of signature but the hard copy must be returned via mail.

The consent designee and witness will verify and document the LAR signed the consent document: By viewing via video conference; or obtaining a photo or scanned copy of the signed consent document or obtaining verbal confirmation from the LAR that he/she signed the consent form.

Once the LAR documentation is confirmed the following signatures must be secured: The consent designee will sign and date the primary consent document; the physician/MLP will sign the physician/MLP consent signature page, and the witness will sign the COVID-19 witness attestation page.

A study team member with EPIC access completes the documentation in EPIC, by opening an encounter for the participant, and entering a note in the Progress Note/NoteWriter section. For COVID-19 Greater Than Minimal Risk patients, the study team member will enter ".COVID19RCHGREATERRISK" for the "COVID-19 Research Consent: Greater Than Minimal Risk" statement and hit "Enter." The study team member will fax the signed completed consent form to EPIC for upload (410-367-7382). The study team will retain the completed consent document in its entirety (i.e., all pages of the consent form) in the study record or participant binder.

Mechanisms for Delivering Informed Consent Electronically.
Our team will pursue the use of MyChart, as a means to deliver the IRB-approved consent document electronically to prospective participants or their LARs via MyChart. Prospective participants will be asked if they have a MyChart account or be asked to establish one in order to access the consent through this platform. The MyChart team will assist our team in creating an electronic delivery mechanism for consent that will have a built in "agree to participate" component.

Site Other than Johns Hopkins
Remote Consent: Individual sites seeking to use a similar remote consent process to the Johns Hopkins clinical site will utilize a plan that complies with FDA guidelines for COVID-19 related research and comply with any local procedural guidelines/institutional policies for remote consent.

Electronic Consent: Sites seeking to use e-consenting will ensure the electronic platform used is FDA Part 11 compliant and will provide documentation of access to a Part 11 compliant system to the IRB as part of initial site onboarding or via a subsequent participating site modification. Sites will also ensure their local institutional policies, guidelines, and practices are followed for electronic consenting.

9.4. Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsors and their agents. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The results of the research study may be published, but subjects' names or identifiers will not be revealed. Records will remain confidential. To maintain confidentiality, the PI will be responsible for keeping records in a locked area and results of tests coded to prevent association with subjects' names. Data entered into computerized files will be accessible only by authorized personnel

directly involved with the study and will be coded. Subjects' records will be available to the FDA, the NIH, the manufacturer of the study product and their representatives, investigators at the site involved with the study, and the IRB.

9.5. Future Use of Stored Specimens

Subjects will be asked for consent to use their samples for future testing before the sample is obtained. The confidentiality of the subject will be maintained. There will be no plans to re-contact them for consent or to inform them of results. The risk of collection of the sample will be the small risk of bruising or fainting associated with phlebotomy however these samples will be taken at the same time as other protocol required samples.
No human genetic testing will be performed on the samples without additional consent for those types of tests.

Five ml of blood samples for future use will be collected at 5 time points (See Schedule of Events). Serum will be frozen in 1-ml aliquots. These samples will be used to answer questions that may arise while the study is underway or after it is completed. If for instance, there were unanticipated AEs, serum could be used to run tests that might help determine the reason for the AEs. Cytokines could be measured, for example.

Samples would not be shared with investigators other than investigators at JHU unless outside investigators had relevant assays or expertise not available to the study investigators. The specimens would remain linked and at JHU for 5 years. Any use of these specimens not specified in the current protocol will be reviewed by the JHU IRB.

9.6. Data management and monitoring

9.6.1. Source Documents

The primary source documents for this study will be the subjects' medical records. If the investigators maintain separate research records, both the medical record and the research records will be considered the source documents for the purposes of auditing the study. The investigator will retain a copy of source documents. The investigator will permit monitoring and auditing of these data, and will allow the sponsor, IRB and regulatory authorities access to the original source documents. The investigator is responsible for ensuring that the data collected are complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected and entered in to the study database/case report form and must be signed and dated by the person recording and/or reviewing the data. All data submitted should be reviewed by the site investigator and signed as required with written or electronic signature, as appropriate. Data entered into the study database will be collected directly from subjects during study visits or will be abstracted from subjects' medical records. The subjects' medical records must record their

participation in the clinical trial and what medications (with doses and frequency) or other medical interventions or treatments were administered, as well as any AEs experienced during the trial.

9.6.2. Data Management Plan

Study data will be collected at the study site(s) and entered into the study database. Data entry is to be completed on an ongoing basis during the study.

9.6.3. Data Capture Methods

Clinical data will be entered into a 21 CFR 11-compliant Internet Data Entry System (IDES). The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

9.6.4. Study Record Retention

The site investigator is responsible for retaining all essential documents listed in the ICH GCP Guidelines. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB/IEC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law. It is the site investigator's responsibility to retain copies of source documents until receipt of written notification to the sponsor.

No study document should be destroyed without prior written agreement between the sponsor and the Principal Investigator. Should the investigator wish to assign the study records to another party and/or move them to another location, the site investigator must provide written notification of such intent to sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. The sponsor must be notified in writing and written permission must be received by the site prior to destruction or relocation of research records.

10. COORDINATING CENTER FUNCTIONS AND MULTI-SITE STUDIES

10.1. **Responsibilities.** A Clinical Coordinating Center (CCC) will be responsible for overall recruitment and retention, data management, monitoring and communication among the enrolling sites, and the general oversight of the conduct of this human subject research project. The CCC for this trial is the Brain Injury Outcomes (BIOS) Center,

located at 750 E. Pratt St., Baltimore, MD 21202. The CCC operates under JHM IRB approval # NA_00010432 of which Daniel Hanley, MD, is the Principal Investigator.

10.2. **IRB Document Management**. There is a plan in place for reviewing site approval documents. Two sIRB coordinators oversee the process of reviewing site approval documents and consent forms prior to sIRB review. The coordinators collaborate with the JHM IRB and conduct web calls with each enrolling site to promptly and adequately pre-review site documents prior to site-specific JHM IRB submissions. The sIRB specialists confirm that each participating site has on file an FWA with OHRP. Throughout the study, the sIRB specialists and CCC site managers will assure that all centers have the most current version of the protocol, which will be stored in the electronic trial management file (eTMF). Site managers will communicate protocol amendments to enrolling site PIs and lead study coordinators via receipt-confirmed email and telephone contact follow-up.

10.3. **Screening and Enrollment Tracking**. Recruitment and retention at the sites will be supported by a centrally managed electronic data collection (EDC) system where data will be entered on every screen and enrollment, including reasons for screen failures, inclusion and exclusion criteria met, and demographics needed for reporting. The eTMF will store any documents involved in the screening and enrollment process. Enrollment reports will be generated every two weeks and reported annually as part of the renewal process.

10.4. **Reporting Protocol Events and Deviations**. A formal Data Management Plan will outline the collection and management of data centrally and at the centers. A formal Data Safety Monitoring Plan will describe the process for reporting and evaluating protocol events and deviations at the enrolling centers. Site-specific protocol events and deviations will be collected in the EDC. Protocol deviations will be characterized according to one of three types (intentional, identified before they occur, and discovered post occurrence) and by which meet the requirement for prompt reporting. Corrective and preventive action (CAPA) plans will be shared with and responded to by sites electronically in the eTMF. Protocol deviation reports will be generated every two to four weeks and reported annually as part of the renewal process.

10.5. **Identifying Enrolling Sites**. As sites are selected, the CCC will notify the JHM IRB, using the template below. Final approval will be withheld until the JHM IRB and the OHSR have all required documentation on file. The protocol will be amended, as a change in research, as each site is selected and prior to onboarding the site. Johns Hopkins will be an enrolling site. If any problems arise with enrolling sites, IRB specialists will communicate with the site contact person named in the application, if necessary.

10.6 **COVID-19 Research Environment.** The selected sites will demonstrate protocol review and protocol approval from institutional Hospital Epidemiology and Infection Control (HEIC) or equivalent office in regards to a COVID-19 positive clinic. Physical

areas in which participants will be seen for consent and/or study visits must be in compliance with standards set by the local HEIC. The HEIC promotes patient safety by reducing the risk of acquiring and transmitting infections.

All local sites must supply sufficient personal protective equipment (PPE) for their study personnel and the study participants. Specific types of required PPE and level of protection will be determined by the local HEIC or equivalent office.

All local sites must inform the CCC of any local restrictions or requirements related to COVID-19 research that may impact the health and safety of the participant and conduct of the study. Any limitations or requirements will be evaluated for study impact by the CCC on a case-by-case basis.

Site Identification Template	Site name and address
	PI name and contact (phone and email)
	Confirmation that the research can be conducted at that site, has an IRB, and that the IRB has completed its approval of the research
	Site FWA number
	An executed agreement to rely on the JHM IRB