Efficacy and Safety of Convalescent Plasma in Treating COVID-19 Hospitalized Patients

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An Open label, Phase 2 Study Evaluating the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19 infection

LIST OF ABBREVIATIONS:

ADR: Adverse Drug Reaction
ADE: Antibody-mediated enhancement of infection
AE: Adverse Event/Adverse Experience
CDC: United States Centers for Disease Control and Prevention
CFR: Code of Federal Regulations
CLIA: Clinical Laboratory Improvement Amendment of 1988
COI: Conflict of Interest
COVID-19: Coronavirus Disease
CP: Convalescent Plasma
CRF: Case Report Form
DMC: Data Management Center
DSMB: Data and Safety Monitoring Board
EUA: Emergency Use Authorization
FCBP: Females of Childbearing Potential
FDA: Food and Drug Administration
GCP: Good Clinical Practice
HBV: Hepatitis B virus
HCPOA: Health care power of attorney
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
HTLV: Human T-cell lymphotropic virus
IB: Investigator's Brochure
ICF: Informed Consent (Informed Consent Form)
ICH: International Conference on Harmonization
ICU: Intensive Care Unit
IEC: Independent ethics committee
IND: Investigational New Drug Application
IRB: Institutional review board
ISBT: International Society of Blood Transfusion
ISM: Independent Safety Monitor
IVIG: Intravenous Immune Globulin
IWRS: Interactive web response system
LOS: Length of stay
MERS: Middle East Respiratory Syndrome
NA: Nuclear antibody
NP: Nasopharyngeal
OP: Oropharyngeal
RBD: Receptor Binding Domain of SARS-Co-V2 virus
RT-PCR: Reverse Transcriptase Real-Time Polymerase chain reaction
PK: Pharmacokinetic
SAE: Serious adverse event
SARS: Severe Acute Respiratory Syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

TACO: Transfusion-associated circulatory overload
T. cruzi: *Trypanosoma cruzi*
TRALI: Transfusion-related acute lung injury
UP: Unanticipated Problem
UPnonAE: Unanticipated Problem that is not an Adverse Event
ZIKV: Zika virus

PROTOCOL SUMMARY:

An Open label, Phase 2 Study Evaluating the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19 infection

Clinical Phase: 2

IND Sponsor: Medical College of Wisconsin; Dr. Mary Beth Graham

Conducted by: Medical College of Wisconsin in collaboration with Versiti as plasma source.

Sample Size: 131 patients in 2 cohorts (ICU cohort called cohort 1 and a hospitalized non-ICU cohort or cohort 2)

Study Population: Hospitalized COVID-19 patients ≥18 years of age with severe symptoms as defined in inclusion criteria and within 21 days of symptom onset.

Study Duration: April 15, 2020 to December 31, 2020

Study Design: This is an open label phase 2 trial assessing the efficacy and safety of anti-SARS-CoV-2 convalescent plasma in hospitalized patients with acute severe respiratory symptoms from COVID-19. Symptomatic patients with clinical or radiological interstitial COVID-19 pneumonia and within 21 days of onset of symptoms will be enrolled in 2 cohorts – an ICU cohort and a hospitalized non-ICU cohort.

Study Assessments: Refer to Table 1 and Section 8

Summary of Outcome measures:

- Transfer to ICU for hospitalized non-ICU patients
- Increased O2 requirement (PaO2/FiO2 ratio or SpO2/FIo2), supplemental oxygen strategy (nasal cannula, high flow nasal cannula, noninvasive ventilation, intubation and invasive mechanical ventilation, rescue ventilation i.e. neuromuscular blocking agents, prone positioning, corticosteroids, ECMO)
- Use if vasopressors, ventilated days, renal support
- ICU LOS, ICU mortality
- Hospital LOS, Hospital mortality
- 28-day mortality

Study Drug:

- SARS-CoV-2 convalescent plasma 2 units
- Study drug will be administered as a single intravenous infusion

Primary Efficacy Objective:

1. Evaluate improvement of sequential organ failure (for ICU cohort)
2. Evaluate improvement in the risk of transfer to ICU and/or death (for non-ICU cohort)

Primary Endpoints:

1. Improvement (Delta) SOFA Score: measured as a change in SOFA score from baseline at the time of plasma infusion to 96 hours post infusion (ICU cohort)
2. Combined primary endpoint of death / intubation (non-ICU cohort)/ ICU transfer (non-ICU cohort)

Secondary endpoints:

1. Type and duration of respiratory support
2. Overall Mortality within first 60 days
3. Hospital LOS and in hospital mortality
4. ICU LOS and ICU mortality
5. Ventilator-free days (non-ICU cohort)
6. Incidence of secondary infections / co infections

Primary Safety Objective:

Evaluate the safety of treatment with high-titer anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19 respiratory symptoms.

Primary Safety Endpoints:

1. Rapid deterioration of respiratory or clinical status on transfusion of SARS-CoV-2 convalescent plasma due to presumed antibody dependent enhancement or other mechanisms
2. Cumulative incidence of all serious adverse events attributed to plasma therapy during the study period: transfusion reaction (fever, rash), transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion related infection

Laboratory Objectives:

1. Anti-SARS-CoV-2 antibody titers at days 0, 4, 7 and 14 (additional days 21 and 28 may be included, as available).
2. SARS-CoV-2 RNA by RT-PCR at days 7 and 14.
3. Research blood draws on days 0, 4, 7 ,14, and 28 to investigate immunology and hematologic pathways in severe COVID-19.

Study population (for both cohorts): Refer to section 5.1 of main protocol

Contents

1. Background and scientific rationale

Since there are no known curative therapeutic options for SARS-CoV-2 infection (and the related clinical disease COVID-19) patients with potentially life-threatening disease, there is considerable interest in passive transfer of immunity using plasma from patients who cleared virus and mounted a successful humoral immune response. Human convalescent plasma or hyperimmune globulin has been used as treatment of many viral illnesses and could be rapidly available when there are sufficient numbers of people who have recovered[1]. These individuals with adequate levels of IgG or IgM titers and confirmed clearance of virus are ideal donors of convalescent plasma. The natural history of this disease with a substantial majority clearing the disease spontaneously lends itself to the development of a strategy around convalescent donor plasma for seriously affected patients[2].

Passive antibody therapy involves the administration of antibodies to a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2009-2010 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic[3-6]. Convalescent plasma or immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with pulsed methylprednisolone[6]. In the 2013 African Ebola epidemic too, a non-randomized study in Sierra Leone revealed a significant increase in survival for those treated with convalescent whole blood relative to those who received standard treatment[5]. A meta-analysis of 32 studies pooling SARS coronavirus infection and severe influenza showed a consistent and overall statistically significant reduction in the odds of mortality following CP therapy, compared with placebo or no therapy[7].

In the ongoing COVID-19 preliminary data have emerged suggesting clinical benefit[8]. Shen et al showed treated 5 patients with COVID-19 pneumonia with convalescent donor derived plasma between day 10 - 20 of hospitalization. All were severely ill with respiratory failure requiring mechanical ventilation (4 patients) or ECMO at the time of therapy. The administered donor plasma had demonstrable anti–SARS-CoV-19 antibodies and in vitro studies demonstrated neutralizing activity. Notably all patients had clinical and virologic improvement in about a week after plasma with resolution of fever, improved SOFA scores and SARS-CoV-2 viral clearance between 1 and 12 days after receipt of plasma. The results are confounded by the co-administration of antiviral treatment primarily with lopinavir/ritonavir (although this therapy was not shown to be effective in a randomized study)[9]. All patients also had an increase in neutralizing antibody titers. Very similar promising results have been reported by a group from China who reported clinical improvement in 10 patients treated with a single 200 mL of convalescent plasma.

The major caveats to these data are the lack of a control group and the subsequent inability to determine the true clinical effect of this intervention or whether patients might have recovered without this therapy. Additionally, the timing of plasma administration

has been pointed out as a matter of debate since it is not clear if earlier administration might have been associated with different clinical outcomes[2]. We believe that the data from Shen et al provide strong evidence to support the possibility of evaluating this in larger cohort involving patients with COVID-19 and moderate to severe illness. Passive antibody administration is currently the only means of providing immediate immunity to susceptible persons and immunity of any measurable kind for COVID-19 patients[10].

In contrast, active vaccination requires the induction of an immune response that takes time to develop and varies depending on the vaccine recipient. Some immunocompromised patients fail to achieve an adequate immune response.

Thus, passive antibody therapy has a storied history going back to the 1890s and is summarized by Casadevall et al[10]. Prior to the development of specific antimicrobial therapy this was in fact a mainstay of therapy. In the case of SARS-CoV-2, there is clear evidence of the development of neutralizing antibodies, both IgM and IgG fairly quickly after infection in patients who demonstrate viral clearance. In a series of 23 patients, To et al showed that viral load peaked during the first week of illness then gradually declined over the second week. IgG and IgM antibodies started to increase on around day 10 after symptom onset, and most patients had seroconversion within the first 3 weeks[11]. Most importantly, IgG and IgM antibody levels against the SARS-CoV-2 internal nucleoprotein (NP) and the surface spike receptor binding domain (RBD) correlated with neutralizing activity. As more individuals contract COVID-19 and recover, the number of potential donors will continue to increase and make this more feasible for the growing number of severely ill individuals too[12].

A general principle of passive antibody therapy is that it is more effective when used for prophylaxis or earlier in the disease course than for treatment of advanced disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease. Another explanation is that antibody works by modifying the inflammatory response, which is also easier during the initial immune response, at which time the patient may not be too symptomatic[13]. ***Our plan is to treat a majority of patients who are sick enough to warrant hospitalization prior to the onset of overwhelming disease. Additionally, a smaller cohort of patients who need ICU level care will be enrolled provided expected life expectancy is >72 hrs. Given the data from Shen et al we feel it is reasonable to treat patients who are on mechanical ventilation but not those with overwhelming disease.***

The plasma product we administer will be collected by Versiti per AABB and GMP approved protocols from recovered asymptomatic individuals who have complete resolution from SARS-CoV-2 infection, virologic clearance and presence of antiviral antibody titers.

There are news reports that convalescent plasma was used for therapy of patients with COVID-19 in China during the current outbreak (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm). Although few details are available from the Chinese experience and published studies involved small numbers of patients, the available information suggests that convalescent plasma administration reduces viral load and was safe.

Ancillary Research Laboratory Studies:

Exploring the inflammatory and hemostatic milieu in severe COVID-19:
Evidence is accumulating that the inflammatory and hemostatic response is uniquely engaged in COVID-infected patients. Coagulopathy, microvascular, arterial, and venous thrombosis are being reported with increasing frequency[14,15]. The response of the immune and hemostatic system to COVID infection is largely unknown. We plan to investigate hemostatic pathways during the hospitalization phase of patients receiving plasma therapies.

Investigating the specificity and affinity of SARS-Co-V2 antibodies:
Although convalescent COVID-19 sera likely have neutralizing antibodies against SARS2-CoV-2, the quantity and quality of neutralizing antibodies in convalescent sera from each individual will vary dramatically. It is not clear which characteristics of SARS-CoV-2-specific antibodies in the infused plasma determine the antiviral potency. Moreover, as noted above administration of convalescent sera possesses risks of causing inadvertent side effects such as immunological reactions, transfusion-related acute lung injury, or antibody-dependent enhancement. In contrast, a human recombinant monoclonal neutralizing antibody against SARS2-CoV-2 can be selected to have the characteristics associated with high antiviral potency and overcome the potential risks, can be produced on a large scale and safely used as prophylactic and therapeutic treatment for SARS-CoV-2 infection. Based on our experience in cloning antigen-specific B cells from human patients and our studies of PF4/heparin-specific B cells, we propose two specific research analyses. First, we will investigate the role of isotype, specificity and affinity in determining neutralization potency of SARS-CoV-2-specific antibodies in COVID-19 convalescent sera and study the antibody responses in COVID-19 patients through single-cell sequencing. Secondly, we will clone RBD-specific antibodies from single B cells of convalescent COVID-19 patients.

The proposed studies will help to identify the most potent sera and monoclonal antibodies from convalescent COVID-19 patients for prophylaxis and/or treatment of COVID-19. These approaches will help prevent SARS-CoV-2 spread among high-risk individuals i.e. frontline health care providers and people that are coming into close contact with patients and will likely be used to treat patients with COVID-19.

2. Known potential risks from clinical trial

a. An important theoretical risk involves the phenomenon of antibody-mediated enhancement of infection (ADE). ADE can occur for several viral diseases and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms for ADE have been described and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain (12). It may be possible to predict the risk of ADE of SARS-CoV-2 experimentally, as proposed for MERS. Since the proposed use of convalescent plasma in the COVID-19 epidemic would rely on preparations with high titers of neutralizing antibody against the same virus, SARS2-CoV-2, ADE may be unlikely. The available evidence from the use of convalescent plasma in patients with SARS1 and MERS (13) and evidence of its use in patients with COVID-19 (Shen et al), suggest it is safe. Nevertheless, caution and vigilance will be required as proposed in the safety end points.

b. Another theoretical risk is that antibody administration to those exposed to SARS-CoV-2 may avoid disease but modify the immune response such that those individuals mount attenuated immune responses, which would leave them vulnerable to subsequent re-infection. In this regard, passive antibody administration before vaccination with respiratory syncytial virus was reported to attenuate humoral but not cellular immunity (14). This concern could be investigated as part of a clinical trial by measuring immune responses in those exposed and treated with convalescent plasma to prevent disease. If the concern proved real these individuals could be vaccinated against COVID-19 when a vaccine becomes available. *These concerns seem modest compared to the possibility of limiting the duration and severity of disease, and avoiding interventions like mechanical ventilation, ARDS and sepsis.*

c. Transfusion associated risk common to any blood products could also be associated with donor plasma including transmission of transfusion transmitted viruses (e.g. HIV, HBV, HCV, etc.), allergic transfusion reactions, anaphylaxis to transfusion, febrile transfusion reaction, transfusion related acute lung injury (TRALI), transfusion associated cardiac overload (TACO), and ABO mediated hemolysis. In order to minimize the risks of disease transmission, standard pathogen reduction techniques will be utilized as per Versiti protocol. Using donors who fulfill donor eligibility requirements, blood donation, and frequent apheresis plasma donation with the exception of recent illness, in this case COVID-19 infection.

3. Known potential benefits of clinical trial

A key potential benefit is treatment for established infection. Convalescent plasma would be administered to those with clinical disease in an effort to reduce their symptoms and mortality. Based on the historical experience with antibody administration, it can be anticipated that *antibody administration relatively early in the course of disease would more effective in preventing disease progression than in the treatment of established severe disease.*

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

4. Investigational plan

4.1 Study Objectives

Primary Efficacy Objective:

1. Evaluate improvement of sequential organ failure (for ICU cohort)
2. Evaluate improvement in the risk of transfer to ICU and/or death (for non-ICU cohort)

Primary Endpoints:

1. Improvement (Delta) SOFA Score measured as a change in SOFA score from baseline at the time of plasma infusion to 96 hours post infusion (ICU cohort)
2. Combined primary endpoint of death / intubation (non-ICU cohort)/ ICU transfer (non-ICU cohort)

Secondary endpoints:

1. Type and duration of respiratory support (see definitions in Section 7.5.1)
2. Overall Mortality within first 60 days
3. Hospital LOS and in hospital mortality
4. ICU LOS and ICU mortality
5. Ventilator-free days (non-ICU cohort)
6. Incidence of secondary infections / co infections

Primary Safety Objective:

Evaluate the safety of treatment with high-titer anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19 respiratory symptoms.

Primary Safety Endpoints:

1. Rapid deterioration of respiratory or clinical status on transfusion of SARS-CoV-2 convalescent plasma due to presumed antibody dependent enhancement or other mechanisms. Since patients in this study are already in respiratory distress, further worsening of respiratory status will be defined as below and causes attributed by treating physician. Any escalation of oxygenation or ventilatory needs within the 12 hours after plasma infusion will be considered as a deterioration. This includes new requirement for supplemental oxygen in a person not on oxygen, an increase of >25% in FiO2; need for non invasive or invasive mechanical ventilation in subjects not requiring these at the time of infusion. In patients already on mechanical ventilation, an increase in PEEP and or FiO2 of >25% will also be considered a respiratory deterioration.
2. Cumulative incidence of all serious adverse events attributed to plasma therapy during the study period: transfusion reaction (fever, rash), transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion related infection

Laboratory Objectives:

1. Anti-SARS-CoV-2 antibody titers at days 0, 4, 7 and 14 (additional days 21 and 28 may be included, as available).
2. SARS-CoV-2 RNA by RT-PCR at days 7 and 14.
3. Research blood draws on days 0, 4, 7,14, and 28 to investigate immunology and hematologic pathways in severe COVID-19.

4.2 Study Definitions:

1. Enrolled: From time consented to participate until designated as a screen failure or have either been discontinued from the study or completed it.
2. Screen Failures: signed informed consent, but then determined to be ineligible or withdraws before being treated.
3. Discontinued: enrolled, but then withdrawn by investigator or subject withdraws consent
4. Completed: Subjects are considered to have completed when they are followed through day 60 or day of death if death occurred prior to day 60

5. Study population

Patients will be enrolled in 2 cohorts independent of each other. Cohort 1 will consist of patients who are admitted to the ICU. Cohort 2 will consist of patients who are admitted to a non-ICU floor. Patients transferring from non-ICU to ICU floors or vice versa will be

analyzed in the cohort corresponding to the location of signing consent. Each cohort will be analyzed independently.

5.1 Eligibility Criteria (for both cohorts)

Inclusion Criteria:

1. Age ≥ 18 years or older
2. Hospitalized as an in-patient with positive COVID-19 test by PCR
3. Presence of symptomatic disease with any one of severe features as below:

    - Respiratory Rate >= 24/min
    - Hypoxia defined as a person requiring >3L/min of supplemental oxygen OR oxygen saturation of <94% on room air
    - New onset or worsening of respiratory symptoms with radiologic confirmation of bilateral ground glass opacities that cannot be attributed to another cause
    - Chief complaint of dyspnea / shortness of breath without meeting above RR or oxygen requirements

4. Patient or patient and witness or LAR / HCPOA is willing and able to provide verbal / telephonic/ physical or electronic informed consent and comply with all protocol and IRB requirements. If patient is unable to consent due to incapacity, health care POA should be defined and able to consent for the patient.
5. Patients are allowed to receive all standard of care treatments and or join other clinical trials.

Exclusion Criteria

1. FCBP with positive pregnancy test (mandatory)
2. Breastfeeding females
3. Receipt of pooled immunoglobulin (e.g. IVIG or other hyperimmune globulin products) in past 14 days. This does not apply to monoclonal antibodies.
4. Mechanical ventilation for > 14 days
5. Days from symptom onset >21 days
6. Expected survival < 72 hours
7. Contraindication to transfusion or history of prior reactions to transfusion blood products including any proven history of TRALI

5.2 Table 1: Schedule of Events

Study period	Screen	Baseline Prior to plasma	Transfusion	Follow-up[6]					Monthly follow-up[6]
Day	-3 to 0	0	0	1	4	7	14	28	60
Eligibility									
Informed consent	x								
Demographic and medical history	x								
COVID-19 symptom screen	x								
Chest x-ray or chest CT	x								
SARS-CoV-2 RT-PCR for eligibility	x								
Serum/urine pregnancy test in FCBP w/in 7 days of study transfusion	x								
ABO type and antibody screen	x								
Treatment									
Donor Plasma Administration			x						
Drug infusion			x						
Study Procedures									
Vital signs	x	x	x[3]	Daily clinical assessments during hospital stay. SOFA score in ICU patients					
Physical examination	x	x							
Symptom screen	x	x							x
Concomitant medications	x	x		x	x	x	x	x	x
SOFA score[2]		x		x	x	x	x		
Adverse event monitoring	x	x	x	Throughout study period					
Laboratory testing									
CBC diff / CMP/ DIC panel		x		x	x	x	x		x[1]
Ferritin/CRP/LDH		x		x	x	x	x		x[1]
Immunoglobulin Panel		x							
SARS-CoV-2 RT-PCR		x[5]							
SARS-CoV-2 antibody research blood sample[4]		x			x	x	x	x[1]	
Research Blood Samples to Versiti[4]		x			x	x	x	x[1]	

1. All labs after the day of discharge from hospital are optional.
2. Refer to appendix 1.
3. Vital signs will be measured immediately prior to infusion, 10-20 minutes after start of infusion, at completion of infusion and 30-60 minutes after the end of the Infusion.
4. Refer to section 14 and appendix 2.
5. Baseline RT PCR for study entry is adequate.
6. +/- 2-day window

5.3 Subject Withdrawal

1. Subjects or HCPOA can terminate study participation and/or withdraw consent at any time without prejudice.
2. Subjects who withdraw from the study who have received study treatment will not be replaced. Subjects who have never received study treatment can be replaced.
3. The investigator may withdraw subjects if they are lost to follow up, non-compliant with study procedures or if the investigator determines that continued participation in the study would be harmful to the subject or the integrity of the study data.
4. Discontinuation of the study: the study sponsor, FDA and IRB all have the right to terminate this study at any time.

6. Treatment

1. Study drug: The investigational product is anti-SARS-CoV-2 convalescent plasma obtained from patients identified as having recovered from COVID-19 as per Versiti plasma collection protocols.
2. Donors and samples will have been screened for transfusion-transmitted infections (as per current AABB and FDA standards) both through the use of the uniform donor questionnaire and FDA mandated blood donor screening tests by Versiti.
3. ABO compatible plasma will be used to reduce risk of hemolysis.

6.1 Rationale for doses

Recommended dose will be 2 units of plasma for all patients.

6.2 Study drug administration

- Drug will be administered once consent, eligibility confirmation, enrollment, and screening/baseline procedures have been completed.
- Infusion rate $\leq$ 500 mL/hour.
- Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given per investigator and clinical care team discretion.
- If an AE develops during infusion, the infusion may be slowed or stopped as per investigator's decision.
    - Most reactions to plasma are relatively minor and the infusion can generally be continued. Infusion site burning and non-allergic systemic effects can generally be managed with slowing of the infusion. Infusion can generally be continued in cases of itching or hives after pausing the transfusion, administering antihistamines, and observing the patient for worsening symptoms.
    - Severe allergic reactions such as, bronchospasm and hypotension, and may require discontinuation of the infusion.

6.3 Concomitant medications

Concomitant medications will be documented on the CRF and these include:

- Prescription medications
- Any other clinical trials
- Over the counter medications
- Herbal treatments/nutritional supplements
- Blood products administered

7. Statistical considerations

Patients will be enrolled in 2 cohorts independent of each other. Cohort 1 will consist of 41 patients who are admitted to the ICU. Cohort 2 will consist of 90 patients who are admitted to a non-ICU floor. The two cohorts will be analyzed independently. For sample size considerations please see section 7.6.

For each cohort, descriptive summaries of continuous and other numeric variables will consist of the summary statistics: median, minimum and maximum values. Categorical variables will be summarized by the frequency and proportion of subjects falling into each category. Unless otherwise indicated, percentages in tables will be column percentages, using the total number of observations in the population as the denominator. Exact confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

7.1 Analysis of AE data

Analysis of AE data will primarily be descriptive based on MedDRA coding of events. The proportion of subjects experiencing an SAE and the proportion experiencing a Grade 3 or higher event will be presented.

7.2 Analysis of anti-SARS-CoV-2 titers

Analysis of titers will also primarily be descriptive, at days 0,4, 7 and 14 post study treatment administration.

7.3 Endpoints

Primary Endpoint:

Cohort 1: Delta SOFA Score (change in SOFA score) from baseline at the time of plasma infusion to 96 hours post infusion (ICU cohort).

The Sequential Organ Failure Assessment (**SOFA**) **Score** is a mortality prediction **score** that is based on the degree of dysfunction of six organ systems. The **score** is calculated on admission and every 24 hours until discharge using the worst parameters measured during the prior 24 hours[16]. Calculation of SOFA score is described in Appendix 1[17].

Cohort 2: Combined primary end point of death, intubation or ICU transfer (non-ICU cohort).

Primary Hypotheses:

Cohort 1: the probability of decrease in SOFA score of at least 2 after 96 hours from the intervention is higher than 20%. An increase to 40% would be clinically meaningful.

Cohort 2: the probability of death, intubation or ICU transfer is lower than 60%. A decrease to 45% would be clinically meaningful.

7.4 Analysis of primary endpoints

The proportion of patients achieving the primary endpoint will be reported with a two-sided 95% exact Clopper-Pearson confidence interval. The primary hypothesis will be evaluated using an exact binomial test at a one-sided 2.5% significance level.

7.5 Analysis of secondary endpoints

7.5.1 Type and duration of respiratory support

The number of patients requiring each type of respiratory support will be tabulated. The duration of support will be summarized with median and inter-quartile range. For the purposes of this protocol respiratory support will be captured and classified in the following categories[18]:

1. Supplemental Oxygen by nasal cannula, simple mask, non-rebreather mask and defined by flow rate in liters/min
2. High Flow Nasal Oxygen with flow rates and FiO2 setting
3. Non-invasive positive pressure ventilation with flow, FiO2 and pressure settings defined
4. Mechanical Ventilation with FiO2, Pressure and ventilator settings defined
5. Extra corporeal Membrane Oxygenation (ECMO).

7.5.2 Overall mortality within first 60 days

The overall survival of the subjects will be estimated using the Kaplan-Meier method and presented with 95% confidence bands. Subjects may be censored if they had a routine discharge (not hospice, or another hospital), and could not be contacted for further follow-up. Overall mortality at 60 days post-intervention will be estimated using the Kaplan-Meier estimate.

7.5.3 Hospital LOS and in-hospital mortality

In-hospital mortality will be estimated as the observed proportion of subjects who died during the hospital stay and presented with a 95% exact Pearson confidence interval. Hospital length of stay will be considered only among subjects discharged alive and will be summarized with median and inter-quartile range.

7.5.4 ICU LOS and ICU mortality

ICU length of stay and mortality will be considered in Cohort 1 and among subjects in Cohort 2 who are admitted to an ICU. ICU mortality will be estimated as the observed proportion of subjects who died during the hospital stay and presented with a 95% exact Clopper-Pearson confidence interval. ICU length of stay will be considered only among subjects discharged alive and will be summarized with median and inter-quartile range.

7.5.5 Ventilator-free days

Ventilator-free days will be considered only in Cohort 1. It will be defined as the number of days during 28 days after the intervention that the subject is alive and does not require ventilator support. Ventilator-free days will be summarized with median and inter-quartile range.

7.6 Sample size considerations

The cohort sizes were selected to achieve at least 80% power of rejecting the null hypotheses at a one-sided 2.5% significance level if the true probability of the primary outcome is at its clinically meaningful value. A single stage exact binomial study design was used.

Cohort 1: With 41 subjects the study will have 80% power to reject the null hypothesis of ≤20% probability of a 2-point decrease in SOFA at a one-sided 2.5% significance level, if the underlying probability is 40%. The treatment will be considered successful if 14 or more subjects achieve the primary endpoint.

Cohort 2: With 90 subjects the study will have 80% power to reject the null hypothesis of ≥60% probability of death, intubation or ICU transfer, if the underlying probability is 45%. The treatment will be considered successful if 44 or fewer subjects achieve the primary endpoint.

8. Study procedures

Consenting Process:

Consent is difficult in patients with acute respiratory symptoms who are in isolation. Therefore, an electronic or phone call or video conference consenting process will be used to document informed consent from patients or HCPOA (refer to section 13.3 for further details). Research staff will make contact info available to patients who have further inquiries about the project. Once a patient consents to participate in the trial, a member of the study team will assign them a unique patient number (UPN). These UPNs will be assigned to subjects sequentially (MCW-COV-001, MCW-COV-002, MCW-COV-003, etc.). Patients are enrolled on the trial once they have consented and are deemed eligible.

Day -3 to -0:

1. Subject informed consent (obtained before performing study related activities)
2. Screening (must be completed before enrollment)
3. Baseline Evaluation (at screening) (much of the information will be obtained from the medical record)
    a. Demographics (age, sex ethnicity, race)
    b. Medical history (timing of exposure to COVID-19 source patient if known, acute and chronic medical conditions, concomitant medications, allergies. Any medical condition arising after consent should be recorded as AE
    c. COVID-19 symptom screen (fevers, cough, shortness of breath), onset of symptoms, source of contagion
    d. Vital signs
    e. Physical exam

f. Chest x-ray or chest CT
g. ABO type and antibody screen documentation or test if not done
h. COVID-19 testing (RT-PCR or rapid test) from any source
i. Pregnancy test (serum or urine) for females of childbearing potential within 7 days prior to infusion
j. Determination of eligibility as per inclusion/exclusion criteria age.
k. HCPOA or witness information

Day 0:

1. Assessment of clinical status by standard symptom and physical examination including calculation of SOFA score in ICU patients. SOFA score will be calculated as per Appendix 1.
2. Study Plasma Administration: 1-2 units of plasma will be transfused. Time at start and end time of infusion will be recorded and vital signs will be measured immediately prior to infusion, 10-20 minutes after start of infusion, at completion of infusion and 30-60 minutes after the end of the infusion.
3. New medical conditions, concomitant medication, and AE evaluation
4. Physical examination
5. CBC with Diff, comprehensive metabolic panel, DIC panel, ferritin, LDH, immunoglobulin panel, and C-reactive protein
6. Research Samples as detailed in Table 1 (Schedule of events)

Days 1-14 (or for duration of hospitalization) – Refer to table 1 for specific day:

1. Vital signs daily
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status
4. New medical conditions, concomitant medication, and AE evaluation
5. Physical examination
6. SOFA score
7. CBC with Diff, comprehensive metabolic panel, CRP, Ferritin, DIC panel, LDH
8. Research Samples as detailed in Table 1 (Schedule of events)

Day 28 (Refer to Table 1):

Follow-up by phone is acceptable if alive and at home.
Current admission; at home vs. in hospital (ICU or not), on supplemental O2 or not, back to work (fully, partially, SNF, nursing home, LTAC)

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. SOFA score if in ICU
3. Assessment of clinical status with physical exam if in hospital / clinic
4. New medical conditions, concomitant medication, and AE evaluation
5. If still hospitalized, follow procedures listed in table 1.
6. Optional labs (CBC with Diff, comprehensive metabolic panel, CRP, Ferritin, DIC panel, LDH; Research Labs) – all labs beyond day 14 are optional.

9. Efficacy, virology measures:

Clinical Efficacy

Clinical assessment will be standard of care subjective symptom assessment and physical examination as documented in daily progress notes. SOFA score will be documented for ICU resident patients.

Virologic measures

1. Serologic positivity and neutralization antibody titers for anti-SARS-CoV-2 at days 0, 4, 7 and 14, whenever possible given sample availability, patient mortality, reluctance to come to MCW for testing.

10. Risks and benefits

Potential Benefits of treatment:

The potential benefits of antiviral treatment with anti-SARS CoV-2 plasma in patients with respiratory symptoms consistent with interstitial pneumonia at high risk for requiring ICU admission are not known. However, it is anticipated that treatment will decrease the risk of disease progression requiring ICU admission and aggressive respiratory support including possible mechanical ventilation (and other ICU support).

Potential benefits of clinical monitoring and virologic testing:

Subjects enrolled in the study may reduce their chances of disease progression.

Potential risks:

1. Risks of plasma: Fever, chills, rash, headache, serious allergic reactions, TRALI, TACO, transmission of infectious agents
2. Risks of phlebotomy: local discomfort, bruising, hematoma, bleeding, fainting
3. Total blood draws will not exceed 100 mL during the entire study
4. Risks of oropharyngeal and throat swab: local discomfort, vomiting

Alternatives:

The alternative to participation in this study is routine care and or other clinical trials. Participation in this trial does not preclude enrollment in any other clinical trial.

11. Safety measures

1. Laboratory evaluations consistent with ongoing standard medical care may include radiographic imaging modalities such as chest x-rays and chest CT.
2. Clinical assessment and monitoring for infusion reaction on day of infusion as per standard of care blood transfusion guidelines.
3. Safety laboratory tests (ABO typing, pregnancy testing, CBC, CRP, and comprehensive metabolic panel) will be performed at the local CLIA-certified clinical laboratory as per schedule of assessments in Table 1.

11.1 Adverse Event

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

Unexpected Adverse event: (UAE) An adverse reaction attributed to infused plasma, the nature or severity of which is not consistent with the risks outlined in the consent form.

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

11.2 Serious Adverse Event (SAE)

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

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

11.2.1 SAEs are reported in the following manner:

All fatal or life-threatening or unexpected and suspected SAEs will be reported to the IRB and all applicable agencies within 24 hours and all other SAEs (non-fatal or non-life-threatening) within 4 calendar days of study site staff awareness.

- Every SAE regardless of suspected causality (e.g., relationship to study drugs or study procedure) occurring after the subject has signed the consent through the 30 days after the last dose of study drugs, AND only SAEs occurring more than 30 days after the last dose of study drugs that the investigator suspects a causal relationship to study plasma, must be reported in the study database SAE section. These will also be reported to the ISM (Dr. Michael Frank as below) and the IRB. All transfusion related AEs and SAEs have to be reported to the hospital blood bank additionally in order to start a transfusion AE investigation.
- All grade 4 and 5 SAEs and any other expedited SAE report to IRB must also be reported to FDA (MedWatch 3500A described below) within five calendar days of MCW study staff's awareness.

- In addition: if the SAE is unexpected and has a suspected relationship to the study drug, site must create a reportable event notice with the MCW IRB, ISM and complete a MedWatch 3500A and submit to FDA:
    - US FDA MedWatch 3500A found here: *http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm*

11.2.2 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

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 of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (sIRB)-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).
- 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.

11.2.3 Adverse Events Not Meeting SAE Definition

- Any medical condition that is present at the time that the participant is screened will be considered as baseline condition and captured on the baseline CRF form, not reported as an AE. All new or worsening AEs that occur after starting study drug until 30 days post last dose of study plasma will be tracked and followed until resolution, stabilization of the event as chronic, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early).
- Changes in the grade of an AE will be documented in the AE CRF to allow an assessment of the duration of the event at each level of severity to be performed. Information to be collected includes event description, time of onset, clinician's assessment of severity, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

11.2.4 Protocol Deviation

A deviation from the IRB-approved study procedures designated as serious:

1. Serious Protocol Deviation: protocol deviation that is also an SAE and/or compromises the safety, welfare or rights of subjects or others
2. Follow safety reporting requirements listed above

11.3 Reporting Interval

All AEs and SAEs will be documented from consenting until study completion at 60 days from study infusion or death or discontinuation from the study. All AEs and SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an adverse event is defined as the

return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

Investigator's Assessment of Adverse Events

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

Assessment of Seriousness

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

Event severity will be assigned according to the scale below

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

2 = Moderate: Some worsening of symptoms but no or minimal medical intervention/therapy required)

3 = Severe: Escalation of medical intervention/therapy required

4 = Life-threatening: Marked escalation of medical intervention/therapy required.

5= Death

Assessment of Association

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

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

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

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

12. Safety Oversight

12.1 Monitoring Plan

1. All AEs and SAEs will be reviewed by protocol team.
2. An Independent Safety Monitor (ISM) will be appointed. The ISM is a physician with expertise in infectious diseases and whose primary responsibility is to provide timely independent safety monitoring. An ISM has the authority to readily access study participant records. The ISM reviews any SAE that occurs at the study site in real time and provides a written assessment. **Dr. Michael Frank, Chief, Division of Infectious Diseases, Medical College of Wisconsin** will serve in this role.

Study monitoring

a. As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor.
b. Informed consent process documents for each subject needs to be available.
c. There is compliance with recording requirements for data points
d. All SAEs are reported as required
e. Individual subjects' study records and source documents align
f. Investigators are in compliance with the protocol.
g. Regulatory requirements as per Office for Human Research Protections-OHRP), FDA, and applicable guidelines (ICH-GCP) are being followed.

12.2 Halting Criteria for the Study

The study enrollment and dosing will be stopped, and an ad hoc review will be performed if any of the specific following events occur or, if in the judgment of the study physician or the ISM, subject safety is at risk of being compromised:

1. Death within one hour of plasma infusion
2. Occurrence of a life-threatening allergic/hypersensitivity reaction (anaphylaxis), manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation, TRALI, TACO.
3. One subject with an SAE specifically associated with study product.
4. Two subjects with a Grade 3 or higher lab toxicity for the same parameter associated with study product.
5. An overall pattern of symptomatic, clinical, or laboratory events that the medical monitor, ISM, or IRB consider associated with study product and that may appear minor in terms of individual events but that collectively may represent a serious potential concern for safety.

6. Any other event(s) which is considered to be a serious adverse event related to the study infusion in the good clinical judgment of the responsible physician and or ISM. These will be appropriately documented.

Halting Criteria/Rules for Subject Infusion

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

- Skin or mucous membrane manifestations: hives, pruritus, flushing, swollen lips, tongue or uvula that do not respond to standard therapy with anti-allergic and steroid medications
- Respiratory compromise: New onset wheezing, stridor, hypoxemia related to infusion
- Any other symptom or sign which in the good clinical judgment of the study clinician or supervising physician warrants halting the infusion. For example, manifestations of anaphylaxis and may warrant an immediate halt prior to meeting full SAE criteria

13. Ethics/Protection of human subjects

13.1 Ethical Standard

We will ensure that the legal and ethical obligations associated with the conduct of clinical research involving human subjects are met.

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

MCW has a Federal wide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP).

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

13.2 Institutional Review Board

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

13.3 Informed Consent Process

The informed consent process will be initiated before a potential subject or their HCPOA agrees to participate in the study and should continue throughout the individual's study participation. The subject or HCPOA will be consented before any procedures are undertaken for the study. The process for consent will be documented in the research records.

Two alternative consent methods will be available for this study:
1. Electronically: transmitting a consent form via email, obtaining e-consent utilizing an iPad, or utilizing a cloud-based system for delivery and communicating in-person with subjects or HCPOA.
2. Phone Call or Video Conference: Example – this method could include utilizing the phone in the subject's room or utilizing video conferencing services such as WebEx, Skype, etc to connect with patient and or HCPOA.

Regardless of the method utilized, a consent form will be provided to the subject either in person by health care staff or electronically.
If consent cannot be obtained electronically or in person, it is required that an impartial witness will be present (via phone or teleconference).

When a witness is being utilized, the following must occur:
1. The witness must be present for the entire consent discussion and confirm that the potential subject's questions have been answered.
2. The investigator must confirm that the potential subject is willing to participate and sign the consent form with the witness present (via phone or teleconference).
3. The potential subject must confirm that he or she wishes to participate and has signed and dated the consent form.

Documenting Informed Consent
1. Electronically
   Example – The consent form can be signed, scanned, and sent via email or fax from the subject to the team. In addition, electronic signatures can be utilized.
2. Photograph
   Example – The subject or research team can photograph the entire signed consent form by camera, cellular phone, etc. and send the picture to the research team. The picture can be taken from outside of the isolation area as long as the signed consent form can be seen clearly.
3. Confirmation
   Example – The impartial witness present for the consenting process can attest that the subject confirmed the he/she wished to participate in the project and signed the consent form.

The method of obtaining informed consent should be included in study records along with the signed consent form (if available). If a signed consent form is not available for the reasons outlined in this document, the study record should include an explanation of which method was used for confirming that the subject signed the consent form as well as the explanation of why the originally signed consent form could not be filed.

An electronic copy of the signed informed consent document will be available to the subject for their records. The consent will explain that subjects may withdraw consent at any time throughout the course of the trial. Extensive explanation and discussion of risks and possible benefits of this investigation will be provided to the subjects in understandable language. Adequate time will be provided to ensure that the subject has time to consider and discuss participation in the protocol.

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

13.4 Subject Confidentiality

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

14. Research Sample Disposition:

Research samples will be drawn from enrolled patients throughout the course of their hospitalization to investigate the early immune response and the impact of treatment. In coordination with these studies, the development of the adaptive, or immune memory response will be investigated. These samples will be drawn in coordination with clinical labs and the blood volume will be limited to 30 ml. These blood samples will be processed and studied at the Versiti Blood Research Institute in the labs of Drs. Demin Wang, Weiguo Cui, Renren Wen, Lisa Baumann Kreuziger, Zheng Ze, Karin Hoffmeister, and Shawn Jobe. Dr. Weiguo Cui as lab investigator will be in overall control of sample security and distribution to other investigators named above. Immunologic and hemostatic assays will be performed on these samples in compliance with Medical College of Wisconsin safety guidelines. Research assays will include in vitro studies of lymphocyte and antibody development, mediators of the immune response particularly circulating cytokines, hemostasis, and platelet function.

Blood samples will be obtained per Table 1 and appendix 2. This will consist of 20ml citrate (blue-topped) and 10ml EDTA (purple-topped) tubes. If the collected blood volume is limited by clinical condition, sample collection will be limited to 10ml citrate and 10ml EDTA initially, then a 10ml citrate tube. Blood samples will be de-identified with only study ID# (refer to section 8), and date/time of collection. These samples will be processed at Versiti Blood Research Institute to obtain platelet-poor plasma (PPP), platelet-rich plasma (PRP), and enriched platelet and peripheral blood mononuclear cell (PBMC) samples. Samples will then be analyzed. Residual de-identified sample will be stored for batched analyses at -70C or in liquid nitrogen.

Proposed research activities will take place in the laboratories at the Versiti Blood Research Institute. Once collected, samples will be shipped deidentified to the Versiti BRI and received by Dr. ui or designee and processed further for research tests as indicated above. Collection, storage, and communication of research samples will be conducted in a manner that is compliant with HIPAA regulations.

Refer to appendix 2 for further collection and shipping instructions.

15. Data management and monitoring

15.1 Source Documents

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

15.2 Data Management Plan

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

a. Data Capture Methods

Clinical data will be entered into a RedCAP database which includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

b. Study Record Retention

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

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

16. References:

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16. Ferreira FL, Bota DP, Bross A, et al: Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 286:1754-8, 2001
17. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22:707-10, 1996
18. Shelly MP, Nightingale P: ABC of intensive care: respiratory support. BMJ 318:1674-7, 1999

APPENDIX 1: SOFA SCORE

Reference: Vincent JL et al, The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine**.** Intensive Care Med. 1996 Jul;22(7):707-10

POINTS ASSIGNED AS BELOW AND ADDED:

Variable	Points
PaO_2/FiO_2, mmHg	
≥400	0
300-399	+1
200-299	+2
100-199 and mechanically ventilated	+3
<100 and mechanically ventilated	+4
Platelets, $\times 10^3/\mu L$	
≥150	0
100-149	+1
50-99	+2
20-49	+3
<20	+4
GLASGOW COMA SCALE	
15	0
13–14	+1
10–12	+2
6–9	+3
<6	+4
Bilirubin, mg/dL (µmol/L)	
<1.2 (<20)	0
1.2–1.9 (20-32)	+1
2.0–5.9 (33-101)	+2
6.0–11.9 (102-204)	+3
≥12.0 (>204)	+4

Mean arterial pressure OR administration of vasoactive agents required (listed doses are in units of mcg/kg/min)	
No hypotension	0
MAP <70 mmHg	+1
DOPamine ≤5 or DOBUTamine (any dose)	+2
DOPamine >5, EPINEPHrine ≤0.1, or norEPINEPHrine ≤0.1	+3
DOPamine >15, EPINEPHrine >0.1, or norEPINEPHrine >0.1	+4
Creatinine, mg/dL (µmol/L) (or urine output)	
<1.2 (<110)	0
1.2–1.9 (110-170)	+1
2.0–3.4 (171-299)	+2
3.5–4.9 (300-440) or UOP <500 mL/day)	+3
≥5.0 (>440) or UOP <200 mL/day	+4

APPENDIX 2: Research Blood Sample Collection and Shipping Instructions

Specimen Collection & Handling

Peripheral blood collection:

Blood samples will be obtained per Table 1 time points.

Approximately 30ml of whole blood will be collected: 20ml in citrate (blue-topped) and 10ml in EDTA (purple-topped) tubes.

If the collected blood volume is limited by clinical condition, sample collection will be limited to 10ml in citrate and 10ml in an EDTA tube initially, then 10ml in a citrate tube.

No pre-processing is required.

Specimen Labeling:

All tubes will be labeled with the study ID# (refer to section 8), and date/time of specimen collection.

Transporting and Storage Requirements:

For all transportations, a requisition should accompany all samples. A copy of the requisition will be retained at the site. Samples should only be collected Monday thru Friday. Samples should be transported to Versiti Blood Research Institute and received by Dr. Cui/designee the same day they are collected. Samples should be kept at ambient temperature until transport. The samples will need to be transported at ambient temperature. Samples should be packed and transported according to IATA regulations.
Research lab staff are available Monday through Friday between the hours of 7 am and 5 pm. Email Dr. Cui's lab to let them know specimens are being transported.

An Open label, Phase 2 Study Evaluating the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19 infection

Specimen Requisition Form

Patient Information:

Patient Study ID #: _____

Peripheral Blood Research Sample Information:

Date of Sample Collection:_____Time of Sample Collection: _____

Time point of collection:

☐ Baseline
☐ Day 4
☐ Day 7
☐ Day 14
☐ Day 28

Person Completing Requisition and Transporting Sample: _____

Phone Number and Email of Person Completing Requisition: _____

Date and Time of Transport of Sample: _____