**Phase IIa Study Exploring the Safety and Efficacy of Convalescent Plasma from Recovered COVID-19 Donors Collected by Plasmapheresis as Treatment for Hospitalized Subjects with COVID-19 Infection**


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# 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 from SARS-CoV2

CRF: Case Report Form

DMC: Data Management Center

DSMB: Data and Safety Monitoring Board

EUA: Emergency Use Authorization

FDA: Food and Drug Administration

GCP: Good Clinical Practice

HBV: Hepatitis B virus

HCIP: Human Coronavirus Immune Plasma

HCV: Hepatitis C virus

HIV: Human immunodeficiency virus

HTLV: Human T-cell lymphotropic virus

IB: Investigator's Brochure

ICF: Informed Consent (Informed Consent Form)

ICH: International Conference on Harmonization

ICU: Intensive Care Unit

IEC : Independent ethics committee

IND: Investigational New Drug Application

IRB: Institutional review board

ISBT: International Society of Blood Transfusion

ISM: Independent Safety Monitor

IWRS : Interactive web response system

MERS: Middle East Respiratory Syndrome

OP: Oropharyngeal

RT-PCR: Reverse Transcriptase Polymerase chain reaction

PK: Pharmacokinetic

PPE: Personal Protective Equipment

SAE: Serious adverse event

SARS: Severe Acute Respiratory Syndrome

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

TACO: Transfusion-associated circulatory overload

T. cruzi: *Trypanosoma cruzi*

TRALI: Transfusion-related acute lung injury

UP: Unanticipated Problem

UPnonAE: Unanticipated Problem that is not an Adverse Event

ZIKV: Zika virus

**PROTOCOL SUMMARY**

**Phase IIa Study Exploring the Safety and Efficacy of Convalescent Plasma from Recovered COVID-19 Donors Collected by Plasmapheresis as Treatment for Hospitalized Subjects with COVID-19 Infection**

**Background**

SARS-CoV-2

The novel coronavirus, SARS-CoV-2, is currently causing a worldwide pandemic with over 700,000 cases as of March 29th, 2020. There is currently no therapy for SARS-CoV-2, and the need for therapeutic options is urgent. The virus appears to cause multiorgan failure through several mechanisms, including a severe inflammatory response leading to acute respiratory distress syndrome.[1]

Convalescent plasma for novel viruses

Passive antibody therapy has been used for prior virus epidemics.[2-6] Reports from outbreaks of severe acute respiratory syndrome (SARS) from coronavirus (SARS-CoV-1) showed that convalescent plasma from recovered patients contains neutralizing antibodies.[7] In the 2013 Ebola epidemic, there was a significant increase in survival (72% vs 56%) for patients receiving convalescent whole blood compared to those who did not.[8] The proposed mechanism of action by which passive antibody therapy works, is thought to be viral neutralization but may also include antibody-dependent cellular cytotoxicity.

**Study Objectives**

Primary Objectives

- Primary objective for patients hospitalized for COVID-19 but not intubated, is to evaluate the efficacy of convalescent plasma in reducing rates of mechanical ventilation
- Primary objective for patients with COVID-19 already intubated is to evaluate the efficacy of convalescent plasma in reducing mortality from COVID-19 related causes at day 30
- To evaluate the safety of convalescent plasma

Secondary objectives

- Duration of hospitalization
- Duration of mechanical ventilation
- Time to symptoms resolution
- Overall survival
- Rate of virologic clearance by nasopharyngeal swab at day 10, 30, 60
- Evaluation of donor parameters including nasopharyngeal swab positivity and titers levels
- Evaluation of the impact of donor titers level (1:64, 1:128, and greater) on efficacy and safety
- Recipient Anti-SARS-CoV2 titer assessment on days 0 (pre-infusion),3,10,30, 60

Exploratory Objectives

These are to be performed at Hackensack Meridian Health Center for Discovery and Innovation

- Plasma product analysis for cytokines, mannose-binding lectin (MBL), procalcitonin (PCT), C-reactive protein (CRP), Human neutrophil lipocalin (HNL), Annexin V, Surfactant protein D (SP-D), as well as microRNAs
- Recipient cytokines and chemokines levels on days 0 (pre-infusion), 3,10,30,60 (optional)
- Host genomics on day 0 (optional)

Safety endpoints

- Rates of adverse events associated with convalescent plasma infusion
- Safety assessment will be performed on infusion days 0 (post infusion), 3, 10, 30, and 60 days

**Inclusion Criteria**

Donor (see Appendix A)

- Age 18-60
- A history of a positive nasopharyngeal swab for COVID-19 or a history of positive titer test.
- At least 14 days from resolution of COVID-19-associated symptoms including fevers
- One negative nasopharyngeal swabs for COVID-19 RNA
- Covid-19 neutralizing antibody ≥1:64
- Adequate venous access for apheresis
- Meets donor eligibility criteria in accordance to Hackensack University Medical Center (HUMC) Collection Facility at the John Theurer Cancer Center (JTCC) if collecting at the JTCC, and all regulatory agencies as describes in SOP 800 01 (Appendix A)
- Required testing of the donor and product must be performed in accordance to FDA regulations (21 CFR 610.40), and the donation must be found suitable (21 CFR 630.30)

Recipient

Recipients age ≥18 years old, are assigned to one of two clinical tracks, track 2 or 3, based on COVID-19 disease severity. Onset of first symptoms < 9 days.

Track 2

- Hospitalized, moderate symptoms requiring medical care for COVID-19 infection
- Symptoms may include fever, dyspnea, dehydration among others
- Hypoxemia may be present but is not a requirement

Track 3

- Requiring mechanical ventilation for the care of COVID-19 infection
- Requiring non-invasive positive pressure ventilation (NIPPV), such as continuous airway pressure (CPAP),bi-level positive airway pressure (BiPAP) or high flow nasal canula (HFNC).

Recipient exclusion criteria

- History of severe transfusion reaction to plasma products
- Infusion of immune globulin within the previous 30 days
- AST or ALT > 10 x upper limit of normal
- Requirement for vasopressors
- COVID-19-associated acute kidney injury requiring dialysis
- DNR status

**Treatment Plan**

Plasma collection

Collection of plasma will be performed on eligible and suitable donors meeting regulatory requirements (Appendix A).

SARS-CoV-2 convalescent plasma consisting of 1 unit of approximately 400-500 mL or 2 units of approximately 200 mL will be collected by apheresis from a volunteer donor who recovered from COVID-19 infection and was found to have a titer of neutralizing antibody $\geq$1:64.

Donors may be referred to an outside licensed Blood Center for plasmapheresis.

Plasma infusion

Fresh or cryopreserved plasma will be infused one time to patients in Track 2 (hospitalized but not mechanically ventilated) or in Track 3 (mechanically ventilated, invasively or non-invasively).

**Statistical Analysis**

For each track, we have considered a multistage sequential design based on the sequential conditional probability ratio test which is more efficient than the Simon's 2-stage design and has the flexibility for unplanned analyses should they become necessary due to slow accrual and/or competing therapies.[17-18]

Track 2 Mechanical ventilation

The phase II trial design for Track 2 is as follows. The first stage analysis will be after 12 patients, if 6 or more of them require mechanical ventilation, we conclude that the therapy is not worth pursuing; and if 0 out of 12 patients requires mechanical ventilation, early evidence for efficacy is established. The maximum discordance probability is 0.00059, which indicates that if 6 or more of the first 12 patients require mechanical ventilation to the therapy, there is very slim (less than 0.059%) chance that the mechanical ventilation rate would be less than 30% should the study continue to enroll all 36 patients. On the other hand, if 0 of the first 12 patients requires mechanical ventilation, it is certain that the trial will meet its goal even if we enroll all 36 patients. This statistical design would have 80% probability to accept the therapy for further trials if the true mechanical ventilation rate is indeed 15% and 10% probability to reject the null hypothesis if the true mechanical ventilation rate is indeed 30%.

Track 3 Mortality

The phase II trial design for Track 3 is as follows. The first stage analysis will be after 6 patients, if 5 or more of them pass away, we conclude that the therapy is not worth pursuing; and if 0 out of 6 patients die, early evidence for efficacy is established. The maximum discordance probability is 0.00091, which

indicates that if 5 or more of the first 6 patients pass away to the therapy, there is very slim (less than 0.091%) chance that the mortality rate would be less than 49% should the study continue to enroll all 19 patients. On the other hand, if 0 of the first 6 patients is alive, it is certain that the trial will meet its goal even if we enroll all 19 patients. This statistical design would have 80% probability to accept the therapy for further trials if the true mortality rate is indeed 25% and 10% probability to reject the null hypothesis if the true mortality rate is indeed 49%.

**Study site**

This is a single institution study conducted at Hackensack University Medical Center (HUMC)/John Theurer Cancer Center at HUMC, Hackensack, NJ. The exploratory laboratory tests will be performed at the Hackensack Meridian Health Center for Discovery and Innovation (CDI)

**PROTOCOL**

**Phase IIa Study Exploring the Safety and Efficacy of Convalescent Plasma from Recovered COVID-19 Donors Collected by Plasmapheresis as Treatment for Hospitalized Subjects with COVID-19 Infection**

## 1. Introduction

### 1.1 General principals of passive antibody therapy

There is currently no proven effective therapy for coronavirus disease (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Donor convalescent plasma has been successfully used for treatment of other viral infections, and thus may provide an option for the treatment of COVID-19 and could be rapidly available from people who have recovered from the disease and can donate plasma.

Passive antibody therapy involves the administration of antibodies against an infectious agent to an afflicted individual for the purpose of treating their disease. In contrast, active vaccination requires the induction of an immune response, which takes time to develop and varies depending on the recipient. Some immunocompromised patients fail to achieve an adequate immune response. Thus, passive antibody administration may in some instances represent the only way of providing immediate immunity to susceptible persons, and more predictable immunity in immunocompromised patients. It also offers the potential for immediate benefit in hospitalized and ICU patients who are critically ill.

Passive antibody was first described in the 1890s, and was the only way to treat certain infectious diseases prior to the development of antimicrobial therapy in the 1940s.[2-6] Experience from prior outbreaks with other coronaviruses such as SARS-CoV-1 shows that convalescent plasma contains neutralizing antibodies to the relevant virus.[7] In the case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy would mediate protection is viral neutralization. However, other mechanisms may be possible, such as antibody-dependent cellular cytotoxicity or phagocytosis. Convalescent serum was also used in the 2013 African Ebola epidemic. A small non-randomized study in Sierra Leone revealed a significant increase in survival for those treated with convalescent whole blood relative to those who received standard treatment.[8]

The only antibody therapy currently available for immediate use in SARS-CoV-2 is found in human convalescent plasma. As more individuals contract COVID-19 and recover, the number of potential donors will continue to increase.

A general principle of passive antibody therapy is that it is more effective when used early in the treatment of disease. Antibody therapy 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.[4] As an example, passive antibody therapy for pneumococcal pneumonia was most effective when administered shortly after the onset of symptoms and there was no benefit if antibody administration was delayed past the third day of disease.[2]

For passive antibody therapy to be effective, enough antibody must be administered. When given to a susceptible person, this antibody will circulate in the blood, reach tissues and provide protection against infection. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin can last from weeks to months. Therefore, the use of a larger amount of plasma collected by apheresis may be preferable to plasma separated from a unit of whole blood.

### 1.2 Experience with the use of convalescent plasma to treat coronavirus infections

In recent times there have been two other epidemics with coronaviruses that were associated with high mortality, SARS1 in 2003 and MERS in 2012. In both outbreaks, the high mortality and absence of effective therapies led to the use of convalescent plasma. The largest study involved the treatment of 80 patients in Hong Kong with SARS.[9] Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. In addition, those who were PCR positive and seronegative for coronavirus at the time of therapy had improved outcomes. There is also some anecdotal information on the use of convalescent plasma in seriously ill individuals. Three patients with SARS in Taiwan were treated with 500 ml of fresh convalescent plasma, resulting in a reduction in plasma virus titer and each survived.[10] Three patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients had neutralizing antibody in their plasma.[11] The latter study highlights a challenge in using convalescent plasma, namely, that some who recover from viral disease may not have high titers of neutralizing antibody.[12] Consistent with this point, an analysis of 99 samples of convalescent sera from patients with SARS showed that 87 had neutralizing antibody with a geometric mean titer of 1:61.[7] This suggests that antibody declines with time or that few patients make high titer responses.

It is also possible that other types of non-neutralizing antibodies are made that contribute to protection and recovery as described for other viral diseases.[13]

Convalescent plasma has been reported in a case series of patients with SARS-CoV-2.[20] Patients received transfusion with 400-500 mL of fresh convalescent plasma with a SARS-CoV-2–specific antibody binding titer greater than 1:1000 and a neutralization titer greater than 40 that had been obtained from 5 patients who recovered from COVID-19. Convalescent plasma was administered between 10 and 22 days after admission. All 5 patients were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital, and 2 are in stable condition at 37 days after transfusion. Since this is the only available data for SARS-CoV2 available, the infusion of a larger volume (400-500mL) of fresh plasma would be supported.

### 1.3 Overview of safety

Historical and current anecdotal data on use of convalescent plasma suggest that it is safe in coronavirus infection. The theoretical risk involves the phenomenon of antibody-dependent enhancement of infection (ADE). 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.[14] Since the proposed use of convalescent plasma in the COVID-19 epidemic would rely on preparations with high titers of neutralizing antibody against the specific virus, SARS2-CoV-2, ADE may be unlikely. The available evidence from the use of convalescent plasma in patients with SARS1 and MERS,[15] and the case series evidence of its use in patients with COVID-19[20] suggests it is safe.

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.[16] This concern will be investigated as part of this clinical trial by measuring immune responses in those exposed and treated with convalescent plasma to prevent disease. If the concern proved real, these individuals could be vaccinated against COVID-19 when a vaccine becomes available. The antibodies used in this study will be derived from serum obtained from convalescent patients and will be subjected to testing protocols used by blood banks and transfusion services. However, as is the case with any biological product, there is a very small risk of allergy or anaphylaxis, transfusion related acute lung injury (TRALI), and transfusion associated circulatory overload (TACO) or passive transfer of potential unknown infectious agents. Most adverse effects are mild and transient including headaches, flushing, fever, chills, fatigue, nausea, diarrhea, blood pressure changes and tachycardia. Late adverse events are rare.

## 2. Study Objectives

### 2.1 Primary objectives

- Primary objective for patients hospitalized for COVID-19 but not intubated, is to evaluate the efficacy of convalescent plasma in reducing rates of progression to mechanical ventilation.
- Primary objective for patients with COVID-19 already intubated is to evaluate the efficacy of convalescent plasma in reducing mortality at day 30.
- To evaluate the safety of convalescent plasma

### 2.2 Secondary objectives

- Duration of hospitalization
- Time to symptoms resolution
- Duration of mechanical ventilation
- Overall survival
- Rate of virologic clearance by nasopharyngeal swab at day 10, 30, 60
- SARS-CoV-2 PCR positivity (RT-PCR) in blood at days 0 (pre-infusion), 3, 10, 30, 60
- Evaluation of the impact of donor titers levels (1:64, 1:128, and greater) on the primary objectives described in 2.1.
- Evaluation of donor parameters including nasopharyngeal swab positivity and titers levels
- Recipient anti-SARS-CoV2 titers assessment on days 0 (pre-infusion), 3, 10, 30, 60

### 2.3 Exploratory objectives

These are to be performed at Hackensack Meridian Health Center for Discovery and Innovation

- Plasma product analysis for cytokines, mannose-binding lectin (MBL), procalcitonin (PCT), C-reactive protein (CRP), Human neutrophil lipocalin (HNL), Annexin V, Surfactant protein D (SP-D), as well as microRNAs
- Recipient cytokines and chemokines levels on days 0 (pre-infusion), 3,10,30,60 (optional)
- Host genomics on day 0 (optional)

### 2.4 Safety endpoints

- Rates of adverse events associated with convalescent plasma infusion will be determined as defined in section 6.3.
- Safety assessment will be performed on post infusion day 0,3,10, 30, and 60 days.

## 3. Eligibility and Exclusion Criteria

### 3.1 Donor

- Age 18-60
- A history of a positive nasopharyngeal swab for COVID-19 or a history of positive titer test.

- At least 14 days from resolution of COVID-19-associated symptoms including fevers
- One negative nasopharyngeal swabs for COVID-19 RNA
- Covid-19 neutralizing antibody ≥1:64
- Adequate venous access for apheresis
- Meets donor eligibility criteria in accordance to regulatory requirements and Hackensack Meridian Health SOP 800 01 "COVID-19 Convalescent Plasma Procurement" (Appendix A).
- Required testing of the donor and product must be performed in accordance to FDA regulation 21 CFR 610.40, and the donation must be found suitable (21 CFR 630.30) (See Appendix A)

3.2 Recipient

Recipients must be ≥18 years old, and have a documented infection with SARS-CoV-2 and belong to either Track 2 or Track 3. Onset of first symptoms < 9 days.

3.2.1 Track 2

- Hospitalized, moderate symptoms requiring medical care for COVID-19 infection
- Symptoms may include fever, dyspnea, dehydration and others
- Hypoxemia may be present but is not a requirement

3.2.2 Track 3

- Patients mechanically ventilated for COVID-19 infection
- Requiring non-invasive positive pressure ventilation (NIPPV), such as continuous airway pressure (CPAP), bi-level positive airway pressure (BiPAP) or high flow nasal canula (HFNC).
-

3.2.3 Recipient exclusion criteria

- History of severe transfusion reaction to plasma products
- Infusion of immune globulin within the previous 30 days
- AST or ALT > 10 times upper limit of normal
- Requirement for vasopressors
- COVID-19-associated acute kidney injury requiring dialysis
- DNR status

## 4. Investigational Plan

4.1 Overall study design

- This is a single arm phase IIa study of convalescent plasma for the treatment of individuals hospitalized with COVID-19 infection.
- Subjects will be considered as having completed the study after 60 (+/- 3) days, unless consent withdrawal or death occurs first.

- Interim analysis will be permitted as described in the statistical section 8.
- The final analysis will be conducted once the last subject completes the day 60 visit or withdraws from the study.

4.2 Number of subjects

- Up to 36 patients in track 2, and 19 patients in track 3 as described in the statistical section 8.

4.3 Overall study duration

- The study begins when the first subject (this will likely be a donor) signs the informed consent. The study will end once the last enrolled subject completes the study (likely a recipient).
- The expected duration of the study is approximately 12 months.

## 5. Treatment Plan

5.1 Donor procedures and evaluation

All activities pertaining to donor recruitment, enrollment, collection, product handling and processing will take place at Hackensack University Medical Center (HUMC) and John Theurer Cancer Center at HUMC. This facility is FDA-registered and AABB accredited, attesting to robust quality oversight of all operations. All donor-related procedures pertaining to this study are detailed in our SOP 800 01 "COVID-19 Convalescent Plasma Procurement" in Appendix A.

5.1.1 Donor recruitment and screening (see Appendix A)

- Mechanism for recruitment will include advertising in the local community where recent outbreaks have occurred.
- Individuals who agree to participate will do so under full informed consent.
- Individuals who agree to participate will undergo pre-donation screening by a clinical health care provider (visit 1).
- Only those individuals who satisfy all criteria for collection as determined through medical evaluation and laboratory testing described in Appendix A will proceed to a second visit (visit 2) during which the collection will take place. Visit 2 will occur within seven days of visit 1.
    1. Visit 1:
        a. History and physical examination if collecting at JTCC
        b. Donor health questionnaire
        c. Nasopharyngeal swab for COVID-19
        d. Blood for SARS-CoV-2 neutralizing antibody
        e. Blood tests as described in SOP 800.01 section "Donor Evaluation and Eligibility" subsection L (Appendix A), for collections at the JTCC
    2. Visit 2:
        a. Donor health questionnaire
        b. Blood tests as described in SOP 800.01 section "Donor Evaluation and Eligibility" subsection L (Appendix A)

c. Apheresis procedure as described in section 5.1.2 and Appendix A if collecting at the JTCC.

5.1.2 Donor plasma collection (see Appendix A)

- The plasma collection will be performed by apheresis at the John Theurer Cancer Center (JTCC) Collection Facility at HUMC as per "COVID-19 Convalescent Plasma Procurement" SOP (Appendix A) or the donor will be referred to an outside licensed Blood Center for plasmapheresis.
- The JTCC houses a FACT accredited Collection Facility, NJ Blood Bank license 10317, FDA (BMT FEI) Registration 3004726780.
- The plasma collection will be performed using either the Trima Accel® System by Terumo BCT (Appendix A SOP 800 01).
- As per routine practice, samples will be collected at the time of donation for testing for transfusion-transmissible infections (all donors), ABO and red cell antibodies (all donors) and HLA antibodies (female donors), in accordance with FDA regulation 21 CFR 610.40, and the donation must be found suitable (21 CFR 630.30).
- Target collection volume: 500mL in a single collection bag or two collection bags of 200mL. The Trima Accel® system considers the total blood volume and will make recommendations to the volume that can be removed safely. Therefore, the collection goal will be either 500mL or the machine recommended maximum volume, whichever is smallest.
- Labeling will be in accordance with FDA regulations 21CFR 606.121.
- The plasma will be maintained in quarantine pending laboratory test results (i.e. infectious screening, ABO and RhD status, Red cell and HLA antibodies).
- If laboratory testing is acceptable (i.e. negative infectious and antibody screening), the products will be appropriately labeled and distributed to hospital blood bank for storage.
- In the event of an abnormal test result, the product will be discarded, and the donor will be notified by the blood center as is standard practice.
    - Donors may donate plasma every $\geq$ 7 days. The donor screening procedure described in section 5.1.1 " visit 2" will need to be repeated for each subsequent donation on the day of plasmapheresis, with the addition of blood for SARS-CoV-2 neutralizing antibody

5.1.3 Product handling

Product handling including labeling, testing, transportation, distribution and record keeping including chain of custody recording will be performed in accordance with regulations and HUMC SOP 800.01 "COVID-19 Convalescent Plasma Procurement" (Appendix A).

5.2 Patient (recipient) procedures and evaluation (see Appendix B)

5.2.1 Day -1 to 0 (pre-infusion)

- Screening
- Informed consent must be obtained before performing study related activities (can be from healthcare proxy if subject unable to provide consent due to medical status)
- Baseline Evaluation (at screening)

1. Demographics (age, sex ethnicity, race)
2. Medical history
    a. Onset of COVID-19 symptoms
    b. Date of positive test
    c. Acute and chronic medical conditions, medications, allergies.
    d. Any medical condition arising after consent should be recorded as an AE
3. COVID-19 symptom screen (fevers, cough, shortness of breath and others)
4. Vital signs
5. Physical examination as last reported in the medical records on current day
6. Documentation of positive nasopharyngeal COVID-19 testing within 10 days (RT-PCR) prior to infusion. If not, repeat.
7. Blood typing, CBC, comprehensive metabolic panel
8. Serological testing: anti-SARS CoV-2 titers
9. Blood SARS-CoV-2 PCR (RT-PCR)
10. Determination of eligibility as per inclusion/exclusion criteria
11. Exploratory blood test (optional) if recipient consents

5.2.2 Day 0 (infusion day)

- Study plasma administration

1. A single unit of fresh plasma will be transfused at an approximate rate of 50 mL per hour x 30 minutes, then the rate may be increased up to 250 mL per hour until completion.
    a. Alternatively, recipients may receive 200 mL to 400 mL of cryopreserved plasma collected at an outside Blood Center. The

cryopreserved plasma will be administered as per standard institutional SOP for fresh frozen plasma infusion.

2. If possible, 10mL of plasma will be collected for research from the infusion line and sent to the CDI
3. The infusion may be slowed or stopped as per investigator's decision for minor transfusion reactions only. The transfusion will be discontinued for any transfusion reactions other than minor allergic reactions.
4. An investigation will be initiated when there are signs of a systemic transfusion reaction.
5. Premedication 30 – 60 minutes prior to the infusion will include 100 mg hydrocortisone IV, acetaminophen 650 mg PO, and diphenhydramine 25 mg IV. Diphenhydramine 25 mg IV and hydrocortisone 100 mg IV may be repeated as needed for an infusion reaction at the discretion of the investigator.
6. Time at start and end of infusion will be recorded
7. Vitals signs should be monitored following Hackensack Meridian Health Blood and Blood Product Administration SOP guidelines:
    a. Temperature, pulse, respirations, and blood pressure pre-infusion (within 30 minutes), 15 minutes after the start, every hour during, if a transfusion reaction is suspected or if there is any change in patient condition, post transfusion (5-15 minutes post)

- COVID-19 symptom screen (fevers, cough, shortness of breath)
- Assessment of clinical status
    1. ICU and mechanical ventilation (invasive or non-invasive) status
    2. Oxygen % requirement
    3. Severe end-organ dysfunction
- New medical conditions, concomitant medication, AE evaluation
- Physical examination, may use as recorded in the medical record from the same day
- CBC, blood chemistry
- Serological testing: anti-SARS CoV-2 titers
- Blood for SARS-CoV-2 PCR (RT-PCR)
- Exploratory blood test for genomics, cytokines/chemokines to be sent to the CDI (optional)

5.2.3 Post infusion day +3, +10 (+/- 48 hours for day 10)

- Vital signs
- COVID-19 symptom screen (fevers, cough, shortness of breath)
- Assessment of clinical status (composite outcome of disease severity)
- New medical conditions, AE evaluation
- Physical examination, may use physical examination from the medical record from the same day

- COVID-19 testing (RT-PCR) from nasopharyngeal or ET secretions if intubated on day 10
- Serological testing: anti-SARS CoV-2 titers if possible.
- Blood for SARS-CoV-2 PCR (RT-PCR)
- Exploratory blood test for genomics, cytokines/chemokines to be sent to the CDI (optional)

5.2.4 Day +30 and +60 ,+/- 3 days (can be remote)

- COVID-19 symptom screen (fevers, cough, shortness of breath)
- Stool for microbiome and viral content if possible
- COVID-19 testing (RT-PCR) from nasopharyngeal sampling
- New medical conditions, AE evaluation
- Serological testing: anti-SARS CoV-2 titers if possible.
- SARS-CoV-2 PCR (RT-PCR) in blood
- Exploratory blood test for genomics, cytokines/chemokines to be sent to the CDI (optional)

## 5.3 Withdrawal criteria

5.3.1 A subject must be withdrawn from study treatment for the following reasons

- Subject has experienced an unacceptable toxicity precluding the completion of plasma infusion.
- The study is terminated by the local health authority, or IRB.

5.3.2 If a subject is withdrawn from study treatment

- The reason(s) for withdrawal must be documented in the subject's medical record and in the CRF.
- The end of treatment (EOT) visit should be performed.
- Subjects must be followed for safety until the time of the follow-up visit or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.
- If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study.

## 5.4 Study Completion

5.4.1 A subject will be considered as completing the study if he or she meets any the following criteria:

- Subject completes the day 60 visit
- Subject dies, and a date of death is available
- Subject is known to have died; however, the date of death cannot be obtained (every effort must be made to obtain the date of death)

- Subject has discontinued study treatment and has withdrawn consent for collection of further follow-up data

## 6. Conduct of study assessment and procedures

### 6.1 Administration of informed consent form

Valid informed consent must be obtained from the study subjects, donor and recipient, before conducting any study-specific procedures pertaining to donor or recipient, using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation. Rescreening of potential subjects is permitted. Recipient consent need not be obtained for a donor to consent and initiate treatment.

### 6.2 Prior and concomitant medications

The medication record will be maintained after signing the ICF to document concomitant medications.

### 6.3 Safety assessments

#### 6.3.1 Adverse events

Adverse events for both donors and recipients will be monitored from the time the subjects sign the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and CRFs regardless of the assumption of a causal relationship with study treatment. The definition, reporting, and recording requirements for AEs are described in Section 8.

#### 6.3.2 Physical examinations

The targeted physical examinations will be symptom-directed evaluations conducted by the investigator or a medically qualified designee. Since subjects (recipients) are highly contagious, a physical examination recorded by a clinician (APN, MD, DO), in the medical record on visit day, will be acceptable.

#### 6.3.3 Performance status

ECOG performance status (table 1) or Karnofsky performance status (table 2) will be assessed. Performance status must be assessed by a medically qualified individual and recorded in the CRF.

Table 1. ECOG Performance Status Grades:

| Grade | Performance Status |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work. |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

Table 2. Karnofsky Performance Status Grades:

| Grade | Performance Status |
|---|---|
| 100 | Normal; no complaints; no evidence of disease. |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 80 | Normal activity with effort; some signs or symptoms of disease. |
| 70 | Cares for self; unable to carry on normal activity or to do active work. |
| 60 | Requires occasional assistance but can care for most of their personal needs. |
| 50 | Requires considerable assistance and frequent medical care. |
| 40 | Disabled; requires special care and assistance. |
| 30 | Severely disabled; hospital admission is indicated although death not imminent. |
| 20 | Very sick; hospital admission necessary; active supportive treatment necessary. |
| 10 | Moribund; fatal processes progressing rapidly. |
| 0 | Dead. |

6.3.4 Infection monitoring

Monitoring for infection other than COVID-19 will be performed on recipient days 0,3,10,30,60.

## 7. Safety Monitoring and Reporting

### 7.1 Adverse events

#### 7.1.1 Definitions

For the purposes of this Protocol, an AE is defined as any untoward medical occurrence associated with the donation or use of a convalescent plasma for COVID-19 whether or not considered related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, or require therapy (eg, hematologic abnormality that requires transfusion).

#### 7.1.2 Reporting

- Adverse events that begin or worsen after initiation of plasma donation or infusion should be recorded on the Adverse Events Form of the CRF. Monitoring for the occurrence of new AEs should be continued for 1 days after the plasma donation and at least 60 days after the plasma infusion. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.
- If an adverse event meets the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s).
- The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

| | |
|---|---|
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Grade 2 | Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living. |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. |

Grade 4 Life-threatening consequences, urgent intervention indicated.

Grade 5 Death due to AE

- The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. This will apply for the donor where a post donation phone call will be placed. For the recipient, occurrence of AEs will be sought on days 0, 3, 10, 30, 60. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:
    1. The severity grade (CTCAE Grade 1 to 5)
    2. Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no)
    3. The start and end dates, unless unresolved at final follow-up
    4. The action taken about study treatment
    5. The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
    6. The seriousness, as per SAE definition provided in section 7.2
- Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements described in section 7.2.2.
- All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy Form in the CRF.
- Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

## 7.2 Serious adverse events

### 7.2.1 Definitions

A SAE is defined as an event that meets at least 1 of the following criteria

- Is fatal or life-threatening

- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
    1. A routine treatment or monitoring of the studied indication not associated with any deterioration in condition
    2. An elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF
    3. A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission
    4. Any social reasons and respite care, in the absence of any deterioration in the subject's general condition
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions
- Constitutes a congenital anomaly or birth defect
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

7.2.2 Reporting

- Information about all SAEs is collected and recorded on the Adverse Event Form of the CRF. The investigator must assess and record the causal relationship of each SAE to the treatment. SEA must be reported in compliance with institutional IRB/DSMD requirements.
- Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

7.3 Data Safety Monitoring Board (DSMB)

This study will be approved and monitored by the HackensackUMC DSMB. The DSMB is responsible for the monitoring of investigator initiated research studies to ensure the safety of participants, the integrity of the data, and the appropriate termination of studies in the event

that undue risks have been uncovered, or it appears that trials cannot be conducted successfully. The DSMB provides multidisciplinary, independent oversight of research studies conducted by HackensackUMC staff and or affiliates. The DSMB can require protocol modifications related to participant safety and to recommend suspension of termination to the IRB and institutional official of any research protocols that fall within its jurisdiction. The DSMB may request that HackensackUMC's Corporate Compliance Department conduct periodic audits to assure that data are being collected and recorded according to the protocol.

The investigator is required to submit monthly monitoring reports which include current enrollment data, adverse event summary data and any other data requested by the DSMB. The DSMB will meet monthly to review the trial progress, adverse event data, and any relevant information such as significant amendments or reviews from IRB submitted by the principal investigator. If significant concerns are raised by the DSMB, the concerns will be forwarded to the PI as well as recommendations made to the IRB, and Institutional Official. Recommendations may include modifying, suspending, or terminating the protocol.

**8. Statistical Analysis**

Patients are clinically divided into Track 2 or Track 3. For each track, we have considered a multistage sequential design based on the sequential conditional probability ratio test which is more efficient than the Simon's 2-stage design and has the flexibility for unplanned analyses should they become necessary due to slow accrual and/or competing therapies.[17-18]

The statistical design is based on the following hypotheses:

For Track 2, the null hypothesis is that the Mechanical Ventilation Rate is at least 30% and the alternative hypothesis is that the Mechanical Ventilation Rate is less than or equal to 15%.

For Track 3, the null hypothesis is that the Mortality Rate is at least 49% and the alternative hypothesis is that the Mortality Rate is less than or equal to 25%.

The design in each track has a type I error rate at 0.10 with statistical power at least 0.80. For Track 2, this statistical design would have 80% probability to accept the therapy for further trials if the true mechanical ventilation rate is indeed 15% and 10% probability to reject the null hypothesis if the true mechanical ventilation rate is indeed 30%. For Track 3, the statistical design would have 80% probability to accept the therapy for further trials if the true mortality rate is indeed 25% and 10% probability to reject the null hypothesis if the true mortality rate is indeed 49%.

For each of the tracks, if a decision for rejecting or accepting the null hypothesis is made based on the interim data at any stage, then the probability that such a decision would be reversed is negligible (less than 0.1%, the maximum discordant probability) should the trial continue to the end and include all patients. This probability is calculated using the SCPRT method and software.[18] This methodology takes the usual fixed sample/single stage design and makes it a multiple-stage design while still retaining the type I and II error. The sample size is calculated with the typical fixed sample test of a proportion. The SCPRT method just makes it multi-stage to allow evaluation of early evidence. While retaining the rigor of

the original fixed sample design. Interim analysis will therefore be performed after each Stage described in Tables 3 and 4. For Track 2 after 12, 24 and 36 patients, and for Track 3 after 6, 12 and 19 patients.

### 8.1 Track 2: Mechanical ventilation

The phase II trial design for Track 2 is as follows. The first stage analysis will be after 12 patients, if 6 or more of them require use of mechanical ventilation, we conclude that the therapy is not worth pursuing, and this will be reported to the DSMB for further guidance. If 0 out of 12 patients requires mechanical ventilation, early evidence for efficacy is established and accrual continues.

The maximum discordance probability is 0.00059, which indicates that if 6 or more of the first 12 patients require mechanical ventilation to the therapy, there is very slim (less than 0.059%) chance that the mechanical ventilation rate would be less than 30% should the study continue to enroll all 36 patients. On the other hand, if 0 of the first 12 patients requires mechanical ventilation, the trial will certainly meet its goal even if we enroll all 36 patients (which is allowed).

This statistical design would have 80% probability to accept the therapy for further trials if the true mechanical ventilation rate is indeed 15% and 10% probability to reject the null hypothesis if the true mechanical ventilation rate is indeed 30%.

**Table 3.** Study design of Track 2

| Stage | Cumulative sample size | Not Promising if number of MVent $\geq$ | Promising if number of MVent $\leq$ |
|---|---|---|---|
| 1 | 12 | 6 | 0 |
| 2 | 24 | 8 | 1 |
| 3 | 36 | 8 | 7 |

*Number of patients requiring mechanical ventilation

## 8.2 Track 3: Mortality

The phase II trial design for Track 3 is as follows. The first stage analysis will be after 6 patients, if 5 or more of them pass away, we conclude that the therapy is not worth pursuing, and this will be reported to the DSMB for further guidance. If 0 out of 6 patients passed away, early evidence for efficacy is established and accrual continues.

The maximum discordance probability is 0.00091, which indicates that if 5 or more of the first 6 patients pass away after the therapy, there is very slim (less than 0.091%) chance that the mortality rate would be less than 49% should the study continue to enroll all 19 patients. On the other hand, if 0 of the first 6 patients die, the trial will certainly meet its goal even if we enroll all 19 patients (which is allowed).

This statistical design would have 80% probability to accept the therapy for further trials if the true mortality rate is indeed 25% and 10% probability to reject the null hypothesis if the true mortality rate is indeed 49%.

**Table 4.** Study design of Track 3

| Stage | Cumulative sample size | Not Promising if number of deaths $\geq$ | Promising if number of deaths$\leq$ |
|---|---|---|---|
| 1 | 6 | 5 | 0 |
| 2 | 12 | 7 | 1 |
| 3 | 19 | 7 | 6 |

## 8.3 Analysis plan

### 8.3.1 Primary endpoints

The primary endpoint of the phase II study is to determine mechanical ventilation rate at 7 days from starting treatment in hospitalized COVID-19 patients (Track 2), and mortality rate at 30 days from starting treatment for patients with COVID-19 (Track 3) receiving new therapies. The above-mentioned rates (response rates) will be computed and reported with an 95% exact binomial confidence interval (CI).

### 8.3.2 Secondary Endpoints

- Describe the rate of virologic clearance at 10 days will be calculated and reported with an 95% exact binomial CI. Viral clearance at a designed follow-up date is defined as the cycle threshold (Ct) of RT-PCT at that designed follow-up date $\geq$ 40.
- Time to symptom resolution (Track 2 and 3)

  Kaplan-Meier analysis will be used to describe time to symptom resolution (Track 1 to 2), the median time with 95% CI will be reported.

  The time to symptom resolution is defined as the time in days from new therapy initiation to the first documented symptom resolution as assessed by local site.

Patients whose symptom are not resolved, who are dead, or lost follow-up on the designed follow-up date will be censored on that date.

- Duration of hospitalization (Tracks 2 to 3)

  Kaplan-Meier analysis will be used to describe the duration of hospitalization (Track 2 to 3), the median time with 95% CI will be reported.

  The duration of hospitalization is defined as the time in days from the first day of hospitalized to the date of discharge or death. Patients who are not discharged, are alive and still in the hospital on the date of closing follow-up, or lost follow-up on the date of closing follow-up will be considered censored on that date.

- Duration of Mechanical Ventilation (Track 3)

  Kaplan-Meier analysis will be used to describe the duration of mechanical ventilation for all evaluable patients (Track 3), the median time with 95% CI will be reported.

  The duration of mechanical ventilation is defined as the time in days from the first day of using mechanical ventilation to the last day of using mechanical ventilation. All evaluable patients will be included and no censoring for this analysis.

- Overall Survival (OS) (Tracks 2 to 3)

  Overall survival will be defined as the time in days from study entry to death. Patients who are alive on the date of closing follow-up will be censored on that date. All events of death will be included, regardless of whether the event occurred while the subject was still taking new therapies, or after the subject discontinued study therapy. If a subject has not died, then the data will be censored according to the following rule: if the subject was lost to follow-up, then data will be censored at the last study visit, or the last contact date, or the date the subject was last known to be alive, whichever is later; if the subject was not lost to follow-up, then data will be censored at the last study visit or the last contact date, whichever is later. OS will be estimated by Kaplan-Meier methodology, and median OS with 95% CI will be reported.

- Safety Assessments (Tracks 2 to 3)

  Overall safety monitoring will be performed throughout the study for each track. The safety of study therapy of patients with COVID-19 will be accessed by evaluating new therapies exposure, adverse events, serious adverse events, and death. And adverse events will be evaluated according to the NCI Common Terminology for Adverse Events (CTCAE) as described in section 7.

- Baseline Characteristics (Tracks 2 to 3)

  For each track, the baseline summary statistics and analyses will be based on characteristics prior to the initiation of new therapies. Frequency and percentages for categorical variables and mean (SD) or median (IQR interquartile range) for the continuous variables based on the normalization of the data.

### 8.3.3 Exploratory

- Descriptive statistics will be used to characterize the genomic expression profiling, immunologic profiling, quantitative viral load, and anti-SAS-CoV-2 titer assessment during the study therapy as well as several follow-up time points. Frequency and percentages for categorical variables and mean (SD) or median (IQR interquartile range) for the continuous variables based on the normalization of the data.
- Univariate test will be performed in terms of identifying the association between baseline genomic expression profiling and the severity of patients' disease (severe disease vs. non-severe disease), Chi-square test or Fisher's exact test for categorical variables, and t-test or its non-parametric version for the continuous variables based on the normalized of the data. These analyses will most likely be in a pairwise fashion given the moderate sample size.
- P-value less than 0.05 will be considered significant. All statistical analyses will be performed using RStudio (Version 0.99.902) and SAS (Version 9.4).

## 9. Regulatory consideration

### 9.1 Good Clinical Practice

The study will be conducted according to the International Conference on Harmonization (ICH), Good Clinical Practice (GCP), the Declaration of Helsinki, Institutional Review Boards (IRB) and in accordance with the U.S. Code of Federal Regulations on Protection of Human Rights (21 CFR 50).

### 9.2 Institutional Review Board (IRB) Review

- The final study protocol and consent form (and any other appropriate documents as applicable) will be approved by the Institutional Review Board (IRB) at Hackensack Meridian *Health*. Approval will be received in writing before initiation of the study.
- Any changes to the study design will be formally documented in protocol amendments and will be approved by the IRB prior to implementation.
- Any amendment to this protocol must also be approved by the IRB and FDA. The written signed approval from the IRB should specifically reference the investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB approval but will be submitted to the IRB for information purposes.
- The investigator must keep a record of all communication with the IRB and, if applicable, between a Coordinating investigator and the IRB. This statement also applies to any communication between the investigator (or Coordinating investigator, if applicable) and regulatory authorities.
- Any advertisements used to recruit subjects for the study must be reviewed by [sponsor] and the IRB prior to use.

### 9.3 Ongoing Information for IRB Committee

As required by legislation and local regulatory requirements, the investigator must submit to the IRB:

- Information on serious or unexpected adverse events as soon as possible
- Annual reports on the progress of the study
- Deviations from the protocol or anything that may involve added risk to subjects

### 9.4 Investigator Responsibilities

- Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations.
- The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions.
- The investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. The investigator is responsible for keeping a record of all

subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

- The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of CRFs and queries.

9.5 Subject information and informed consent

- The investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.
- Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the investigator's study files and a copy given to the study subject.
- In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the investigator's study files and a copy given to the study subject.

9.6 Confidentiality

- The patient charts, collected data, and all analysis of the data will adhere to HIPAA & institutional patient confidentiality requirements.
- More specifically, a coding system will be used for which a unique identifier (study ID number) will be assigned to each patient name and contact details. Only the study number will be included in the data collection tool, data analysis software and potential publications. The list with the direct identifiers (for the purposes of linking data and keeping track of patients) will be stored separately in a secure server at each site.
- Analytical datasets will be stored on secure servers that also limit access to the investigator team. Should results of the study be published or reported, individual names or other identifying information will not be used.

9.7 Retention of records

Records will be retained in accordance with regulatory, organizational and sponsor requirements, but no less than six (6) years following the completion of the research.

Disposal of records will be done in such a manner that no identifying information can be linked to research data.

## 10. Data handling and recordkeeping

### 10.1 Data/documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained.

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/case report form and must be signed and dated by the person recording and/or reviewing the data. All data submitted should be reviewed by the site investigator and signed as required with written or electronic signature, as appropriate. Data entered into the study database will be collected directly from subjects during study visits or will be abstracted from subjects' medical records. The subjects' medical records must record their participation in the clinical trial and what medications (with doses and frequency) or other medical interventions or treatments were administered, as well as any AEs experienced during the trial.

### 10.2 Data management

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. Clinical data will be entered into an electronic case report form. The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

**APPENDIX A**

**COVID-19 Convalescent Plasma Procurement SOP BMT 800 01**

- BMT 800 01, appendices a- k
- BMT 800 01, referenced SOPs

## APPENDIX B

**Recipient schedule of assessment**

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