1. PROTOCOL SUMMARY

Long Title: Convalescent Plasma to Limit Coronavirus Associated Complications: A Randomized, Double-Blind, Controlled, Phase 2 Study Comparing the Efficacy and Safety of Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 non-immune) Plasma Among Outpatients with Symptomatic COVID-19.

Short Title: CSSC-004

Clinical Phase: 2

IND Sponsor: Johns Hopkins University

Conducted By: Johns Hopkins University

Sample Size: 1344

Study Population: Ambulatory/outpatient subjects aged 18 years of age and older who are positive by molecular test for SARS-CoV-2 AND have at least one symptom of COVID-19.

Study Duration: April 27, 2020 to December 31, 2022

Study Products:

Active Product: Human coronavirus immune plasma (HCIP): Plasma collected by apheresis from a volunteer donor who has recovered from COVID-19 and who has serum SARS-CoV-2 antibody titer ≥ 1:320 and after July 2021 meets FDA criteria for high titer plasma.

Control Product: Plasma collected from a volunteer donor prior to January 1, 2020 will not be tested for SARS-CoV-2 antibodies. Plasma collected after December 31, 2019 will be confirmed as SARS-CoV-2 seronegative.

Study Design:

This randomized, double-blind, controlled, phase 2 trial will assess the efficacy and safety of HCIP to reduce the risk of hospitalization or death, the duration of symptoms and duration of nasopharyngeal or oropharyngeal viral shedding. Adults 18 years of age or older, regardless of risk factors for severe illness may participate. A total of approximately 1344 eligible subjects stratified 50:50 in the <65 vs ≥ 65 age range will be randomized in a 1:1 ratio to receive either HCIP or control plasma.

The following will be assessed in all subjects:

- Clinical measures of safety and efficacy: Day 0 (baseline) to Day 28 and 90.
- Serum antibody titer to SARS-CoV-2: Day (-1 or 0), 14, 28 and 90
- SARS-CoV-2 RNA levels in fluid from nasopharyngeal or oropharyngeal swabs: Day (-1 or 0), 14 and 28.

Primary Efficacy Objective:

Evaluate the efficacy of treatment with HCIP in reducing hospitalization and death among outpatient adults who have molecular detection test-confirmed COVID-19 AND have developed any symptoms of COVID-19 including but not limited to fever, cough, or other COVID associated symptoms like anosmia.

Primary Efficacy Endpoint:

Cumulative incidence of COVID-19 related hospitalizations or deaths prior to hospitalization in treatment versus control groups by Day 28.

Primary Safety Objective:

Evaluate the safety of treatment with HCIP and control plasma in symptomatic outpatient subjects presenting with a positive SARS-CoV-2 molecular test.

Primary Safety Endpoints:

- Cumulative incidence of treatment-related serious adverse events (SAE) categorized separately as either severe transfusion reactions or Acute Respiratory Distress Syndrome (ARDS) during the study period
- Cumulative incidence of treatment-related grade 3 and 4 adverse events (AE) during the study period

Secondary Efficacy Endpoints:

- Compare serum SARS-CoV-2 antibody titers between active and control groups at Days (-1 or 0), 14, 28 and 90.
- Compare the rates and duration of SARS-CoV-2 RNA positivity (by RT-PCR) of nasopharyngeal or oropharyngeal fluid between active and control groups at days (-1 or 0), 14 and 28.

Tertiary Efficacy Endpoints

- Compare the levels of SARS-CoV-2 RNA between active and control groups at days (-1 or 0), 14 and 28.
- Compare time to hospital disease severity measured by ICU admission, invasive mechanical ventilation or time to death in hospital.
- Assess rate of participant-reported secondary infection of household contacts
- Compare blood oxygen saturation levels as measured by pulse oximetry (where available) between active and control groups through Day 28.
- Assess time to resolution of COVID-19 symptoms based on temperature logs and symptom score sheets.
- Assess treatment effect heterogeneity by age (as continuous variable).
- Compare donor antibody titer to primary, secondary and tertiary endpoints

Study Population:

Inclusion Criteria for Enrollment:

- ≥ 18 years of age
- Competent and capable to provide informed consent
- Positive molecular test for presence of SARS-CoV-2 in fluid collected by saliva for antigen, oropharyngeal or nasopharyngeal swab
- Experiencing *any symptoms of COVID-19 including but not limited to fever* (T> 100.5º F)*, cough, or other COVID associated symptoms like anosmia.*

- ≤ 8 days since the first symptoms of COVID-19
- ≤ 8 days since first positive SARS-CoV-2 molecular test
- Able and willing to comply with protocol requirements listed in the informed consent.
- SARS-CoV-2 vaccine status can be either no vaccine receipt or vaccine receipt from day 0 to 90 before onset of symptoms with a positive molecular test. (receipt of COVID-19 vaccine does not exclude a participant with < 8 days of symptoms and a positive test.

Exclusion Criteria:

- Hospitalized or expected to be hospitalized within 24 hours of enrollment
- Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator would affect subject safety and/or compliance
- History of prior reactions to transfusion blood products
- Inability to complete therapy with the study product within 24 hours after enrollment
- Receiving any treatment drug for COVID-19 within 14 days prior to screening evaluation (monoclonal antibodies, , compassionate use or study trial related). Steroid treatment at any time does not affect study eligibility.

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List of Abbreviations and Definition of Terms

AABB	American Association of Blood Banks
ADR	Adverse Drug Reaction
ADE	Antibody-mediated enhancement of infection
AE	Adverse Event/Adverse Experience
ARDS	Acute Respiratory Distress Syndrome
CCC	Clinical Coordinating Center
CDA	Center for Clinical Data Analytics
CDC	United States Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendment of 1988
COI	Conflict of Interest
COVID-19	Coronavirus Disease
C-RAC	Community Research Advisory Council
CRF	Case Report Form
CMP	Comprehensive Metabolic Panel
CRMS	Clinical Research Management System
DCC	Data Coordinating Center
DMC	Data Management Center
DMID	NIH Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
her	Electronic Health Record
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCIP	Human Coronavirus Immune Plasma
HCV	Hepatitis C virus
HEIC	Hospital Epidemiology and Infection Control
HIV	Human immunodeficiency virus
HTLV	Human T-cell lymphotropic virus
IB	Investigator’s Brochure
ICF	Informed Consent (Informed Consent Form)
ICH	International Conference on Harmonization

ICU	Intensive Care Unit
ICTR	Institute for Clinical and Translational Research
IEC	Independent ethics committee
IND	Investigational New Drug Application
IRB	Institutional review board
ISBT	International Society of Blood Transfusion
ISM	Independent Safety Monitor
IWRS	Interactive web response system
MERS	Middle East Respiratory Syndrome
NYBC	New York Blood Center
OP	Oropharyngeal
PER	Protocol Event Report
PK	Pharmacokinetic
PPE	Personal Protective Equipment
SAE	Serious adverse event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SMC	Safety Monitoring Committee
TACO	Transfusion-associated circulatory overload
T. cruzi	*Trypanosoma cruzi*
TRALI	Transfusion-related acute lung injury
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event
ZIKV	Zika virus

2. BACKGROUND AND SCIENTIFIC RATIONALE

There are currently no proven treatment 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 prevention and treatment of other infections and thus may provide an option for 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 treating an infectious disease caused by that agent. In contrast, active vaccination requires the induction of an immune response to the vaccine 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[1, 2]. Experience from prior outbreaks with other coronaviruses, such as SARS-CoV-1 shows that convalescent plasma contains neutralizing antibodies to the relevant virus[3]. In the case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy would mediate protection is viral neutralization. However, other mechanisms may be possible, such as antibody dependent cellular cytotoxicity and/or phagocytosis. Convalescent serum was also used in the 2013 African Ebola epidemic. A small non-randomized study in Sierra Leone revealed a significant increase in survival for those treated with convalescent whole blood relative to those who received standard treatment[4].

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

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 more 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[5]. 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[6].

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 viral neutralization. Depending on the antibody amount and

composition, the viral neutralization conferred by the transferred immunoglobulin can last from weeks to months.

2.1 Experience with Use of Convalescent Plasma Against Coronavirus Disease

In the 21st century, there were two other epidemics with coronaviruses that were associated with high mortality, SARS-COV-1 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[7]. 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. The case fatality rate was 12% (n=80) with convalescent plasma and 17% (n=1755) without convalescent plasma in historic controls*. 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[8]. Three patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients had neutralizing antibody in their plasma[9]. 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[10]. 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.

With Polio in the 1950s gamma globulin provided 80% protection from acquiring polio virus for 5 weeks[11]. In Argentine hemorrhagic fever the Case fatality rate was 1% (n=91) with convalescent plasma and 16% (n=97) without convalescent plasma[12]. During the Spanish flu 1918 pandemic the case fatality rate was 16% (n=336) with convalescent plasma and 37% (n=1219) without convalescent plasma[13]. For the H1N1 influenza in 2009 the severe disease case fatality rate was 20% (n=20) with convalescent plasma and 54% (n=73) without convalescent plasma[14].

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[15, 16]. 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.

2.2 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[17]. 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 SARS-COV-1 and MERS[18], 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[19].This concern will be investigated as part of this clinical trial by measuring immune responses in those exposed and treated with convalescent plasma to prevent disease. If the concern proved real these individuals could be vaccinated against COVID-19 when a vaccine becomes available.

Passive antibodies are derived from human plasma. The antibodies used in this study will be derived from plasma obtained from convalescent patients and will be subjected to testing protocols that are similar to those used by blood banks and transfusion services. However, as is the case with any biological product, there is a very small risk of allergy/anaphylaxis, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), passive transfer of potential unknown infectious agents or infections, or accidental receipt of an incompatible blood product. 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.

2.3 Known Potential Benefits

A potential benefit is societal: If the time to viral clearance is faster, the risk of further transmission (R naught) might be reduced and the epidemic slowed. Convalescent plasma can 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.

3. INVESTIGATIONAL PLAN

3.1 Study Objective and Endpoint

3.1.1 Primary Efficacy Objective

Evaluate the efficacy of treatment with HCIP in reducing hospitalization and death prior to hospitalization among outpatient adults who have molecular detection test-confirmed COVID-19 AND have developed any symptoms of COVID-19 including but not limited to fever, cough, or other COVID associated symptoms like anosmia. For CSSC-004, the following were put into the clinical events scale as hospitalization equivalents: 1) a stay of >24 hours for observation in an emergency department, field hospital, or other healthcare unit; 2) any receipt of O2 for >24 hours, outside of a hospital.

Primary Efficacy Endpoint:
Cumulative incidence of COVID-19 related hospitalizations or deaths prior to hospitalization in treatment versus control groups by Day 28.

3.1.2 Primary Safety Objective

Evaluate the safety of treatment with HCIP and control plasma in symptomatic outpatient subjects presenting with a positive SARS-CoV-2 molecular test.
Primary Safety Endpoint:

1. Cumulative incidence of treatment-related serious adverse events categorized separately as either severe transfusion reactions or Acute Respiratory Distress Syndrome (ARDS) during the study period
2. Cumulative incidence of treatment-related grade 3 and 4 adverse events during the study period

3.1.3 Secondary Efficacy Endpoint

1. Compare serum anti-SARS-CoV-2 titers between active and control groups at days (-1 or 0), 14, 28 and 90
2. Compare the rates and duration of SARS-CoV-2 RNA positivity (by RNA detection test) of nasopharyngeal or oropharyngeal fluid between active and control groups at days (-1 or 0), 14 and 28

3.1.4 Tertiary Efficacy Endpoint

1. Compare the levels of SARS-CoV-2 RNA between active and control groups at days (-1 or 0), 14 and 28
2. Compare time to hospital disease severity measured by ICU admission, invasive mechanical ventilation or time to death in hospital.
3. Assess rate of participant-reported secondary infection of household contacts
4. Compare blood oxygen saturation levels as measured by pulse oximetry (where available) between active and control groups through Day 28
5. Assess time to resolution of COVID-19 symptoms based on temperature logs and symptom score sheets.
6. Assess treatment effect heterogeneity by age (as continuous variable).
7. Compare donor antibody titer to primary, secondary and tertiary endpoints.

3.2 Definitions

1. Enrolled: From time consented to participate until designated as a screen failure or have either been discontinued from the study or completed it.
2. Randomized: when a randomization number is assigned
3. Screen Failures: signed informed consent, but then determined to be ineligible or withdraws before being randomized
4. Discontinued: randomized, but then withdrawn by investigator or withdraws consent
5. Completed: Subjects are considered completed when they are followed through to Day 90 or died before that.
6. 6. Hospitalization Equivalent: a stay of >24 hours for observation in an ED, field hospital, or other healthcare unit or any receipt of O2 for >24 hours, outside of hospital

3.3 Study Population

3.3.1 Inclusion Criteria:

1. ≥ 18 years of age
2. Competent and capable to provide informed consent
3. Positive RNA molecular test for presence of SARS-CoV-2 in fluid collected by saliva for antigen, oropharyngeal or nasopharyngeal swab
4. Experiencing *any symptoms of COVID-19 including but not limited to fever* (T> 100.5º F),
   cough, or other COVID associated symptoms like anosmia.
5. ≤ 8 days since the first symptoms of COVID-19
6. ≤ 8 days since first positive SARS-CoV-2 molecular test
7. Able and willing to comply with protocol requirements listed on the informed consent
8. SARS-CoV-2 vaccine status can be either no vaccine receipt or vaccine receipt from day 0 to 90 before onset of symptoms with a positive molecular test. (receipt of COVID-19 vaccine does not exclude a participant with < 8 days of symptoms and a positive test..

3.3.2 Exclusion Criteria:

1. Hospitalized or expected to be hospitalized within 24 hours of enrollment
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. History of prior reactions to transfusion blood products
4. Inability to complete therapy with the study product within 24 hours after enrollment
5. Receiving any treatment drug for COVID-19 within 14 days prior to screening evaluation (monoclonal antibodies, off label, compassionate use or trial related). Steroid treatment at any time does not affect study eligibility.

3.3.3 Subject Withdrawal

1. Subjects can terminate study participation and/or withdraw consent at any time without prejudice.
2. Randomized subjects who withdraw from the study will not be replaced.
3. 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
4. Discontinuation of the study: The study sponsor, FDA and IRB all have the right to terminate this study at any time.

3.3.4 Randomization and Intervention

1. Subjects will be recruited for enrollment into two age groups (<65 vs ≥ 65 years of age) of approximately equal number.
2. Subjects within each age group will be randomized using an interactive web response system (IWRS) in a 1:1 ratio to receive HCIP or control plasma.

3.3.5 Identification, Recruitment and Retention of Subjects

To ensure the trial accrues and retains the number and diversity of participants required to assess the primary, secondary and tertiary 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. Recruitment methods and intensity may be adjusted to achieve enrollment of roughly equal number of subjects into the two age groups. Overall, the trial will aim to enroll a trial cohort in which 50% are < 65 and 50% are ≥ 65 years old. Depending on the pattern of enrollment, overall and by site, the trial leadership may direct some or all sites to modify their recruitment procedures in order to achieve the desired age distribution of participants in the trial.

<u>Community Engagement</u>
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. In partnership with the Recruitment Innovation Unit (RIC) of the CTSA, we have established a variety of recruitment materials and modalities to maximize outreach for recruitment: broad targeted

advertisements (ex. brochures, flyers, web pages, etc), direct-to-patient (ex. health system portal communications, waiting rooms, or clinical team referrals), and social and community networks (ex. social media, community events). Recruitment materials and scripts will be approved by the IRB prior to use.

Broad Targeted Recruitment

Research recruitment flyers and brochures have been created to be placed in public areas, including clinics, COVID-19 testing areas, and medical offices, as well as to be sent to local clinicians to share with eligible patients who may be interested in the study. These materials include the study website www.CovidPlasmaTrial.org as well as study email address.

We have developed text for use on the ResearchMatch website (https://www.researchmatch.org/). Research Match is a secure online tool that matches potential participants with research studies. The study can also be found on www.clinicaltrials.gov (NCT#04373460)

Around the country, state and local health departments have set up websites providing information on COVID-19 symptoms, treatment, and research opportunities. For example, the state of Maryland has set up a website, COVIDConnect (https://health.maryland.gov/covidconnect/Pages/Home.aspx). Among user choices is the option, "I'm interested in potential research or clinical study opportunities." As of May 20, 2020, 630 people have expressed interest in clinical trials and studies. Public interest in COVID-19 research is vital for effective and efficient study recruitment, and promotes local community stakeholder engagement. As a recruitment tool, we have created a study description which includes local study contact information to be posted on state, county, and city health department websites near our study sites. Participating study sites will be responsible for creating similar listings and for coordination with their state, county, and city health departments.

At the Johns Hopkins site, we will list the study on a list of COVID-19 related studies, Trials@Hopkins, and handouts of study information, all created and maintained by the JHU ICTR. Local sites may list the study description on similar institutional sites, databases, or handouts, as per local institution guidelines and policies.

At Johns Hopkins site, HOPE is an ICTR-maintained registry of COVID-19 studies. This study will be listed on the ICTR RIU website of enrolling studies for review by the general public. The ICTR will be using social media campaigns to drive people to this landing page highlighting how they can participate in COVID-19 studies.

The study website address may be reached through the domain name www.CovidPlasmaTrial.org. This domain name points to the URL https://hopkinsinfectiousdiseases.jhmi.edu/research/convalescent-plasma-studies/. The website is hosted on the Johns Hopkins Infectious Diseases website. A script has been developed for the videotaping of Dr. David Sullivan describing the study. The video may be posted on the study website. Users will be directed to the website in our brochures, flyers, email auto reply, MyChart text, and ResearchMatch text.

Healthcare Provider Recruitment

For targeted recruitment, we will make special efforts to recruit healthcare providers and staff who have tested positive for COVID-19. Having a vested interest in early treatment, 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. We will insure healthcare employees will not be recruited to enroll in research by their direct supervisor. The electronic medical records of healthcare workers will not be used as the initial general screening method for potential participants. The electronic medical records can be accessed after identification from the list of SARS-CoV-2 positives. To recruit healthcare providers, we also plan to place brochures and flyers in locations visited by healthcare workers in public spaces such as the cafeteria and public bulletin boards, as well as Digital Signage throughout the hospital. In addition, at Johns Hopkins site, we are adding a description of the study to the Healthcare workers list of studies maintained by the ICTR https://ictr.johnshopkins.edu/coronavirus/hcw-studies/

Direct to Patient Recruitment

EHR-based Recruitment

We will engage the Center for Clinical Data Analytics (CCDA) (or local equivalent) to search the EHR for codes related to COVID testing results and/or COVID illness for inpatient (if COVID-19 testing was done while an inpatient), outpatient and Emergency Department records. Additionally, referring physicians and Emergency Department providers who identify potential participants for the study will be a source of study recruitment. At Johns Hopkins, CCDA query of EPIC (local EHR system) will generate a daily list of patients who test positive for COVID-19. The list of SARS-CoV-2 positives can be other health care centers or testing sites that may refer test positive individuals interested in clinical research for contact. Patients meeting study eligibility criteria will be contacted by the study team. CCDA results may be used to send MyChart (or equivalent EHR-based communication) notifications to adult persons matching CCDA search criteria. Participants may also be recruited via other EHR systems (ex. CRISP) as per IRB approved IRB Waiver of HIPAA Privacy Authorization (Form 4). Participating study sites may use similar EHR-based recruitment methods in compliance with local regulations and practices regarding use and deployment as established by their local institutions. Recruitment letters, sample text, and other materials will all be approved by IRB prior to use.

Direct Physician Referral

To reach additional COVID-19 positive patients who may be tested at community testing centers (ex. VEIP stations, pharmacy parking lots, Urgent Care centers, etc) and not have available test results in EHR system, we plan to reach out to referring physicians directly to request that they share study information with their patients. We have created “Dear Doctor” letters which describe the study and will accompany study flyers or brochures. These materials will be emailed to local physicians who treat or refer patients for COVID-19 testing (ex. Primary care physicians, internists, pulmonologists, ENTs, geriatric specialists, etc) with a request to share forward the information to any patients who may be interested in and eligible for the study. Participating study sites will be responsible for contacting local physicians at their locations.

Digital Signage Displays

To increase research participant recruitment, at Johns Hopkins site we will contract with the Department of Brand Management and Production, to display elements of our recruitment poster as digital signage on the electronic plasma screens at all locations throughout JH Medicine in the Baltimore and Washington metro areas. The poster will be included in a rotation of other JHMI messages. It will appear approximately three times per hour. The content of the digital poster is the same as the content of our printed brochure and will include IRB number and approval date, name of the PI, short descriptive study name, and study contact information. Multi-center study sites will be responsible for creating similar digital message (if applicable for their location), including local site contact information.

Social and Community Network Recruitment

Social Media outreach, such as Facebook, Twitter, CraigsList, etc., in our experience has proven to be an effective method of research recruitment. We propose several different iterations of a social media posting and/or paid ad, including photographs. Our social media outreach will include, but not be limited to Facebook and Twitter. A script has been developed for the videotaping of Dr. David Sullivan describing the study; the video may be posted on social media platforms. At Johns Hopkins site, we will utilize existing JH social media outlets, including but not limited to the JH ICTR, JHU SOM, BSPH, and SON. Multi-center study sites will be responsible for creating similar social media listings, with space for their local site contact information.

Media resources such as newspaper advertisements, television news channel feature reports, radio public service announcements, etc. may be additional recruitment resources to be considered in the future. All such media advertisements will be approved by IRB and coordinated with local institution Media Relations team and/or Communications team to ensure compliance with institutional guidelines.

Survey

To supplement the need for a call center, yet capture participant contact information in response to our recruitment efforts, we are utilizing a HIPAA-compliant survey tool. The survey link will appear on our web page: www.CovidPlasmaTrial.org. Survey text is included in the IRB application. In addition to participant contact information, the survey solicits basic COVID-19 related questions to ascertain if the survey responder may be a potential candidate for study inclusion. Via the survey, participants will be provided with a list of participating study sites and their addresses, so that the participant may choose at which study site they wish to participate. If a participant's residence is not within a 200-mile radius of a study site, the participant will be informed we do not have a study site near them, but to please contact their local hospital for potential COVID-19 research participation opportunities. The study team will have access to survey responses and will contact the potential participants who select their study site as location of participation.

Pre-Screen/Screening

Phone calls will be made by the study team to potential participants identified through EHR, registries, survey responses, direct physician referrals, and those individuals who

respond to research ads and recruitment materials.

Study coordinators will maintain the Telephone Pre-Screening Log which will be used to record contact by persons interested in study participation. The log will record the subject name, screening number, and recruitment method and eligibility inclusion/exclusion criteria. The log will be reviewed on a regular basis to identify issues which limit inclusion.

An IRB-approved Telephone Pre-Screening Script will be used to direct conversation with potential participants who respond to recruitment materials. Potential participants will be asked "how did you hear about the study" in an effort to gauge effectiveness of recruitment methods.
The script provides information about the study and asks screening questions related to inclusion and exclusion criteria. If at the end of the interview it is determined the person may be a candidate for study enrollment, an in-person screening visit is scheduled.

Potential participants will be encouraged to share study information and study contact phone number with friends/family who may be interested in participating in the study.

The local 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.

3.4 Study Product

3.4.1 Overview of Study Product

Study product: The investigational product, HCIP, is anti-SARS-CoV-2 convalescent plasma. HCIP will be collected by apheresis from healthy adults identified as having recovered from COVID-19. Healthy adult donors with SARS-CoV-2 antibody titers ≥ 1:320 by an FDA approved test will donate plasma to be used in the trial. After July 2021 the new March 9 EUA for high titer hospital plasma may be used to qualify plasma for study use including Euroimmun ration ≥3.5. The antibody testing will be performed in a CLIA certified laboratory. Potential donors who meet these qualification standards will be referred to an FDA-registered blood center where donors will be evaluated according to current blood donation requirements; plasma will then be collected as fresh frozen plasma (FFP) or plasma frozen within 24 hours of phlebotomy (PF24). Plasma will be distributed to the participating study site's hospital for blinding.

Control plasma will be provided to the participating site's hospital from FDA-registered blood centers as fresh frozen plasma (frozen within 8 hours) or plasma frozen within 24 hours (PF24) collected prior to 1/1/2020 and will not be tested for SARS-CoV-2 antibodies. Plasma collected after December 31, 2019 will be confirmed as SARS-CoV-2 seronegative.

Plasma will be transfused according to hospital standard operating procedures. Active

arm will receive a minimum of 175 ml of HCIP. Control arm will receive a minimum of 175 ml of control plasma

Both active and control products will be provided to the transfusion team in standard plasma unit bags, with a study specific ISBT label and will be identical in appearance.

3.4.2 Blood Centers

All activities pertaining to donor recruitment, enrollment, and collection and processing will initially take place at New York Blood Center/NYBC and/or other FDA-registered blood centers like Vitalant, American Red Cross or others. Subsequent donations may be obtained locally at FDA-registered blood centers, including Johns Hopkins/AAMC (detailed in protocol IRB00248402).

3.4.3 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. Control arm plasma from collections prior to 1 January 2020 will not be tested for SARS-CoV-2 antibodies. Plasma collected after December 31, 2019 will be confirmed as SARS-CoV-2 seronegative. Fresh frozen plasma is safely stored for more than a year. We will secure sources for the ~750 doses necessary study at the outset.

3.4.4 Rationale for Dosing

Dose calculation is based on 1 unit (200-250 mL) of plasma with anti-SARS-CoV-19 titers of >1:320 and 1 unit of standard control plasma. For the purposes of the proposed trial, we required titers ≥1:320. The current FDA Guidance (April 2020) recommends neutralizing antibody titers ≥ 1:160. A pilot study in China showed most (39/40) convalescent donors had titers ≥1:160 (Duan K, et al.medRxiv. 2020:2020.03.16.20036145). On March 9, 2021 the FDA issued a new EUA for use of convalescent plasma for hospitalized patients restricting to high titer defined by Euroimmun ration greater than 3.5 as well as more than a dozen other tests (https://www.fda.gov/media/141477/download). In April 2021, serial communication 10 (CRMTS 13251). The FDA agreed that the new high titer standard with a EUROIMMUN ratio greater than 3.5 may be used to qualify plasma for study use going forward.

A plasma dose of 200 mLs is 7% of the total plasma volume for a 60kg individual with titer reduction to about 1:15 after dilution into the recipient.

Study Drug Administration

- Plasma will be administered within 24 hours of enrollment.
- Transfusions will be performed by qualified/skilled personnel in settings equipped to handle potential complications of transfusion. We have planned to administer transfusion of convalescent plasma in a hospital or ambulatory clinic setting.
- Transfusion rate ≤ 500 mL/hour
- Medicines to minimize mild transfusion reactions during occurrence (e.g. acetaminophen, diphenhydramine) may be given at the discretion of the investigator.
- If an AE develops during transfusion, the transfusion may be slowed or stopped as per

investigator's decision.

- Management of transfusion-associated AE will follow AABB guidelines; anything more than a simple allergic transfusion reaction, the transfusion will be discontinued and investigated appropriately (i.e. per standard practice guidelines).

4. STATISTICAL CONSIDERATIONS

4.1 Sample Size and Power Considerations

The planned sample size for the trial is a total of 1344 (1280*1.05 to allow a 5% oversample) subjects with a target goal (but not binding) of at least an equal number among those <65 and ≥ 65 years of age (n=672) or a slight bias towards those ≥65 years of age (no more than 40%:60% ratio), randomized in a 1:1 ratio to HCIP vs SARS-CoV-2 non-immune control plasma.

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

1. The primary analysis will compare the efficacy of convalescent plasma in reducing the risk of hospitalization. We assume a one-sided Type I error rate (alpha) of 0.05 as we are interested in superiority and Type II error rate (beta) of 0.2. We also present in Table 1 below the sample size needed under 90% power.
2. We assumed that the probability of hospitalization for those <65 years of age is 0.15 and for those ≥65 years of age is 0.30 (data from CDC MMWR[21]). We then allowed the sample to be equally weighted among young to old (i.e., 50:50) as well as 40:60, 30:70, and 20:80. Therefore, we weighted the age specific risk for hospitalization accordingly to determine the overall samples risk under control plasma. We want to ensure that there are both younger and older individuals represented in the trial so we can assess effect heterogeneity by continuous age as a tertiary objective.
3. It is anticipated that very few of these subjects will be randomized and not start study plasma transfusion (and so be excluded from the primary analysis) or be lost to follow-up prior to resolution of symptoms (and so have missing data for the primary endpoint).
4. Furthermore, we assume that the treatment effect of HCIP will be a reduction in risk between 15% and 60%. To estimate the sample size, we used the weighted age stratified risks and assumed this risk was by day 15 (such that the cumulative incidence for hospitalization or death prior to hospitalization no longer increases afterwards) for the controls and the treated group was the control risk reduced between 15 to 75%. Using these assumptions and data, we used an exponential model to identify the lambda parameter and the package 'powerSurvEpi' for the R statistical software was then used to calculate the sample sizes for these scenarios.
5. In Table 1 below, we provide the total sample size according to three of the recruitment ratios of <65:≥65 years of age, 80 or 90% power, and three effect sizes of 25%, 30% and 35% as percent reduction in the rate of hospitalization. In Figure 1 below we provide under 80% power, the sample sizes needed to detect the treatment effect between 15 and 60% reduction in risk and according to different age recruitment ratios. In table 2 with inclusion of 268 (~300) subjects with a target of a minimum ratio of 50:50 for <65:≥65 years of age, we expect to detect at least a 50%

reduction in hospitalizations under 80% power. This is a 20% hospital rate in control and 10% in convalescent plasma treated. If the effect size in hospital rate reductions is 40% than a sample size of 455 will be needed. An overall reduction in hospital rates from 20% to 10% necessitates a sample size of 268 with 80% power. 85 subjects will be the sample size for a reduction rate from 20% to 5%.

6. Therefore, with a sample size of 1344 (1280*1.05 to allow for potential losses) with a target of a minimum ratio of 50:50 for <65:≥65 years of age, we expect to detect at least a 25% reduction in the rate of hospitalization under 80% power and a 30% reduction in rate of hospitalization with 90% power. From the curve in Figure 1, an overall reduction in hospital rates from 20% to 10% necessitates a sample size of 268 with 80% power. Eighty-five subjects will be the sample size for a reduction rate from 20% to 5%.

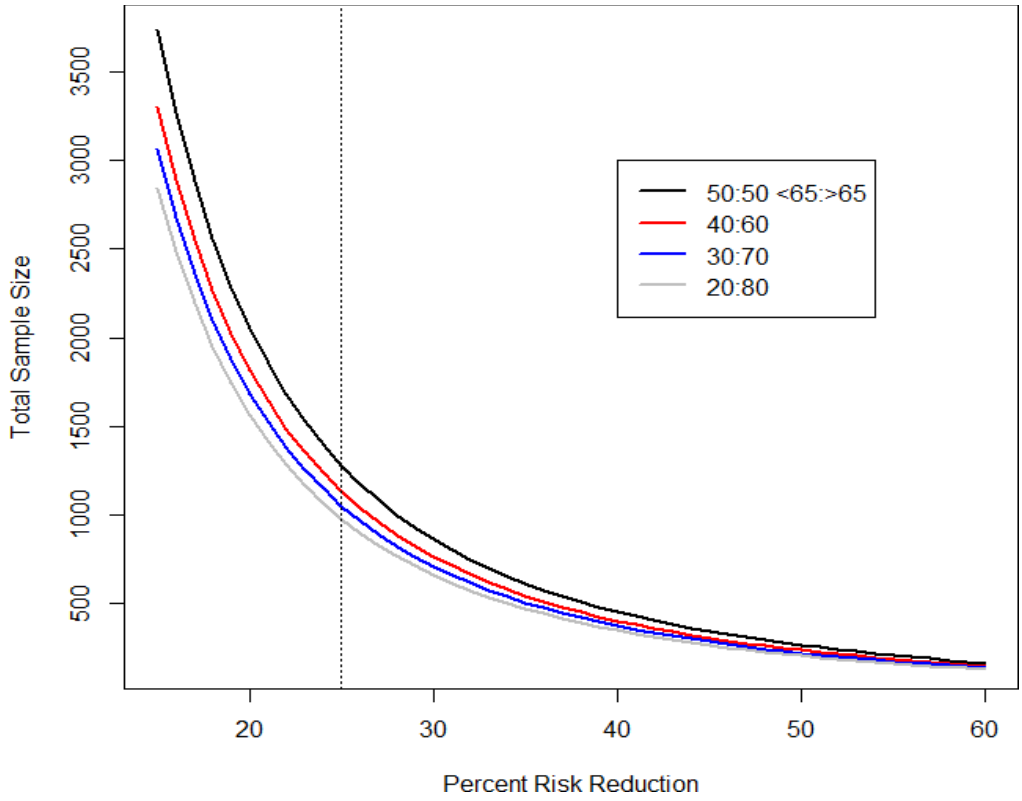
Table 1 Sample sizes according to effect sizes, recruitment ratios of younger to older participants, and two levels of power

Power:	80% Power			90% Power		
Hospital rate Reduction	25%	30%	35%	25%	30%	35%
< 65: ≥ 65						
50:50	1280	864	615	1772	1196	852
40:60	1134	767	546	1571	1062	757
30:70	1052	712	507	1457	985	703

Table 2 Sample sizes according to effect sizes, recruitment ratios of younger to older participants, and two levels of power

Power:	80% Power			90% Power		
Hospital rate Reduction	40%	50%	60%	40%	50%	60%
< 65: ≥ 65						
50:50	455	268	167	630	371	232
40:60	404	239	149	560	331	207
30:70	376	222	139	521	308	193

Figure 1 Sample size by treatment effect for HCIP as a percent hospital rate reduction for four different ratios of recruitment of those <65 to ≥ 65 years of age



Note: Sample size by treatment effect for HCIP as a percent hospital rate reduction for four different ratios of recruitment of those <65 to ≥ 65 years of age. Hospital events are 20% in this figure. Assumed an exponential model, alpha of 0.05, power of 0.8, risk by day 15 is a weighted average of the age specific CDC data[21].

Sample Size Re-Estimation Plan

Our original sample size calculation was based on assumptions reflective of the event rate and associated age distribution in the control population at the beginning of the pandemic. If the event rate in the control group differs from our assumptions during the design of CSSC-004, we may see a decrease in power. To reduce the risk of an underpowered study, we propose to conduct a sample size re-estimation at the first safety interim analysis (5% of participants completing 28-day follow-up) and again at 25% of participants completing 28-day follow-up. We propose to use the overall rate of the primary outcome for the purpose of sample size re-estimation. If this rate is lower than our assumptions for the sample size calculation, additional participants may be needed to achieve adequate statistical power. We will consult with the DSMB on any proposed changes to the sample size estimation. This decision will include considerations for safety data from CSSC-004 that will also be provided to the DSMB. The study team along with our collaborators at the Department of Defense will determine the feasibility of the increased sample size based on the availability of convalescent plasma and impact on funding.

4.2 Statistical Analysis

4.2.1 General Statistical Considerations.

All subjects that enter the study will be accounted for in the final clinical report, whether or not they are included in the analysis. All reasons for exclusion will be documented for those subjects. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. Baseline values for all parameters will be the most recent value prior to administration of any dose of study product. SAS/STAT (release 15.1 or higher) will be used for the clinical data analyses.

4.2.1.1 Analysis of AE Data

All subjects who received any amount of study drug will be included in the safety population. A summary of all adverse events that were reported will be presented by Medical Dictionary for Regulatory Activities® (MedDRA®-version 23.0 or higher, March 2020) coded (System Organ Class and Preferred Term) by highest severity. There will be one report by highest severity for each subject for that adverse event. Relationship to study treatment, action taken, event, and event outcome will be summarized within and across dosing groups. AE will be compared between randomized arms using Fisher's Exact Test.

Serious adverse events will be described in narratives that include subject demographics, treatment date, event, date of onset, relationship to study treatment and the descriptions of actions and outcomes during the event. Any deaths occurring in the study will be summarized in narrative with the demographics, treatment duration, cause of death, date of death and additional information surrounding that serious adverse event. Deaths, SAEs, and events resulting in study discontinuation will also be tabulated.

Safety laboratory data will be transformed prior to analysis as defined in the SAP. Summaries and changes from baseline will be presented for each evaluation time point. Changes from baseline will also be presented using shift tables for selected laboratory parameters.

4.2.1.2 Final Statistical Analysis Plan (SAP)

A final SAP for the analysis and presentation of data from this study will be prepared before database lock. The following is an overview of planned analyses.

4.2.1.3 Overview of Planned Analyses

Primary endpoint: Our primary hypothesis is that by providing anti-SARS-CoV-2 plasma, the cumulative incidence of hospitalization or death prior to hospitalization will

be lower than those receiving control plasma over the course of follow-up. Therefore, our analysis will be a time to event analysis examining the effect of anti-SARS-CoV-2 plasma. We will estimate the survival function for each treatment arm in order to estimate the risk difference over time as well as the restricted mean survival time which is the area under the survival function and provides the expected mean time to hospitalization, as defined in section 3.2, or death up to time t^{22}. Our approach will be to estimate the cumulative incidence using the doubly robust estimator based upon targeted minimum loss based estimator as described by Diaz et al (2019). Results of the analysis for the primary endpoint will be presented both as unadjusted (crude) and adjusted for covariates. By adjusting for baseline covariates that are related to the outcome, we increase precision. This TMLE based approach was shown to increase precision by around 10% to 20% over an inverse probability weighted or augmented inverse probability weighted estimator [Diaz 2019].

Variables chosen for adjustment are specifically for increasing precision in estimates of treatment efficacy and thus must be predictive of disease outcome [Diaz et al, Lifetime Data Anal (2019):25]. To identify the adjustment variables, we will utilize a hybrid approach of pre-specifying some variables and using an algorithmic approach to identify variables to adjust for among pre-specified candidate variables. Variables that we are near certain to be predictive of outcome will be adjusted for. Age has been consistently related to worse outcomes for COVID-19 and therefore will be included in analyses for adjustment. Other pre-specified variables that will be candidates for inclusion in primary analysis will be determined via an algorithmic approach and these variables will include: clinical site, race, ethnicity, sex, category of exposure, hematology factors and other laboratory markers (i.e., CBC and metabolic panels), body mass index, ABO blood group, targeted physical exam, time between SARS-CoV-2 exposure or symptom onset and transfusion of plasma, time between when plasma was donated and transfusion of plasma, distance between where donor provided plasma and participant being transfused, and prior comorbidities that have specifically been associated with worse COVID-19 outcomes including: asthma, chronic kidney disease, chronic lung disease (COPD, idiopathic pulmonary fibrosis, cystic fibrosis), diabetes, hemoglobin disorders (thalassemia, sickle cell disease), immunocompromised (cancer, HIV, organ transplantation, prolonged use of corticosteroids), chronic liver disease, hypertension, and serious heart conditions (heart failure, coronary artery disease, cardiomyopathies, pulmonary hypertension), smoking status, dementia, down syndrome, pregnancy, stroke/cerebrovascular disease, and substance use disorder [updated to reflect CDC website revised on 5/4/2021 and Guan et al Eur Respir J. 2020 May; 55(5)].
To determine which of these pre-specified candidate variables to be included, we will conduct variable selection by random survival forest in the entire sample (i.e., not including an indicator term for treatment arm) and blinded to treatment allocation. The variable importance and 95% confidence intervals [Ishwaran et al Statistics in Medicine. 2019;38] shall be used to identify predictive variables for the outcome and included in analytical models. Specifically, variables in which the 95% CI for the variable importance from the random forest does not contain 0 will be adjusted for. This should reduce the number of variables that the analysis adjusts in order to minimize the degrees of freedom that are use while allowing the analysis to include the variables that have the most correlation with the outcome in order to maximize precision. This hybrid approach

will be done on the full sample and not include the treatment arm (i.e., among entire sample without controlling for convalescent or control plasma) in order to identify the prognostic baseline variables for entire sample.

Intention-to-Treat Approach. All analyses will be conducted with a modified intention-to-treat approach, which excludes randomized subjects who do not initiate infusion transfusion 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 to which they were randomized[26-28]. Finally, statistical inference will use a one-sided Type 1 error rate of 0.05 and 95% confidence intervals (see below under section 8.3 Halting Criteria for Study for effect of interim analyses).

4.2.1.4 Analysis of Anti-SARS-CoV-2 Antibody Titer

Analysis of titers will also primarily be descriptive, comparing the geometric mean titers at days -1 or 0, 14, 28 and 90 between the randomized arms. Furthermore, it is of interest to describe the entire distributions of anti-SARS-CoV-2 titers by randomized arms and contrast these distributions. Therefore, we will use quantile regression in order to describe whether there is a shift or change in the titer distribution between randomized arms [29]. 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 -1 or0, 14 and 28, we will account for the correlation within individuals using a cluster bootstrap in order to properly estimate the p-value and 95% confidence intervals.

4.2.1.5. 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 (-1 or 0), 14,28 and 90 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 (-1 or 0), 14 and 28.

However, we can estimate a minimum and maximum amount of time that an individual was positive. For instance if an individual first negative at day 3 after positive on day 1, then we know that this individual became negative between day 1 and 3. 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.

4.2.1.6 Analysis of SARS-CoV-2 RNA levels

Similar to the secondary aim of comparing the anti-SARS-CoV-2 antibody 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.

4.2.1.7 Analysis of Disease Severity

A secondary hypothesis is that individuals receiving anti-SARS-CoV-2 convalescent plasma are likely to have less disease severity than control. Our primary endpoint examines time to hospitalization, for this we will examine our clinical event scale for disease severity at the 28th day visit (allowing for visit window). The event scale is:

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
   or
   a stay of >24 hours for observation in an ED, field hospital, or other healthcare unit*
   or
   any receipt of O2 for >24 hours, outside of hospital*
5. Not hospitalized, but with clinical and laboratory evidence[1] of COVID-19 infection (symptomatic infection)

The analysis for this will the doubly robust estimator that will be used is that as outlined by Benkeser et al. (2020) based upon a non-parametric extension of the log-odds ratio by Diaz et al. (2016).

4.2.1.8 Rate of Participant Reported Secondary Infection of Housemates

Participants will be assessed for the number of individuals that live in the same house as well as by the end of follow-up the number of individuals that became sick during their convalescence. Therefore, in order to estimate whether anti-SARS-CoV-2 plasma has had an effect on secondary infections, we will use a binomial model in which each individual living in the house is a Bernoulli trial. We will account for clustering by household using generalized estimating equations.

4.2.1.9 Oxygen Saturation Levels Over Time

[1] Positive molecular testing for SARS-CoV-2

*with surge of infections in December 2020 and hospitals becoming more full, these two were put into the clinical events scale as hospitalization equivalents

Participants will self-assess their oxygen saturation levels using home pulse oximetry, when available. Therefore, we will compare the oxygen saturation levels between treatment arms during follow-up using quantile regression similar to above analyses.

4.2.1.10 Time to Resolution of COVID-19 Symptoms

One of our secondary hypotheses is that among those randomized to anti-SARS-CoV-2 plasma, the time to resolution of symptoms from the symptom score sheet that are included in the CDC guidelines for quarantine will be reduced. Therefore, our analysis will be a time to event analysis examining the effect of anti-SARS-CoV-2 plasma. Furthermore, we wish to assess the effect heterogeneity due to age. We will estimate the survival function for each treatment arm in order to estimate the risk difference over time as well as the restricted mean survival time which is the area under the survival function and provides the expected mean time to resolution of symptoms up to time t[22]. The analysis of time to resolution of symptoms is complicated by the fact that some individuals will be precluded from having this event due to another event. Specifically, some individuals may die during the course of their disease. Therefore, this is a setting which is known as competing risks and an area with which we have much expertise[29-33].

We will treat death during COVID-19 as a competing event to our primary outcome of interest being resolution of symptoms. However, we do not expect the number of deaths to be large but will be different by age. We have powered this study to identify treatment effect at day 3 and will estimate the risk difference between the cumulative incidence curves over the entirety of follow-up until day 90. A specific interest in 90 day symptoms exists due to the potential for post-acute sequelae of SARS-CoV-2. Our approach will be to estimate the cumulative incidence using a non-parametric estimator for competing risks (i.e., Aalen- Johansen estimator) stratified by age intervals and treatment group. In order to increase power in a clinical trial, we will adjust for baseline covariates that are related to the outcome using inverse probability of treatment weights[25, 23]. Furthermore, we will also estimate a parametric survival model for competing risk settings which will also increase efficiency. Specifically, we will use a parametric mixture model[34, 35, 30]. Because a parametric model assumes a specific distribution which may not always be an appropriate assumption, we will use a flexible distribution. Specifically, specifically 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 will be used[25]. Furthermore, we will allow for interaction between covariates and time to allow for non-proportionality. The factors that we will adjust for are those that likely to contribute to development of infection such as age, being immunocompromised, and presence of additional comorbidities. 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. The current recommendation for competing risk data is to estimate both the cause- specific hazard ratio (or each cause-specific hazards) and the sub distribution hazard ratios or the cumulative incidence function. This is to provide as much information such that fuller inferences can be made about the time-to-event processes that are occurring[34,30,

36-38
.

Given the interest in PASC, we will also assess the number of symptoms between treatment arms at the 28th day visit and 90th day visit using a Poisson or negative binomial model depending on potential for over dispersion choosing the best model by the lowest Aaike's Information Criterion. We will adjust for potential variables as above using the algorithmic approach.

4.2.1.11 Assessing for the Potential Treatment Effect Heterogeneity by Age

We will assess whether the treatment effect varies by age. The trial will be recruiting individuals regardless of age and therefore, we shall attempt to analyze treatment heterogeneity by age. This will be done by allowing for interaction terms between the indicator for treatment arm and age as a continuous variable using the methods described for the primary analysis. The relationship between the modification of treatment effect by age may not be linear with age and therefore we will allow for non-linearity using splines. Additionally, we will examine treatment heterogeneity by age using categories (for example <40, 40-<65, ≥65) as well as by a binary indicator for age being above the median age (see statistical analysis plan for more details).

4.2.1.12 Medical Condition Risk Factors

We have designed the initial study by using age related risk for serious COVID-19 infection by weighting proposed target sample by age rather than by risk factors for medical conditions like diabetes, lung, heart or liver disease within the age strata. While we are including pregnant women, the outcome of plasma during pregnancy will require a larger subgroup recruitment just the medical risk factors. Nevertheless, we will assess treatment effect heterogeneity by medical co-morbidities. One approach will be to use each type of co-morbidity, a sum of number of co-morbidities, or a scale such as the Charlson Comorbidity Index.

4.2.1.13 Analysis of secondary and tertiary endpoints if participant receives convalescent plasma after endpoint hospitalization through expanded access.

Individuals may receive convalescent plasma through the National Expanded Access or other IND programs occurs after randomization. While this does not lead to confounding, analyses that are affected by this (i.e., secondary efficacy endpoints) may be biased due to the potential of selection bias if we try to analyze the data as per-protocol. The intention to treat analysis is not biased but no longer truly reflect the efficacy that was originally envisioned in a hypothetical perfect trial. Essentially, these individuals are not adhering to the protocol for the treatment arm they were randomized to. In order to deal with this and estimate a per-protocol effect, we can artificially censor these individuals when they deviate from the protocol of the single transfusion at baseline that they were randomized to. In order to mitigate the selection bias that censoring these individuals when they receive convalescent plasma in the hospital that may occur, we will use inverse probability censoring weights, which allows for informative censoring.

4.3 Endpoints

Primary Efficacy Objective: Evaluate the efficacy of treatment with HCIP in outpatient adults who have molecular detection test-confirmed COVID-19 AND have developed any symptoms of COVID-19 including but not limited to fever, cough, or other COVID associated symptoms like anosmia.

Primary Efficacy Endpoint:
Cumulative incidence of COVID-19 related hospitalizations or deaths prior to hospitalization in treatment versus control groups by the Day 28 visit. COVID-19 related hospitalizations will be adjudicated using a three member panel. Each member will independently come to a decision on whether the hospitalization was or was not related to COVID-19 using as much information that could be provided such as hospital discharge forms. Classification of whether the hospitalization was due to COVID-19 will be by majority decision of the panel.

Primary Safety Objective: Evaluate the safety of treatment with HCIP and control plasma in symptomatic outpatient subjects presenting with a positive SARS-CoV-2 molecular test.

Primary Safety Endpoints:
1. Cumulative incidence of treatment-related serious adverse events categorized separately as either severe transfusion reactions or Acute Respiratory Distress Syndrome (ARDS) during the study period.
2. Cumulative incidence of treatment-related grade 3 and 4 adverse events during the study period.

Secondary Efficacy Endpoints:
1. Compare anti-SARS-CoV-2 titers between active and control groups at days (-1 or 0), 14, 28 and 90
2. Compare the rates and duration of SARS-CoV-2 RNA positivity (by RNA detection test) of nasopharyngeal or oropharyngeal fluid between active and control groups at days (-1 or 0), 14 and 28.

Tertiary Efficacy Endpoint
1. Compare the levels of SARS-CoV-2 RNA between active and control groups at days (-1 or 0), 14 and 28
2. Compare time to hospital disease severity measured by ICU admission, invasive mechanical ventilation or time to death in hospital.
3. Assess rate of participant-reported secondary infection of household contacts
4. Compare blood oxygen saturation levels as measured by pulse oximetry (where available) between active and control groups through Day 28
5. Assess time to resolution of COVID-19 symptoms based on temperature logs and symptom score sheets
6. Assess treatment effect heterogeneity by age (as continuous variable).
7. Compare donor antibody titer to primary, secondary and tertiary endpoints

5. STUDY PROCEDURES, EVALUATIONS AND SCHEDULES

5.1 Clinical Evaluations:

The following clinical evaluations will be performed at the times indicated in Section 6 (Study Visits) and Appendix A (Schedule of Events). Any abnormalities identified during the evaluations listed below will be graded according to the EDC dictionary.

5.2 Medical history:

Study staff will interview subjects to collect personal medical histories, including illnesses, surgeries, and medications; and demographic data, including name, sex, age, race, and ethnicity.

5.2.1 Physical Examination:

Complete physical exam by study team member will include a skin examination (partially disrobed); height, weight, vital sign measurements (oral temperature, respiratory rate, heart rate, and blood pressure); examination of the head, eyes, ears, throat, lungs, heart, abdomen, extremities, joints, spine, and other sites as directed by symptoms by a study physician.

5.2.2 Vital Signs:

Vital signs will be collected as indicated in Section 7. Vital sign evaluation will include measurement of temperature, pulse rate, respiratory rate, and blood pressure (systolic and diastolic).

5.2.3 Clinical (local) and Central Laboratory Evaluations:

The following clinical laboratory tests will be completed at time points as specified in Section 6.4 (Study Visits) and Appendix A (Schedule of Events)

Complete Blood Count: (approximately 5 ml blood): WBC, RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, Platelet Count, MPV and Differential (Absolute - Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils)

Serum Chemistry: (approximately 4 mL blood): Albumin, Alkaline Phosphatase, ALT, AST, Calcium, Bicarbonate, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen C-Reactive Protein

Blood oxygen saturation: Percent oxygen saturation of blood as measured by finger pulse oximetry (where available)

Other Laboratory Evaluations to be processed centrally: The following laboratory tests will be completed at time points as specified in Section 6 (Study Visits) and Appendix A (Schedule of Events)

Antibody levels: Serum SARS COV-2 antibody by ELISA, neutralization test or other FDA-approved test

SARS-CoV-2 levels: Upper respiratory tract fluid (nasopharyngeal or oropharyngeal swab) for presence and level of SARS-CoV-2 RNA by RT-PCR

5.2.4 Concomitant Medications

- Prescription medications
- Blood products

5.2.5 Prohibited Medications

Before enrollment, any approved or investigational drug with established activity against SARS-CoV-2.

5.2.6 Hospital Rescue Treatments After Primary Endpoint

In the event that a participant is hospitalized, the subject and study coordinators shall remain blinded. The participant can receive "rescue" therapy with Expanded Access Program convalescent therapy or other allowed or approved medications for hospital treatment of severe COVID-19. The date of receipt of rescue therapy whether additional convalescent therapy or another measure shall be recorded in the data capture system. The participant should still attend follow up research appointments upon discharge. The research study team should obtain research blood and swab on day 14 or 28 if applicable in the hospital in the allowable windows. Hospitalization is not an event for which the participant or research study staff change blinding status.

5.3 Efficacy, Virologic and PK Measures

Clinical Efficacy (clinical event scale of disease severity)

1. Death
2. Requiring mechanical ventilation and/or in ICU due to COVID-19
3. non-ICU hospitalization due to COVID-19, requiring supplemental oxygen;
4. non-ICU hospitalization due to COVID-19, not requiring supplemental oxygen;
5. Hospital visit but not admitted
6. A stay of >24 hours for observation in an ED, field hospital, or other healthcare unit
7. any receipt of O2 for >24 hours, outside of hospital
8. Rate of participant-reported secondary infection of housemates
9. Compare levels of oxygenation between treatment arms over course of follow-u

Virologic measures

1. Rates and duration of SARS-CoV-2 PCR positivity (RT PCR) at days (-1 or 0), 14 and 28
2. Peak quantity levels of SARS-CoV-2 RNA at days (-1 or 0), 14 and 28

Pharmacokinetic (PK) measures: Anti-SARS-CoV-2 titers at days (-1 or 0), 14, 28

and 90.

Upon recruitment of 20 donors, we will measure the viral growth inhibition titers of SARS-CoV-2 neutralizing antibodies compared to the current FDA benchmark neutralizing titer of 1:8160. However, the ability to detect neutralizing antibodies for SARS-CoV-2 through true viral neutralization in culture is time consuming. Other approaches include in-house ELISA tests for the receptor binding subdomain on the external spike glycoprotein trimer, which correlate with viral culture neutralization in previous coronavirus work. Finally, there are an increasing number of non-FDA validated, commercial ELISA tests with the entire spike glycoprotein trimer or nucleocapsid as capture proteins. The viral specificity of these commercial ELISA assays for antibodies to the more frequent common cold beta coronavirus like OC43 or the rare SARS-CoV-1 as well as sensitivity for SARS-CoV-2 antibodies is evolving in the ongoing pandemic. Therefore, we will compare the SARS-CoV-2 donor plasma neutralizing titer levels to the whole protein commercial ELISAs being adopted by hospitals versus the receptor binding domain ELISAs. The goal will be to accurately determine the correlation of serum antibody titers measured by the two ELISA assays to virus neutralization titers determined with SARS-CoV-2 live virus.

5.4 Study visits

Day -1 or 0 Visit (in person in an appropriate location for patients with positive COVID-19 per local policy)

- Informed consent (obtained before performing study related activities preferably by remote consent)
- Screening (must be completed before randomization)
- Baseline Evaluation (at screening)

Screening

1. Demographics (Age, sex, ethnicity, race)
2. Medical history dates of first and last exposure to COVID-19 source patient (if known), acute and chronic medical condition, medications, allergies. Any medical condition arising after consent should be recorded as AE. Date and source institution of positive result of previous SARS-CoV-2 positive test)
3. COVID-19 symptom screen (dates of onset and resolution of fever, cough, shortness of breath, diarrhea, anosmia); date and level of highest recorded temperature
4. Vital signs (temperature, degrees F; pulse, beats per minutes; respirations per minute; BP, systolic and diastolic, mm Hg)
5. Physical examination (neurological, respiratory, cardiac, abdomen, skin
6. Collection of nasopharyngeal or oropharyngeal swab for COVID-19 testing (RNA detection test) prior to transfusion (not for clinical testing)
7. Collection of blood for:
   - ABO typing, unless documentation of ABO type from medical record
   - SARS-CoV-2 antibody (Stored for later research analysis)

- Comprehensive metabolic panel (CMP) and CRP- CLIA
- Complete blood count (CBC) CLIA
- Stored plasma and serum specimen for future studies

8. 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. Results must be received and documented on the case report form prior to transfusion.
9. Determination of eligibility as per inclusion/exclusion criteria
10. Provision of daily diary form for subject to complete twice daily (preferably morning and evening) through Day 14, including cough (frequency and intensity of episodes), shortness of breath (frequency and intensity of episodes), anosmia (frequency and intensity of episodes), other symptoms (frequency, intensity, time of onset), oral temperature, and blood oxygen saturation.
11. Provision of oral digital thermometer and pulse oximeter (where available) and training on use. Staff-observed and subject-acquired data should be entered on CRF as the temperature, pulse and blood oxygen saturation.

Day 0 (in person in an appropriate location for patients with positive COVID-19 per local policy)

Treatment Visit

1. Randomization of eligible subject in IWRS
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (composite outcome of disease severity)
4. Collection and review of AE, New medical conditions, concomitant medication, AE evaluation
5. Physical examination
6. Collection of nasopharyngeal or oropharyngeal swab for COVID-19 testing if not obtained on Day -1 (RNA detection test) prior to transfusion (not for clinical testing)
7. Collection of blood if not obtained on day -1 for
   i. SARS-CoV-2 antibody (Stored for later research analysis)
   ii. Comprehensive metabolic panel (CMP) and CRP- CLIA
   iii. Complete blood count (CBC) CLIA
   iv. Stored plasma and serum specimen for future studies
8. Study Plasma Administration: A single unit of plasma will be transfused. Time at start and end of transfusion will be recorded and Vital signs will be measured immediately prior to transfusion, 10-20 minutes after start of transfusion, at completion of transfusion and 30-60 minutes after the end of the transfusion.
9. Draw plasma and serum 15 to 30 minutes after transfusion for research antibody levels for peak antibody levels

Day 1 (Phone Call) window of +1 day

Phone call to recipient for review of subject diary, symptom screen and AE assessment.

Day 3 (Phone Call) window of -1 or +1 day

Phone call to recipient for review of subject diary, symptom screen and AE assessment.

Day 5 (Phone Call) window of -1 or +1 day

Phone call to recipient for review of subject diary, symptom screen and AE assessment.

Day 7 (Phone Call) window of -1 or +1 day

Phone call to recipient for review of subject diary, symptom screen and AE assessment.

Day 10 (Phone Call) window of -1 or +1 day

Phone call to recipient for review of subject diary, symptom screen and AE assessment.

Day 14 window of -3 or +3 days (in person in an appropriate location for patients with positive COVID-19 per local policy)*

1. Vital signs
2. Blood oxygen saturation
3. Review of subject diary, symptom screen and AE assessment
4. Physical examination
5. Blood specimens for CBC, CRP, CMP
6. SARS-CoV-2 antibody, plasma and serum specimens for future studies (Stored for later research analysis)
7. Nasopharyngeal or oropharyngeal swab for SARS-CoV-2 testing (RNA detection test) (not for clinical testing)

Day 28 (Clinic) window of -3 or +3 days

1. Vital signs
2. Blood oxygen saturation
3. AE assessment
4. Physical examination
5. Blood specimens for CBC, CRP & CMP CLIA
6. SARS-CoV-2 antibody, plasma and serum specimens for future studies (Stored for later research analysis)
7. Nasopharyngeal or oropharyngeal swab for SARS-CoV-2 testing (RNA detection test) (not for clinical testing)

Day 90 (Clinic) window of -8 or +8 days

1. Interim medical history and AE assessment
2. Vital signs
3. Physical examination (if indicated)
4. Blood specimens for CBC, CRP&CMP- CLIA
5. SARS-CoV-2 antibody, plasma and serum specimens for future studies (Stored for later research analysis)

A chart review for vaccine status will be conducted for all participants, including those who have completed their day 90 visit.

Unscheduled pre-vaccine- Optional unscheduled visit prior to receipt of vaccine for CBC, CMB, CRP and research plasma and serum. Continue with other regular schedule visits.
Procedure for determination of COVID-19 positive or COVID-19 negative clinic visit.

Current CDC criteria for release from quarantine which aligns with present JHH guidelines are inclusive of all of the below. These are subject to change and future changes to instructions for protective isolation will be followed during the implementation of this protocol.

i. At least 3 days (72 hours) have passed *since recovery* defined as resolution of fever without the use of fever-reducing medications AND

ii. Improvement in respiratory symptoms (e.g., cough, shortness of breath) AND

iii. At least 7 days have passed *since symptoms first appeared.*

Because a viral swab will be performed on Day 14 and the duration of viral infectivity, irrespective of RNA viral levels after onset of symptoms has yet to be determined, the participant should receive the viral swab in the COVID-19 positive clinic on Day 14. The day 28 clinic visit and day 90 can be performed in a non COVID-19 clinic in accord to CDC and local HEIC guidelines.

Current JHH HEIC clinic guidelines for patients based on changing data and the situation are found at these links:

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

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

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

1. RISKS AND BENEFITS

1.1 Potential Benefits of treatment.

The potential benefits of antiviral treatment with anti-SARS CoV-2 plasma in patients with COVID-19 will decrease the risk of developing progressive symptomatic disease or decrease the severity of illness should it develop.

Potential benefits of clinical monitoring and virologic testing
Subjects enrolled in the study will undergo close clinical and virologic monitoring that could facilitate early symptomatic COVID-19 resolution 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 to Participation

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 the safety of HCIP and control plasma and compare rates and severity of transfusion-related and not related adverse events.
2. Clinical evaluations: Vital signs and symptom screen as described in Section 6, Study Procedures, Evaluations and Schedules
3. Safety laboratory tests will be performed as described in Section 6, Study Procedures, Evaluations and Schedules

1.2 Definitions

Adverse 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)

1. An SAE is any adverse event that results in any of the following outcomes:
2. Death;
3. Life-threatening (immediate risk of death);
4. Inpatient hospitalization or prolongation of existing hospitalization;
5. Persistent or significant disability or incapacity;
6. Congenital anomaly/birth defect;
7. 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.
8. 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.
An expedited IND safety report will be used to notify the FDA IND division of each serious unexpected suspected adverse reactions according to FDA regulations, part 312 and Guidance for Industry and Investigators: Safety Reporting Requirements for INDS and BA/BE Studies effective March 28, 2011. In accordance with these regulations, this protocol has a pre-specified monitoring plan for determining if subjects receiving the intervention are at higher risk for mortality and will only report a death as an expedited IND safety report if there is evidence of a causal relationship between the intervention and/or the study drug and the event resulting in death. In addition, an expedited IND safety report will be used to notify the FDA if there is an imbalance between the arms suggesting there is a reasonable possibility that the intervention or the control caused any of the pre-specified safety endpoints. Otherwise, the occurrence of these safety endpoints will be reported on an annual basis.

Written IND Safety reports will include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events will be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events will be submitted to the FDA, the JHM sIRB, and all participating investigators for local IRB review within 15 calendar days of the CCC first learning of the event.

Unanticipated Problem (UP)

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

Protocol Deviation

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

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

1.3 Reporting Processes

Documentation of AEs. All AEs and SAEs will be documented on the CRF from time of signing of the informed consent form. 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.

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

Assessment of Seriousness

Event seriousness will be determined according to the protocol definition of an SAE

Assessment of Severity

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

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

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

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

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

5= Death

Assessment of Association.

Is the event related to investigational treatment categories to be used for this study are:

- Not related
- Unlikely
- Possible
- Probable
- Definite

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.

7. SAFETY OVERSIGHT

7.1 Monitoring Plan

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

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

3. A Data and Safety Monitoring Board (DSMB), composed of experts without conflicts of interest, will be established. The Board will review the study before initiation and at least monthly thereafter. The Board will review safety, efficacy (including the interim analysis), study progress, and conduct of the study. The following have accepted and will serve on DSMB (and are working on their contracts) :

- Pablo Tebas University of Pennsylvania (as DSMB Chair)
- Roy F. Chemaly, MD Anderson Cancer Center
- Joe Massaro, Boston University School of Public Health
- Keith Kaye, University of Michigan

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

Maya McKean-Peraza
Project Leader for the DSMB for CSSC001 and CSSC004
Government Trials & Networks
Duke Clinical Research Institute
300 W. Morgan Street, Office 425
Durham, NC 27701
maya.mckean.peraza@duke.edu | trialinnovationnetwork.org | dcri.org

A Clinical Events Committee (CEC) has been established by the Grant Principal Investigators consisting of three expert members, including the Chairman, without conflicts of interest to independently review Serious Adverse Events (SAEs) of patients who were hospitalized to evaluate the relatedness to COVID and the severity of hospitalization and determine clinical safety and efficacy outcomes. Any SAE event that does achieve consensus for hospitalization related to COVID or severity of hospitalization will be discussed with all three adjudicators to review

definitions and provide any other documentation for that event that may assist in achieving consensus. If non-consensus remains, Dr Rodriguez, CEC Chairman will have the deciding vote.

Ron Rodriguez, MD Member and Chairman
Virology and Trial Safety

Joanna Daily, MD Member
Microbiology and Immunology

Panagis Galiatsatos, MD Member
Pulmonary and Critical Care Medicine

7.2 Study Monitoring

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

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

Research monitors will verify that:

1. There is documentation of the informed consent process and signed informed consent documents for each subject
2. There is compliance with recording requirements for data points
3. All SAEs narratives 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.

7.3 Halting Criteria for the Study

The study enrollment and dosing will be stopped, potentially permanently, 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:

1. Unexpected death of a dosed subject in relation to transfusion
2. An overall pattern of symptomatic, clinical, or laboratory events that the medical monitor, DSMB consider associated with study product and that collectively may represent a serious potential concern for safety.

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 300 participants in each arm and with the following assumptions 1) 18% in the HCIP treatment arm are expected to progress to

hospitalization, and 2) 1.4% of these enrolled individuals progress to death, the probability of observing one death in either arm is likely (Table 3). 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 more than 3 deaths occur in intervention arm that the DSMB would need to consider stopping due to safety concerns as more than 3 deaths would be highly unlikely (Table 4). There will be two planned formal reviews of the safety data after approximately 5 percent and 20 percent of participants have accumulated 30-day outcome data. These first two interim analyses will not involve efficacy data, in an effort to conserve alpha spending.

Table 3 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	Control Plasma arm Expected Symptomatic N=148 participants	Anti-SARS-CoV-2 Plasma arm Expected Symptomatic N=111 participants
1.4%	0.88	0.79
2.7%	0.98	0.95

Table 4 For 1, 2, 3, or 5 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	0.018	(0.0004, 0.098)	0.533	0.030	(0.0007, 0.158)	0.372
2	0.037	(0.005, 0.127)	0.175	0.061	(0.007, 0.202)	0.078
3	0.056	(0.012, 0.154)	0.040	0.091	(0.019, 0.243)	0.011
5	0.0.093	(0.031, 0.203)	<0.001	0.152	(0.0511, 0.319)	<0.001

7.4 Special considerations for ARDS

Given that ARDS is a significant potential consequence of COVID-19 and potentially a sign of ADE, we will monitor participants for development of ARDS as a medical consequence of concern by monitoring differences between participants receiving control plasma and anti-SARS-CoV-2 plasma. Given that we plan to recruit 300 participants in each arm and with the following assumptions 1) 18% progress to hospitalization in the control arm, 2) 10.8% progress to hospitalization in the treatment arm (a 40% reduction in risk), and 3) in an abundance of caution *as a worst case scenario* we will assume that 40% of ADE 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 5). Specifically, we would expect *six* participants in the control and *two* participants in the treatment arm to develop ARDS (table 6). After at least 50% of trial participants have 28 day 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 ask 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 5 Binomial Probability of at least one ARDS case among each treatment arm for a worst-case scenario of 40 and 50% of hospitalized participants progressing to ARDS

Proportion Developing ARDS	Standard Plasma arm Expected Symptomatic N=148 participants	Anti-SARS-CoV-2 Plasma arm Expected Symptomatic N=111 participants
40%	>0.999	>0.999
50%	>0.999	>0.999

Table 6 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 hospitalized

	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
10				0.30	(0.156, 0.487)	0.290
15	0.28	(0.165, 0.416)	0.072	0.45	(0.281, 0.636)	0.595
20	0.37	(0.243, 0.513)	0.680	0.61	(0.421, 0.771)	0.0.020
25	0.46	(0.326, 0.604)	0.405	0.76	(0.577, 0.889)	<0.001
30	0.56	(0.414, 0.691)	0.0.025	0.91	(0.757, 0.981)	<0.001

Upon completion of this review, the DSMB 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 spend some of our alpha level with each interim analysis.

7.5 Planned Interim Analysis

7.5.1 Stopping guidelines

Stopping guidelines for a formal efficacy evaluation will occur for efficacy and futility once 40% of the 28 day outcome data have accumulated. We use a non-binding Hwang-Shih-DeCani spending function with gamma=-4, which approximates the O'Brien-Flemming boundaries, for both upper and lower bounds. This results in an interim analysis Z-value boundary of 2.68 (nominal p=0.0037, spent alpha=0.0037) for the upper bound and -0.59 (p=0.277, spent beta=0.0148) for the lower. For final analysis the Z-value is 1.66 (p=0.049, spent alpha=0.0463, spent beta=0.1852) for a one-sided test with Type 1 of 0.05. For a stricter one sided test with Type 1 of 0.025, the Z-value boundaries would be interim: 2.90; final: 1.98 for the upper bounds and interim:-0.39; final: 1.98 for the lower bounds. During this planned interim analysis, the study team may request, after consultation with the DSMB, to recalculate the sample size after observation of the primary outcome proportion in the control arm if initial estimates of that proportion are not accurate. In this case, there would be no adjustment for the effect size to be detected (the detectable reduction in the primary outcome in the active study arm relative to the control arm). The DSMB will be unmasked for analyses but keeping investigators blinded to the treatment arms. This interim analysis will adjust for factors related to mortality including age and presence of cardiopulmonary comorbidities.

7.6 Rules for Halting Plasma Transfusion

Transfusion of plasma will be halted, and will not be restarted, if any of the following manifestations of anaphylaxis develop:

- 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 transfusion. 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

8. ETHICS/PROTECTION OF HUMAN SUBJECTS

8.1 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.

8.2 Institution 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.

8.3 Informed Consent Process

The informed consent process will be initiated before a volunteer agrees to participate in the study and should continue throughout the individual's study participation. Participants in this trial are initially under investigation for SARS-CoV-2 infection, necessitating remote consent. Therefore, for we will follow the IRB's guidance as issued in the document "Informed Consent for Human Subjects Research at Johns Hopkins during the COVID-19 Emergency." Following administration of the Telephone Pre-Screening Script and determination that the caller is a study participant, the research coordinator will send the written consent form to the participant via email or text for their review. Participants without email or text capabilities will be sent a hard copy of the written consent form via US Postal Service.

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

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

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

To reduce the risk of transmission, the hard-copy consent by the isolated participant will not be removed from the participant's space. A separate copy of the informed consent form will be used to secure the following: the signature and date of the consent designee,

the signature and date of physician/MLP ("mid-level provider") on the appropriate signature page and the signature and date of the witness on the COVID-19 witness attestation page. The consent designee will return all signed components as one combined document to a study team member.

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

Consenting a LAR for decisionally impaired participants

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

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

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

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

The consent designee and witness will verify and document the LAR signed the consent document: By viewing via video conference; or obtaining a photo or scanned copy of the

signed consent document or obtaining verbal confirmation from the LAR that he/she signed the consent form.

Once the LAR documentation is confirmed the following signatures must be secured: The consent designee will sign and date the primary consent document; the physician/MLP will sign the physician/MLP consent signature page, and the witness will sign the COVID-19 witness attestation page. The study team will retain the completed consent document in its entirety (i.e., all pages of the consent form) in the study record or participant binder.

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

Provision of information to participants having a language or hearing impairment and non-English speakers will follow IRB recommendations as outlined during the COVID pandemic.

Sites Other than Johns Hopkins

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

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

8.4 Subject Confidentiality

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

involved with the study, and the IRB.

8.5 Future Use of Stored Specimens

Subjects will be asked for consent to use their samples for future testing before the sample is obtained. The confidentiality of the subject will be maintained. 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.

Human genetic testing may be performed on the samples as per participant choice.

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 have 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.

8.6 Data Management and Monitoring

8.6.1 Source Documents

Source documents for this study will include the subjects' medical records and study record documents. 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 into 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.

8.6.2 Data Management Plan

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

participant data (IPD) collected in this study, including data dictionaries, will be made available to other researchers after the end of the study.

8.6.3 Data Capture Methods

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

8.6.4 Study Record Retention

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

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

10 COORDINATING CENTER FUNCTIONS AND MULTI-SITE STUDIES

10.1. **Responsibilities.** A Clinical Coordinating Center (CCC) will be responsible for overall recruitment and retention, data management, monitoring and communication among the enrolling sites, and the general oversight of the conduct of this human subject research project. The CCC for this trial is the Brain Injury Outcomes (BIOS) Center, located at 750 E. Pratt St., Baltimore, MD 21202. The CCC operates under JHM IRB approval # NA_00010432 of which Daniel Hanley, MD, is the Principal Investigator.

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

enrolling site PIs and lead study coordinators via receipt-confirmed email and telephone contact follow-up.

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

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

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

10.6 **COVID-19 Research Environment**- The selected sites will demonstrate protocol review and protocol approval from institutional Hospital Epidemiology and Infection Control (HEIC) or equivalent office in regards to a COVID-19 positive clinic. Physical areas in which participants will be seen for consent and/or study visits must be in compliance with standards set by the local HEIC. The HEIC promotes patient safety by reducing the risk of acquiring and transmitting infections.

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

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

Prior to initiation, study sites will provide documentation of:

1. Local HEIC approval or equivalent,
2. Sufficient access to personal protective equipment (PPE) and other resources to carry out the protocol to keep both the subjects and the study personnel safe,
3. Policies about local restrictions and requirements on COVID-19 related research

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

10.6 Participating Sites: Participating sites are listed on clinicaltrials.gov (NCT: 04373460).

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APPENDIX A

Schedule of Events

Study period	Screen	Baseline	Trans-fusion								
Day (windows)	-1 to 0	0	0	1 (+1)	3 (-1 or +1)	5 (-1 or +1)	7 (-1 or +1)	10 (-1 or +1)	14 (-3 or +3)	28 (-3 or +3)	90 (-8 or +8)
Informed consent	x										
Demographic and Medical history	x										
COVID-19 symptom screen	x										
SARS-CoV-2 molecular test review of prior test report	x										
Pregnancy test[1]	x										
Blood typing ABO[2]	x										
Randomization		x									
Drug transfusion			x								
Study Procedures											
Vital signs	x	x	xxx[3]						x	x	x
Phone call				x	x	x	x	x			
Physical examination neuro, lung cardiac, abdominal, skin	x		x						x	x	x
Symptom screen (COVID-19 related)	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	
Adverse event monitoring		x	x	x	x	x	x	x	x	x	x
Temperature (self-administer)	x	x	x	x	x	x	x	x	x	x	
Pulse oximetry (self-administer)	x	x	x	x	x	x	x	x	x	x	
CBC, CRP and CMP	x								x	x	x
SARS-CoV-2 RNA detection test[4]	x								x	x	
SARS-CoV-2 antibody	x								x	x	x
Blood for future testing (plasma and serum)	x		X post transfusion						x	x	x

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

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

[3] Vital sign testing: immediately prior to transfusion, 10-20 minutes after start of transfusion, at completion of transfusion and 30-60 minutes after the end of the transfusion

[4] Sites include nasopharyngeal or oropharyngeal