PROTOCOL SUMMARY:

Long title: Convalescent Plasma to Treat Coronavirus - Associated Severe Pulmonary Complications: A Feasibility Study Assessing the Safety of Multiple Doses of Anti-SARS-CoV-2 Plasma in Mechanically Ventilated Intubated Patients with Respiratory Failure due to COVID-19

Short title: CPPulm-001

Clinical Phase: 1

IND Sponsor: Johns Hopkins via a National IND, or IND Exemption for Human Plasma

Conducted by: UPMC, Cedars Sinai, Johns Hopkins and other potential sites

I. **Study Design**: This is a single-arm feasibility study to assess the safety of anti-SARS-CoV-2 convalescent plasma (CP) in intubated, mechanically ventilated patients with confirmed COVID-19 pneumonia by chest X-ray or chest CT.

II. **Study Population**: Mechanically ventilated intubated COVID-19 patients aged 18 years or older.

III. **Study Duration**: March 30, 2020 to December 31, 2022.

IV. **Sample Size**: 30

V. **Covariates**: The following will be evaluated in all subjects:

a. age, sex, comorbidities, date of symptoms, type of admission, APACHE II score, modified SOFA score, clinical status, vital signs including temperature, respiratory rate, oxygen saturation, oxygen requirement, CBC with neutrophil counts, lymphocytes count, chest x-ray, chest CT
b. TRALI (incidence 1:5000 transfusions) within 12 hours of CP infusion
c. Safety – T(0) baseline, daily while in ICU, weekly in the hospital, day 28, day 60 Blood specimens for immune antibody correlatives[1] to SARS-CoV-2 as feasible.
d. **Study Agent:** SARS-CoV-2 convalescent plasma (1-2 units; ~200-600 mL) from MALE DONORS, prefer AB blood type

Primary Objective: To determine feasibility of patients in the ICU receiving CP for COVID-19-induced respiratory failure.

[1] Measured via initial anti-SARS-CoV-2 ELISA and serum neutralizing antibody titer to SARS-CoV-2.

Primary Endpoint: To determine feasibility of providing CP to patients with COVID-19-induced respiratory failure

Key Secondary Endpoint: To determine overall survival

Other Exploratory Outcomes:

1. Ventilatory free days and mechanical ventilatory parameters (e.g FiO2, PEEP, plateau pressure, driving pressure)
2. ICU mortality and LOS
3. Hospital mortality and LOS
4. 28-day and 60-day mortality
5. Multi-organ failure (and other ICU support e.g., dialysis, vasopressors)
6. Number of patients developing TRALI based on CDD Hemovigilance Criteria https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf

Study population:

Inclusion Criteria

1. 18 years of age or older
2. Hospitalized with COVID-19 respiratory symptoms and confirmation via COVID-19 SARS-CoV-2 RT-PCR testing.
3. Subject or proxy (including by phone) is willing and able to provide written or virtual informed consent and comply with all protocol requirements.
4. Intubated
5. Consent to storage of specimens for future testing.

Exclusion Criteria

1. Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products).
2. Severe multi-organ failure, hemodynamic instability.
3. Other documented uncontrolled infection.
4. Severe DIC needing factor replacement, FFP, cryoprecipitate.
5. On dialysis.
6. Active intracranial bleeding.
7. Clinically significant myocardial ischemia.

LIST OF ABBREVIATIONS

ADR: Adverse Drug Reaction
ADE: Antibody-mediated enhancement of infection
AE: Adverse Event/Adverse Experience
CDC: United States Centers for Disease Control and Prevention
CFR: Code of Federal Regulations

CLIA: Clinical Laboratory Improvement Amendment of 1988
COI: Conflict of Interest
COVID-19: Coronavirus Disease
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
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
NA: Nuclear antibody
NP: Nasopharyngeal
OP: Oropharyngeal
RT-PCR: Reverse Transcriptase Real-Time Polymerase chain reaction
PK: Pharmacokinetic
SAE: Serious adverse event
SARS: Severe Acute Respiratory Syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
TACO: Transfusion-associated circulatory overload
T. cruzi: *Trypanosoma cruzi*
TRALI: Transfusion-related acute lung injury
UP: Unanticipated Problem
UPnonAE: Unanticipated Problem that is not an Adverse Event
ZIKV: Zika virus

1. Background and scientific rationale

Beyond supportive care, there are currently no proven therapeutic options for pneumonia due to coronavirus disease (COVID-19), the infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Human convalescent plasma is an option for treatment of COVID-19 and will be available when sufficient numbers of people

have recovered. Such persons should have high titer neutralizing immunoglobulin-containing plasma.

Passive antibody therapy involves the administration of antibodies against pathogens in susceptible or infected individual for the purpose of preventing or treating disease due to that agent. In contrast, active vaccination requires the induction of an immune response that takes time to develop with responses that vary among recipient; some immunocompromised patients fail to achieve an adequate immune response. Thus, passive antibody administration is the only means of providing immediate immunity to susceptible persons and immunity of any measurable kind for highly immunocompromised patients.

Passive antibody therapy dates back to the 1890s. Prior to this, it was the only means of treating many infectious diseases before the advent of antimicrobial therapy in the 1940s (1,2). Experience from prior outbreaks with other coronaviruses, such as SARS-CoV-1 shows that convalescent plasma contains neutralizing antibodies to the virus (3). In the case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy would mediate protection is viral neutralization. However, other mechanisms may be possible, such as antibody dependent cellular cytotoxicity and/or phagocytosis. Convalescent serum was also used in the 2013 African Ebola epidemic. A small non-randomized study in Sierra Leone revealed a significant increase in survival among those treated with convalescent whole blood relative to those who received standard treatment (4).

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

For passive antibody therapy to be effective, a sufficient amount of antibody must be administered. When given to a COVID-19 susceptible person, this antibody will circulate in the blood, reach tissues and mitigate infection severity. Depending on antibody amount and composition, the protection conferred by transferred immunoglobulin can last from weeks to months.

2. Experience with the use of convalescent plasma against coronavirus diseases

In the 21st century, there were two other epidemics with coronaviruses that were associated with high mortality, SARS-CoV-1 in 2003 and Middle Eastern Respiratory Syndrome (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-CoV-1 (7). Those who were RT-PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis.

Reports highlighting the mechanism and limitations of convalescent plasma therapy come from small case series. SARS plasma virus titers were reduced in three Taiwanese survivors of SARS following treatment with 500 ml of convalescent plasma (8). In South

Korea, three patients with MERS were treated with convalescent plasma, but only two or the donors were shown to have produced neutralizing antibodies (9). This second study highlights a challenge in using convalescent plasma, namely, that some who recover from viral disease may not have high titers of neutralizing antibody (10). Of note, analysis of convalescent sera from 99 MERS survivors showed that only 87 had neutralizing antibody with a geometric mean titer of 1:61. This suggests that antibody declines with time and/or that few patients make high titer responses. *The plasma product we administer will be collected 14-21 days after symptom resolution and antibody titers will be assessed. Otherwise the donor will fulfill all of the standard donor criteria.*

Importantly, there are reports that convalescent plasma was used for therapy of patients with COVID-19 in China during the current outbreak (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm). Although few details are available from the Chinese experience and published studies involved small numbers of patients, the available information suggests that convalescent plasma administration reduces viral load and was safe. 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 (11).

3. Potential risks

a. The theoretical risk involves the phenomenon of antibody-mediated enhancement of infection (ADE). ADE can occur for several viral diseases and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms for ADE have been described and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain (12). It may be possible to predict the risk of ADE of SARS-CoV-2 experimentally, as was proposed for MERS. Since the proposed use of convalescent plasma in the COVID-19 epidemic would rely on preparations with high titers of neutralizing antibody against the same virus, SARS2-CoV-2, ADE may be unlikely. Evidence from the use of convalescent plasma in patients with SARS1 and MERS (13), and anecdotal evidence of its use in patients with COVID-19 (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm), suggest it is safe. Nevertheless, caution and vigilance will be required in for any evidence of enhanced infection.

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

duration and severity of disease, and avoiding interventions like mechanical ventilation, ARDS and sepsis.

c. There are risks associated with any transfusion of plasma including transmission of transfusion transmitted viruses (e.g. HIV, HBV, HCV, etc.), allergic transfusion reactions, anaphylaxis to transfusion, febrile transfusion reaction. Donors will fulfill donor requirements for whole blood donation and frequent apheresis plasma donation with the exception of recent illness, in this case COVID-19 infection.

d. Transfusion related acute lung injury (TRALI): This study will administer up to 10 units of plasma (1-2 doses per day, every-other-day dosing for 5 doses) to patients with ARDS, or at risk of progression to ARDS. These patients are at increased risk of TRALI due to increased inflammatory state with high IL-6 and IL-8 levels. TRALI is caused by anti-HLA or anti-neutrophil antibodies in donor plasma. Therefore, to reduce the risk of TRALI, patients on the protocol will receive CP from **male donors, only** (lower chance of anti-HLA antibodies), and will preferentially use AB blood-type plasma.

e. Transfusion associated cardiac overload (TACO): occurs due to the osmotic load of the plasma. Treating clinicians will carefully monitor volume status, weight gain > 1kg/day, and urine output, and may withhold CP for patients with unresolved TACO from prior transfusions. Judicious use of diuretics to mitigate TACO is encouraged.

f. Hemolysis should ABO incompatible plasma be administered.

4. Potential benefits

Assessing the feasibility of a treatment protocol for established COVID-19 infection, a now prevalent disease without other proven therapeutic options the key potential benefit of this study. Convalescent plasma would be administered to those with clinical disease in an effort to reduce their symptoms and mortality. The purpose of this feasibility study is to assess whether CP administration late in disease course is safe. Future studies and other companion protocols will address whether there is an optimal time to start CP administration, and whether there is an optimal dose, donor, or neutralizing antibody content.

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

5. Investigational plan

5.1 Study Objectives

Primary Objective: Determine feasibility of patients in the ICU receiving CP for COVID-19-induced respiratory failure.

Key Secondary Endpoint: Survival

Other Exploratory Outcomes:

1. Ventilatory free days and mechanical ventilatory parameters (e.g FiO2, PEEP, plateau pressure, driving pressure)
2. ICU mortality and LOS
3. Hospital mortality and LOS
4. 28-day and 60-day mortality
5. Multi-organ failure (and other ICU support e.g., dialysis, vasopressors)
6. Number of patients developing TRALI based on CDC Hemovigilance Criteria https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf

Other Exploratory Endpoints:

1. Cumulative incidence of serious adverse events during the study period: transfusion reaction (fever, rash), transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion related infection
2. Tolerability of plasma transfusions in critically ill recipients
3. Anti-SARS-CoV-2 titers at days 0 and when available.
4. Rates and duration of SARS-CoV-2 PCR positivity (RT-PCR) at days 0 and if further available.

5.2 Definitions

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

5.3 Study population

Inclusion Criteria for Enrollment

1. Patients 18 years of age or older
2. Hospitalized and intubated in the ICU with COVID-19 respiratory symptoms and confirmation via COVID-19 SARS-CoV-2 RT-PCR testing. Patient or proxy is willing and able to provide written informed consent and comply with all protocol

requirements, or requirement for informed consent is WAIVED due to the inability to communicate with the patient and unable to identify legally authorized representative.

3. Consents to storage of specimens for future testing, or consent waived.

Exclusion Criteria

1. Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products).
2. Severe multi-organ failure, hemodynamic instability.
3. Other documented uncontrolled infection.
4. Severe DIC needing factor replacement, FFP, cryoprecipitate.
5. On dialysis.
6. Active intracranial bleeding.
7. Clinically significant myocardial ischemia.

Table: Schedule of Events

Study period	Screen	On Study Treatment						
Day	-14 to 0	0	2	4	6	8	14	28
Eligibility								
Informed consent or WAIVER (includes proxy)	x							
Demographic and Medical history; SOFA score	x		x	x	x	x	x	x
COVID-19 symptom screen	x							
SARS-CoV-2 RT-PCR for eligibility	x							
Pregnancy test for females of childbearing age	x							
ABO[2]	x							
Study Drug Administration								
Convalescent Plasma Infusion		x	x	x	x	x		
Study Procedures								
Vital signs	x	x	x	x	x	x	x	x
Physical examination	x		x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x
Adverse event monitoring		x	x	x	x	x	x	x
Laboratory testing								
CBC and CMP		x	x	x	x	x	x	x
SARS-CoV-2 RT-PCR[3]		x						
SARS-CoV-2 antibody		x	x	x	x	x		
Blood for future testing (excess sample available and stored)		x	x	x	x	x	x	x

5.4 Subject Withdrawal

1. Subjects can terminate study participation and/or withdraw consent at any time without prejudice.
2. 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
3. Discontinuation of the study: The study sponsor, FDA and IRB all have the right to terminate this study at any time

[2] At least 2 assessments of ABO type on file, with one in the 90 days prior to enrollment
[3] Sites could include nasopharyngeal and throat
[4]The assessments performed on day 28 will be repeated on days 60 and 90.

5.5 Treatment

1. Subjects will receive open-label screened plasma from COVID-19+ clinically resolved individuals (14 days post-resolution). Dosing of single or double plasma units (weight based < or > 90Kg) will be administered on days 0, 2, 4, 6, and 8, or until extubation or futility (if either occurs before day 8) is determined by the ICU.
2. Doses can be omitted at the discretion of the treating clinician (e.g., TRALI events are 100% donor-dependent and do not prohibit future transfusions).
3. Study drug: The investigational product is anti-SARS-CoV-2 convalescent plasma obtained from MALE patients identified as having recovered from COVID-19 with COVID-19+ antibody titers.
4. Male donors and samples will be screened for infections transmitted via transfusion (e.g. HIV, HBV, HCV, WNV, HTLV-I/II, *T.cruzi*, ZIKV) both through the use of the uniform donor questionnaire and FDA mandated blood donor screening tests. Plasma will be collected using apheresis technology or whole blood collection in accordance with standard FDA and blood bank protocols.

6. Rationale for doses

For a 70 kg person, plasma volume is estimated at 2800 mL (40 mL/kg x 70 kg). Baseline antibody titer may be present or absent.

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.

In practical terms this is 1-2 units of FFP per patient based on < or > 90kg. Treating clinician can decide to give 1 unit if the patient is at high risk of circulatory overload.

6.1 Study drug administration

- Infusion rate £ 500 mL/hour
- Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given per investigator and clinical care team discretion.
- If an AE develops during infusion, the infusion may be slowed or stopped as per investigator's decision.
    - Most reactions to plasma are relatively minor and the infusion can generally be continued. Infusion site burning and non-allergic systemic effects can generally be managed with slowing of the infusion. Infusion can generally be continued in cases of itching or hives after pausing the

transfusion, administering antihistamines, and observing a lack of symptom progression.
- Severe allergic reactions such as, bronchospasm and hypotension, and may require discontinuation of the infusion.

6.2 Concomitant medication
s will be documented on the CRF

- Prescription medications
- Over the counter medications
- Herbal treatments/nutritional supplements
- Blood products

Prohibited Therapies: No off-label therapies are prohibited (patients may receive concomitant tocilizumab, hydroxychloriquine, azithromycin, remdesivir, Kaletra, statins, interferons, etc.) but patients are not permitted to enroll in more than one clinical trial at the same time.

7. Statistical considerations

7.1 Statistical Analysis

Descriptive summaries of continuous and other numeric variables will at least consist of the following summary statistics: median, minimum and maximum values. We will analyze events including number of doses of CP administered, survival, organ function. Categorical variables will be summarized by the frequency and proportion of subjects falling into each category. Unless otherwise indicated, percentages in tables will be column percentages, using the total number of observations in the population (*n*=30). Percentages will be rounded to one decimal place, and thus may not always add up to exactly 100%. Clinical laboratory values will be first reported in using International System of Units (SI). Exact confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

7.2 Analysis of AE data

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

The main AEs of interest relate to **transfusion-associated toxicities, TRALI, TACO and antibody-associated worsening of infection.** We will attempt to distinguish these entities using Consensus Criteria, but will also report respiratory parameters, body weight, and relationship of AEs to CP infusion, so that post-hoc assessment of AEs can be performed.

7.3 Analysis of anti-SARS-CoV-2 titers

Analysis of titers will also primarily be descriptive, comparing the geometric mean titers at days 0 and when available from excess plasma from clinical specimens (that will be stored). These assays are being developed by the CP Virology Subgroup in the trial consortium (ELISA, neutralizing Ab assays).

8. Study Procedures

Day -1 to 0:

A. Screening
B. Subject informed consent (or proxy consent, including by phone)
C. Baseline Evaluation (at screening) (much of the information will be obtained from the medical record)
    1. Demographics (Age, sex ethnicity, race)
    2. Medical history (timing of exposure to COVID-19 source patient, onset of respiratory symptoms, acute and chronic medical condition, medications, allergies. Any medical condition arising after consent should be recorded as AE
    3. COVID-19-induced respiratory failure for eligibility
    4. Vital signs
    5. COVID-19 testing (RT-PCR) from nasopharyngeal or other sources if available (sputum, stool, bronchoalveolar lavage fluid).
    6. Blood typing, CBC, comprehensive metabolic panel
    7. Serological testing: anti-SARS CoV-2 titers
    8. Stored samples for future studies
    9. Urine or serum pregnancy test for females of childbearing potential will be noted.

DAY 0:

1. Enrollment of eligible subjects
2. Study Plasma Administration: 1-2 units of plasma (weight-based as above) will be transfused. Time at start and end of infusion will be recorded and Vital signs will be measured immediately prior to infusion, 10-20 minutes after start of infusion, at completion of infusion and 30-60 minutes after the end of the infusion
3. Assessment of clinical status, physical examination
4. New medical conditions, concomitant medication, AE evaluation
5. Blood typing, CBC, comprehensive metabolic panel
6. Serological baseline testing for anti-SARS CoV-2 titers
7. Stored samples for future studies (cytokines, etc)

Day 1-9 (or for duration of ICU stay)

1. Vital signs daily including SpO2
2. Daily Ventilatory requirements (FiO2, PEEP, respiratory rate)
3. Assessment of clinical status including new medical conditions, AE evaluation for potential toxicities prior to subsequent every other day dosing of CP (up to day 8) by the ICU attending physician in coordination with the study team
4. Treating physician is permitted to withhold study treatment (skip a scheduled infusion of CP) if he/she judges that the patient is at excessive risk of TACO (TRALI is 100% donor-dependent), or if toxicity from the previous dose has not resolved. The patient may remain on study and receive subsequent doses if toxicities have resolved, weight is stable, respiratory status is stable or improving, etc. We will record the number of doses given and the reason for each skipped dose.
5. physical examination
6. CBC, comprehensive metabolic panel as clinically indicated
7. Serological testing anti-SARS CoV-2 titers when available from excess plasma
8. Stored samples for future studies

Day 10-27:

Key parameters are 1) survival; 2) inpatient status versus outpatient status (ICU or not); 3) persistent respiratory failure or extubation; 4) clinical data such respiratory support (supplemental O2 or not); 5) if discharged, SNF, nursing home, LTAC versus home recovered, back to work (fully, partially)

1. Respiratory status
2. Assessment of overall clinical status
3. New medical conditions, AE evaluation

Day 28 and 60:

1. Respiratory status
2. Assessment of overall clinical status
3. New medical conditions, AE evaluation

9. Efficacy, virology and PK measures

Clinical Efficacy

1. Survival (days)
2. Duration (days) of ventilatory support in ICU and mechanical ventilatory requirements (FiO2, PEEP, rate, mode etc)
3. ICU mortality and LOS
4. Hospital mortality and LOS
5. 28-day and 60-day mortality
6. Multi-organ failure (and other ICU support e.g., dialysis, pressors)
7. Number of patients developing TRALI based on Consensus Definition

Virologic measures

1. Rates, levels and duration of SARS-CoV-2 RNA in NP swabs by RT-PCR at days 0 and subsequent clinical testing. Other specimen types that may be tested and available (*eg.,* BAL fluid, tracheal secretions, sputum, etc.) or when RT-PCR assays are validated for additional sources (*i.e.,* stool, blood).
2. Serologic positivity and neutralization antibody titers for anti-SARS-CoV-2 at days 0 when specimens available for post-treatment (additional days 28 and 60 may be included, if available).

10. Risks and benefits

Potential Benefits of treatment:

The potential benefits of antiviral treatment with anti-SARS CoV-2 plasma in patients with respiratory failure, intubated due to pneumonia or ARDS. However, it is anticipated that treatment may decrease disease severity and ICU stay.

Potential benefits of clinical monitoring and virologic testing:

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

Potential risks:

1. Risks of plasma: Fever, chills, rash, headache, serious allergic reactions, TRALI, TACO, transmission of infectious agents
2. Risks of phlebotomy: local discomfort, bruising, hematoma, bleeding, fainting,
3. Total blood draws will not exceed 500 mL
4. Risks of oropharyngeal and throat swab: local discomfort, vomiting

Alternatives:

The alternative to participation in this study is routine care.

11. Safety measures

1. Safety Evaluations will assess for the safety of high titer anti-SARS-CoV-2 plasma and determine if it is higher, lower or the same as standard plasma
2. Clinical evaluations: Vital signs and symptom screen on days 0-9, days 10-27 and days 28, 60.
3. Laboratory evaluations consistent with ongoing medical care may include radiographic imaging modalities such as chest x-rays and chest CT.
4. Safety laboratory tests (ABO typing, pregnancy testing, CBC, and comprehensive metabolic panel) will be performed at the local CLIA-certified clinical laboratory on days 0, 2, 4, 6, 8, 14, 28 and as clinically indicated.

Event (AE)

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

Serious Adverse Event (SAE)

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

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

Unexpected Adverse event: (UAE) An adverse reaction, the nature or severity of which is not consistent with the investigator's brochure.

Serious and Unexpected Suspected Adverse Reaction (SUSAR)

Unanticipated Problem (UP)

Unanticipated Problem that is not an Adverse Event (e.g. breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.
Protocol Deviation: Deviation from the IRB-approved study procedures. Designated serious and non-serious

1. Serious Protocol Deviation: Protocol deviation that is also an SAE and/or compromises the safety, welfare or rights of subjects or others
2. Safety Reporting Requirements

Reporting Interval

All AEs and SAEs will be documented from the first administration of study product until completion or un-enrollment from the study. All AEs and SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an adverse event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

At any time after completion of the study, if the investigator becomes aware of a SAE that is suspected to be related to study product

Investigator's Assessment of Adverse Events

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

Laboratory abnormalities will be reported as AEs if there is a 2 s.d. increase above baseline.

Assessment of Seriousness

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

Event severity will be assigned according to the scale below

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

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

3 = Severe: Escalation of medical intervention/therapy required

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

5= Death

Assessment of Association

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

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

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

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

12. Safety Oversight

Monitoring Plan

1. All AEs and SAEs will be reviewed by the protocol team in real time.
2. A medical monitor will be appointed by the sponsor for safety oversight of the clinical study.
3. A data safety monitoring board (DSMB), will be established and comprised of independent experts without conflict of interests will be established. The Board will review the study before initiation and at least quarterly thereafter. The Board will review study data to evaluate the safety, efficacy, study progress, and conduct of the study

4. An Independent Safety Monitor (ISM) will be appointed. The ISM is ideally a physician with expertise in infectious diseases and critical care (Henry Masur, MD will be asked) and whose primary responsibility is to provide timely independent safety monitoring. An ISM is in close proximity to the study site and has the authority to readily access study participant records. The ISM reviews any SAE that occurs at the study site in real time and provides a written assessment.

Study monitoring

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

Halting Criteria for the Study

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

1. Death within one hour of plasma infusion

2. Occurrence of a life-threatening allergic/hypersensitivity reaction (anaphylaxis), manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation.

3. An overall pattern of symptomatic, clinical, or laboratory events that the medical monitor, ISM, or SMC consider associated with study product and that may appear minor in terms of individual events but that collectively may represent a serious potential concern for safety.

4. Any other event(s) which is considered to be a serious adverse event in the good clinical judgment of the responsible physician. This will be appropriately documented.

Upon completion of this review and receipt of the advice of the ISM or SMC, DMID will determine if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol.

Halting Criteria/Rules for Subject Infusion

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

- Skin or mucous membrane manifestations: hives, pruritus, flushing, swollen lips, tongue or uvula
- Respiratory compromise: dyspnea, wheezing, stridor, hypoxemia
- A decrease in systolic blood pressure to < 90 mmHg or >30% decrease from baseline or a diastolic drop of >30% from baseline.
- Tachycardia with an increase in resting heart rate to > 130bpm; or bradycardia <40 that is associated with dizziness, nausea or feeling faint.
- 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

13. Ethics/Protection of human subjects

1. Ethical Standard

UPMC, Cedars Sinai and Johns Hopkins and all other potential participating institutions are and will be committed to the integrity and quality of the clinical studies it coordinates and implements. All sites will ensure that the legal and ethical obligations associated with the conduct of clinical research involving human subjects are met. The information provided in this section relates to all sites participating in this research study

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

In addition, all sites have a Federal wide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP).

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

2. Institutional Review Board

The UPMC, Cedars Sinai and Johns Hopkins IRBs will initially review this protocol and all protocol-related documents and procedures as required by OHRP and local requirements before subject enrollment. We will also pursue single IRB if possible, for maximal efficiency.

3. Informed Consent Process

The informed consent process will be initiated before a volunteer agrees to participate in the study and should continue throughout the individual's study participation. The subject will sign the informed consent document before any procedures are undertaken for the study. A copy of the signed informed consent document will be given to the subject for their records. The consent will explain that subjects may withdraw consent at any time throughout the course of the trial. Extensive explanation and discussion of risks and possible benefits of this investigation will be provided to the subjects in understandable language. Adequate time will be provided to ensure that the subject has time to consider and discuss participation in the protocol.
The consent will describe in detail the study interventions/products/procedures and risks/benefits associated with participation in the study. The rights and welfare of the subjects will be protected by emphasizing that their access to and the quality of medical care will not be adversely affected if they decline to participate in this study.

4. Subject Confidentiality

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

14. Future Use of Stored Specimens

Subjects will be asked for consent to use their samples for future testing before the sample is obtained. The confidentiality of the subject will be maintained. They will be no

plans to re-contact them for consent or to inform them of results. The risk of collection of the sample will be the small risk of bruising or fainting associated with phlebotomy however these samples will be taken at the same time as other protocol required samples. Excess blood samples will be collected and stored when feasible, including plasma, serum and buffy coats, will be frozen in 1-ml aliquots. These samples will be used to answer questions that may arise while the study is underway or after it is completed, and may be shared with other investigators with expertise in virology, immunology, genetics and other disciplines. If for instance, there were unanticipated AEs, serum could be used to run tests that might help determine the reason for the AEs. Cytokines could be measured, for example.

15. Data management and monitoring

a. Source Documents

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

Data Management Plan

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

b. Data Capture Methods

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

c. Study Record Retention

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

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

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