PROTOCOL #843003 (PENNCCP-02): AN OPEN-LABEL, CONTROLLED, PHASE 1, SAFETY AND EXPLORATORY EFFICACY STUDY OF CONVALESCENT PLASMA FOR SEVERELY ILL, HOSPITALIZED PARTICIPANTS WITH COVID-19 PNEUMONIA CAUSED BY SARS-COV-2

NCT04397757

VERSION DATE: 28-AUG-2020

8032 Maloney Bldg. | 3400 Spruce St | Philadelphia, PA 19104-6061 | Tel: (215) 662-4484 | Fax: 215-614-0378
www.med.upenn.edu/ocr

CLINICAL RESEARCH PROTOCOL

INVESTIGATIONAL PRODUCT(S):		Penn COVID-19 Convalescent Plasma
STUDY NUMBER(S):	**IRB Number**	843003
	Other Protocol Identifiers	PennCCP-02
PROTOCOL(S) TITLE:		An Open-Label, Controlled, Phase 1, Safety and Exploratory Efficacy Study of Convalescent Plasma for Severely Ill, Hospitalized Participants with COVID-19 Pneumonia Caused by SARS-CoV-2
IND NUMBER		20836
REGULATORY SPONSOR:		University of Pennsylvania 3400 Spruce Street; 8032 Maloney Building Philadelphia, PA, 19104
FUNDING SPONSOR(S):		University of Pennsylvania
MEDICAL DIRECTOR		Katharine J. Bar, MD
ORIGINAL PROTOCOL DATE:		15-Apr-2020
VERSION NUMBER:		Version 4
VERSION DATE:		28-Aug-2020

Table of Contents

Table of Tables

Abbreviations

ACIP	Advisory Committee on Immunization Practices
ALT	alanine aminotransferase
AE	adverse event
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BMT	bone marrow transplant
BP	blood pressure
CDC	The Centers for Disease Control and Prevention
CMV	cytomegalovirus
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
ECMO	extra corporeal membrane oxygenation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug Application
IRB	institutional review board
ISBT	International Society of Blood Transfusion
IVIG	intravenous immune globulin
JAMA	Journal of the American Medical Association
LIP	Licensed Individual Practitioner
MMWR	Morbidity and Mortality Weekly Report
MN	microneutralization
NAT	nucleic acid testing
OTC	over the counter
PCCP	Penn COVID-19 Convalescent Plasma
PCR	polymerase chain reaction
PK	pharmacokinetic
RSV	respiratory syncytial virus
SAE	serious adverse event
SARS	severe acute respiratory syndrome
TRALI	transfusion-related acute lung injury
VIG	vaccinia immune globulin

1 STUDY SUMMARY

1.1 Synopsis

Title:	An Open-Label, Controlled, Phase 1, Safety and Exploratory Efficacy Study of Convalescent Plasma for Severely Ill, Hospitalized Participants with COVID-19 Pneumonia Caused by SARS-CoV-2.
Short Title:	COVID-19 Convalescent Plasma for Hospitalized Population
Study Description:	This open-label, controlled, phase 1 trial will assess the safety and efficacy of convalescent plasma in severely ill, hospitalized participants with pneumonia due to COVID-19. This study will enroll adults 18 years old and older, including pregnant women. A total of 80 eligible participants will be randomized to receive either 2 units of convalescent plasma collected from ABO-compatible donors who have recovered from COVID-19 and standard of care (treatment arm) or standard of care alone (control arm). Participants in the treatment arm will receive 2 units of convalescent plasma on Study Day 1 in addition to standard of care. Participants will be assessed on study Day 1 (pre-dose), 30 minutes after each unit of plasma, on all Study Days while hospitalized, and Study Days 15, 22, 29, and 60. All participants will undergo a series of safety and efficacy, assessments. Blood samples will be collected on Days 1 (prior to plasma administration), 3, 8, 15, 29, and 60. Oropharyngeal or endotracheal samples will be collected on Days 1 (prior to plasma administration), 3, 5, 8, 11, and 15.
Objectives:	**Primary Objectives** The overall objective of the study is to evaluate the safety and explore the efficacy of treatment with convalescent plasma plus standard care vs. standard care alone in hospitalized participants with confirmed COVID-19 disease. **Secondary Objectives** For the secondary objectives, we will compare treatment and control arms with clinical severity scales.
Primary Endpoint:	The primary safety objective will be assessed by the cumulative incidence of serious adverse events (SAEs) at Study Day 29. The primary efficacy objective will be assessed by comparison of clinical severity between participants in the treatment versus control arms, as measured by a modified 8-point ordinal severity score on Study Day 29. The modified score treats all participants who have reached levels 1-3 as recovered.

Secondary Endpoints:

SECONDARY OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
1. Evaluate the clinical efficacy of convalescent plasma administration by comparing treatment vs. control arms. • **Clinical Severity** ○ Ordinal scale: ▪ Time to recovery, defined by time to levels 1-3 on the ordinal scale ▪ Time to an improvement of one category and two categories from Day 1 using an ordinal scale. ▪ Participant clinical status using ordinal scale at Days 3, 5, 8, 11,15, 22, and 29. ▪ Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29.	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Day 15, 22, and 29. • Clinical status assessment (8-point ordinal scale) includes: 1. Not hospitalized, no limitations on activities. 2. Not hospitalized, limitation on activities and/or requiring home oxygen; 3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 5. Hospitalized, requiring supplemental oxygen; 6. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 7. Hospitalized, on invasive mechanical ventilation or ECMO. 8. Death

- National Early Warning Score (NEWS):
  - Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first
  - Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS
- Oxygenation:
  - Oxygenation free days to Day 29.
  - Incidence and duration of new oxygen use during the study.
- Non-invasive ventilation/high flow oxygen:
  - Non-invasive ventilation/high flow oxygen - free days to Day 29.
  - Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.
- Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO):
  - Ventilator / ECMO free days to Day 29.
  - Incidence and duration of new mechanical ventilation or ECMO use during the study.

- NEWS assessed daily while hospitalized and on Days 15 and 29.
- Days of supplemental oxygen (if applicable)
- Days of non-invasive ventilation (if applicable).
- Days of high flow oxygen (if applicable).
- Days of invasive mechanical ventilation (if applicable).
- Days of ECMO (if applicable).

- **Hospitalization**
  - Duration of hospitalization.
- **Mortality**
  - Survival time
  - 14-day mortality
  - 28-day mortality

- Days of hospitalization
- Date and cause of death (if applicable)

2. Evaluate the safety of convalescent plasma administration comparing treatment vs. control arms by:

- Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29.
- Changes in WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT over time (analysis of lab values in addition to AEs noted above).

- SAEs
- Grade 3 and 4 AEs
- WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if lab collection is possible).

EXPLORATORY OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Evaluate the clinical efficacy of convalescent plasma administration as compared to active drug (*e.g.,* Remdesivir) recipients in DMID Protocol Number: 20-0006 or other relevant COVID-19 Protocols • **Clinical Severity** ○ Ordinal scale: ▪ Time to recovery, defined by time to levels 1-3 on the ordinal scale ▪ Time to an improvement of one category and two categories from Day 1 using an ordinal scale. ▪ Participant clinical status using ordinal scale at Days 3, 5, 8, 11,15, 22, and 29. ▪ Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29. ○ National Early Warning Score (NEWS): ▪ Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first ▪ Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS. ○ Oxygenation: ▪ Oxygenation free days to Day 29. ▪ Incidence and duration of new oxygen use during the study. ○ Non-invasive ventilation/high flow oxygen: ▪ Non-invasive ventilation/high flow oxygen - free days to Day 29. ▪ Incidence and duration of new non- invasive ventilation or high flow oxygen use during the study.	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Day 15, 22, and 29. • NEWS assessed daily while hospitalized and on Days 15 and 29 • Days of supplemental oxygen (if applicable) • Days of non-invasive ventilation (if applicable). • Days of high flow oxygen (if applicable).

○ Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO): ▪ Ventilator / ECMO free days to Day 29. ▪ Incidence and duration of new mechanical ventilation or ECMO use during the study.	• Days of invasive mechanical ventilation (if applicable). • Days of ECMO (if applicable).
Evaluate the virologic efficacy of convalescent plasma as assessed by: • Percent of participants with detectable SARS-CoV-2 in OP or ET samples at Days 3, 5, 8, 11, and 15. • Quantitative SARS-CoV-2 in OP or ET samples at Days 3, 5, 8, 11, and 15. • Qualitative SARS-CoV-2 in OP or ET samples at Days 3, 5, 8, 11, and 15.	• Quantitative and Qualitative PCR for SARS-CoV-2 in OP or ET swab at Day 1; Days 3, 5, 8, 11, and 15.
Evaluate the timing and titer of anti-SARS-CoV-2 antibody responses after convalescent plasma administration Evaluate the timing and quality of SARS-CoV-2 cellular responses after convalescent plasma administration Evaluate the change in inflammatory responses with convalescent plasma administration	• Plasma antibody binding and neutralization on Day 1; Days 3 8, 15, 29, and 60 • Cellular responses in whole blood on Day 1; Days 3, 8, Days 15 29, and 60 • Plasma and cellular markers of inflammation on Day 1; Days 3, 8, 15, 29, and 60
Evaluate the change in clinical status (by clinical severity score) to the change in inflammatory markers	• Ferritin, C Reactive Protein, D-Dimer, Fibrinogen, Erythrocyte Sedimentation Rate, Triglycerides, IL-6 on Study Day 1, 3, 5, 8, 11, 15, 29, and 60 (when available).

Study Population: Severely-ill, hospitalized adults ≥18 years old with COVID-19 pneumonia

Phase: Phase I

Enrolling Sites: This is a single site study conducted in the Hospitals of the University of Pennsylvania.

Description of Study Intervention: This open label, randomized, controlled, phase I study will assess the administration of 2 units of convalescent plasma collected from ABO-compatible donors who have recovered from COVID-19. Participants will be randomized 1:1 to receive either convalescent plasma on Study Day 1 in addition to standard care or standard care alone.

Study Duration: We expect the study to last 6 months from initiation

Participant Duration:	An individual participant will complete the study in about 60 days, from screening at Day -1 or 1 to follow-up on Day 60 ± 5 days

1.2 Key Roles and Study Governance

Sponsor: University of Pennsylvania	**Medical Director**
[redacted]	[redacted]
University of Pennsylvania	University of Pennsylvania
3400 Spruce Street; 8032 Maloney Building Philadelphia, PA 19104	[redacted]
[redacted]	Phone Number: [redacted]
Email: [redacted]	Email: [redacted]

1.3 Schema

Not applicable.

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

Coronavirus disease (COVID-19), the syndrome caused by SARS-CoV-2, causes significant morbidity and mortality in a subset of infected individuals. In the most severely affected individuals, COVID-19 causes pneumonia and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. There are currently no effective biomedical therapies available, beyond supportive therapy, to treat COVID-19. Convalescent plasma from individuals who have recovered from COVID-19 may contain high titer anti-SARS-CoV-2 neutralizing antibodies that could help treat the disease.

2.2 Background

2.2.1 COVID-19

Emerging infectious diseases can be defined as "infections that have newly appeared in a population or have existed previously but are rapidly increasing in incidence or geographic range." [1, 2] Over the last decade there has been an increase in recognized emerging or re-emerging infectious diseases. This includes, but is not limited to Nipah virus, Lassa virus, Hantavirus, Hendra virus, West Nile virus, avian influenza, severe acute respiratory syndrome (SARS), Middle Eastern respiratory syndrome (MERS), and COVID-19 caused by SARS-CoV-2. For emerging diseases that have no treatment, the use of convalescent plasma is often invoked.

COVID-19, the clinical disease caused by SARS-CoV-2, was first recognized in a cluster of pneumonia cases in Wuhan, China in late 2019 [48]. Since then, COVID-19 has rapidly evolved into a pandemic of unprecedented scope. As of April 1, 2020, COVID-19 had infected over a million individuals and resulted in more than 50,000 deaths worldwide (JHU CRS site). In the United States, the COVID-19 epidemic is growing in prevalence, with more than 200,000 diagnosed infections and more than 5,000 deaths (JHU CRS site).

COVID-19 has a range of clinical severity, with a proportion of patients experiencing severe disease, causing pneumonia, acute respiratory distress syndrome, and hypoxic respiratory failure requiring mechanical ventilation. For severely ill COVID-19 patients, there are currently no effective biomedical interventions beyond supportive care. Due to the morbidity and mortality occurring in severe COVID-19 disease, the testing of additional therapeutic options is warranted. One potential therapeutic that is rapidly available is the use of convalescent plasma as passive immunotherapy.

2.2.2 Passive Immunotherapy in Coronavirus Disease

Over the past 20 years, two other coronaviruses have caused epidemics and substantial morbidity and mortality. SARS, first detected in 2003, and MERS, first detected in 2012, both caused severe disease in a proportion of infected individuals. The lack of effective therapeutics led to the use of passive immunotherapy with convalescent plasmas. In a large, single-arm, open-label study from Hong Kong, 80 SARS patients with disease that had progressed on the standard of care therapies received passive immunotherapy [29]. The convalescent plasma was obtained from SARS patients who were afebrile for at least 7 days and 14 days from initial presentation. Of the 80 SARS-infected study participants receiving plasma, 33 experienced a study-defined "good outcome" by meeting discharge criteria within

22 days from plasma administration. More frequent good outcomes were seen in participants receiving plasma early (within 14 days of presentation) and before development of SARS antibodies. Importantly, no immediate adverse events were noted.

For COVID-19, there have been two recently published case series describing a total of 15 individuals treated with convalescent plasma. In the first publication, Shen and colleagues described five critically ill COVID-19 patients with laboratory-confirmed disease, acute respiratory distress syndrome (ARDS) on mechanical ventilation, and high viral loads, who received plasma between day 10 and 22 of hospitalization. All five participants experienced clinical improvement after plasma administration, with improvement in respiratory function in all five and hospital discharge in three of the five [30]. The second report describes ten severely ill participants who received 1 unit of COVID-19 convalescent plasma between day 10 and 20 of symptomatic disease [31]. Of the ten plasma recipients, three were supported by mechanical ventilation, five were receiving high- or low-flow supplemental oxygen, while two were not receiving supplemental oxygen. After plasma administration, clinical disease generally improved in terms of required oxygen support, lung imaging, and lab abnormalities, including leukopenia and some inflammatory markers. Importantly, there were no serious adverse events in either report. Although these trials are both small and uncontrolled, they describe generally safe and positive clinical responses to COVID-19 convalescent plasma administration. They also highlight the need for controlled trial data to determine the clinical utility of COVID-19 convalescent plasma administration.

2.2.3 Passive Immunotherapy in Other Viral Infection

A number of viral diseases are treated with antibody preparations with variable results. These antibody preparations can be given as either convalescent plasma or intravenous immunoglobulin (IVIG). Curative treatment with IVIG is rare. Red blood cell aplasia caused by parvovirus B19 infection is the only recognized viral infection in which treatment with IVIG may eradicate the infection. [3, 4] However, there is considerable evidence that immune globulin preparations may modify the natural history of viral diseases. These are summarized below.

Influenza: Passive immunotherapy with convalescent plasma has been studied in many contexts against various strains of influenza. A cohort study of patients with severe H1N1 2009 disease in Hong Kong compared outcomes in patients who received convalescent plasma with those who declined enrollment to the study, demonstrating a lower mortality in the plasma recipients [26]. A multicenter, prospective, double-blind, randomized trial of H1N1 2009-immune plasma formulated into immunoglobulin, H-IVIG vs. normal IVIG. H-IVIG treatment was associated with significantly lower 5- and 7-day post-treatment viral loads [27]. Recently, a large United States multi-center, double-blinded trial of high-titer vs. low-titer anti-influenza plasma in individuals with severe influenza A. The high-titer plasmas conferred no significant clinical benefit over the non-immune plasmas [28].

Cytomegalovirus (CMV): CMV enriched immune globulin preparations have shown benefit when used in combination with ganciclovir in the treatment of CMV pneumonia. [5] This immune globulin preparation is also utilized in the treatment of ganciclovir-resistant CMV infections.

Respiratory Syncytial Virus (RSV): In adult bone marrow transplant (BMT) patients with RSV pneumonia, combination therapy using aerosolized ribavirin and standard IVIG (500 mg/kg every

other day for 12 days) for the treatment had a 22% mortality rate, compared to a historical mortality rate of 70%. [6] In pediatric BMT patients with RSV pneumonia, patients treated with combination aerosolized ribavirin and RSV antibody enriched IVIG (RespiGam®) had a 9.1% mortality, compared with a historical 50-70% mortality rate of such patients given ribavirin alone. [7]

Vaccinia Virus: Certain complications of vaccination with the vaccinia virus (smallpox vaccine) are treated with vaccinia immune globulin (VIG). These included generalized vaccinia, eczema vaccinatum, and progressive vaccinia. There have been no controlled trials of the efficacy of VIG. However, anecdotal experience suggests that treatment with VIG for these conditions is beneficial, and is now considered the standard of care. [8]

Hepatitis A: IVIG has also been shown useful in hepatitis A. Persons who have been recently exposed to hepatitis A and who have not been previously vaccinated with hepatitis A are recommended to receive standard IVIG as post-exposure prophylaxis. This is based on data that showed IVIG, when administered within 2 weeks following an exposure to hepatitis A, is greater than 85% effective in preventing hepatitis A. [9] IVIG can also attenuate the clinical expression of hepatitis A infection when given later in the incubation period. [10] Standard IVIG is used because it does contain sufficient anti-hepatitis A antibodies.

Hepatitis B: For patients with hepatitis B and cirrhosis undergoing orthotopic liver transplant, hepatitis B hyperimmune IgG is given pre-operatively and post-operatively to prevent reinfection with hepatitis B. This has been shown to be 50-85% effective in preventing recurrence of hepatitis B in the transplanted liver. [11, 12] This efficacy may be improved with the concurrent use of the antiviral lamivudine. [12]

Rabies: Rabies hyperimmune IgG is the standard recommended therapy after exposure to the rabies virus/rabid animal. [13]

Argentine Hemorrhagic Fever: Convalescent plasma from survivors is the standard of care and has been shown to reduce mortality from 50% to 4% if therapy is initiated within 8 days after disease onset. [14]

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

2.3.1.1 Risk of Plasma Transfusions

Common risks of plasma transfusions may include one or more of the following: fever, rash, hives, or headache. Other more serious risks are rare and may include the following: serious allergic reactions including anaphylaxis, bacterial infections, or viral infections like hepatitis B, hepatitis C, and human immunodeficiency virus (HIV).

Transfusion-related acute lung injury (TRALI) may occur, but this risk is minimized by screening female donors for anti-HLA class I and class II antibodies in this study. TRALI is characterized by a clinical constellation of symptoms including dyspnea, hypotension and fever. Although the precise

pathogenesis of TRALI remains unknown, it has been shown to be related to the transfusion of anti-HLA class I and anti-neutrophil antibodies most often from plasma from multiparous women (antibodies presumably generated during pregnancy) or donors who have received multiple blood transfusions though the introduction of universal leukoreduction of blood products has largely mitigated the production of HLA antibodies in response to transfusion. The risk of TRALI was reported as 1 out of 5000 transfusions in 2005 before these safety measures were put into place. [15]

The infused plasma volume of 2 units is roughly 500 mL, so there is the risk of volume overload in the recipient, which could cause pulmonary edema. Participants with preexisting conditions who may not tolerate this volume of plasma will be excluded from this study, but this condition could still occur in recipients.

There is also a possible increased risk of thrombotic events associated with plasma transfusion in severely-ill patients. This has been reported in cancer, trauma, and surgical patients [32, 33, 34, 35]. It is possible that an increased risk of thrombotic events, including deep vein thrombosis or pulmonary embolism, could accompany plasma administration in severely-ill patients. There are case reports of pulmonary emboli occurring after administration of IVIG and plasma therapy, though definitive studies assessing risk are lacking. [16] In one series 5 of 10 participants critically ill with H1N1 were shown to have pulmonary emboli. [17] This high percentage has not been shown in other H1N1 series, and pulmonary emboli have been shown to develop in approximately 10-15% of critically ill adults. [18] However, the potential risk of pulmonary embolism exists.

2.3.1.2 Risk of Antibody-Mediated Enhancement (ADE) of Infection

There is a theoretical risk that the antibodies within convalescent plasma could enhance SARS-CoV-2 infection. ADE has been reported in several other virus infections, usually in the setting of antibodies that cross-react between two related viral strains (e.g., Dengue infection) or weak or non-neutralizing antibodies (HIV-1) [36, 37]. We have seen minimal virus evolution, to date, in the COVID-19 pandemic, making cross-reactive antibodies less likely. Convalescent plasma from recently infected individuals likely contains high-titer neutralizing antibodies, making a predominantly weak or non-neutralizing effect less likely. Further, reports of convalescent plasma use in SARS and COVID-19, though few and uncontrolled, have not suggested enhanced infection 26, 30]. Continued study and assessment for ADE is warranted.

2.3.1.3 Risk of Antibody-Mediated Acute Lung Injury

There is a theoretical risk of antibody-mediated acute lung injury with convalescent plasma administration. Antibody-mediated acute lung injury has been reported in a nonhuman primate model of SARS-CoV-1 [38]. In this study, rhesus macaques with anti-SARS-CoV-1 antibodies via active or passive immunization, demonstrated pro-inflammatory lung responses during acute SARS infection. This phenomenon has not been reported in the observational reports of convalescent plasma administration in either SARS-CoV-1 or COVID-19, but remains a theoretical concern, especially in plasma administration during acute or early infection.

2.3.1.4 Risk of Decreased Protective Immunity

Immune responses to past Coronavirus diseases, including SARS and MERS, have been shown to be transient and directly related to the severity of illness. Patients with asymptomatic or mild disease had lower titer and less durable markers of immunity, including antibody responses [39]. Mechanistically, antibody-based therapy aims to neutralize and/or clear virus, leading to less antigen for immune recognition and response maturation. Thus, it is possible that modifying the course of disease and decreasing viral antigen burden could hamper the duration or magnitude of protective immune responses after COVD-19 recovery. This theoretical effect should be further investigated, and convalescent plasma-treated individuals considered for enhanced vaccination strategies, as they are developed. The risk of decreased protective immunity is outweighed in moderately and severely individuals requiring hospitalization and/or ventilation, for whom the immediate risks of disease are more substantial.

2.3.1.5 Risk of Plasma Transfusions Interaction with Immunization

The Advisory Committee on Immunization Practices (ACIP) advises that people who receive plasma products wait 7 months (assuming they receive 10 mL/kg) from administration of the plasma before receiving the measles vaccine (given as MMR - mumps, measles and rubella) or the varicella (chickenpox) vaccine. This is because these are live virus vaccines, and antibodies in the plasma may limit the immune response to the vaccine. Antibody-containing blood products do not interfere with the immune response to yellow fever vaccine and are not believed to interfere with the response to live typhoid, live attenuated influenza, rotavirus, or zoster vaccines. While both varicella and zoster vaccines use an attenuated varicella virus, the zoster vaccine is at least 14 times greater amount of virus than that found in varicella vaccine explaining the difference in ACIP recommendations. The amount of plasma administered in this study is 20-30% less than in the ACIP guidance (7-8 mL/kg for most participants), so the deferral period is likely slightly less (i.e., 5-6 months). [40].

In a separate document, ACIP stresses the importance of rubella and varicella immunity among women of child-bearing age and recommends “the postpartum vaccination of women without evidence of immunity to rubella or varicella with MMR, varicella, or MMRV vaccines should not be delayed because of receipt of anti-Rho(D) globulin or any other blood product during the last trimester of pregnancy or at delivery. These women should be vaccinated immediately after giving birth…[41]. While not explicitly stated, we assume this supersedes the deferral considerations above. Attempts by the sponsor to clarify this issue directly with ACIP were unsuccessful.

2.3.1.6 Risk of Phlebotomy

The primary risks of phlebotomy include local discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, and rarely hematoma, infection, or fainting. At the time of enrollment and during study visits, each participant will be asked about participation in other research studies to ensure that blood draws do not exceed the following amounts for all research protocols combined: 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period for adults, and no more than 5 mL/kg may in a single day (no more than 9.5 mL/kg may be drawn over any 8-week period) for persons under the age of 18.

2.3.1.7 Risk of Nasopharyngeal Swab

The primary risk of a nasal swab is local discomfort. Rarely, there can be local bleeding from the nasal mucosa, which is controlled with local measures such as pressure or packing with gauze.

2.3.1.8 Risk of Oropharyngeal Swab

The primary risk of an oropharyngeal swab is local discomfort. This swab can stimulate the gag reflex, and very rarely vomiting.

2.3.1.9 Risk of Endotracheal Aspirate

The primary risk of endotracheal aspirate is cough, and rarely can cause a small amount of bleeding.

2.3.2 Known Potential Benefits

2.3.2.1 Benefits of Treatment

The benefits of antiviral treatment with convalescent immune plasma in patients with severe COVID-19 disease are unknown. However, it is possible (and it is the hypothesis), that convalescent plasma in addition to standard of care (i.e., supportive care and institutional and/or medical provider recommended therapies) will more rapidly decrease viral replication, reduce the duration and severity of illness, reduce complications, and improve outcomes after infection with COVID-19 compared to not receiving convalescent plasma.

2.3.2.2 Alternatives

The alternative to participation in this study is routine standard of care, which can include supplemental oxygen, fluids, and other symptomatic treatments. Additional treatments for this type of participants may include experimental antivirals and/or immunomodulators (e.g., hydroxychloroquine) determined by clinical practice and the rapidly evolving evidence base.

2.3.3 Assessment of Potential Risks and Benefits

There is a substantial risk of morbidity and mortality in COVID-19 disease, especially in intubated, mechanically ventilated patients. Mortality rates vary across clinical cohorts, but recent reports suggest mortality rates up to 28% in hospitalized patients in China (REFS). At this time, there are no effective COVID-19 therapeutics and standard of care involves supportive therapy (e.g., oxygen, fluids), with consideration of a variety of unproven, experimental treatments (e.g., antivirals and immunomodulators).

The administration of blood products, including plasma, is a common and well tolerated clinical option used in multiple indications. There are limited reports of the effects of convalescent plasma for COVID-19, with just two small observational studies describing a total of 15 patients, to date [30, 31]. The experience from these studies and studies of convalescent plasma in other viral infections suggest that plasma administration is safe and well tolerated and may confer clinical benefit. Thus, for severe COVID-19 disease, the possible therapeutic benefit of convalescent plasma outweighs the minimal safety risks.

2.3.3.1 Assessment of Potential Risks and Benefits in Pregnant Individuals

2.3.3.1.1 Rationale for inclusion of Pregnant Women in COVID-19 clinical research

There is growing consensus on the ethical and practical need to more proactively consider inclusion of pregnant women in clinical research, including in COVID-19 studies [42]. Formal studies provide evidence-based guidance on treatment options for application in medically compromised pregnancies. The supervision of the patient and the quality of the data acquired in formal, preferably controlled, studies is superior to that received in the post-marketing environment. Safety and efficacy information will be obtained sooner and with fewer pregnant women and fetuses exposed than if the drug information is obtained following its release on the market (recognizing, as with all drugs, that some objectives cannot be met until widespread use occurs). In particular, advocacy groups recommend that pregnant women should be included in clinical research when participation in a study provides potential therapeutic benefit and the anticipated benefits exceed the anticipated risks and when their exclusion cannot be justified by scientific rationale [43] .

2.3.3.1.2 Risks and Benefits of plasma and antibody administration in Pregnant Women

The use of fresh frozen plasma in pregnancy is considered standard of care and is used for several conditions, including massive bleeding or coagulation disorders, as described in clinical society guidelines, (eg, the British Royal College of Obstetrics and Gynaecologists) [44]. Further, the use of antibody preparations, like IVIG, are used commonly to treat autoimmune or coagulation disorders and to protect the fetus from maternal antibody disorders [45, 46, 47]. The known risks of plasma infusion, including TRALI and volume overload complications discussed above for all populations, remain issues for pregnant women, but have not been reported in higher frequency or severity. Given the frequent and generally safe experience with plasma administration and the potential benefit of plasma in severe-disease, administration of convalescent plasma is regarded as a reasonable strategy to evaluate.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives

The overall objective of the study is to evaluate the safety and explore the efficacy of treatment with convalescent plasma plus standard care vs. standard care alone in severely ill hospitalized participants with confirmed COVID-19 disease.

The primary safety objective will be assessed by the cumulative incidence of serious adverse events (SAEs) at Study Day 29.

The primary efficacy objective will be assessed a comparison of the clinical severity between participants in the treatment versus control arms, where severity is measured by the modified 8-point ordinal clinical severity scale at Day 29. The modified score treats all participants who have reached levels 1-3 as recovered.

3.2 Secondary Objectives and Endpoints

For the secondary objectives, we will compare treatment and control arms based on the following list of clinical endpoints which capture different aspects of disease severity.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
1. Evaluate the clinical efficacy of convalescent plasma administration by comparing treatment vs control arms • **Clinical Severity** ○ Ordinal scale: ▪ Time to recovery, defined by time to levels 1-3 on the ordinal scale ▪ Time to an improvement of one category and two categories from Day 1 using an ordinal scale. ▪ Participant clinical status using ordinal scale at Days 3, 5, 8, 11,15, 22, and 29. ▪ Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29.	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Day 15, 22, and 29. • Clinical status assessment (8-point ordinal scale) includes: 1. Not hospitalized, no limitations on activities. 2. Not hospitalized, limitation on activities and/or requiring home oxygen; 3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 5. Hospitalized, requiring supplemental oxygen; 6. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 7. Hospitalized, on invasive mechanical ventilation or ECMO; 8. Death
○ National Early Warning Score (NEWS): ▪ Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first ▪ Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.	• NEWS assessed daily while hospitalized and on Days 15 and 29.
○ Oxygenation: ▪ Oxygenation free days to Day 29. ▪ Incidence and duration of new oxygen use during the study.	▪ Days of supplemental oxygen (if applicable)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
○ Non-invasive ventilation/high flow oxygen: ▪ Non-invasive ventilation/high flow oxygen - free days to Day 29. • Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.	• Days of non-invasive ventilation (if applicable). • Days of high flow oxygen (if applicable).
○ Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO): ▪ Ventilator / ECMO free days to Day 29. ▪ Incidence and duration of new mechanical ventilation or ECMO use during the study.	• Days of invasive mechanical ventilation (if applicable). • Days of ECMO (if applicable).
• **Hospitalization** ○ Duration of hospitalization.	• Days of hospitalization
• **Mortality** ○ Survival Time ○ 14-day mortality ○ 28-day mortality	• Date and cause of death (if applicable)
2. Evaluate the safety of convalescent plasma plus standard care vs. standard of care alone by: • Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29. • Changes in WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT over time (analysis of lab values in addition to AEs noted above).	• SAEs • Grade 3 and 4 AEs • WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).

3.3 Exploratory Objectives and Endpoints

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Exploratory	
Evaluate the clinical efficacy of convalescent plasma administration as compared to active drug (*e.g.,* Remdesivir) recipients in DMID Protocol Number: 20-0006 or other relevant COVID-19 Protocols • **Clinical Severity** ○ Ordinal scale: ▪ Time to recovery, defined by time to levels 1-3 on the ordinal scale ▪ Time to an improvement of one category and two categories from Day 1 using an ordinal scale. ▪ Participant clinical status using ordinal scale at Days 3, 5, 8, 11,15, 22, and 29. ▪ Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29.	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Day 15, 22, and 29.
○ National Early Warning Score (NEWS): ▪ Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first ▪ Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.	NEWS assessed daily while hospitalized and on Days 15 and 29.
○ Oxygenation: ▪ Oxygenation free days to Day 29. ▪ Incidence and duration of new oxygen use during the study.	Days of supplemental oxygen (if applicable)
○ Non-invasive ventilation/high flow oxygen: ▪ Non-invasive ventilation/high flow oxygen - free days to Day 29. ▪ Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.	• Days of non-invasive ventilation (if applicable). • Days of high flow oxygen (if applicable).
○ Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO): ▪ Ventilator / ECMO free days to Day 29. ▪ Incidence and duration of new mechanical ventilation or ECMO use during the study.	• Days of invasive mechanical ventilation (if applicable). • Days of ECMO (if applicable).

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Evaluate the virologic efficacy of convalescent plasma as assessed by: • Percent of participants with detectable SARS-CoV-2 in OP or ET samples at Days 3, 5, 8, 11, and 15. • Quantitative SARS-CoV-2 in OP or ET samples at Days 3, 5, 8, 11, and 15. • Qualitative SARS-CoV-2 in OP or ET samples at Days 3, 5, 8, 11, and 15.	• Quantitative and Qualitative PCR for SARS-CoV-2 in OP or ET swab at Day 1; Days 3, 5, 8, and 11 (while hospitalized) and Days 15, if available.
Evaluate the timing and titer of anti-SARS-CoV-2 antibody responses after convalescent plasma administration	• Plasma antibody binding and neutralization on Day 1 (prior to plasma administration); Days 3, 8, 15, 29, and visit Day 60.
Evaluate the timing and quality of SARS-CoV-2 cellular responses after convalescent plasma administration	• Cellular responses in whole blood on Day 1(prior to plasma administration); Days 3, 8, 15, 29, and visit Day 60.
Evaluate the change in inflammatory responses with convalescent plasma administration	• Plasma and cellular markers of inflammation on Day 1(prior to plasma administration); Days 3, 8, 15, 29, and visit Day 60.
Evaluate the change in clinical status by 8-point ordinal scale and/or NEWS with change in inflammatory markers	• Ferritin, C Reactive Protein, D-Dimer, Fibrinogen, Erythrocyte Sedimentation Rate, Triglycerides, IL-6 on Study Day 1, 3, 5, 8, 11, 15, 29 (when available).
Evaluate the safety of convalescent plasma administration as compared to active drug (*e.g.,* Remdesivir) recipients in DMID Protocol Number: 20-0006 • Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29. Changes in WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT over time (analysis of lab values in addition to AEs noted above).	• SAEs • Grade 3 and 4 AEs WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).
Compare the safety of plasma plus standard care vs. standard care alone by cumulative incidence of serious adverse events by day 60	• SAEs

4 STUDY PLAN

4.1 Study Design

80 participants will be enrolled and randomized. All participants will be followed through Study Day 60. The study population will consist of adults >18 years of age hospitalized, intubated and mechanically ventilated with confirmed COVID-19 pneumonia caused by SARS-CoV-2.

This randomized, controlled, open-label, phase 1 trial will assess the safety and efficacy of convalescent plasma in severely ill, hospitalized participants with pneumonia due to COVID-19. This study will enroll adults over the age of 18, including pregnant women.

A total of 80 eligible participants will be randomized 1:1 to either receive standard care and 2 units of convalescent plasma collected from ABO-compatible donors who have recovered from COVID-19 or standard care alone. Participants in the treatment arm will receive convalescent plasma on Study Day 1 in addition to standard care. Participants will be assessed daily while hospitalized through Study Day 29. Participants discharged from the hospital will be asked to attend remaining study visits at Study Days 15, 22, 29, and 60. The Study Day 22 visit may be conducted by phone. All participants will undergo a series of safety, efficacy, and laboratory assessments. Blood samples will be collected on Days 1 (prior to plasma administration), 3, 5, 8, 11, 15, 29, and 60. Oropharyngeal or endotracheal samples will be collected as possible on Days 1 (prior to plasma administration), 3, 5, 8, 11, and 15. Given the COVID-19 restrictions and the difficulty some of the participants might have to attend an in person visit after hospital discharge, the collection of Day 60 data for primary and secondary endpoints and the collection of Day 60 research samples for exploratory tests may be performed up to 90 days following the Day 60 visit.

4.2 Scientific Rationale for Study Design

This randomized, open-label trial is intended to evaluate the effect of treatment with convalescent plasma in hospitalized COVID-19 patients. There are no data from randomized, controlled trials demonstrating clinical benefit for any therapies for COVID-19. Further, there are no randomized, controlled studies of passive immunotherapy for coronavirus related disease, including SARS, MERS, and COVID-19. Thus, quality evidence from controlled trials is valuable.

The current standard of care for COVID-19 patients is unclear and in flux. Several treatment options are recommended for COVID-19 patients as per Departmental or Hospital system guidelines, but none are FDA-approved nor supported by strong clinical trials evidence. Given the potential severity of disease in COVID-19 patients and the limited validated treatment options available, the study will include hospital system- or medical provider-directed standard of care treatments in both treatment and control arms, including experimental or non-FDA approved therapeutics.

There are three possible benefits of a plasma infusion that may be unrelated to any binding of SARS-CoV-2 viruses by antibodies in the plasma:

- Volume load
- Oncotic load

- Fc binding – The Fc of the antibodies (the non-virus binding end of the antibody) present in plasma (both influenza and other antibodies) will bind to receptors in the body. This binding may modulate the immune response. It is for this reason that IVIG (concentrated antibody preparations) is sometimes used in autoimmune diseases. Volume load would have the largest effect. This volume effect could be beneficial, though a volume load in an ill population may also increase the risk to the subject.

Nonimmune plasma was considered as a placebo, but there may be cross-reactive antibodies in this plasma that would complicate analysis and/or nonspecific immune modulating effects from Fc binding. A half-normal saline with albumin was entertained as a better physical representation of study plasma, but this approach has several shortcomings. First, the albumin will provide oncotic pressure, i.e., it would not be a true inactive placebo. Second, the sequential labeling in the blood bank would be difficult to replicate on this compound, and therefore the labeling would be able to distinguish placebo from active plasma. Therefore, it would still need to be masked. Finally, identification of plasma donor without recent COVID-19 is challenging, given the limited availability of serologic assays to disprove recent infection. Thus, many asymptomatic donors may have recently been infected COVID-19 and their plasma would not serve as a control.

Given the potential for increased risk with a saline control, and the inability to effectively blind the study (discussed below) immune plasma will be compared with standard care (i.e., there is no comparator infusion, saline or other). If a treatment effect is determined to exist, then subsequent studies can dissect the components of the treatment effect (volume load, Fab binding of virus, Fc binding with immune modulation, and oncotic pressure).

This study is not blinded. Saline or other controls would be significantly different in appearance compared to plasma. Plasma needs to be distributed from blood banks. However, hospital blood banks do not have the capabilities of distributing placebo. Conversely, pharmacies could not distribute the study plasma. Hospitals have systems for double-checking administration of blood products, as well as documentation of the administration of blood products in the hospital record (paper or electronic). Mechanisms for documentation of administration of a study drug would not be sufficient for documentation of a blood product, and the mechanisms for documentation of plasma products would not be amenable to documentation of a blinded study product. Therefore, effectively blinding the study, wherein there is high likelihood that the investigative team does not know whether the participant received plasma or saline, was not felt to be practical.

Participants will be randomized in a 1:1 ratio. Higher ratios were considered (i.e., 2:1 or 3:1 active:control); however this would hamper the assessment of the control rate of the various efficacy assessments, making planning future confirmatory studies difficult.

4.3 Justification for Dose

Plasma volume in adults can be estimated by multiplying actual body weight in kilograms by 40 mL/kg. [19] For 70-kg person, the plasma volume would be estimated to be 2800 mL (40 mL/kg x70 kg).

Standard plasma dosing is 2 units, (~200-250 mL per unit). At the discretion of the principal investigator, patients less than 90kg or with concern for volume overload, may receive 1 unit of plasma.

The volume of a unit of plasma is 200-250 mL. Therefore, the study dose of 2 units of plasma could be equal to as much as 500 mL. A plasma volume of 500 mL at an anti-SARS-CoV-2 titer of 1:160 would increase the titer in the plasma to approximately 1:25; then fall to 1:13 after equilibration with the extravascular space.

The dose of anti-SARS-CoV-2 antibodies needed to modify COVID-19 clinical disease is not known. The range of anti-SARS-CoV-2 titers in individuals who have recovered from COVID-19 is not fully characterized; in the recently described cohort of 5 patients receiving convalescent plasma, anti-SARS-CoV-2 titers ranged from 1:1,800 to 16,200 by ELISA for IgM and ELISA for IgG, and 1:80 to 1:480 to neutralizing antibody (Shen JAMA 2020). A second observational description of convalescent plasma in China identified ten donors. In their cohort of 40 plasma donors, 39 had neutralizing antibody titers >1:160, while a single donor had titers of 1:32, as determined by plaque reduction assay (Duan PNAS 2020).

In Influenza studies, Rockman et al demonstrated in a H5N1 model in ferrets, that achieving a HI titer of 1:8 with a hyperimmune IVIG without any other antivirals was sufficient in preventing death if given early in the illness (during fever), and in delaying death if given at the onset of severe disease. [20]

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the Day 60 visit shown in the Schedule of Activities (SoA), Appendix 12.1. Given the COVID-19 restrictions and the difficulty some of the participants might have to attend an in person visit after hospital discharge, the collection of Day 60 data for primary and secondary endpoints and the collection of Day 60 research samples for exploratory tests may be performed up to 90 days following the Day 60 visit.

5 STUDY POPULATION

5.1 Inclusion Criteria

1. Adult ≥18 years of age

2. Laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other authorized or approved assay in any specimen collected within 72 hours prior to enrollment.

   Note – An exception must be requested to the Sponsor if ≥72 hours since positive test.

3. Hospitalized in participating facility.

4. Documentation of pneumonia with radiographic evidence of infiltrates by imaging (e.g., chest x-ray or CT scan).

5. Abnormal respiratory status that is judged worse than baseline by the investigator and as documented at any point within 24 hours prior to randomization, consistent with ordinal scale levels 5, 6 or 7, specifically defined as:

   - Room air saturation of oxygen (SaO2) < 93%, OR
   - Requiring supplemental oxygen, OR
   - Tachypnea with respiratory rate ≥30

6. Patient or proxy is willing and able to provide written informed consent and comply with all protocol requirements

5.2 Exclusion Criteria

1. Contraindication to transfusion (e.g., severe volume overload, history of severe allergic reaction to blood products), as judged by the investigator.
2. Clinical suspicion that the etiology of acute illness (acute decompensation) is primarily due to a condition other than COVID-19

3. Receipt of other investigational therapy as a part of another clinical trial.

   a. *Note: investigational therapies used as part of clinical care, (eg, remdesivir, hydroxychloroquine) are permissible.*

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

After the screening evaluations have been completed, the investigator or designee is to review the inclusion/exclusion criteria and determine the participant's eligibility for the study.

Only the reason(s) for ineligibility will be collected on screen failures. Participants who are found to be ineligible will be told the reason(s) for ineligibility.

Individuals who do not meet the criteria for participation in this study (screen failure) because of an abnormal laboratory finding may be rescreened once.

5.5 Strategies for Recruitment and Retention

5.5.1 Recruitment

Screening will begin with a brief discussion with study staff. If patient is mechanically ventilated and both studies are open to enrollment, information about both PennCCP-01 and PennCCP-02 will be provided to all potential participants and or legally authorized representative. Information regarding the risks and benefits and scientific aims of the single arm study PennCCP-01 and the randomized, controlled study PennCCP-02 will be presented. If patient is ineligible for PennCCP-01, information about this randomized study only will be presented to potential participants (or legally authorized representative) and questions will be asked to determine potential eligibility. Screening procedures can begin only after informed consent is obtained by a Study Investigator.

5.5.2 Retention

Retention of participants in this trial is very important for determining the primary endpoint. As such, after hospital discharge, participants will be reminded of subsequent study visits and every effort will be made to accommodate the participant's schedule to facilitate follow-up within the specified visit window. Additionally, there are many circumstances that influence the ability to obtain outcome information after discharge. Follow-up visits may be conducted by phone if in-person visits are not feasible. Data and samples may be collected from subject's home, office, or hospital visits.

5.5.3 Costs

There is no cost to participants for the research tests, procedures/evaluations and study product while taking part in this trial. Procedures and treatment for clinical care including costs associated with hospital stay may be billed to the participant, participant's insurance or third party.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

Participants in the treatment arm will receive standard care plus 2 units of COVID-19 convalescent plasma on Study Day 1. Participants will receive plasma compatible with their blood type (per standard blood bank practice).

6.1.2 Dosing and Administration

Participants will be randomized 1:1, stratified on mechanical ventilation and receipt of remdesivir at baseline, to receive either PCCP and standard care (treatment arm) or standard care alone (control arm).

For those participants assigned to the treatment group, the study plasma should be administered as soon as possible. Before administration of study plasma, the investigator must check for appropriate investigational study label on the plasma bag.

The calendar date and 24-hour clock time for study plasma administration should be recorded for the start and end of each infusion. The two infusions should be separated by at least 1 hour after the end of the first and the start of the second infusion in order to assess for any immediate AEs from the first unit. The interval may be extended if clinically indicated. This should be noted on the infusion record and will not be considered a protocol violation.

If an AE considered related to the administration of the investigational product occurs during infusion, the infusion may be slowed temporarily or permanently discontinued, as deemed appropriate by the investigator. As a guide, local side effects (e.g., infusion site burning), nonallergic systemic effects (e.g., chills), and mild allergic reactions (itching, hives) can generally be alleviated by slowing the rate of infusion, whereas serious allergic side effects (e.g., wheezing, hypotension) should result in the cessation of study plasma infusion. The treating investigator is ultimately responsible for making the decision to slow or stop study plasma infusion. If the infusion is discontinued, the participant should be treated according to best available local practices and procedures, and the Principal Investigator should notify the Sponsor Medical Director and HUP Blood Bank. Reason(s) for premature discontinuation of any plasma infusion must be documented in the medical record (source document) and on the CRF.

As with any foreign protein, allergic reactions to dose administration are possible. Therefore, appropriate drugs such as Benadryl® and epinephrine and medical equipment to treat acute allergic reactions must be immediately available, and study personnel must be trained to recognize and treat allergic reactions. If generalized urticaria, hypotension, or anaphylaxis occurs, the infusion of plasma should be immediately discontinued. Treatment should be given in an appropriate timeframe as medically indicated.

All participants will be observed for at least 1 hour after administration of study plasma. Appropriate medical treatment should be given as needed based on best available local practices and procedures.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

The Penn Blood Bank will release a thawed product, in a bag containing between 200-250 mL. The Principal Investigator will ensure an adequate accountability of the investigational product

6.2.2 Formulation, Appearance, Packaging, and Labeling

The product ready to be administered will be provided in a bag labelled using an ISBT-128 compliant label and will include the investigational product language as required by regulation. Product Storage and Stability.

Product will be stored in the HUP Stem Cell Laboratory until it is released to the PI at the time of transfusion.

6.2.3 Preparation

Preparation: Frozen product will be transported from the HUP Stem Cell Laboratory back to the HUP Blood Bank to be thawed before issuing to the patient's transfusion team.

6.3 Measures to Minimize Bias: Randomization and Blinding

Individuals will be randomized to the intervention or control arm in a 1:1 ratio. Randomization will occur in a blinded fashion using Redcap. Allocation will be determined using a permuted block algorithm with varying block sizes. We will stratify randomization based on whether or not a patient is on mechanical ventilation and on remdesivir at baseline. Though the intervention will not be blinded, we will attempt to minimize bias by blinding study personnel, such as individuals running laboratory assays, to the extent that it is possible.

6.4 Study Intervention Compliance

Not applicable.

6.5 Concomitant Therapy

All participants will be monitored throughout the study for use of concomitant medications. Any prescription medications including IVIG, blood products, over-the-counter (OTC) preparations, herbal remedies, and/or nutritional supplements taken during the study period must be recorded on the CRF.

It is also anticipated that participants may be treated with antibacterial agents, either for concomitant infection, or bacterial superinfection. The final decision for antibiotics (need, drug[s] and dose) and other medications will be made by the treating physician (except as noted below under Prohibited Medications).

6.5.1 Rescue Medicine

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants will be considered to have completed the study if they are followed through Study Day 60 (+ 90 days) and complete the final study visit (or followed through to death at or before 60 days).

7.1 Discontinuation of Study Intervention

Participants (or their legal surrogates if participants become unable to make informed decisions) can terminate study participation at any time without prejudice. If a participant terminates participation before completing the study, the reason for this decision will be recorded in the CRF. Participants who withdraw from the study will not be replaced.

Participants who indicate interest in withdrawing from the study should also be asked permission to be contacted at Day 29 and Day 60 (+90 days) by telephone for vital status (date of discharge, disposition, and any adverse events that occurred during the study). This is not considered full withdrawal of consent, but the modified consent for limited follow-up should be noted in the medical record.

Participants who fully withdraw consent will not be contacted further.

7.2 Participant Discontinuation/Withdrawal from the Study

The investigator also has the right to withdraw participants from the study. Participants may be withdrawn from the study for either of the following reasons:

- The participant is lost to follow-up.
- The investigator believes that continuation in the study would be detrimental to the participant.

If appropriate, the participant should not be fully withdrawn but rather have limited further study interventions. This limited follow-up would entail contacting the participant on Day 29 by telephone for vital status (date of discharge, disposition, and any AEs that occurred during the study). The reason for withdrawal from the study is to be recorded on the CRF.

If a non-serious AE is unresolved at the time of discontinuation, efforts should be made to follow up until the event resolves or stabilizes, the participant is lost to follow-up, or there is some other resolution of the event. The investigator is to make every attempt to follow all SAEs to resolution.

7.3 Lost To Follow-Up

Participants who miss a study visit should be contacted to reschedule. If participants cannot be contacted immediately, attempts should continue until study completion. Lost to follow-up is defined as unsuccessful contact after at least two documented telephone calls and one written letter.

Any participant withdrawn from the study will not be replaced.

8 STUDY ASSESSMENT AND PROCEDURES

8.1 Screening and Efficacy Assessments

For all efficacy assessments and follow-up visits, refer to SoA (Table 4) for procedure to be done, and details below for each assessment.

8.1.1 Screening Procedures

After the informed consent, some or all of the following assessments are performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Confirm the positive SARS-CoV-2 test result.
    - If the original sample was >72 hours prior to planned randomization, an exception must be requested to the Sponsor.
- Take a focused medical history, including the following information:
    - Day of onset of COVID-19 signs and symptoms
    - History of chronic medical conditions related to inclusion and exclusion criteria
    - Medication allergies
    - Review medications and therapies for this current illness taken in the 7 days prior to Day 1 and record on the appropriate CRF.
- Women of childbearing potential should be counseled to either practice abstinence or use at least one primary form of contraception from screening through Day 60.
    - Acceptable forms of contraception include barrier methods, copper or hormonal IUDs, implantable hormonal contraception, or oral contraceptives.
    - Note: If a woman is either postmenopausal (i.e., has had ≥12 months of spontaneous amenorrhea) or surgically sterile (i.e., has had a hysterectomy, bilateral ovariectomy (oophorectomy), or bilateral tubal ligation), she is not considered to be of childbearing potential
- Obtain height and weight (height can be self-reported)
- Review results of recent radiographic imaging (x-ray or CT scan)
- Perform a targeted physical exam focused on lung auscultation
- Check a SpO2

- Obtain blood for screening laboratory evaluations if not done as part of routine clinical care in the preceding 48 hours:
    - type and screen
- Clinical screening laboratory evaluations will be performed locally by the site laboratory.
- The overall eligibility of the participant to participate in the study will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team.
- Study participants who qualify will be immediately randomized.

8.1.1.1 Screening Procedures in Pregnant Women

To best understand risk and benefit of study enrollment for pregnant women, we will follow this SOP for consideration of enrollment.
Standard Operating Procedure for Pregnant Patients:

1. Maternal Fetal Medicine (Obstetrical service managing pregnant patients) consults Infectious Diseases
2. Obstetrics (OB) and Infectious Diseases (ID) study physicians discuss possible enrollment in study, considering factors including fetal gestational age, maternal co-morbidities, severity of COVID-19 disease, volume status.
3. Discussion between OB, ID, patient (if possible) and patient legally authorized representative on risks and benefits of study.
4. With enrollment and plasma administration: close observation in acute setting (eg, in COVID-19 unit, ICU or Labor & Delivery)
5. Continue close monitoring after plasma administration. Participants will be followed through the 60 days of the study. Data will not be collected after the Day 60 visit nor will data be collected on neonates.

The volume of venous blood to be collected is presented in Table 2.

8.1.2 Measures of clinical support, limitations and infection control

On each study day while hospitalized through Study Day 29, the following measures for the previous day will be recorded. i.e., on Day 3, Day 2 measures are assessed as occurring anytime in that 24 hour period (00:00 to 23:59h):

- Hospitalization
- Oxygen requirement
- Non-invasive mechanical ventilation (via mask) requirement

- High flow oxygen requirement.
- Invasive mechanical ventilation (via endotracheal tube or tracheostomy tube) requirement.
- ECMO requirement.
- Ongoing medical care preventing hospital discharge (COVID-19 related or other medical conditions)
- Limitations of physical activity (self-assessed).
- Isolated for infection control purpose

If drawn for clinical care, record inflammatory markers, including:

- Ferritin, C Reactive Protein, D-Dimer, Fibrinogen, Erythrocyte Sedimentation Rate, Triglycerides, IL-6.

If and when a participant is discharged from the hospital, they will continue with study visits as an outpatient, for all Study Days that are applicable, including Days 15, 29, and 60. Outpatient visits will involve the participant returning to clinic, unless other reasonable accommodations for evaluations and blood draws can be arranged. Day 22 Study visit can be as a phone call. Given the COVID-19 restrictions and the difficulty some of the participants might have to attend an in person visit after hospital discharge, the collection of Day 60 data for primary and secondary endpoints and the collection of Day 60 samples for exploratory tests may be performed up to 90 days following the Day 60 visit. For these participants, the Day 60 data may be obtained from the information already entered in the clinical records by any clinician, or by contacting the participant by phone up to 90 days following the Day 60 visit to obtain retrospective data.

8.1.3 Ordinal Scale

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. From the measures collected in 8.1.2.1, this ordinal scale can be constructed.

The scale used in this study is as follows:

1. Not hospitalized, no limitations on activities.
2. Not hospitalized, limitation on activities and/or requiring home oxygen;
3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
5. Hospitalized, requiring supplemental oxygen;

6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
7. Hospitalized, on invasive mechanical ventilation or ECMO;
8. Death

By assessing the individual components however, alternative scales can be constructed.

8.1.4 National Early Warning Score (NEWS)

NEWS has demonstrated an ability to discriminate participants at risk of poor outcomes. (Smith, 2016). This score is based on 7 clinical parameters (see Table 1). The NEWS is being used as an efficacy measure. This should be evaluated at the first assessment of a given study day and prior to administration of study product. The 7 parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment and a numeric score given for each parameter (e.g., a RR of 9 is one point, oxygen saturation of 92 is two points). This is recorded for the day obtained. i.e., on Day 3, Day 3 score is obtained and recorded as Day 3.

Table 1: National Early Warning Score (NEWS)

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

Level of consciousness = alert (A), and arousable only to voice (V) or pain (P), and unresponsive (U).

8.2 Exploratory Assessments

8.2.1 Virologic and Serologic Assays

OP swabs or ET samples and blood will be collected on Day 1 3, 5, 8, 11, and 15 and stored as outlined in the MOP. Blood samples will be collected on Day 1, 3, 8, 15, 29 and Day 60 visit The assays used to detect and characterize virologic and immune responses are in development or experimental in nature. Therefore, while viral and immunologic responses to convalescent plasma therapy are thought to be an important endpoint, considering the limitations above, they are listed as exploratory endpoints.

8.2.2 Alternative Ordinal Scales

Given the limited clinical data available for COVID-19, the best construct of ordinal scale is not known. Additional data may be used to construct different ordinal scales to test their utility in a treatment study. These are hypothesis generating and will not be submitted as part of a final CSR.

8.3 Safety and Other Assessments

Study procedures are specified in the SOA. A study physician licensed to make medical diagnoses and listed on the 1572 will be responsible for all trial-related medical decisions.

- Physical examination: A symptom-directed (targeted) physical examination will be performed at screening and when needed to evaluate possible adverse event(s) (i.e. any new symptoms). No physical exam is needed for routine study visits.

- Clinical laboratory evaluations:

    - Fasting is not required before collection of laboratory samples.

    - Blood will be collected at the time points indicated in the SOA. Clinical laboratory parameters include WBC, differential, Hgb, PLT, Creatinine, glucose, total bilirubin, AST, ALT, and PT.

    - This testing will be performed at each clinical trial site in real time.

Table 2: Venipuncture Volumes[1]

	Screen	**Baseline**							
Day +/- Window	**-1 to 1**	**-1 to 1**	**3±1**	**5±1**	**8±1**	**11±1**	**15±2**	**29±2**	**60±5**
Type and screen	**X 10 mL**								
Safety hematology, chemistry, liver tests		X 10 mL	X 10 mL	X 10 mL	X 10 mL	X 10 mL	X 10 mL	X 10 mL	
Blood for plasma/ serum and cells, including research assays		X 32 mls	X 32 mL		X 32 mL		X 32 mL	X 24 mL	X 32 mL

Total volume	10 mL	42 mL	42 mL	10 mL	34 mL	10 mL	42 mL	34 mL	32 mL
Total volume all study days									264 mL

1 See SOE for specific tests to be performed.
2 Total volume calculated assumes no routine clinical laboratory results that can be used for the screening, baseline, and safety laboratory values.
3 Samples may be collected for up to 90 days following the Day 60 visit.

8.3.1 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

If a physiologic parameter (e.g., vital signs, or laboratory value) is outside of the protocol- specified range, then the measurement may be repeated once if, in the judgment of the investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition or was an error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Events (AE)

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

Given the nature of severity of the underlying illness, participants will have many symptoms and abnormalities in vital signs and laboratory values. All Grade 3 and 4 AEs will be captured as AEs in this trial.

8.4.2 Definition of Serious Adverse Events (SAE)

A SAE is defined as “An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or

- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant 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, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

"Life-threatening" refers to an AE that at occurrence represents an immediate risk of death to a participant. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE.

All SAEs, as with any AE, will be assessed for severity and relationship to study intervention by the Principal Investigator or qualified sub-investigator and will be recorded on the appropriate CRF.

All SAEs will be followed through resolution or stabilization by the Principal Investigator or qualified sub-investigator.

8.4.3 Classification of an Adverse Event

The determination of seriousness, severity, and causality will be made by the Principal Investigator or qualified sub-Investigator upon medical judgment. Qualified sub-investigator includes but is not limited to physicians, physician assistants, and nurse practitioners.

8.4.3.1 Severity of Event

All AEs and SAEs will be assessed for severity, according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) (see Appendix 12.2).

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the participant's usual activities of daily living.

- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

- Severe (Grade 4): Events that are potentially life threatening.

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop dates (duration) of each reported AE will be recorded on the appropriate CRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

8.4.3.2 Relationship to Study Intervention

For each reported adverse reaction, the PI and Sponsor must assess the relationship of the event to the study product using the following guideline:

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

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to PCCP administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the PCCP (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the PCCP, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to PCCP administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the <study intervention>) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- Unrelated – The AE is completely independent of PCCP administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.3.3 Expectedness

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

8.4.4 Time Period and Frequency for Event Assessment and Follow-Up

Safety will be assessed by monitoring and recording potential adverse effects using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017 at each study visit. Participants will be monitored by medical histories, physical examinations, and other studies. If the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) (See Appendix 12.2) grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the participant, the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade (DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1 (July 2017). See Appendix 12.2.

2. Duration (start and end dates)

3. Relationship to the study treatment or process – [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?

4. Expectedness to study treatment or process – [Unexpected – if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol].

5. Action taken with respect to study or investigational treatment or process (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

7. Whether the event is serious

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

For this study, all Grade 3 and 4 AEs, all SAEs occurring from the time the informed consent is signed through the Day 60 visit will be documented, recorded, assessed, and reported. In addition, any grade 1 or 2 or higher hypersensitivity reaction is also reported as an AE.

8.4.5 Adverse Event Reporting

8.4.5.1 Reporting Period

Adverse events will be reported from the time of informed consent until study completion.

8.4.5.2 Investigator Reporting: Notifying the Study Sponsor

Information on all AEs should be recorded on the appropriate CRF.

Every SAE, regardless of suspected causality (e.g., relationship to study product(s) or study procedure(s) or disease progression) must be reported to the sponsor within **24 hours** of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported to the Sponsor as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

Send the SAE report to the psom-ind-ide@pobox.upenn.edu indicating the protocol number and the study product.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer.

8.4.5.3 Investigator Reporting: Local Reporting Requirements

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

8.4.6 Serious Adverse Event Reporting

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered related to the Penn COVID-19 Convalescent Plasma, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the Penn COVID-19 Convalescent Plasma caused the event. Study endpoints that are serious

adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the Penn COVID-19 Convalescent Plasma and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The SAE reports to the Sponsor should be sent to: psom-ind-ide@pobox.upenn.edu indicating the protocol number and the study product

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction per applicable regulations. In addition, the sponsor must notify the FDA, as applicable and all participating investigators of potential serious risks, from clinical trials or any other source, as per the applicable regulation.

A SUSAR is any SAE where a causal relationship with the study product or process or procedure is at least reasonably possible but is not listed in the IB, Package Insert, and/or Summary of Product Characteristics

8.4.7 Reporting Events to Participants

The Sponsor does not plan to report adverse events to participants unless it is required by regulation, the IRB or FDA.

8.4.8 Events of Special Interest

There are no events of special interest in this protocol.

8.4.9 Reporting of Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug or process may have interfered with the effectiveness of a contraceptive medication or method. Pregnancy is not a contraindication to receipt of plasma transfusion and will not be reported or followed if not associated to an adverse event.

8.5 Unanticipated Problems

8.5.1 Definition of Unanticipated Problems (UP)

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

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

UP are generally non-medical events, as medical events would be capture under AEs.

8.5.2 Unanticipated Problem Reporting

Unanticipated problems (UPs) such as:

- Post-marketing withdrawal of a drug, device, or biologic used in a research protocol due to safety concerns.
- FDA ban of a drug, device, or biologic used in a research protocol due to safety concerns.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the participant to remain on the study
- Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.) should be reported by the investigator to the Sponsor and the reviewing Institutional Review Board (IRB). The UP report will include the following information:
- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported as any other SAE.
- Any other UP will be reported to the Sponsor and IRB within 3 days of the investigator becoming aware of the problem.

8.5.3 Reporting Unanticipated Problems to Participants

The Sponsor does not plan to report adverse events to participants unless it is required by regulation, the IRB or FDA.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

- **Primary Safety Endpoint:** Cumulative incidence of serious adverse events (SAEs), i.e. the proportion of individuals with at least one SAE, at Day 29.

- We hypothesize that 2 units of convalescent plasma will be safe and will not result in a difference in SAE rates between the experimental and control arms. The analysis will be primarily descriptive summaries by arm. We will calculate the proportion of individuals that experience at least one SAE by arm, along with 95% Clopper Pearson confidence intervals. We expect any related AE to happen relatively shortly after infusion but will assess the AE at all study timepoints. Overall SAE rates, those broken down by system organ class and preferred term will be summarized.

- **Primary Efficacy Endpoint:** Comparison of clinical severity between patients on the experimental versus control arms, determined by the modified 8-point ordinal severity score on Study Day 29. The modified score treats all subjects who have reached levels 1-3 as recovered.

- The key parameter of interest will be the comparison of clinical severity between individuals receiving the experimental intervention versus control, as measured by a clinical severity score that takes into account the modified 8-point ordinal severity score in a prioritized manner. For the modification, recovery will be defined by reaching levels 1-3 on the 8-point ordinal severity score. The null hypothesis is that experimental individuals will have the same median severity as control individuals. The severity score is based on a procedure by Shaw and Fay 2016 [21], which ranks participants based on their Day 29 ordinal severity. All survivors better than non-survivors, individuals with shorter recovery times as better, and individuals with shorter times to death as worse. For individuals who survive but had not yet recovered by Day 29, they will be ranked according to their Day 29 ordinal severity, with individuals achieving the same ordinal severity being ranked according to time to reaching that level of severity. More details are provided in the Statistical Analysis Plan (SAP). This type of severity score, or prioritized outcome, has been advocated in many settings such as infectious disease and cardiovascular outcome settings [22,24,25]. This analysis will have more power to detect differences than looking only at one individual endpoint. Shaw and Fay 2016 showed this test statistic can be interpreted as a weighted average of the log-rank type test statistic for survival and the one for time to recovery amongst survivors. The individual endpoints, time to recovery and time to death, will also be examined as secondary endpoints.

- **Secondary Efficacy Endpoint(s):** Comparison between arms of time to recovery and survival.

- The null hypothesis is that the two arms will have the same recovery time and the same survival time. Kaplan-Meier survival curves will be calculated by arm and compared with a Peto-Peto generalized Wilcoxon test. In the event that deaths that occur, the cumulative incidence of recovery will be estimated and compared between groups using Gray's test, which will be able to capture a lower time to recovery due to either a slower event rate or a higher death rate. For interpretive purposes the cause specific hazard ratios for will also be calculated for each event type,

survival and recovery, along with the Peto-Peto test. In the event of no deaths, time to recovery will be summarized with the Kaplan-Meier and compared using the Peto-Peto generalized Wilcoxon test. Analyses of other secondary endpoints listed in Section 3.2 are listed below in Section 9.4.

9.2 Sample Size Determination

A total of 80 participants are expected to enroll and be randomized in a 1:1 fashion to one of two study arms. Sample sizes are determined by desire to estimate safety and to provide a preliminary idea of efficacy. Given patients will be hospitalized at enrollment, we expect very low missing data rates for early safety and efficacy endpoints. We also expect to be able to have good follow-up post discharge until the end of the study. Patients will be analyzed for safety if they receive at least one dose of the experimental treatment. For efficacy endpoints, analyses will be according to the intent-to-treat principle and outcomes on all enrolled participants will be included for analysis. All power calculations assume Type I error rate of alpha=0.05. Power calculations were done using STATA/SE v16.0.

With a sample size of 40 for a given arm, the expected probability of observing zero or at least one adverse event at varying underlying adverse event rates under a binomial distribution is shown below in Table 3. At this sample size, it is likely to see at least one person with an adverse event even with relatively small rates of adverse reactions. For example, 40 individuals in one arm, there is an 80% chance of observing at least one individual with an event if the underlying AE rate is 4%. The analysis of AE rates will primarily be descriptive due to the lack of power to make formal comparisons with the control arm.

Table 3. Probability of detecting zero individuals or at least one individual with an Adverse Event (AE) for a variety of different underlying AE rates and sample size N =40

AE rate	Pr(0 events)	Pr(1+ event)
0.001	0.96	0.04
0.005	0.82	0.18
0.01	0.67	0.33
0.02	0.45	0.55
0.03	0.30	0.70
0.04	0.20	0.80
0.05	0.13	0.87
0.10	0.01	0.99

While the sample size is driven by safety considerations, we also consider the operating characteristics of the proposed sample size for the analysis of the primary and secondary efficacy endpoints. The primary efficacy outcome is a comparison of the clinical severity score. The severity score is based on

a procedure by Shaw and Fay 2016 [21], which ranks all survivors better than non-survivors, individuals with shorter recovery times as better, individuals with shorter times to death as worse, and non-recovered survivors ranked according to their Day 29 severity score. We considered the power to reject the null hypothesis that there is a 50-50 chance that the individuals receiving the experimental treatment had lower severity compared to the control arm. The analysis of the Win Ratio [22], which simply ranks the experimental participant with a matched control participant as either better or worse by considering the time to death, if evaluable, and otherwise considers the patient ranking according to the time to recovery, or time to Day 29 severity score if not-recovered, and reduces to a simple binomial proportion. For 40 matched experimental-control pairs, we have over 80% power to reject the null proportion= 50% if the experimental treatment is associated with a 80% or higher probability of having better severity than a control participant. The proposed analysis for this endpoint, described in the previous section, is expected to have even better power by also considering the timing of the event and not just the binary outcome of better or worse [21].

One can also consider the power to detect a difference in the secondary survival and recovery time endpoints. Given the sample size of 40 per arm, only very large differences would be detectable with 80% power. For example, we will have about 80% power to detect a difference between arms if the underlying event rate was 0.50 vs 0.80. Power calculations rely on the Pearson's chi-squared test approximation; log-rank statistics provided similar power to detect a hazard ratio of about 0.30.

9.3 Populations for Analyses

- The **safety analysis set** includes all participants who received any amount of the study intervention and for whom post-infusion safety data are available.

- The **per-protocol (PP) analysis set** comprises all participants who completed 1 or 2 unit infusions, have no important protocol deviations, and have valid endpoint data available. These will be documented and tabulated.

- The **intent-to-treat analysis set** includes all participants who were randomized.

9.4 Statistical Analyses

9.4.1 General Approach

Descriptive statistics (mean, standard deviation, minimum, median interquartile range, and maximum values for continuous variables; and frequencies and percentages for categorical variables) will be computed for all study variables for the above populations. Unless otherwise specified, a complete case analysis will be considered such that missing values will not be replaced, and calculations will be done on available reported values. If there is a substantial amount of missing data we may consider imputation methods and adjust the analyses accordingly. Analyses will primarily be descriptive; estimates will be presented with 95% confidence intervals. Any significance testing will be done at the 0.05 level. Details for the primary and key secondary analyses are provided below. A formal Statistical Analysis Plan (SAP) will be developed prior to performing analyses of the study endpoints.

9.4.2 Analysis of the Primary Endpoint(s)

The primary safety endpoint is cumulative incidence of serious adverse events (SAEs) at Day 29, calculated separately by arm as the percent of individuals who had at least one SAE by Day 29. The SAE rate at all other time points of the study will also be calculated. The overall SAE incidence will be presented, as well as separately by system organ class and preferred term groupings. Percentages will be based on the number of participants who were treated (the safety analysis set). Additional frequencies will be presented with respect to maximum severity and to relationship to COVID19 and study product. Multiple occurrences of the same AE will be counted only once according to the highest occurring grade and relationship to study product/COVID19.

The primary efficacy endpoint is the clinical severity score and will be calculated based on all randomized individuals (the intent-to-treat set). The key parameter of interest will be the comparison of clinical severity between individuals receiving the experimental intervention versus control, as measured by a clinical severity score that takes into account the survival time, recovery time, and Day 29 severity score for survivors who had not recovered by Day 29. Recovery is defined by time to reaching levels 1-3 in the 8-point ordinal scale. The severity score for the primary efficacy endpoint is calculated based on a procedure proposed by Shaw and Fay 2016 [21], which ranks all survivors better than non-survivors, individuals with shorter recovery times as better, and individuals with shorter times to death as worse. Shaw and Fay 2016 showed this test statistic can be interpreted as a weighted average of the log-rank type test statistic for survival and the one for time to recovery amongst survivors. If there are participants who survive to Day 29 but have not yet recovered, their clinical severity will be determined by their Day 29 ordinal severity score, using time to reach that level to rank those who had the same Day 29 ordinal severity. It is anticipated that this analysis will have more power to detect differences than looking only at only an individual endpoint. Secondary endpoints will include a comparison of each of the individual endpoints: time to recovery and survival. Further details for the statistical analysis will be provided in the SAP

9.4.3 Analysis of the Secondary Endpoint(s)

Key secondary efficacy endpoints include survival and time to recovery and will generally be calculated using the intent-to-treat set. Kaplan-Meier survival curves will be calculated by arm and compared with a Peto-Peto generalized Wilcoxon test. In the event that deaths that occur, the cumulative incidence of recovery will be estimated and compared between groups using Gray's test, which will be able to capture a lower time to recovery due to either a slower event rate or a higher death rate. For interpretive purposes the cause specific hazard ratios for will also be calculated for each event type, survival and recovery, along with the Peto-Peto test. In the event of no deaths, time to recovery will be summarized with the Kaplan-Meier and compared using the Peto-Peto generalized Wilcoxon test.

Cumulative incidence curves will be considered for time-to-event endpoints, treating death as a competing risk. Gray's test, or if the cause-specific hazard ratio was of interest the log-rank test, will be used to compare groups. Binary proportions will be estimated along with Clopper-Pearson 95% confidence intervals and compared between arms using Fisher's exact test. Continuous endpoints will be summarized with means, SD and normal 95% confidence intervals; Wilcoxon rank-sum will be used to compare arms for continuous endpoints. Ordinal endpoints (e.g. 8-point clinical severity score) will be summarized by their multinomial proportions across the different categories at Study Day 15,

22 and 29. An exact Mann-Whitney test will be used to test for whether the ordinal clinical severity was higher in one arm versus the other for ordinal endpoints. Further details for the analysis of secondary endpoints will be provided in the Statistical Analysis Plan.

9.4.4 Safety Analyses

The primary outcome is summaries by arm of the cumulative incidence of SAE, as described in Section 8.4.2. Safety endpoints include death through Day 29, SAEs, discontinuation of study drug infusions, and Grade 3 and 4 AEs. Safety events will be analyzed as individual events and as part of a composite endpoint (e.g. any SAE). Proportions at specific study time points and by arm, e.g. Day 15, 22, 29 and 60, will be tabulated, as well as a Kaplan-Meier curve for death and time to first event for the composite endpoint. Each AE will be counted once for a given participant and graded by severity and relationship to COVID-19 or study intervention. AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by system organ class, duration (in days), start- and stop-date. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be summarized. Analyses will be primarily descriptive.

Events that would result in immediate study pause for DSMB review and the potential stopping of the study include: transfusion reactions or coagulopathic events. Plasma transfusion is a safe and commonly used treatment and so we do not anticipate additional SAE, above what these critically ill patients would experience as part of their baseline risk.

9.4.5 Baseline Descriptive Statistics

Baseline characteristics will be summarized for the treatment and control groups. For continuous measures, the mean and standard deviation will be summarized. Categorical variables will be described by the number and proportion in each category. Of interest will be participant demographics, e.g. age, gender, race, as well as clinical and laboratory variables describing co-morbidities and disease severity at baseline. P-values for significance testing between groups, e.g., Fisher's exact test for proportions or Wilcoxon Rank Sum for continuous, will be considered but differences between groups interpreted primarily qualitatively.

9.4.6 Planned Interim Analyses

A Data Safety Monitoring Board (DSMB) will monitor ongoing results to ensure participant well-being and safety as well as study integrity. The DSMB will be convened for a detailed review of safety data after 10 patients have been enrolled and reached day 15 or at 2 months, whichever comes first, and then as needed. No formal statistical interim analyses are planned. Events that would result in immediate study pause for DSMB review and the potential stopping of the study include: transfusion reactions or coagulopathic events. Plasma transfusion is a safe and commonly used treatment and so we do not anticipate additional SAE, above what these critically ill patients would experience as part of their baseline risk.

The study team will provide the DSMB Committee reports of enrollment, baseline characteristics, follow-up rates, and safety data.

9.4.7 Sub-Group Analyses

Subgroup analyses for the primary and key secondary efficacy outcomes will be considered to see where the differences between the treatment and control groups varied across the following subgroups: age, sex, and duration of symptoms prior to enrollment. A forest plot will display confidence intervals across subgroups. We do not expect to have enough sample size to conduct formal interaction tests to determine whether the effect of treatment varies by subgroup.

9.4.8 Tabulation of Individual Participant Data

The time course of participants clinical and laboratory markers will be considered. Frequency of evaluation varies across clinical and laboratory assessments. Adverse event and clinical evaluation will occur daily while individual is in hospital and otherwise include Day 15, 22, 29, and 60. Laboratory measures will generally occur at days 3, 5, 8 and 11 while participant is in hospital. The full list of evaluations are shown in the Schedule of Activities (Appendix 12.1).

9.4.9 Exploratory Analyses

We will analyze a number of biomarkers of immune response and virologic efficacy. Binary proportions will be estimated along with Clopper-Pearson 95% confidence intervals. Continuous endpoints will be summarized with means, SD and normal 95% confidence intervals; for skewed data, non-parametric statistics, such as the median and interquartile range will be considered. Trends over time will be assessed descriptively, as well as with linear mixed effects models if appropriate. We will also consider the clinical efficacy of convalescent plasma administration as compared to active drug (e.g., Remdesivir) recipients in DMID Protocol Number: 20-0006. Analysis of all comparative endpoints will be similar to that for the comparison of the treatment and control groups, as described in Section 9.4.3. Further details will be provided in the SAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

Consent forms describing in detail the Penn COVID-19 Convalescent Plasma, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting the study intervention.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant or legally authorized representative (LAR) where appropriate, and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants/LAR will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants/LAR should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent, either electronically or wet ink signature prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. To avoid paper and bio-contaminants, this will be done via electronic means. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If the participant is able to consent, the process will be done in person and documentation of the participant's consent will be recorded electronically following the University of Pennsylvania IBB guidance.

10.1.2 Study Discontinuation and Closure

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

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the participants; interests.

10.1.3 Confidentiality and Privacy

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

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

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

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

10.1.4 Future Use of Stored Specimens and Data

Secondary Human Participant Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other ''primary'' or ''initial'' activity, such as the data and samples collected in this protocol. Any use of the sample or data for secondary research purposes, however, will be presented in a separate protocol and require separate IRB approval.

Participants will be asked for consent to collect additional blood, the use of residual specimens, and samples for secondary research. Extra blood will be drawn for secondary research during each visit when a study blood samples are obtained.

The stored samples will be labeled with barcodes and a unique tracking number to protect participant's confidentiality. Secondary research with coded samples and data may occur; however, participant confidentiality will be maintained as described for this protocol. An IRB review of the secondary research using coded specimens is required.

Samples designated for secondary research use may be used for understanding the SARS-CoV-2 infection, the immune response to this infection, and the effect of therapeutics on these factors.

Samples will not be sold for commercial profit. Although the results of any future research may be patentable or have commercial profit, participants will have no legal or financial interest in any commercial development resulting from any future research.

There are no direct benefits to the participant for extra specimens collected or from the secondary research. No results from secondary research will be entered into the participant's medical record. Incidental findings will not be shared with the participant, including medically actionable incidental findings, unless required by law.

Participants may withdraw permission to use samples for secondary use at any time by notifying the study doctors or nurses in writing. If the participant subsequently changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

10.1.5 Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB operates under the rules of an approved charter that is written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study sponsor.

10.1.6 Clinical Monitoring

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the Office of Clinical Research monitoring team.

- In an effort to ensure the safety of the study personnel and the monitors during the COVID-19 pandemic, monitoring of the study data will be primarily remote until the restrictions in place as a consequence of the COVID-19 pandemic are lifted.

- The site should ensure that all safety related information is in an electronic record or scanned into a secure access application that the monitor can access. Source data verification will be conducted between electronic record and the sponsor EDC.

- The Sponsor will be provided copies of monitoring reports within the time period set by the DSMP.

- Details of clinical site monitoring are documented in a Data Safety Monitoring Plan (DSMP). The DSMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. The DSMP is written to allow non safety related items to be deferred to later visits if necessary and therefore some items may be deferred to a later visit that can be conducted in person. Close out visits will need a follow up in person visit, at a later date.

- Independent audits or compliance reviews may be conducted by University of Pennsylvania Office of Clinical Research to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the MP.

10.1.7 Quality Assurance and Quality Control

All monitoring and audits are to be performed according to ICH GCP E6(R2).

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

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

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

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

10.1.8 Data Handling and Record Keeping

10.1.8.1 Data Collection and Management Responsibilities

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

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

Clinical and laboratory data will be entered into a 21 CFR Part 11-compliant electronic data capture system (EDC) that includes individual user account level password protection. The EDC used to support this trial is Penn CTMS (Velos version 9) which supports compliant eCRF collection, audit trail capabilities and facilitates source data verification.

10.1.8.2 Study Records Retention

Study related records, including the regulatory file, study product accountability records, consent forms, participant source documents and electronic records should be maintained until the Sponsor and provides notice

10.1.9 Protocol Deviations

The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

If the assessment is determined to be of limited impact (minor deviation), the documentation for this assessment and the outcome should be reported to the Sponsor at the time of annual report. Reporting to the IRB should follow specific local requirements.

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- having the potential to adversely affect participant safety; OR
- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the participant's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

These scenarios should be reported to the Sponsor within 10 business days of discovery. Reporting to IRB should follow local requirements.

10.1.10 Publication and Data Sharing Policy

Following completion of the study, results of this research will be sent for publication in a scientific journal. As this is an adaptive study and given the public health urgency to disseminate results, data from individual comparisons (i.e. the initial 2 study arms) can be published when those arms are fully enrolled and all participants in those arms are followed through to completion of the study.

Data will be available immediately following publication, with no end date, with data sharing at the discretion of the Sponsor. Publication may occur prior to completion of a final clinical study report for the entire trial.

Any publication, press release, and sharing of data for any reason must be shared with sponsor prior to release.

The investigator is responsible for authoring a final clinical study report and sharing with the sponsor team. The Clinical Study Report will be issued within 12 months of data lock and the results summary will be posted to clinicaltrials.gov. A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.11 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore,

persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 Additional Considerations

10.2.1 Research Related Injuries

The PI will assess participant AEs.

Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions. No financial compensation will be provided to the participant by the Sponsor or the participating site for any injury suffered due to participation in this trial.

10.3 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
0.5	16-May-2020	• Original version	
2.0	04-May-2020	• Update eligibility criteria and study endpoints • Add rational for inclusion of pregnant women • Updates to the statistical section • Administrative changes	• To address IRB and FDA stipulations • To address FDA non-hold comments on IND Advice letter • For clarification purposes
2.1	05-May-2020	• Addition of stratified randomization based on participant's receipt of Remdesivir.	• To allow statistical analysis based on the use of Remdesivir as standard care.
2.2	05-May-2020	• Match sample collection dates along the protocol	• Consistency along the protocol
V2.5	12-May-2020	• Clarification of secondary endpoint and inclusion criteria	• For clarity purposes
V3	21-May-2020	• Clarification of primary efficacy endpoint	• To address FDA request
V4	28-Aug-2020	• Clarification of follow up time frame.	• For clarification purposes

11 REFERENCES

1. Morse SS: Factors in the emergence of infectious diseases. Emerg Infect Dis 1995, 1(1):7-15.

2. Bean WJ, Schell M, Katz J, Kawaoka Y, Naeve C, Gorman O, Webster RG: Evolution of the H3 influenza virus hemagglutinin from human and nonhuman hosts. J Virol 1992, 66(2):1129-1138.

3. Nour B, Green M, Michaels M, Reyes J, Tzakis A, Gartner JC, McLoughlin L, Starzl TE: Parvovirus B19 infection in pediatric transplant patients. Transplantation 1993, 56(4):835-838.

4. Koduri PR, Kumapley R, Valladares J, Teter C: Chronic pure red cell aplasia caused by parvovirus B19 in AIDS: use of intravenous immunoglobulin--a report of eight patients. Am J Hematol 1999, 61(1):16-20.

5. Reed EC, Bowden RA, Dandliker PS, Lilleby KE, Meyers JD: Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. Ann Intern Med 1988, 109(10):783-788.

6. Whimbey E, Champlin RE, Englund JA, Mirza NQ, Piedra PA, Goodrich JM, Przepiorka D, Luna MA, Morice RC, Neumann JL et al: Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syncytial virus disease in adult bone marrow transplant recipients. Bone Marrow Transplant 1995, 16(3):393-399.

7. DeVincenzo JP, Hirsch RL, Fuentes RJ, Top FH, Jr.: Respiratory syncytial virus immune globulin treatment of lower respiratory tract infection in pediatric patients undergoing bone marrow transplantation - a compassionate use experience. Bone Marrow Transplant 2000, 25(2):161-165.

8. Medical Management of Smallpox (Vaccinia) Vaccine Adverse Reactions: Vaccinia Immune Globulin and Cidofovir. http://www.bt.cdc.gov/agent/smallpox/vaccination/mgmt-adv-reactions.asp

9. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1999, 48(RR-12):1-37.

10. Kluge T: Gamma globulin in the prevention of viral hepatitis. A study on the effect of medium size doses. Rev Int Serv Sante Armees 1963, 36:Suppl 59-68.

11. Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, Bismuth H: Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med 1993, 329(25):1842-1847.

12. Engler S, Sauer P, Klar E, Stremmel W, Kallinowski B: Prophylaxis of hepatitis B recurrence after liver transplantation with lamivudin and hepatitis B immunoglobulin. Transplant Proc 2002, 34(6):2285-2287.

13. Human rabies prevention--United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1999, 48(RR-1):1-21.

14. Ruggiero HA, Perez Isquierdo F, Milani HA, Barri A, Val A, Maglio F, Astarloa L, Gonzalez Cambaceres C, Milani HL, Tallone JC: [Treatment of Argentine hemorrhagic fever with convalescent's plasma. 4433 cases]. Presse Med 1986, 15(45):2239-2242.

15. Bux J: Transfusion-related acute lung injury (TRALI): a serious adverse event of blood transfusion. Vox Sang 2005, 89(1):1-10.

16. Alliot C, Rapin JP, Besson M, Bedjaoui F, Messouak D: Pulmonary embolism after intravenous immunoglobulin. J R Soc Med 2001, 94(4):187-188.

17. Intensive-care patients with severe novel influenza A (H1N1) virus infection - Michigan, June 2009. MMWR Morb Mortal Wkly Rep 2009, 58(27):749-752.

18. Moser KM, LeMoine JR, Nachtwey FJ, Spragg RG: Deep venous thrombosis and pulmonary embolism. Frequency in a respiratory intensive care unit. Jama 1981, 246(13):1422-1424.

19. Sekimoto M, Fukui M, Fujita K: Plasma volume estimation using indocyanine green with biexponential regression analysis of the decay curves. Anaesthesia 1997, 52(12):1166-1172.

20. Rockman S, Maher D, Middleton D: The use of hyperimmune serum for severe influenza infections*. Crit Care Med 2012, 40(3):973-975.

21. Shaw PA, Fay MP. A rank test for bivariate time-to-event outcomes when one event is a surrogate. Statistics in medicine. 2016 Aug 30;35(19):3413-23.

22. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. European heart journal. 2012 Jan 1;33(2):176-82.

23. Zhou F Lancet 2020, Chen N Lancet 2020; Wang D JAMA 2020; Guan W-J NEJM 2020

24. Evans SR, Rubin D, Follmann D, Pennello G, Huskins WC, Powers JH, Schoenfeld D, Chuang-Stein C, Cosgrove SE, Fowler Jr VG, Lautenbach E. Desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR). Clinical Infectious Diseases. 2015 Sep 1;61(5):800-6.

25. Shaw PA. Use of composite outcomes to assess risk–benefit in clinical trials. Clinical Trials. 2018 Aug;15(4):352-8.Shaw PA.

26. Hung IF, To KK, Lee CK, Lee KL, Chan K, Yan WW, Liu R, Watt CL, Chan WM, Lai KY, Koo CK, Buckley T, Chow FL, Wong KK, Chan HS, Ching CK, Tang BS, Lau CC, Li IW, Liu SH, Chan KH, Lin CK, Yuen KY: Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis* 2011, 52(4):447-56.

27. Hung IFN, To KKW, Lee CK, Lee KL, Yan WW, Chan K, Chan WM, Ngai CW, Law KI, Chow FL, Liu R, Lai KY, Lau CCY, Liu SH, Chan KH, Lin CK, Yuen KY: Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. *Chest* 2013, 144(2):464-473.

28. Beigel JH, Aga E, Elie-Turenne MC, Cho J, Tebas P, Clark CL, Metcalf JP, Ozment C, Raviprakash K, Beeler J, Holley HP Jr, Warner S, Chorley C, Lane HC, Hughes MD, Davey RT Jr; IRC005 Study Team: Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial. Lancet Respir Med 2019, 7(11):941-950.

29. Cheng Y, Wong R, Soo Y,Wong W, Lee C, Ng M, Chan P, Wong K, Leung C, Cheng G: Use of Convalescent Plasma Therapy in SARS Patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005 Jan;24(1):44-6. doi: 10.1007/s10096-004-1271-9.

30. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L: Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020. doi: 10.1001/jama.2020.4783.

31. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X: Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A*. 2020, pii: 202004168. doi: 10.1073/pnas.2004168117.

32. Zander AL, Olson EJ, Van Gent JM, Bandle J, Calvo RY, Shackford SR, Peck KA, Sise CB, Sise MJ, King BS: Does resuscitation with plasma increase the risk of venous thromboembolism? *J Trauma Acute Care Surg* 2015 Jan;78(1):39-43.

33. Nilsson KR, Berenholtz SM, Garrett-Mayer E, Dorman T, Klag MJ, Pronovost PJ: Association between venous thromboembolism and perioperative allogeneic transfusion. *Arch Surg* 2007 Feb;142(2):126-32.

34. Gangireddy C, Rectenwald J, Upchurch G, Wakefield T, Khuri S, Henderson W, Henke P: Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. *Journal of Vascular Surgery* 2007 Feb; 45(2): 341-342.

35. Abu-Rustuma N, Richard S, Wilton A, Lev G, Sonoda Y, Hensley M, Gemignani M, Barakat R, Chi D: Transfusion utilization during adnexal or peritoneal cancer surgery: Effects on symptomatic venous thromboembolism and survival. Gynecologic Oncology 2005; 99(2): 320-326.

36. Halstead SB: Pathogenesis of dengue: challenges to molecular biology. *Science* 1988, 239(4839):476-81.

37. Takada A, Kawaoka Y: Antibody-dependent enhancement of viral infection: molecular mechanisms and in vivo implications. *Rev Med Virol*. 2003, 13(6):387-98.

38. Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, Tang H, Nishiura K, Peng J, Tan Z, Wu T, Cheung KW, Chan KH, Alvarez X, Qin C, Lackner A, Perlman S, Yuen KY, Chen Z: Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI Insight. 2019 Feb 21;4(4). pii: 123158.

39. Alshukairi AN, Khalid I, Ahmed WA, Dada AM, Bayumi DT, Malic LS, Althawadi S, Ignacio K, Alsalmi HS, Al-Abdely HM, Wali GY, Qushmaq IA, Alraddadi BM, Perlman S: Antibody Response and Disease Severity in Healthcare Worker MERS Survivors. Emerg Infect Dis 2016, 22(6).
40. CDC Yellow Book, Chapter 2, General Recommendations for Vaccination & Immunoprophylaxis: https://wwwnc.cdc.gov/travel/page/yellowbook-home-2014.

41. MMWR Morb Mortal Wkly Rep. 2011 Jan 28;60(RR02):1-60.

42. LaCourse S, John-Stewart G, Adams Waldorf K: Importance of inclusion of pregnant and breastfeeding women in COVID-19 therapeutic trials. Clinical Infectious Diseases. 2020, https://doi.org/10.1093/cid/ciaa444
43. Shields, KE. Pregnancy and the Pharmaceutical Industry, Elsevier Press, 2019. https://www.nichd.nih.gov/sites/default/files/inline-files/Preg_Women_Clin_Trials_2019.pdf

44. Royal College of Obstetricians and Gynaecologists (2015), *Blood Transfusion in Obstetrics* (Guide No. 47). Retrieved from https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-47.pdf

45. Winkelhorst D, Murphy MF, Greinacher A, Shehata N, Bakchoul T, Massey E, Baker J, Lieberman L, Tanael S, Hume H, Arnold DM, Baidya S, Bertrand G, Bussel J, Kjaer M, Kaplan C, Kjeldsen-Kragh J, Oepkes D, Ryan G: Antenatal management in fetal and neonatal alloimmune thrombocytopenia: a systematic review. Blood. 2017 Mar 16;129(11):1538-1547.

46. Gamez J, Salvado M, Casellas M, Manrique S, Castillo F. Intravenous immunoglobulin as monotherapy for myasthenia gravis during pregnancy. J Neurol Sci. 2017;383:118–122. doi:10.1016/j.jns.2017.10.037

47. Winkelmann A, Rommer PS, Hecker M, Zettl UK. Intravenous immunoglobulin treatment in multiple sclerosis: A prospective, rater-blinded analysis of relapse rates during pregnancy and the postnatal period. CNS Neurosci Ther. 2019;25(1):78–85. doi:10.1111/cns.12985

48. Huang Y, Cheng W, Zhao N, Qu H, Tian J: CT screening for early diagnosis of SARS-CoV-2 infection. *Lancet Infect Dis* 2020 Mar 26. pii: S1473-3099(20)30241-3. doi: 10.1016/S1473-3099(20)30241-3. [Epub ahead of print]

12 APPENDIX

12.1 Schedule of Activities (SoA)

The following page outlines all of the assessments to be conducted during the study. A detailed presentation of assessments immediately follows the table.

Table 4: Schedule of Activities

	Screen	Baseline	Study Period				
	While inpatient			While inpatient or as outpatient visits			
Day +/- Window	**−1 or 1**	**1**	**Day 2 to 29**	**15[7] ± 2**	**22[7] ± 3**	**29[7] ± 3**	**60[7] ± 5[10]**
ELIGIBILITY							
Informed consent	X						
Demographics & Medical History	X						
Targeted physical exam	X						
Review SARS-CoV-2 results	X						
STUDY INTERVENTION							
Randomization		X					
Administration of investigational plasma		X					
STUDY PROCEDURES							
Vital signs including SpO_2		X[4]	Daily until discharge or Day 29 of hospitalization	X		X	X
Clinical data collection[1]		X[4]	Daily until discharge or Day 29 of hospitalization	X	X[8]	X	X
Targeted medication review		X[4]	Daily until discharge or Day 29 of hospitalization	X		X	X
Adverse event evaluation		X[4]	Daily until discharge or Day 29 of hospitalization	X	X	X	X
SAFETY LABORATORY							
Type and Screen	X[2,3]						
Safety hematology, chemistry and liver tests		X[4,5,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized[5,6]	X[9]		X[9]	
Pregnancy test for females of childbearing potential	X[2,3]						
RESEARCH LABORATORY							
Oropharyngeal swab or endotracheal sample		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X			

Blood for research		X[5]	Day 3, 8, (all ± 1 day)	X		X	X

1 Refer to Section 8.1 of the protocol for details of clinical data to be collected including ordinal score, NEWS, oxygen requirement, mechanical ventilator requirement, etc.
2 Screening laboratory tests include: ALT, AST, creatinine (and calculate an estimated glomerular filtration rate (eGFR)), and pregnancy test.
3 Laboratory tests performed in the 48 hours prior to enrollment will be accepted
4 Baseline assessments should be performed prior to study drug administration. Laboratory tests performed as part of routine clinical care in the 24 hours prior to first dose will be accepted for the baseline safety laboratory tests. Baseline may be the same as the screening laboratory tests.
5 Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT.
6 Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing. Window during the study period is ±1 day.
7 In-person visits are preferred but recognizing quarantine and other factors may limit the participant's ability to return to the site for the visit. In this case, these visits may be conducted by phone and blood and OP can be coordinated remotely.
8 Phone call at Day 22 is to assess clinical status (ordinal scale), adverse events, readmission to a hospital, and mortality only.
9 Safety laboratory tests on Day 15 and 29 if still hospitalized or returns to the site for the visit or at home visit.
10 The collection of Day 60 data for primary and secondary endpoints and the collection of Day 60 samples for exploratory tests may be performed up to 90 days following the Day 60 visit.

12.2 Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1 (July 2017)

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1 - July 2017)pdf