Convalescent Plasma to Reduce Complications Associated with COVID-19 Infection: A Randomized Trial Comparing the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 Plasma vs. Standard Plasma in Hospitalized Patients with COVID- 19 Infection

Dated: October 16, 2020

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Version 1.8

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Protocol signature page:

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Elliott Bennett-Guerrero, M.D.	x_____	_____
Name of Investigator of Record	Signature of Investigator of Record	Date

In developing this protocol, we reviewed, adopted and adapted some of the helpful strategies and language outlined in the National COVID-19 Convalescent Plasma Project protocols that are posted for free and immediate use (https://ccpp19.org/status.html ; 3 protocols listed from John Hopkins as well as the Mayo Clinic). We are grateful for these examples.

PROTOCOL

Long Title: Convalescent Plasma to Reduce Complications Associated with COVID-19 Infection: A Randomized Trial Comparing the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 Plasma vs. Standard Plasma in Hospitalized Patients with COVID- 19 Infection

Short title: Convalescent Plasma vs. Standard plasma for COVID-19 Infection

Clinical Phase: 1/2

IND Sponsor: Elliott Bennett-Guerrero, M.D.

Conducted by: Stony Brook University

Study Locations: Stony Brook University Hospital locations (Stony Brook Hospital and Southampton Hospital). Convalescent plasma that has been collected and stored frozen at Stony Brook Hospital's blood bank will be transported frozen, stored, thawed, and dispensed by Southampton Hospital's blood bank, which is also a licensed blood bank. Written authorization has been obtained from the FDA on May 29, 2020 that no shipping license is required for shipment of this COVID-19 convalescent plasma to the blood bank of the IRB approved location/site.

Sample Size: 500 (interim DSMC safety/efficacy assessments at 100 and 250 patients randomized)

Study Population: Hospitalized patients >18 years of age with a PCR confirmed diagnosis of COVID-19, and within 14 days from admission to Stony Brook Hospital or any hospital.

Study Duration: 90 days post randomization

Study Design: This randomized placebo-controlled trial will assess the efficacy and safety of anti-SARS-CoV-2 convalescent plasma in hospitalized patients with a PCR confirmed diagnosis of COVID-19 and within 14 days from admission to Stony Brook Hospital (or another hospital if transferred to Stony Brook). A total of 500 eligible subjects will be randomized in a 4:1 ratio to receive either high titer anti-SARS-CoV-2 plasma or control (standard plasma). For individuals who are eligible for the study, but there is no eligible compatible convalescent plasma available at that time, these patients will be followed as a non-randomized third study group. If plasma becomes available within the eligible time period (within 14 days from admission to Stony Brook Hospital or another hospital), then patients will be removed from this group and randomized.

Randomization will be stratified by illness severity, defined as hospitalized patients not on a ventilator vs. patients on a ventilator at the time of randomization.

The following will be assessed in all subjects at the time of randomization (or consent if in the "observational" arm who have no matching plasma) and then at pre-specified time points up to maximum 90 pays post randomization:

- Age, sex, comorbidities, date of symptoms, level of care (ICU vs not), vital signs including temperature, respiratory rate, oxygen saturation, oxygen requirement, and CBC with neutrophil counts, lymphocytes count, CRP, chest x-ray, chest CT (if available from routine care)
- Safety (AEs) and efficacy: Day 0 (baseline), 1, 2, 3, 7, 14, and 28 days and once monthly at 60 (50-70) and 90 (80-100) days post randomization through review of the electronic medical record (EMR) and telephone calls to the subject.
- Antibody titer (either a drop of blood for point of care [POC] test or 3 ml EDTA tube for each time period, or total of 18 ml for these) to SARS-CoV-2: Days 0, 1, 7, 14, 21 and 28 through hospital discharge and only required in the first 100 subjects randomized. If available, a drop of blood will also be tested on a "research only" plate for antibodies to the spike protein (FDA approved plate we are using measures antibodies to the NP portion of the virus).
- Type and Screen, if one for this admission does not already exist (6 ml tube by venipuncture or from an indwelling catheter)
- Outcome measures: number of days on mechanical ventilation, time to extubation, new incidence of intubation, ICU admission, ICU length of stay, total hospital LOS, all-cause mortality, resolution of symptoms (normalization of temperature and reduced need for oxygen [example, 50% facemask down to 2 L Nasal Cannula]).

Study Agent:

- SARS-CoV-2 convalescent plasma (equivalent to 2 units of plasma, or approximately total volume of 450-550 mL collected by apheresis from a volunteer who recovered from COVID-19 infection and has high IgG levels of antibody to SARS-CoV-2 antibody determined by a FDA EUA approved (FDA 2020) quantitative IgM and IgG assay (Chembio Diagnostics, Inc. Medford, NY). See FDA "Policy for Diagnostic Tests for Coronavirus Disease-2019 during the Public Health Emergency", March 16, 2020. Goal is for antibody titers approximately > 1:320 but per FDA's April 3, 2020 guidance we can go down to a titer of 1:80 if higher titer plasma is not available.
- Standard plasma (equivalent to 2 units of plasma, or approximately total volume of 450-550 mL) with presumed or documented low levels of IgG as per above.

Primary Efficacy Objective: Reduction in progression of COVID-19 associated pulmonary dysfunction manifested by high oxygen and in some case ventilator requirements.

Primary Endpoint: Ventilator free days through 28 days post randomization. This endpoint is established in critical care trials (e.g. ICU-ROX trial; NEJM 2020). Patients who never require mechanical ventilation through 28 days are assigned 28 days, i.e. best outcome. Patients who

die are assigned the worst outcome, i.e. 0 ventilator free days. We define a ventilator day as one that either requires endotracheal intubation, or tracheostomy with any need for a ventilator, even if only pressure support ventilation. Non-invasive ventilation (e.g. BIPIP, CPAP, Hi-flow NC) are not considered "ventilator days".

Secondary endpoints:

1. Death (rates and time to event) through 90 days post randomization
2. Length of Hospital Stay
3. Length of ICU stay
4. Oxygen requirement (highest, i.e. lowest PaO2/FiO2 ratio per day,) will be recorded from routine clinical data on Day 0 (baseline), 1, 2, 3, 7, 14, and 28 but only while the subject is hospitalized.
5. Change in antibody levels to SARS-CoV-2 post transfusion of plasma
6. Resolution of clinical symptoms (normalization of temperature, reduced need for oxygen)
7. Improvement of ≥2 points in World Health Organization (WHO) Ordinal Scale for oxygen requirement
8. Quality of life (SF-36) at approximately 90 days post randomization.

Primary Safety Objective: Evaluate the safety of treatment with high-titer anti-SARS-CoV-2 plasma versus control (standard plasma) in hospitalized patients with COVID-19 infection.

Primary Safety Endpoints:

1. Acute (within 60 minutes) deterioration of respiratory or clinical status on transfusion of SARS-CoV-2 convalescent plasma
2. Cumulative incidence of serious adverse events: transfusion reaction (fever, rash) during and within 1 hours after infusion, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion related infection within 28 days of infusion

These safety endpoints, and other AEs, will be reviewed by the trials internal blinded Safety Monitor and sent to the DSMB, IRB, and FDA as appropriate (see section 7).

2. Study Population

To ensure fairness, potential subjects will be pre-screened according to a process that includes a daily "lottery": to determine the order in which to approach patients (see SOP).

Inclusion Criteria for Enrollment

1. Patients must be 18 years of age or older

2. Hospitalized with COVID-19 infection and a confirmed diagnosis of COVID-19 SARS-CoV-2 from RT-PCR testing.
3. Patient (or Legally Authorized Representative) is willing and able to provide written informed consent and comply with all protocol requirements.
4. If female must not be pregnant and/or breastfeeding.

Exclusion Criteria

1. Female subjects with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period. The protocol will be amended to allow participation of these individuals when processes are in place that can ensure the safety of the donated plasma to the pregnant woman and fetus/baby.
2. In the treating physician's opinion, the patient cannot tolerate a 450-550 mL infusion of plasma over up to 8 hours (4 hours max per unit), even if prophylaxed with intravenous diuretic, e.g. furosemide 20-80 mg, which is commonly done in critically ill or low EF patients
3. Receipt of pooled (polycolonal) immunoglobulin or any intravenous polyclonal immunoglobulin (IVIG) in past 30 days. Receipt of a monoclonal antibody is not an exclusion.
4. Contraindication to transfusion or history of prior reactions to transfusion blood products
5. **Unable to randomize patient within 14 days of admission to Stony Brook Hospital (or any other hospital if a transfer to Stony Brook Hospital). This definition is consistent with our desire to focus on patients relatively early in the disease process, e.g. NOT patients many weeks into the disease. Admission date is an objective measure, unlike "onset of symptoms", which is very challenging to accurately predict in many patients.** The time from onset of symptoms may play a role in plasma treatment response (Roback 2020). A prior study using convalescent plasma during the 2003 SARS outbreak showed that patients who received the transfusion earlier had better outcomes (Cheng 2003). Preliminary data from Chembio serial assays, and anecdotal reports from other investigators, suggest that many individual do not mount an immune response 2-3 weeks after infection, so convalescent plasma may be effective in this early stage window.

Above prescreening for eligibility should occur within 72 hours prior to randomization if eligible.

3. Background

COVID-19 infection from the SARS-CoV-2 virus has become a global pandemic. It is estimated that approximately 50% of humans on Long Island might become infected by May of

2020, leading to significant human suffering, death, and economic disruption. Mortality rates are very high in the elderly and in patients with underlying comorbidities. However, even relatively healthy individuals of middle age with COVID-19 infection often require ICU care and in some cases mechanical ventilation.

Currently there are no specific treatments for COVID-19 pneumonia and its associated acute respiratory distress syndrome (ARDS), other than routine supportive ICU care. In the absence of proven, effective anti-viral agents for SARS-CoV2, the use of "plasma therapy" may be our only option for the next few months or so. Serum or plasma therapy for infectious diseases dates to the 1890s, and has been used as a potential treatment in the SARS (Mair-Jenkins 2015), MERS, and now in recent COVID-19 (Shen 2020) outbreaks. However, clinical trials are necessary in order to show that this therapy can be useful in COVID-19 (Tanne 2020). This is especially true since some well-controlled trials of convalescent serum in other respiratory viral diseases have failed to show benefit (Beigel et al. 2019; Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial).

Plasma from many individuals who have recovered from COVID-19 appears to contain antibodies to the virus that can be used as a potential therapy, although there are currently limited data on whether these antibodies are neutralizing/protective. The objectives of randomized placebo controlled trial are to determine if the administration of convalescent plasma can reduce complications associated with COVID-19.

4. Investigational Plan

Subject Withdrawal

I. Subjects can terminate study participation and/or withdraw consent at any time without prejudice.
II. Randomized subjects who withdraw from the study will not be replaced.
III. The investigator may withdraw subjects if they are lost to follow up, non-compliant with study procedures or if the investigator determines that continued participation in the study would be harmful to the subject or the integrity of the study data
IV. Discontinuation of the study: The study sponsor, FDA and IRB all have the right to terminate this study at any time

Intervention including Study product acquisition, Study product administration, Study product accountability

I. Subjects are randomized in a 4:1 ratio to receive treatment with SARS-CoV-2 convalescent plasma vs. SARS-CoV-2 non-immune plasma. This allows for potential benefit for a high percentage of patients (80%) but still allows for a control group to assess safety and efficacy of this unproven therapy.

II. Study Drug: The investigational product is anti-SARS-CoV-2 convalescent plasma. Patients identified as having recovered from COVID-19 will serve as potential donors. Testing using the CHEMBIO DIAGNOSTICS quantitative IgM and IgG antibody assay (described below, and conditionally FDA approved- see Package Label) will identify those with presumed titers >1:320 for donation, as evidenced by an IgG reader value approximately >300. However, per FDA's April 3, 2020 guidance we can go down to a titer of 1:80 if higher titer plasma is not available. Potential donors (see donor eligibility section) will be screened for all routine transfusion-transmitted infections (e.g. HIV, Hep BV, Hep CV, West Nile virus, HTLV-I/II, *T. cruzi* , syphilis /T. Pallium and Babesia) and will be collected using apheresis technology. This is similar to standard blood bank protocols. Type compatible (type-specific or ABO-compatible) convalescent plasma units will be issued to suitable patients by trained hospital staff. Type and screen will be obtained in potential recipients to be screened for ABO and Rh determinations and unexpected antibodies.

III. The active arm will receive convalescent plasma, which will be delivered by intravenous transfusion at a dose of approximately 2 units (total volume range 450-550 ml, each unit over approximately 1-4 hours (maximum) (see VI. below).

IV. The control arm will receive approximately 2 units (total volume range 450-550) of non-immune plasma, each unit over approximately 1-4 hours (maximum) (see VI below). See rationale for this comparator group below.

V. The Blood Bank will not be blinded to study arm assignment, however, patients, clinicians, and study personnel will be blinded using a Blood Bank approved label for the bag. Some unblinded study personnel (Team M) are assigned to interface with the Blood Bank, randomize patients, transport plasma, and measure antibody levels in plasma and/or whole blood, but they will not be involved in any other study activities for any subjects.

VI. The duration of plasma infusion can be longer, e.g. up to maximum 8 hours (maximum 4 hours per approximate 250 ml unit), if significant ventricular dysfunction (e.g. LV or RF Ejection Fraction< 40%, or if the patient has overt volume overload). A diuretic, e.g. furosemide 20-80 mg IV push, can be co-administered if there is concern for volume overload. Extending the duration to this maximum or co-administering diuretic will be left to the discretion of the treating physician, e.g. hospitalist or intensive care M.D.

VII. All patients will be actively monitored during this time for allergic or other immediate reactions as per routine hospital policy. Continued monitoring for changes in clinical status will occur after the transfusion, including checking vital signs (heart rate, blood pressure, temperature, respiratory rate, and blood oxygen

levels) and sending laboratory tests as necessary. Halting Criteria/Rules for Subject Infusion are detailed below and all halting events will be reported to the DSMB (see section 7).

VIII. Whole blood or plasma antibody titer (either a drop of blood for POC test or 3 ml EDTA tube for each time period, or total of 18 ml for these) to SARS-CoV-2 will be measured at Days 0, 1, 7, 14, 21 and 28 only through hospital discharge and is only mandatory in the first 100 subjects. If available, a drop of blood will also be tested on a "research only" plate for antibodies to the spike protein (FDA approved plate we are using measures antibodies to the NP portion of the virus).

IX. Type and Screen (6 ml tube) obtained by venipuncture or from an indwelling catheter, if not already available for this hospital admission.

X. For all of the above testing, i.e. Type and Screen (6 ml), and serial antibody testing (up to 18 ml), the maximum blood removed will be 24 ml.

XI. NO SPECIMENS ARE BEING COLLECTED FOR FUTURE UNSPECIFIED RESEARCH. Per FDA's request (April 13, 2020 Guidelines) whenever feasible, we will collect 1-2 ml of plasma to be frozen for later measurement of neutralizing anti-COVID antibody levels once this assay is up and running at Stony Brook. FDA states "*When measurement of neutralizing antibody titers is not available, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date*."

XII. Unused convalescent plasma, not being tested for antibodies to SARS-CoV-2, will be destroyed per Hospital guidelines.

Halting Criteria/Rules for Subject Infusion

Infusion of study drug will be paused/halted if any of the following manifestations of anaphylaxis develop:

- Skin or mucous membrane manifestations: hives, pruritus, flushing, swollen lips, tongue or uvula
- Respiratory compromise: dyspnea, wheezing, stridor, worsening hypoxemia
- A >30% decrease from baseline in mean arterial pressure.
- Tachycardia with an increase in resting heart rate to > 130bpm; or bradycardia <40 that is associated with dizziness, nausea or feeling faint.
- Syncope
- Confusion
- Any other symptom or sign, which in the good clinical judgment of the study clinician or supervising physician warrants halting the infusion. For example, the rapid onset of gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and cramps, for instance, may be manifestations of anaphylaxis and may warrant an immediate halt prior to meeting full SAE criteria

If a reaction is detected, the infusion will be paused and the treating team will employ standard treatment including antihistamines, H2 blockers and small doses of hydrocortisone if needed, as well as epinephrine injections in severe cases. The treating team, with consultation with the Transfusion Service physician on call, will evaluate if, and when, it is safe to restart the infusion following standards of transfusion reactions.

Rationale for Dosing

There are no specific data for plasma dosing in COVID-19 infection to support a specific dose. However, the general consensus is that with these initial trials, we need to administer a large enough volume, e.g. approximately 500 ml, to avoid treatment failures due to insufficient dosing. This is important since we are not concentrating the IgG, which while potentially useful, will take more time for centers to develop. The vast majority of patients will tolerate 2 units of plasma over 4 hours (maximum 8 hours for the 2 units, i.e. maximum 4 hours per unit, in rare cases), especially since the protocol allows for concomitant administration of a rapid acting diuretic such as furosemide 20-80 mg IV push. We will amend the protocol to modify the dose volume if new data emerge that provide justification for changing our dose. The table below show data we have compiled. Note that 4 of these 5 studies have no rigorous control group. The Hopkins study is more of a prophylaxis trial, which is why a lower volume (200-250 ml) may be effective in those patients.

In addition, in an NIH funded multicenter randomized blinded trial for treatment of influenza (Beigel et al. 2019. Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial), 2 units of convalescent plasma were not effective compared with 2 units of standard plasma. This supports the idea that a control arm is needed in these protocols. That being said, the virus being treated in this negative trial was different, which may explain the lack of efficacy observed.

Protocol Date on file	Site	Study Type	Patients	Size	Conv. Plasma	Placebo
3/29/2020	Johns Hopkins	Conv. Plasma vs. Control	Adults Exposed to COVID-19 (not showing symptoms)	150	1 unit (200-250 mL) of plasma with anti-SARS-CoV-19 titers expected to have titer >1:64	1 unit of standard plasma

3/25/2020	Johns Hopkins	single-arm feasibility study to assess the safety of anti-SARS-CoV-2 convalescent plasma	Mechanically Ventilated Patients	30	Standard plasma dosing is 2 units, (~200-250 mL per unit) with detectable COVID-19 antibody titer. At the discretion of the treating physician, patients less than 90kg may receive 1 unit of plasma for the first 1-2 doses and increase to 2 units per dose if tolerated.	x
3/25/2020	Mayo clinic w /JH	Convalescent Plasma to Limit Coronavirus Associated Complications: An Open label, Phase 2A Study of High-Titer Anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19	Hospitalized COVID-19 patients aged ≥18 years of age with respiratory symptoms within 3 to 7 days from the beginning of illness	5	(1-2 units; ~300-600 mL at neutralization antibody titer *>1:160. (Note this is a moving target as assays develop*)	X
March 25, 2020	Shen, Shenzhen China (JAMA)	Treatment of critically ill patients with conv. Plasma	Severe pneumonia and mechanical ventilation	5	2 consecutive transfusions of 200 to 250 mL of ABO-compatible convalescent plasma (400 mL of convalescent plasma in total) (Donor serum specific ELISA ab titer higher than 1:1000,	x

					neutralizing antibody titer>40)	
3/23/2020	Duan Shanghai China Chi CTR 2000030048 Not peer reviewed	Treatment of critically ill patients with conv. Plasma	Severe, hospitalized I think they were all on another drug – "Nine patients received arbidol-monotherapy or combination therapy with Remdesivir or ribavirin,or peramivir, while one patient received ribavirin monotherapy"	10	1 dose of 200 mL convalescent plasma (CP) derived from recently recovered donors with the neutralizing antibody titers above 1:640	x

Rationale for Standard Plasma Control Arm and Blinding

It is critical that the trial include a blinded control group in order to determine if this intervention is safe and effective. The trial's independent DSMB will review safety data, including halting of infusions and SAEs, to determine if there are unacceptable risks to patients receiving either convalescent or standard plasma.

Beigel et al's study results and discussion (Beigel et al. 2019. Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial) highlight the need for a blinded control group of standard plasma. This multicenter NIH funded randomized trial showed that 2 units of convalescent plasma were not effective compared with 2 units of standard plasma. This result would not have been possible without the control arm. They discuss the possibility of increased study withdrawals of patients randomized to the "control" arm if this is not masked.

Beigel et al. also mention that there is a lack of alternative strategies to provide a blinded comparator. Yellow multivitamin dyed saline and albumin have different colors and/or consistency. Studies in critically ill patients suggest that albumin is associated with worse outcome (BMJ. 1998 Jul 25;317(7153):235-40. Human albumin administration in critically ill patients: systematic review of randomised controlled trials). Therefore, if albumin is used in the control group and outcome is worse in this arm we will not know if this is due to a lack of antibodies to SARS-CoV-2 or if it is due to a harmful affect from the albumin. If a vitamin is used

as a dye, then our results will be confounded by potential effects of the vitamins including vitamin C (Marik PE. J Thorac Dis. 2020 Feb;12(Suppl 1):S84-S88. doi: 10.21037/jtd.2019.12.64. Vitamin C: an essential "stress hormone" during sepsis).

Moreover, other trials are taking the same approach. For example, the Johns Hopkins study entitled “Convalescent Plasma to Stem Coronavirus: A Randomized, blinded Phase 2 Study Comparing the Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. control (SARS-CoV-2 non-immune plasma) among Adults Exposed to COVID-19” is using a blinded standard plasma comparator.

Plasma Donors:

Consent/Screening (Visit 1)

Mechanism for identifying donors

- Mechanism for recruitment will include advertising in the local community where recent outbreaks have occurred. Flyers might be placed on the bulletin boards in the Stony Brook HSC. Potential donors will also be identified through a sister study occurring at Stony Brook. This study is examining the presence or absence of antibodies in multiple groups of patients, including those with a known diagnosis of COVID-19.
- Individuals who agree to participate to donate plasma will do so under full informed consent; consent will be a modified version of a standard donation consent form i.e. content specific to the trial will be included along with the intended use for the donated plasma.
- Individuals who agree to participate will undergo pre-donation screening as below prior to their first plasma donation unless they have been symptom free for at least 28 days in which case, per FDA Guidelines, a negative PCR test is not required. In addition, FDA guidelines only require repeat of the transmittable- disease-test (TDT) markers within 30 days prior to donation.

Eligibility for plasma donors:

As per the current FDA guidelines, COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood. Required testing must be performed and the donation must be found suitable. Additional considerations for donor eligibility should be addressed, as follows (as per FDA Guidance March 24, 2020, and Revised FDA Guidance April 3, 2020 and April 13, 2020. Of note the revised FDA guidance allows exceptions/modifications to some of the routine donor selection criteria, see below.):

I. Past diagnosis of COVID19 by either:
    a. Positive PCR test (FDA Emergency Use Authorization (EUA) laboratory test), or

b. Presence of antibodies (positive serology) as detected by an FDA approved laboratory test (see below).

II. Complete resolution of symptoms for at least 14 days prior to donation (still requires negative PCR test to allow donation). We will follow FDA's April 8, 2020 guidance for COVID-19 plasma donors that allows plasma donations from individuals without a negative PCR test who have been fully recovered for at least 28 days.

III. Donors negative for HLA antibodies. Human Leukocyte Antigen (HLA) testing (5 ml tube) will be obtained by venipuncture in all donors.

IV. Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood for plasma donors who have been symptom free between 14 and 27 days per new FDA guidance. A partial list of available tests can be accessed at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations.

V. Defined SARS-CoV-2 neutralizing antibody titers, optimally greater than 1:320 (but allowed as low as 1:80 per new FDA guidance if higher titer plasma not available), using the conditionally FDA approved Chembio assay (see Package Label), defined as an IgG reader value approximately >300. Subjects will be informed whether their results meet criteria to be eligible for plasma donation, or if a retest is recommended if it is suboptimal, or if testing is negative for antibodies to COVID-19. These results are documented in the individuals EMR under their screening visit note. . If available, a drop of blood will also be tested on a "research only" plate for antibodies to the spike protein (FDA approved plate we are using measures antibodies to the NP portion of the virus) and these "research only", not FDA approved test results will not be shared with the subject. In addition, per FDA's request (April 13, 2020 Guidelines), whenever feasible, we will collect 1-2 ml of plasma to be frozen and later measured for neutralizing anti-COVID antibody levels once this assay is up and running at Stony Brook. FDA states "When measurement of neutralizing antibody titers is not available, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date."

VI. Standard infectious disease marker testing, also known as TDTs, e.g. HIV, Hep BV, Hep CV, West Nile virus, HTLV-I/II, *T. cruzi* , syphilis /T. Pallidum and Babesia, will be performed on blood obtained during the screening visit and sent to the routine clinical laboratory that routinely does these tests on coded samples for the Blood Bank. This routine screening must be negative prior to moving on to a donation visit. Any positive results from these markers will be shared with the subject as per standard donor protocols.

VII. Type and screen (5 ml) will also be obtained in potential donors to be screened for ABO and Rh determinations and for the presence of unexpected antibodies. Individuals with antibodies in this screen will not be eligible to donate plasma.

VIII. Complete blood count (CBC), approximately 4 mL, will also be obtained to confirm adequate hemoglobin level per standard Blood Bank donor requirements. For repeat donation visits, the Blood Bank will check the adequacy of hemoglobin with their point of care test using a finger stick per their routine process used in all individuals prior to blood product donation

IX. Serum protein electrophoresis pattern and protein composition (6 ml venipuncture) per FDA guidance/Code of Federal Regulations.

X. Must meet all usual donation criteria for apheresis, e.g. weight, hemoglobin, which are part of routine screening and the routine donor questionnaire. Revised FDA Guidance now allows exceptions/modifications to some of the routine donor selection criteria, *April 2, 2020 FDA STATEMENT Coronavirus (COVID-19) Update: FDA Provides Updated Guidance to Address the Urgent Need for Blood During the Pandemic*:
    a. For male donors who would have been deferred for having sex with another man: the FDA has changed the recommended deferral period from 12 months to 3 months.
    b. For female donors who would have been deferred for having sex with a man who had sex with another man: the FDA has changed the recommended deferral period from 12 months to 3 months.
    c. For those with recent tattoos and piercings: the agency FDA has changed the recommended deferral period from 12 months to 3 months.
    d. For those who have traveled to malaria-endemic areas (and are residents of malaria non-endemic countries): the FDA has changed the recommended deferral period from 12 months to 3 months. In addition, the guidance provides notice of an alternate procedure that permits the collection of blood and blood components from such donors without a deferral period, provided the blood components are pathogen-reduced using an FDA-approved pathogen reduction device.
    e. For those who spent time in certain European countries or on military bases in Europe who were previously considered to have been exposed to a potential risk of transmission of Creutzfeldt-Jakob Disease or Variant Creutzfeldt-Jakob Disease, the FDA is eliminating the recommended deferrals and is recommending allowing reentry of these donors.
    f. Of note, none of the above changes impact the need for negative transmittable disease testing as already included in the protocol.

XI. At least 18 years of age

XII. For all of the above testing of donors, i.e. Type and Screen, HLA , infectious markers testing, antibody testing, serum protein electrophoresis, we will remove up to 50 ml via venipuncture.

Following selection of an appropriate donor as above, potential donors will have their plasma collected (between approximately 500-1000 mLs, maximum 10.5 ml/kg per routine practice including blood sampling/testing) via an approved device by qualified Apheresis technical staff. Additional donation(s) can take place weekly but only if repeat antibody testing reveals return of high IgG antibody levels. Routine blood bank required transmissible disease testing (TDT) is required at least every 30 days. Collections will take place at Stony Brook Hospital's licensed and accredited pheresis/blood bank unit on Level 5. If there is a shortage of plasma from our plasma collection process, we will allow the use of acquired convalescent plasma from other licensed sites/vendors, e.g. the American Red Cross, New York Blood Center. Convalescent plasma being collected from these sites must conform per Federal Regulations (FDA) to the

same guidance we are using for our plasma collections at Stony Brook, so it should be as safe and effective as the plasma we collect at Stony Brook.

Donation Visit plan (Visit 2)

Collecting and Processing

Prior to donation, the donor will need to complete several increasingly stringent levels of review. They must complete a standard donor history questionnaire at the screening visit and prior to any plasma donation. At the time of presentation at the blood center (i.e. see Visit 2 below), a determination of resolved infection will have already been made, and blood bank personnel will confirm that the subject feels well per their usual interview process.

- Standard apheresis plasma collection will be performed per routine standard operating procedure at the certified and licensed collection facility (Stony Brook Hospital).
- Target collection volume: at least 500 ml but maximum 10.5 ml/kg per American Association of Blood Bank guidelines including blood sampling; this will allow for splitting (separation) into daughter units
- The plasma will be processed per routine practice; it may be frozen and thawed per standard blood bank protocol prior to dispensing to a recipient.
- The plasma will be maintained in quarantine at the hospital's Blood Bank until it needs to be dispensed.

Control arm plasma

The control arm plasma follows identical collection and processing procedures, but will have been collected from community blood donors with no overt history of COVID-19 infection and ideally a low IgG anti-CoV-2 antibody level defined as less than 25 on the CHEMBIO point of care assay (see below).

Antibody Assay

The antibody assay we will use was developed at Chembio Diagnostic Systems Inc. Chembio is a publicly traded company (Nasdaq:CEMI) on Long Island, NY that already markets several approved point of care assays including HIV, Zika, and Ebola. [redacted]

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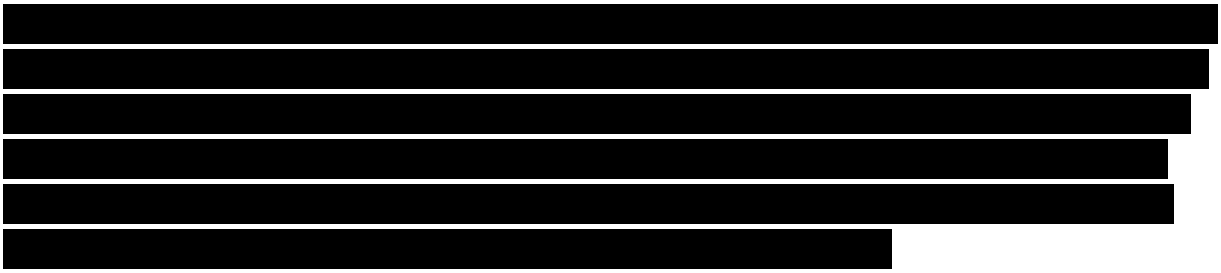

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5. Data Collection From Plasma Recipients:

Data collection will include routine demographics (age, sex, race/ethnicity), history of present illness (e.g. onset of symptoms, signs, testing results for COVID-19, chest x-ray or CT findings from clinically ordered testing), past medical history to include comorbidities, hospital course, and outcomes such as death, duration/occurrence of mechanical ventilation, supplemental oxygen, ICU admission and duration, and length hospital stay. IgM and IgG antibody levels will be monitored over time for at least the first 100 patients, starting prior to randomization and through 14+ days if still hospitalized. Clinical symptoms such as average daily temperature and oxygen levels will also be collected. Most of these data will be abstracted from the electronic medical record, but patients will be actively monitored for safety. Follow-up clinical data are collected at 14, 21, 28 and 90 days from the EMR and telephone calls. Subjects will not be asked to return for visits after discharge. We will also assess patient quality of life at 90 days after treatment using the SF-36 (telephone call), as well as the location of the patient (discharge location, in hospital, death). Many of our outcomes are based on time. We plan to use the time of randomization the start time for most of these outcomes. Time from onset of symptoms, admission to the hospital, and study entry are likely to be important covariates. If these factors are unbalanced, we will account for this in the planned analyses below. Data will be transcribed into a dedicated study REDCap database, and then exported for statistical analyses.

6. Statistical Methods

All analyses will be presented by treatment group. Descriptive summaries of all outcomes and covariates will be presented. All analyses will be conducted as an intent to treat

approach, which includes all randomized subjects. All statistical analyses will use a two-sided Type 1 error rate of 0.05 and 95% confidence intervals.

We are currently uncertain of the size of the observational group (i.e., those who qualified for the study but did not have a donor match at the time, and remained in the observational group). If the sample size is large enough, we will include this observational group as a third study arm. Alternatively, we may add these individuals to the plasma control group if and only if all outcomes and covariates are equivalent. This could be done in the form of a sensitivity analysis. Any analyses specifically referencing 2 groups below will be revised to three groups if appropriate (e.g., t-tests will be revised to ANOVA).

Randomization:

Patients will be randomized in a 4:1 plasma to placebo ratio using permuted block randomization. Randomization will be stratified by non-intubated vs. intubated patients. The total number of target patients is 500, with 400 in the plasma treatment group and 100 in the placebo control group. Our target enrollment ratio is 2 to 1 for the randomization strata to promote inclusion of more patients with less severe disease who may benefit more from convalescent plasma. Randomization lists will be generated using SAS software, and implemented using an interactive web response randomization tool in REDCap.

Primary Outcome and Power Analysis:

The primary outcome in this study is total number of ventilator-free days from randomization to day 28 (ICU ROX, NEJM 2020). We are defining ventilator free days as the total number of calendar days or proportions of calendar days of (assisted breathing per definition earlier) during the first 28 days after randomization. All study participants who never require intubation will be assigned a time of 28 days. All patients who die by day 28 will be considered to have a time of 0 ventilator-free days. Ventilator free days will be compared by study group using a Wilcoxon rank sum test. We believe that an average difference of 2.5 ventilator-free days (SD 6) is a clinically meaningful difference between groups, but the measure of variance is truly unknown for this population. We have calculated the sample size based on this moderate effect size of 0.42, but we have also added an 18% inflation to allow for a possible interim analysis (if requested by the DSMC) and to account for a range of uncertainty in the standard deviation of days. We have also built in a 7% buffer to allow for possible study withdrawals, even though this is expected to be minimal. Using a 90% power and alpha of 0.05%, the final study size needed is 500 participants, with 400 plasma treatment patients and 100 placebo patients. We will also stratify this analysis by our randomization strata (intubated vs. non-intubated). The change (improvement) in WHO Ordinal Scale will be calculated daily for all randomized patients prior to discharge (or day 28, whichever is earlier), with

improvement defined as patients with a ≥2 point improvement to be consistent with previous trials. The worst (highest amount of support) on any given 24 hour period will be used, with 24 hour periods starting at the time the plasma infusion begins (or time of randomization if no plasma received). This will be analyzed as the proportion in each arm with a ≥2 point improvement, and analyzed in both the ITT (all randomized) as well as Per Protocol (randomized and receiving 2 units of assigned plasma) populations. The time to a ≥2 point improvement will also be determined in both arms using survival analysis, again both in the ITT as well as Per Protocol populations.

Secondary Outcomes:

Death: As a secondary outcome, we will examine all-cause mortality through 90 days post randomization in two ways: as a dichotomous variable (yes/no), and as a time to event (number of days from treatment/placebo to death). Chi-square tests, multivariable logistic regression, and cox proportional hazards models (with Kaplan Meier survival curves) may be used for these analyses.

WHO Ordinal Scale: Many clinical trials related to COVID-19 use the WHO Ordinal Scale as either a primary or secondary endpoint. This is promulgated by the World Health Organization (https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf). It is a 9 point scale, however, since our trial focuses on hospitalized patients we will collapse Scores 0, 1, and 2 (all outpatients) into 1 single score. So 1= no longer hospitalized (i.e., discharged)2= hospitalized, not on oxygen, 3= hospitalized, on nasal cannula or face mask, 4= hospitalized, high flow nasal cannula or bipap, 5= hospitalized, intubated, 6= hospitalized, ECMO, 7= dead. This will be calculated daily (prior to discharge) for all randomized patients.

Immune response: The trajectories of whole blood or plasma IgM and IgG will be plotted over time and compared in the treatment group vs. the placebo group for all patients with this data. The first sample will be taken prior to administration of the treatment/placebo, and repeated samples will be taken after the intervention through hospital discharge. Average antibody levels at each time point will be compared using t-tests.

*Resolution of Clinical Symptoms: T*emperature will be monitored for all patients per routine hospital policy. Average daily scores (during the first 7 days while in hospital, after randomization) will be recorded. Time to temperature normalization will be compared between the two groups using log-rank tests (with Kaplan-Meier curves).

SF-36: 90 day quality of life (as measured by the SF 36) will be assessed by study arm using Wilcoxon rank sum tests.

Adverse Events: Analysis of adverse data will primarily be descriptive based on the coding of events. The proportion of subjects experiencing an SAE will be compared between randomized arms using Fisher's Exact Test.

7. Data and Safety Monitoring Plan, Regulatory, Registration

Registration: The trial was registered (NCT04344535) prior to subject enrollment at clinicaltrials.gov per Federal guidelines.

Regulatory: The trial will be conducted under an IND.

Data and Safety Monitoring:

Adverse event Definitions:

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes exacerbation of pre-existing conditions and intercurrent illnesses. This definition of "adverse event" will be applied to all study subjects beginning at the time of randomization.

Serious Adverse Event

A Serious Adverse Event (SAE) is an AE, whether considered related to the study product or not, that:

1. Results in death during the period of protocol-defined surveillance
2. Is life threatening: defined as an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death were it more severe
3. Requires inpatient hospitalization (or prolongation of existing hospitalization): defined as at least an overnight stay in the hospital or emergency ward for treatment that would have been inappropriate if administered in the outpatient setting
4. Results in a persistent or significant disability/incapacity

Relationship categories for Adverse Events are as follows:

For purposes of reporting to IRB and the FDA, AEs will also be characterized as Related or Not-Related per FDA's Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies, December 2012 (see below).

Related There is a reasonable possibility that the adverse event may be related to the study drug.

Not related There is not a reasonable possibility that the adverse event may be related to the study drug.

Safety-Related Recording and Reporting to **Internal Safety Monitor**

The study will have an internal blinded Safety Monitor (Sharon Nachman, MD, Professor of Pediatrics, Associate Dean for Research, Renaissance School of Medicine). This individual will be responsible for reviewing safety data (below) and making recommendations to the PI on what data should be reported to the DSMB, IRB, and/or FDA.

Any event that occurs during protocol-specified AE reporting periods (see Table AA), following plasma donation (donors) or infusion with study product (recipients), is to be considered an AE and should be evaluated as a potential Expedited AE, with reporting within 48 hours of knowledge of event to the internal safety monitor (not IRB or FDA unless it meets their reporting criteria- see below). The current section outlines which events which should be recorded on eCRFs for inclusion in the database.

Table AA:

1. Within 24 hours of infusion or donation
    a. Hypotension requiring new initiation of vasopressors
    b. Rash
    c. Any other event which leads to acute stopping of IgG infusion
    d. Death
2. Within 7 days of infusion or donation
    a. Organ failure*, grade 4 (this includes worsening of underlying comorbid conditions)
    b. Grade 4 liver, kidney or hematologic toxicity
    c. Death
3. Within 28 days of infusion or donation
    a. Organ failure*
    b. Grade 4 liver, kidney or hematologic toxicity
    c. Death

Grading table for adverse events

Severity	Defined
Grade (0) None	Not applicable

Severity	Defined
Grade (1) Mild	No medical intervention required; may include use of over-the-counter medications managed by the caregiver for treatment of symptoms
Grade (2) Moderate	Outpatient medical intervention by a health care provider required; may include use of over-the-counter and/or prescription medications
Grade (3) Severe	Prolonged medical intervention required
Grade (4) Life threatening	Illness requiring continued hospitalization with intensive care
Grade (5) Death	Event resulting in fatal outcome to the participant

Organ Failure/Grade 4 SAE Definitions:

1) CNS: new stroke
2) Cardiovascular: new myocardial infarction (defined as troponin above ULN and new pathologic Q wave by ECG or overt clinical evidence of MI)
3) Pulmonary: new pulmonary embolus (note: intubation/mechanical ventilation is the primary endpoint for the study so per FDA guidelines does **not** require AE reporting for this endpoint)
4) Renal: new hemodialysis (does not include patient already on HD but given plasma on "off day"
5) Liver: new INR > 1.8 (without alternative cause, e.g. Coumadin or other drug affecting INR)
6) Hematologic: a) new platelet count <50,000, or, b) arterial or venous thrombosis requiring surgical treatment or thrombolytic, e.g. TPA, treatment.

Note that if a condition exists at baseline, i.e. prior to plasma infusion, e.g. platelet count is <50 at baseline, but then increases to >50, that if it subsequently decreases to 50 this will trigger the AE definition.

Safety-Recording and Reporting to **IRB and FDA** and **Internal Safety Monitor**

Plasma has been administered to millions of patients and has a well-known safety profile. In this study, plasma is collected, processed, stored, and administered per established FDA and hospital approved guidelines. It is only the quantity of antibodies in the plasma, and its "off-label" use to treat COVID-19 infection, which differentiates it from usual "on-label" use in hospitalized patients, where it is used extensively. In addition, hospitalized patients with COVID-19 infection are usually very ill and experience a multitude of adverse events, almost all of them likely related to their underlying condition.

We will record and report to IRB and FDA AEs occurring within 28 days of plasma infusion that are serious, unexpected, and related to the study per FDA reporting guidelines.

Adverse events (other than SAEs) which in the opinion of the principal investigator meet the criteria for an unanticipated problem involving risk to subjects or others (unanticipated, reasonably related to the research as defined above, and increase risk to subjects), and occurring within 28 days of plasma infusion will also be recorded and reported to the IRB and FDA.

SUSAR:(S)AEs that occur within 28 days of plasma infusion and that are serious, unexpected, reasonably related to the study, **and** informative to the IRB or FDA as a single event per FDA's Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies, December 2012, will be **reported** in an **expedited** manner to the IRB within 5 days of knowledge of the event, and to the FDA no later than 15 calendar days after the sponsor determines that the suspected adverse reaction or other information qualifies for reporting to the FDA.

Results of aggregate safety analysis suggesting that (S)AEs or death occur more frequently in the treatment group will also be reported to the IRB and FDA according to the above timelines.

DSMC:

The trial will have 3 member independent Data and Safety Monitoring Committee (DSMC) also known as DSMB. Per the DSMC's Charter, the DSMC will review all deaths, infusion halts, and recorded AEs on a rolling basis as well as in aggregate on a monthly basis. The DSMC will inform the investigators if there are concerns that warrant revision to the consent form or other change to study procedures. After the 100th randomized subject and the 250th randomized subject reach the 28-day post-randomization time point, plus allowance of up to 2 weeks for preparation of a report to DSMC, the DSMC will review the available data for futility, safety, and efficacy but it will be the DSMC's decision whether inferential/statistical testing for efficacy is necessary. There will be no formal stopping rules for these analyses.

The blood bank policies will be followed throughout the study and if the blood bank staff need to report according to their standard guidelines they will do so separate from the study group reporting.

Informed Consent:

Patients must be able to provide written informed consent or a legally authorized representative must be able to provide written informed consent. Individuals will be provided with as much time as they need to read the consent form, ask questions to the study team, and

confer with others. Refusal to participate will not alter their hospital care or post-hospitalization management.

Confidentiality of Data:

A REDCAP Database, created by the trial's data manager, will be used for data collection. This Database will sit behind the firewall at Stony Brook University and will only be accessible to study personnel using a secure login/password protected program. Electronic data will be stored on password protected computers in password-protected, Stony Brook Medicine IT controlled folders or encrypted folders (e.g. SB IT created BOX folders) setup by the SB Research IT group. Paper records will be stored in a locked file cabinet in a secure location within the hospital.

Risks, Benefits, and Procedures to Minimize Risk to Subjects

Risks to donors.

Likely:

Pain and bruising where the needles are put into the arms

Transient lowered platelet count. Platelet counts usually return to normal levels within two to four weeks after collection of the plasma.

Less Likely:

Lightheadedness

Nausea

Citrate reaction - to prevent clotting, citrate will be used mixed in the machine as an "anticoagulant". Citrate can bind to the calcium, and cause hypocalcemia. Hypocalcemia related symptoms include numbness and tingling of the fingertips or around the mouth. This can be treated with calcium including oral Tums depending on severity, or calcium pills (at least 1200 mg daily) for 5 days.

Rarely:

Chills, fainting during the procedure

Large amount of bleeding/bruising where the needles in the arm veins are located

Loss of blood from a breakdown of the apheresis machine. About 1½ cups of blood is reported if the machine breaks. This is unlikely to cause any harm or require transfusion replacement.

There is a small (about 1 in 1,200) risk of being hospitalized for observation of side effects from the procedure, (for example, lightheadedness, nausea).

These volume changes risks will be minimized by continued hydration the day of the procedure and monitoring of pulse and blood pressure during and shortly after

Benefits to donor:

Donors will not receive direct benefit from having this procedure. This study may help cure or stop the progression of the recipient's disease, which will limit further exposure of donors and their community to the disease under study.

Risks for recipients.

Acute risks:

1. Volume overload: The intended plasma infusion could represent additional volume to already fluid overloaded patients. We acknowledge this risk and therefore exclude patients in whom the treating physician does not think it is safe to proceed, even with the countermeasures below. Volume overload will be promptly monitored by continuous measurements of output related to input and other routine clinical measures. Diuretics will be utilized to allow removal of accumulated fluids if needed. Also, to further minimize risks, extended infusion for up to 4 hours per unit (8 hours for both units) will be considered in such patients.
2. Acute allergic reactions to the infused plasma. These infusions will be done under hospital acute care monitoring. If reactions are detected, the infusion will be paused and the treating team will employ standard treatment including antihistamines, H2 blockers and small doses of hydrocortisone if needed, as well as epinephrine injections in severe cases. The treating team, with consultation with the Transfusion Service physician on call, will evaluate if and when it is safe to restart the infusion following standards of transfusion reactions.

Intermediate term risks

1. Antibody-mediated enhancement of infection (ADE): ADE can occur for several viral diseases and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms for ADE have been described and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain [Wan Y, ET AL, Molecular mechanism for antibody-dependent enhancement of coronavirus entry. Journal of Virology. 2020; 94, (7). However, 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, so ADE may be unlikely. The available evidence from the use of convalescent plasma in patients with SARS1 and MERS [8], and (9) anecdotal evidence of its use in patients with COVID-19, suggest it is safe. Nevertheless, caution and vigilance will be required in

monitoring for any evidence of enhanced infection within the 90-day study period follow-up.

2. 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. This risk is less applicable to our patient cohort because this is a treatment study and not a prophylactic study.

3. Risk of administering virus to recipients if donor is not virus free: although a possible risk, this will be minimized by following steps advised by the FDA as well as other trial criteria. This includes enrolling asymptomatic donors after a total of 14 days from beginning of symptoms and, in donors who have been symptom free for less than 28 days, documenting a negative viral PCR test (Per FDA Guidelines). The above follows FDA's revised guidelines on required testing for recovered COVID plasma donors.

4. There are theories that administration of convalescent plasma for COVID-19 may lead to increased risk of thrombosis and/or lung injury (Cao H. and Shi Y, Convalescent Plasma: possible therapy for novel coronavirus disease 2019, Transfus Med Rev, in press; Dzik S., Transfus Med Rev, in press).

Long term risks:

Theoretical risks that inflict long-term harm include infections with hepatitis, HIV, and other known blood- borne viruses. This will be minimized by stringent donor screening and is not expected to occur.

<u>Benefits to recipient.</u>

If this study meets its primary and secondary endpoints of safety and efficacy, recipients of convalescent plasma may have reduced viral load, accelerated time to recovery and hence fewer complications, which may ultimately increase their chances of survival.

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