1. PROTOCOL SUMMARY:

Long title: Convalescent Plasma to Stem Coronavirus: A Randomized, blinded Phase 2 Study Comparing the Efficacy and Safety 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:

Conducted by: Johns Hopkins University

ClinicalTrials.gov Registration: NCT04323800

Sample Size: 150

Study Population: Subjects aged 18 years of age and older who have experienced a high risk 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 open label 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* and at higher risk for severe illness** may participate. A total of 150 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).

*High risk exposure as defined by CDC: Living in the same household as, being an intimate partner of, or providing care in a nonhealthcare setting (such as a home) for a person with symptomatic laboratory-confirmed COVID-19 infection *without using recommended precautions* for home care and home isolation

**Higher risk for severe illness as defined by CDC: $\geq$ 65 years of age, residence in a nursing home or long-term care facility, chronic lung disease or moderate to severe asthma, heart disease, immunocompromising condition including cancer treatment, severe obesity (body mass index [BMI] $\geq$ 40), uncontrolled diabetes, renal failure, liver disease

The following will be assessed in all subjects:

- Safety and efficacy: Day 0 (baseline), 1, 2, 3, 7, 14, and 28 and once monthly at 2-3 months. May be performed by telemedicine on days when laboratory testing not scheduled.
- Blood antibody titer to SARS-CoV-2s: Day 0, 1, 3, 7, 14, 90
- SARS-CoV-2 PCR from nasopharyngeal aspirate or the equivalent: Day 0, 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; ~200-250 mL collected by pheresis from a volunteer who recovered from COVID19 disease. If SARS-CoV-2 neutralizing antibody titers can be conducted would optimally use blood with titers > 1:320)
- Standard plasma collected prior to December 2019

Primary Efficacy Objective: Evaluate 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 at day 28.

Primary Endpoint: Cumulative incidence of composite outcome 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[1] of COVID-19 infection

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 grade 3 and 4 adverse events during the study period
2. Cumulative incidence of serious adverse events during the study period

Secondary 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 0, 1, 3, 7, 14 and 90.
2. Compare the rates and duration of SARS-CoV-2 PCR positivity (RT PCR) amongst the anti-SARS-CoV-2 convalescent plasma and control (SARS-CoV-2 non-immune plasma) groups at days 0, 3, 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 0, 7, 14 and 28

[1] Positive PCR for SARS-CoV-2

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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) High risk exposure to person with COVID-19 within 96 hours of enrollment (and 120 hours of receipt of plasma)

   High risk exposure as defined by CDC: Living in the same household as, being an intimate partner of, or providing care in a nonhealthcare setting (such as a home) for a person with symptomatic laboratory-confirmed COVID-19 infection *without using recommended precautions* for home care and home isolation

3) Higher risk for severe illness as defined by CDC (any of the following):
   a) ≥ 65 years of age
   b) Residence in a nursing home or long-term care facility
   c) Chronic lung disease or moderate to severe asthma
   d) Heart disease
   e) Immunocompromising condition including cancer treatment
   f) Severe obesity (body mass index [BMI] ≥40)
   g) Uncontrolled diabetes
   h) Renal failure
   i) Liver disease

1.1.2. Exclusion Criteria

1. Receipt any blood product in past 120 days
2. Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect subject safety and/or compliance
3. Symptoms consistent with COVID-19 infection (fevers, acute onset cough, shortness of breath) at time of screening
4. Nucleic acid testing evidence of COVID-19 infection at time of screening
5. History of prior reactions to transfusion blood products
6. inability to complete therapy with the study product within 24 hours after enrollment

2. LIST OF ABBREVIATIONS

ADR: Adverse Drug Reaction
ADE: Antibody-mediated enhancement of infection

AE: Adverse Event/Adverse Experience
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
CRF: Case Report Form
DMC: Data Management Center
DSMB: Data and Safety Monitoring Board
EUA: Emergency Use Authorization
FDA: Food and Drug Administration
GCP: Good Clinical Practice
HBV: Hepatitis B virus
HCIP: Human Coronavirus Immune Plasma
HCV: Hepatitis C virus
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
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
OP: Oropharyngeal
RT-PCR: Reverse Transcriptase Polymerase chain reaction
PK: Pharmacokinetic
PPE: Personal Protective Equipment
SAE: Serious adverse event
SARS: Severe Acute Respiratory Syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
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 33 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 73 non-randomized study in Sierra Leone revealed a significant increase in survival for those 74 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 serum. The antibodies used in this study will be derived from serum 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. Compare the anti-SARS-CoV-2 convalescent plasma and control (SARS-CoV-2 non-immune plasma) groups anti-SARS-CoV-2 titers at days 0, 1, 3, 7, 14 and 90

II. Compare the rates and duration of SARS-CoV-2 PCR positivity (RT-PCR) amongst the anti-SARS-CoV-2 convalescent plasma and control (SARS-CoV-2 non-immune plasma) groups at days 0, 7, 14 and 28

III. Compare the peak quantity 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 0, 7, 14

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. High risk exposure as defined by CDC, to person with COVID-19 within 96 hours of enrollment (and 120 hours of receipt of plasma)

   High risk exposure as defined by CDC: Living in the same household as, being an intimate partner of, or providing care in a nonhealthcare setting (such as a home) for a person with symptomatic laboratory-confirmed COVID-19 infection *without using recommended precautions* for home care and home isolation

3. Higher risk for severe illness as defined by CDC (any of the following):

   (a) ≥ 65 years of age
   (b) Residence in a nursing home or long-term care facility
   (c) Chronic lung disease or moderate to severe asthma
   (d) Heart disease
   (e) Immunocompromising condition including cancer treatment
   (f) Severe obesity (body mass index [BMI] ≥40)
   (g) Uncontrolled diabetes
   (h) Renal failure
   (i) Liver disease

4.3.2. Exclusion Criteria for Enrollment

1. Receipt any blood product in past 120 days
2. Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principle investigator, would affect subject safety and/or compliance
3. Symptoms consistent with COVID-19 infection at time of screening: Acute respiratory tract infection (sudden onset of at least one of the following: cough, fever, shortness of breath) AND with no other etiology that fully explains the clinical presentation
4. Laboratory evidence of COVID-19 infection (i.e. RT-PCR) at time of screening
5. A history of previous allergic reaction meeting definitive case definition criteria, at least severe severity, and probable or definite Imputability per NHSN/CDC criteria[i]

Table: Schedule of Events

Study period	Screen	Baseline	Transfusion	Follow up						
Day	-1 to 0	0	0	1	3	7	14	28	60	90
Eligibility										
Informed consent	x									
Demographic and Medical history	x									
COVID-19 symptom screen	x									
SARS-CoV-2 RT-PCR for eligibility	x									
Pregnancy test [2]	x									
ABO[3]	x									
Study Drug Administration										
Randomization		x								
Drug infusion			x							
Study Procedures										
Vital signs	x	x	xxxx[4]	x	x	x	x			
Physical examination[5]	x		x	x		x				
Symptom screen	x	x	x	x	x	x	x	x	x	
Concomitant medications	x	x	x							
Assessment of composite outcome of disease severity[6]		x		x	x	x	x	x	x	
Adverse event monitoring		x	x	x	x	x	x	x	x	
Laboratory testing										
CBC and CMP		x		x		x	x			
SARS-CoV-2 RT-PCR[7]		x			x	x	x			
SARS-CoV-2 antibody		x		x	x	x	x			x
Blood for future testing		x		x	x	x	x			

[2] Urine pregnancy test for women of childbearing potential

[3] Assessment of ABO type on file

[4] 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

[5] Done remotely if feasible

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

[7] Sites could include nasopharyngeal, throat, blood, stool

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. If SARS-CoV-2 neutralizing antibody titers can be conducted would optimally use blood with titers > 1:320 for donation. 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. Active arm will receive 1 unit of anti-SARS-CoV-2 plasma. If SARS-CoV-2 neutralizing antibody titers can be conducted would optimally use blood with titers > 1:320)
IV. Control arm will receive 1 unit of SARS-CoV-2 non-immune plasma
V. Both active and control drugs will be in standard plasma unit bags, with a study-specific ISBT label. study products will be labeled with the following statement: "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (see 21 CFR 312.6 (a)).

4.3.5. Randomization

Subjects enrolled in the study will be randomized using an interactive web response system (IWRS) to receive study drug vs place at a 1:1 ratio.

Blood product and rationale for doses

4.3.6. Collection

All activities pertaining to donor recruitment, enrollment, and collection and processing will take place at [New York Blood Center/NYBC or similar organization]. NYBC is one of the largest independent, community-based, nonprofit blood centers in the United States. It is operational in multiple states i.e. it is not confined to New York. NYBC has a longstanding research program and is well versed in the regulatory and ethical aspects of research, including clinical trials. The organization is FDA-licensed and AABB (American Association of Blood Banks) accredited attesting to robust quality oversight of all operations.

4.3.7. Identification of plasma donors and recruitment

- Mechanism for recruitment will include advertising in the local community where recent outbreaks have occurred.
- Individuals who agree to participate will do so under full informed consent; consent will be a modified version of a standard donation consent form i.e. content specific to the trial will be included along with the intended use for the donated plasma.
- Individuals who agree to participate will undergo pre-donation screening by clinical health care providers independent of the blood center (visit 1); only those who satisfy all criteria for collection as determined through evaluation and laboratory testing will proceed to a second visit (visit 2) during which the collection will take place.

4.3.8. Inclusion criteria for convalescent plasma collection

- COVID-19 convalescent plasma will only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15).
- Additional considerations for donor eligibility are as follows:
    - Prior diagnosis of COVID-19 documented by a laboratory test
    - Complete resolution of symptoms at least 14 days prior to donation
    - Female donors negative for HLA antibodies or male donors
    - Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood.
    - Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)

*For the purposes of the trial, recent recommendations pertaining to donor deferral related to COVID-19 will not apply

4.3.9. Identification of plasma recipients; recruitment and retention

To ensure the trial accrues and retains the number and diversity of participants required to assess the primary and secondary endpoints, a recruitment and retention risk and needs assessment to identify areas of concern and opportunities for engagement will be

conducted. We will use an ongoing evaluation process, which will include iterative feedback from the recruitment reports and study participants and will guide implementation activities and adapt as needed.

For recruitment of community members, we will engage the Johns Hopkins ICTR's Community Research Advisory Council (C-RAC), led by Cheryl Dennison Himmelfarb, PhD, MSN, RN, and the ICTR's Recruitment Innovation Unit to provide feedback regarding community recruitment and retention.

For targeted recruitment, we will make special efforts to recruit healthcare providers and staff with potential COVID exposure. Having a vested interest in remaining healthy, while being exposed to numerous persons with COVID, we feel targeting this population will offer a rich pool of participants. We will take special precautions to not put undue pressure on this population to consent or continue participation.

A portfolio of recruitment materials will be used, such as:

- Broad targeted advertisements (e.g., brochures/flyers, web advertisements, and media)
- Direct-to-patient (e.g., mail, health system portals, calls, waiting rooms, or clinical team)
- Social and community networks (e.g., social media or community events)

Study coordinators will maintain Screening Logs which will be reviewed on a regular basis to identify issues which limit inclusion. Potential strategies to be employed regarding screening and recruitment include:

Pre-Screen/Screening

- Phone calls will be made to potential participants identified through EHR, registries, and those who respond to ads.
- Potential participants will be contacted using MyChart (an Epic EHR product) pending IRB approval. The communication text is outlined in the document, *EHR-based Recruitment Communication*.
- Potential participants will be encouraged to share study information and study contact phone number with friends/family who may interested in participating in the study
- Potential participants will be invited to register on ResearchMatch
- Potential participants will be asked "how did you hear about the study"

Consenting

- Potential participants will be given opportunities to ask questions about the study
- Study team members will begin building rapport with participants

- By the use of CRMS, the participant's enrollment will be noted in their Epic medical record.

Potential strategies to promote retention of participants could include:

- Return of results
- Phone calls
- Reminder emails

The study team will be responsible for participant attrition and missed visits. Team leaders will provide missed visit status reports including the reason why the visit was missed to the Data Coordinating Center (DCC). The DCC will compile reports to generate a master log of participant attrition and missed visits. This log will be monitored to guide and inform continuous process improvement.

4.4. Pre-donation screening

Given that the blood center is not equipped to collect nasopharyngeal and throat swabs, initial assessment of resolved infection per CDC criteria, will need to be performed by the screening provider. At time of presentation at the blood center (i.e. see Visit 2 below), a determination of resolved infection will have already been made.

Visit 1:

- Informed consent obtained by clinical provider
- Pre-donation screening (clinical and laboratory assessment of CDC criteria for resolved infection)
- Collection for samples for SARS-2-CoV antibody and RNA testing (2 EDTA and 1 clotted tube)

Visit 2

Eligible "donors" who have satisfied the above criteria for plasma collection will be invited to return to donate

4.4.1. Collection and processing

- Standard apheresis plasma collection will be performed per routine standard operating procedure at the collection facility (NYBC)
- As per routine practice, samples will be collected at time of donation for testing for transfusion-transmissible infections (all donors), ABO and red cell antibodies (all donors) and HLA antibodies (female donors).

- Target collection volume: ~450-600mL; this will allow for later splitting (separation) into 200-250mL daughter units
- The plasma will be processed per routine practice; it will be frozen within 24hrs of collection per AABB standards
- The plasma will be maintained in quarantine at the blood center pending laboratory test results (i.e. infectious screening, ABO and RhD status, Red cell and HLA antibodies)
- If laboratory testing is acceptable (i.e. negative infectious and antibody screening), the products will be distributed to hospital blood bank for storage
- In the event of an abnormal test result, the product will be discarded and the donor will be notified by the blood center as is standard practice

4.4.2. Control arm plasma

The control arm plasma follows identical collection and processing procedures, but will have been collected from community blood donors prior to documented SARS-CoV-2 in the United States (i.e., to be conservative all control arm plasma will be from collections prior to 31 December 2019).

Potential risks of donation

Apheresis collections are routinely performed and are generally well tolerated. However, risks that are addressed in a standard donation consent form include the following:

1. Risks of phlebotomy: local discomfort, bruising, hematoma, bleeding, fainting (incl. vasovagal reactions), nerve injury
2. Risks of apheresis: bleeding/hypercoagulability, air embolism
3. Allergic reactions (including anaphylaxis)
4. Discovery of a disease that the donor was previously unaware of (e.g. viral hepatitis, HIV, Chagas)

4.4.3. Rationale for dosing

We will utilize 1 unit (200-250 mL) of plasma with anti-SARS-CoV-19 titers expected to have titer >1:64[8] and 1 unit of standard plasma

Dosing was based on experience with previous use of convalescent plasma therapy in SARS where 5 mL/kg of plasma at titer $\geq$ 1:160 was utilized [European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology. 2005;

8 This refers to total antibody level. With regards to SARS-CoV-2 neutralizing antibody titers, if testing can be conducted would be optimally greater than 1:320

24(1):44-6.]. Historical precedence allowing for 0.25 of treatment dose for prophylaxis was taken into account. Hence, considering first order linear proportionality, 3.125mL/kg of plasma with titer >1:64 would provide equivalent immunoglobulin level to one quarter of 5ml/kg plasma with titer ≥ 1:160. For a typical patient (~80 Kg) this would result in 250 mL of plasma (3.125ml/kg x 80kg = 250 mL > 1:64).

4.5. Study drug administration

- Drug will be administered within 24 hours of randomization
- Transfusions will be performed by qualified persons in settings equipped to handle potential complications of transfusion **NEED LANGUAGE FOR THIS**
- Infusion rate ≤ 500 mL/hour
- Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given
- If an AE develops during infusion, the infusion may be slowed or stopped as per investigator's decision.
    - Outside of a simple allergic reaction, the transfusion will be stopped and an investigation initiated when there are signs of a systemic transfusion reaction. **CHECK IF LANGUAGE OK**
    - Allergic reactions such as, bronchospasm and hypotension, generally require discontinuation of the infusion.

4.5.1. Concomitant medications will be documented on the CRF

- Prescription medications
- Over the counter medications
- Herbal treatments/nutritional supplements
- 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 150 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 two-sided Type I error rate (alpha) of 0.05 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. 20% incidence of symptomatic disease in exposed individuals treated with SARS-CoV-2 non-immune plasma
d. 5% incidence of symptomatic disease in exposed individuals treated with anti-SARS CoV-2 plasma

We estimate a sample size of 150 patients (75 in each arm) would be sufficient to detect a difference in outcomes between those two arms with a power of 0.8.

5.2. Statistical Analysis

Primary endpoint:
Our primary hypothesis is that by providing anti-SARS-CoV-2 plasma, the incidence of developing infection as well as severity of infection will be decreased as compared to those randomized to standard plasma. Our primary endpoint is composed of several different clinical events as markers for disease severity that a participant may experience from progressing to not hospitalized, but symptomatic and laboratory evidence of COVID-19 disease to death. We will analyze the primary endpoint as a monotonically increasing composite event. That is individuals are allowed to progress to more severe stages during follow-up but will not move in the other direction. By doing this we can conduct a time to event analysis (note that a time-to-event analysis is equivalent to an analysis examining the probability of outcome at 28 days when there are complete follow-up and more appropriate when there is censoring) as we will be able to capture some of the outcomes such as hospitalization (with or without supplemental oxygen), requiring mechanical ventilation and/or admitted into ICU, and death in continuous time (i.e., on day of occurrence). However, other outcomes such as positive PCR for SARS-CoV-2 will only be measured on certain days (3, 7, and 14) of follow-up. With a mixture of events that will be captured irrespective of follow-up visit as well as an outcome that can only be measured on

specific days, how individuals are censored due to loss-of-follow-up could potentially bias results[ii]. Therefore, our analytical plan is to break the composite event into each event type, conduct a time-to-event analysis from the point of randomization to each of the events in order to estimate the cumulative hazard function. Once we have the cumulative hazard function for each event type, we will calculate the overall cumulative incidence curves for the composite event as well as partition this space into the appropriate event types (e.g., of the overall cumulative incidence, what proportion is due to death, due to mechanical ventilation/ICU, due to hospitalization with supplemental oxygen, etc.). Partitioning the overall composite cumulative incidence into the various event types is analogous to estimating the cumulative incidence of each event type using competing risk methods [iii]. Our approach to estimating the specific event type cumulative hazard function will start with the non-parametric Aalen-Johansen estimator and then move to a flexible Weibull parametric model that allows for a variety of curvature to the hazard function and thus reduce the required distributional assumptions for parametric time-to-event models[iv]. Furthermore, we will allow for interaction between covariates and time to allow for non-proportionality. Additionally, to increase power in a clinical trial, we can adjust for baseline covariates that are related to the outcome[v] . Therefore, we will adjust for factors that likely to contribute to more severe disease such as age, immune compromised, and whether individual has comorbidities. Finally, depending on amount of losses-to-follow-up, we will use inverse probability of censoring weights to mitigate the potential for informative censoring[vi]. In order to check the fit of the parametric model, we will graphically assess the parametric cumulative incidence curves to that of the non-parametric estimator. If a good fit is not achieved, we will add additional splines to the flexible Weibull parametric model and/or modify the interaction between covariates and time to allow for additional flexibility in the model over follow-up time.

All analyses will be conducted with a modified intention-to-treat approach, which excludes randomized subjects who do not initiate an infusion of the study plasma. Furthermore, because this is essentially non-adherence to the randomization process, we will use inverse probability of selection weights to account for the individuals who do not initiate the treatment they were randomized to[vii].

Finally, statistical inference will use a two-sided Type 1 error rate of 0.05 and 95% confidence intervals (unless a Bonferroni correction is necessary due to interim analyses as requested by the DSMB – see below under section 8.3 Halting Criteria for Study). Because the analysis requires multiple steps to properly study the multiple levels of the outcome, we will use bootstrap methods to estimate the p-value and 95% confidence intervals.

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 anti-SARS-CoV-2 titers

Analysis of titers will also primarily be descriptive, comparing the geometric mean titers at days 0,1,3,7 and 14 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[viii]. 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, 3, 7, and 14, we will account for the correlation within individuals using a cluster bootstrap in order to properly estimate the p-value and 95% confidence intervals.

5.2.3. Analysis of rates and duration of SARS-CoV-2 PCR Positivity

Analysis of the rate and duration of SARS-CoV-2 PCR positivity between the randomized arms will primarily be descriptive examining proportion positive at days 0, 3, 7, and 14 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 PCR 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 PCR positivity will only be acquired at days 0, 3, 7, and 14. 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 3 and then is positive at day 7 but negative at day 14, then we know that this individual became positive between day 0 and 3 and negative between day 7 and 14. Therefore, the minimum amount of time positive is 5 days (day 8 – day 3) 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 5 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.

5.2.4. 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: Cumulative incidence of composite outcome 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[9] of COVID-19 infection

Primary Safety Endpoints:

1. Cumulative incidence of grade 3 and 4 adverse events during the study period
2. Cumulative incidence of serious adverse events during the study period

Secondary Endpoints

1. Anti-SARS-CoV-2 titers at days 0, 1, 3, 7 and 14.
2. Rates and duration of SARS-CoV-2 PCR positivity (RT-PCR) at days 0, 7

6. STUDY PROCEDURES

Day -1 to 0

A. Screening (must be completed before randomization)
B. Informed consent (obtained before performing study related activities)'
C. Baseline Evaluation (at screening)

1. Demographics (Age, sex ethnicity, race)

9 Positive PCR for SARS-CoV-2

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
5. Physical examination[10]
6. COVID-19 testing (RT-PCR) prior to infusion, from nasopharyngeal aspirate or equivalent, throat and stool (optional) samples
7. Blood typing, CBC, comprehensive metabolic panel
8. Serological testing: anti-SARS CoV-2 titers
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 enrollment may be used for the pregnancy test.
11. Determination of eligibility as per inclusion/exclusion criteria

Day 0

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)
4. Assessment of clinical status (composite outcome of disease severity)
5. New medical conditions, concomitant medication, AE evaluation
6. Physical examination
7. COVID-19 testing (RT-PCR) from nasopharyngeal aspirate or equivalent, throat and stool (optional) samples
8. Blood typing, CBC, comprehensive metabolic panel
9. Serological testing: anti-SARS CoV-2 titers
10. Stored samples for future studies

Day 1

1. Vital signs
2. COVID-19 symptom screen (fevers, cough, shortness of breath
3. Assessment of clinical status (composite outcome of disease severity)
4. New medical conditions, AE evaluation

10 All physical examinations will be done remotely whenever feasible

5. Physical examination
6. CBC, comprehensive metabolic panel
7. Serological testing: anti-SARS CoV-2 titers
8. Stored samples for future studies

Day 3

1. Vital signs
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (composite outcome of disease severity)
4. New medical conditions, AE evaluation
5. COVID-19 testing (RT-PCR) from nasopharyngeal aspirate or equivalent, throat and stool (optional) samples
6. Serological testing: anti-SARS CoV-2 titers
7. Stored samples for future studies

Day 7

1. Vital signs
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (composite outcome of disease severity)
4. New medical conditions, AE evaluation
5. Physical examination
6. COVID-19 testing (RT-PCR) from nasopharyngeal aspirate or equivalent, throat and stool (optional) samples
7. Serological testing: anti-SARS CoV-2 titers
8. Stored samples for future studies

Day 14

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (composite outcome of disease severity)
3. New medical conditions, AE evaluation
4. physical examination
5. CBC, comprehensive metabolic panel
6. Serological testing: anti-SARS CoV-2 titers
7. Stored samples for future studies

Day 28

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

Day 60

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

6.1. EFFICACY, VIROLOGIC AND PK MEASURES

Clinical Efficacy (composite outcome 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[11] of COVID-19 infection

Virologic measures

1. Rates and duration of SARS-CoV-2 PCR positivity (RT PCR) at days 0, 7 and 14
2. Peak quantity levels of SARS-CoV-2 RNA at days 0, 7 and 14

Pharmacokinetic (PK) measures: Anti-SARS-CoV-2 titers at days 0, 1, 3, 7 and 14.

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.

11 Positive PCR for SARS-CoV-2

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: Vital signs and symptom screen on days 0,1,3,7,14 and symptom screens on days 28 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 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. 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. 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 serious and non-serious

1. Serious Protocol Deviation: Protocol deviation that is also an SAE and/or compromises the safety, welfare or rights of subjects or others
2. Non-Serious Protocol Deviation: Other protocol deviation

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.

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 meet Grade 1 or higher criteria. The grading of the laboratory AEs will be based on the toxicity tables in https://www.niaid.nih.gov/research/dmid-safety-reporting-pharmacovigilance

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 Toxicity Tables. For parameters not included in the Toxicity Table the following definitions will be used:

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 will be appointed by the sponsor for safety oversight of the clinical study.
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
4. An Independent Safety Monitor (ISM) will be appointed. The ISM is a physician with expertise in infectious diseases and whose primary responsibility is to provide timely independent safety monitoring. An ISM is in close proximity to the study site and has the authority to readily access study participant records. The ISM reviews any SAE that occurs at the study site in real time and provides a written assessment to DMID.

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. 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. Two subjects with an unexpected SAE associated with study product.

IV. Four subjects with a Grade 3 or higher toxicity for the same MEDRA coded event reported as 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.

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 [ix], 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) [x]. 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). These data will be presented to the masked DSMB so that they may objectively evaluate and determine whether they would like to be unmasked. 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 (1) see a clinically meaningful difference between trial arms that trigger an unmasking of the DSMB and (2) if so do they require a formal interim analysis. At any point should the DSMB asked to be unmasked and require a formal interim analysis, we will examine the difference in treatment arms for mortality. This interim 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 placebo 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 placebo 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 (1) see a clinically meaningful difference between trial arms that trigger an unmasking of the DSMB and (2) if so, do they require a formal interim analysis. At any point should the DSMB asked to be unmasked and require a formal interim analysis for safety, we will examine the difference in treatment arms for development of ARDS. 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 worst 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 placebo 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, DMID will determine if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol. Should the trial not be stopped at this time

point, the final analysis would need to account the number of interim analyses that were conducted. Therefore, we would penalize any final analysis dividing our 0.05 alpha in half for each interim analysis (i.e., Bonferroni correction).

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 FWA00005834.

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. Johns Hopkins Medicine IRB Role as the Single IRB for Other Participating Sites

All Johns Hopkins sIRB-approved study materials and required local context forms will be distributed to participating sites to complete their local context review. Sites will be immediately notified of changes to the protocol/master consent that may affect local context at their site. Enrollment information will be obtained from sites to include in JHM sIRB continuing reviews. Reporting of any site protocol events or deviations that meet JHM IRB requirements for prompt reporting will be directed by the coordinating center.

9.4. Informed Consent Forms

The consent form will include two parts: a master consent [Part 1] that discusses the study broadly and a site-specific consent information form [Part 2] that discusses institutionally-required consent language.

9.5. 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 subject will sign the informed consent document before any procedures are undertaken for the study. A copy of the signed informed consent document will be given to the subject for their records. 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.

9.6. Adults Lacking the Capacity to Consent

Members of the study team will provide documentation that the patient's primary care physician's opinion is that a suitable period of lucidity can be obtained in order for the potential participant to express understanding of the research study agreement. This assessment is specifically accomplished by conversing at length with the potential participant, answering questions, and validating key points of the study, and noting any signs of fluctuating, progressive, limited, or complete decisional impairment. Incompetence to provide informed consent may be a temporary result of the participant's condition (e.g., the participant is unconscious or sedated) or may result from cognitive impairment produced by the disease or medical condition that impairs mental capacity.

If the primary care physician's assessment of subject incompetence is noted, the opinion of a second physician will be obtained. In this case, informed consent will be sought by a legally authorized representative defined by institutional guideline as an individual or other entity authorized under state law to consent on behalf of the research participant. The Legal Authorized Representative would sign the written consent form.

Reassessment of the competency of the subject's condition to provide informed consent would be reevaluated on an ongoing basis by the primary providers. As soon as competence is deemed appropriate, the subject would be approached to provide informed consent.

When a potential subject's cognitive capability is deemed insufficient for consent due to the severity of their medical condition, an attempt to gain assent from the subject will be attempted. A general sense of the purpose and procedures of the study will be communicated to the subject, and their assent will be documented by obtaining their signature on the assent line of the consent form. The subject's LAR will be approached to provide informed consent for participation in the trial.

Standard practice for transplant patients is to have a designated LAR and for this LAR to be readily available for health care questions on behalf of the patient. In any event, the patient's primary care physician or unit nurse will be consulted to identify the LAR for the subject. In the

event that an LAR is not available, the Maryland Surrogate Decision Making law will be followed. When this person is available to speak with a member of the study team in the hospital ward in which the potential subject is present, the written consent form will be explained in detail, page by page, to the LAR. The process is estimated to take between 30 and 60 minutes. Understanding will be ascertained by asking the LAR to repeat key provisions of the consent form on behalf of the subject.

9.7. 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.

9.8. Prompt Reporting Requirements

Federal regulations require that institutions engaging in human subjects research have written procedures to ensure investigators properly report certain events to the Institutional Review Board ("IRB"). This policy defines those events that require prompt reporting the Johns Hopkins Medicine (JHM) IRB. The policy applies to all research studies that are overseen by the JHM IRB.

9.8.1. Reporting Timeframe

For the purposes of this policy, "prompt" means as soon as possible after the event is discovered, but in all cases within 10 working days after discovery of the event. Reportable deaths must be reported within 72 hours after discovery.

9.8.2. What Events Must be Promptly Reported to the IRB?

The following types of events must be promptly reported to the IRB:

A. UPIRSO:

All potential “unanticipated problems involving risks to subjects or others”(“UPIRSO”). An event is considered an UPIRSO when it meets all of the following criteria:

(1) It is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the population being studied; Unexpected events could be either medical or non-medical events.

(2) It is related or possibly related to participation in the research (i.e. there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

and,

(3) It places subjects or others [e.g. study team members or relatives of a subject] at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

B. POTENTIAL SERIOUS OR CONTINUING NON-COMPLIANCE:

Non-Compliance is defined by the Organization as the failure to follow the research protocol, federal, state, or local laws or regulations governing human subjects research, institutional policies, or the requirements or determinations of the IRB. Only incidents that may qualify as serious or continuing non-compliance must be promptly reported:

(1) Serious Non-compliance is defined by the Organization as non-compliance that either (a) significantly harms or poses an increased risk of significant harm to subjects or others, or (b) significantly compromises the rights and welfare of the subjects or the integrity of the Organization’s human research protection program.

(2) Continuing Non-compliance is defined by the Organization as a pattern of non-compliance that significantly compromises the scientific integrity of the study or the rights and welfare of the subjects or the integrity of the Organization’s human research protection program. When applying this definition, particular consideration may be given by the IRB to activity that recurs after a previous report has been evaluated by the IRB and corrective action has been instituted.

C. OTHER EVENTS THAT REQUIRE PROMPT REPORTING:

In addition the above, investigators must also promptly report the following:.

1) Potential Breaches of Confidentiality: Any unauthorized disclosure of subject's personally identifiable information. Please Note: Potential breaches of confidentiality that involve protected health information (PHI) must also be reported promptly to the HIPAA Privacy Officer. Please see guidance for further detail.

2) Incarceration of a participant in a study not approved by the IRB to involve prisoners and the study team plans to continue study activities with prisoners while incarcerated.

3) Unresolved Subject Complaints: Complaints of subjects when the complaint indicates unexpected risks or cannot be resolved by the research team.

4) Other events: There may be other events that should be promptly reportable to the IRB. If you have questions about whether an event is immediately reportable, please contact a Human Research Compliance Associate in the Office of Human Subjects Research.

Events that do not meet the above criteria should be summarized and reported to the IRB at the time of continuing review. Please see the companion reportable event guidance for additional information about the types of events that are reportable under this policy.

9.8.3. Procedure for Reporting to IRB

The PI has the ultimate responsibility to review each event and determine if it meets any of the above reporting criteria. Events that require prompt reporting shall be reported to the IRB via a Protocol Event Report (PER) in eIRB per the JHM timelines defined above and/or as defined by the external IRB if applicable.

9.8.4. Review of Event and Institutional Reporting

Each PER will be reviewed by the IRB. Upon receipt, the event will be assessed to determine the level of review required. The IRB is authorized to take any actions necessary to address the event, including but not limited to:

1) Requiring modification of the study protocol, informed consent, or other aspects of the study;

2) Requiring notification of subjects;

3) Requiring monitoring or auditing;

4) Suspending or terminating the research;

5) Referring the event to organizational officials for their consideration;

6) Requiring further reporting of the event to regulatory agencies or sponsors.

As part of its review, the IRB is responsible for determining whether an event qualifies as an UPIRSO, Serious Non-compliance, and/or Continuing Non-compliance. Only a convened IRB may make a formal finding that an event(s) constituted an UPIRSO, Serious Non-compliance, and/or Continuing Non-compliance. Such findings require additional reporting by the Institution.

9.9. 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. They 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.
Five ml of blood samples 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.

9.10. Data management and monitoring

9.10.1. 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.

9.10.2. 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.

9.10.3. 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.

9.11. Record Retention Guidance

The Principal Investigator (PI) of a study approved by a JHM IRB is required to retain records associated with a human subjects research project pursuant to Organization Policy 115.2.

9.11.1. JHM Organization Requirements

Original data must be retained for at least 5 years from the date of publication. Beyond that, where questions have been raised regarding the validity of the published data, investigators must preserve the original data until such questions have been resolved to the satisfaction of the Organization and any involved government agencies. The director

or chair of each department or research unit must decide whether to preserve original data for a given number of additional years or for the life of the unit.

9.11.2. HIPAA

Under the HIPAA Privacy Rule, subjects have the right to ask Hopkins for an accounting of certain disclosures of their identifiable health information for a period dating 6 years from the date of the last covered disclosure. To ensure that Hopkins can meet this accounting requirement, investigators must retain study records, along with records of all disclosures of study information, for at least 7 years after either of the following (whichever is later):

The last subject has completed his or her participation in the study; or,

The date of the last disclosure of identifiable health information from study records, if disclosures continue after all subjects have completed the study. [45 CFR 164.528]

This requirement to retain study records and to account for disclosures also applies to research that involves the secondary use of medical records or other identifiable health information.

9.11.3. Federally-Funded Research and FDA-Regulated Research

DHHS regulations require that, "records relating to research which is conducted shall be retained for at least 3 years after completion of the research." [45 CFR 46.115(b)]

For Investigational New Drug (IND) research, the FDA requires that sponsors and investigators retain "records and reports required by this part for 2 years after a marketing application is approved for the drug; or if an application is not approved for drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA so notified."

9.11.4. 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.

REFERENCES

i

1. NHSN Biovigilance Component Hemovigilance Module Surveillance Protocol v2.5.. Atlanta, GA, USA: Centers for Disease Control and Prevention, 2018.

ii

iii

2. Lesko CR, Edwards JK, Moore Rd and Lau B. Censoring for Loss to Follow-up in Time-to-event Analyses of Composite Outcomes or in the Presence of Competing Risks. Epidemiology, 2019 Nov;30(6):817-824
3. Calkins KL, Canan CE, Moore RD, Lesko CR and Lau B. An application of restricted mean survival time in a competing risks setting: comparing time to ART initiation by injection drug use. BMC Med Res Methodol. 2018 Mar 9;18(1):27.
4. Lesko CR and Lau B. Bias Due to Confounders for the Exposure-Competing Risk Relationship. Epidemiology 2017 Jan;28(1):20-27.
5. Cole SR, Lau B, Eron JJ, Brookhart MA, Kitahata MM, Martin JN et al. Estimation of the standardized risk difference and ratio in a competing risks framework: application to injection drug use and progression to AIDS after initiation of antiretroviral therapy. Am J Epidemiol.2015 Feb 15;181(4):238-45.
6. Lau B, Cole SR, Gange SJ. Parametric mixture models to evaluate and summarize hazard ratios in the presence of competing risks with time-dependent hazards and delayed entry. Stat Med. 2011 Mar 15;30(6):654-65.
7. Lau B, Cole SR. Moore RD, Gange SJ. Evaluating competing adverse and beneficial outcomes using a mixture model. Stat Med. 2008 Sep 20;27(21):4313-27.

iv

8. Royston P and Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002 Aug 15;21(15):2175-97.

v

9. Colantuoni E and Rosenblum M. Leveraging prognostic baseline variables to gain precision in randomized trials. Stat Med. 2015 Aug 15;34(18):2602-17.
10. Steingrimsson JA, Hanley DF, Rosenblum M. Improving precision by adjusting for prognostic baseline variables in randomized trials with binary outcomes, without regression model assumptions. Contep Clin Trials. 2017 Mar;54:18-24.

vi

vii

11. Willems S, Schat A, van Noorden MS and Fiocco M. Correcting for dependent censoring in routine outcome monitoring data by applying the inverse probability censoring weighted estimator. Stat Method Med Res. 2018 Feb;27(2):323-335.
12. Howe CJ, Cole SR, Lau B, Napravnik S and Eron JJ Jr. Selection Bias Due to Loss to Follow Up in Cohort Studies. Epidemiology. 2016 Jan;27(1):91-7.

13. Caine LE and Cole SR. Inverse probability-of-censoring weights for the correction of time-varying noncompliance in the effect of randomized highly active antiretroviral therapy on incident AIDS or death. Stat Med. 2009 May 30;28(12):1725-38.
14. Howe CJ, Cole SR, Lau B, Napravnik S and Eron JJ Jr. Selection Bias Due to Loss to Follow Up in Cohort Studies. Epidemiology. 2016 Jan;27(1):91-7.

viii

15. Roger Koenker, Quantile Regression. Cambridge University Press, May 5, 2005

ix

x

16. Wu JT, LeungK, Bushman M, et al. Estimating Clinical Severity of COVID-19 from the transmission dynamics in Wuhan, China. *Nature Med*