Long title: Pilot Study for Use of Convalescent Plasma Collected from Patients Recovered from COVID-19 Disease for Transfusion as an Empiric Treatment during the 2020 Pandemic at the University of Chicago Medical Center

Short title: COVID-19 Convalescent plasma

Conducted by: University of Chicago Medical Center

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PROTOCOL SUMMARY:

Sample Size: Total sample size = 160 subjects. We expect to recruit 150donors and 10 recipient subjects of convalescent plasma (CP). The donor subject number is because plasma received from the donors will also be screened for HLA alloantibody and ABO compatibility according to routine blood bank guidelines. The recipient subject number is to ensure the feasibility of the protocol.

Study Population: Recipient subjects will be hospitalized patients aged 18 years or older with severe or life-threatening COVID-19 disease within 21 days or less from beginning of illness. Donor subjects will be people aged 18 years or older who are able to donate blood per standard blood bank guidelines; have prior diagnosis of COVID-19 documented by a laboratory test; and have complete resolution of symptoms at least 28 days prior to donation.

Study Duration: April 1, 2020 to December 31, 2022

Study Design: This a prospective open label pilot study to assess the feasibility of delivering anti-SARS-CoV-2 convalescent plasma to hospitalized patients aged 18 years of age or older, with severe or life-threatening COVID-19 disease less than 21 days from the beginning of their illness. We plan a targeted recruitment of 100 total eligible donor to donate plasma. A total of 10 eligible recipient subjects will receive anti-SARS-CoV-2 plasma after eIND application to the FDA has been approved for each individual subject.

The following will be assessed in all donor subjects

- Biomarker tests performed in the research lab (e.g. antibody titer, cytokine levels)
- Donor questionnaire
- Donors screened as above must be otherwise eligible, give consent, and successfully donate plasma, as part of a whole blood (WB)

The following will be assessed in all recipient subjects:

- Feasibility: is plasma given to the recipient
- All demographic and clinical data contained in the electronic medical record, as well as hospital administrative data for enrolled patients. This data includes age, sex, comorbidities, date of symptom onset, type of admission, APACHE score, SOFA score, clinical status, vital signs including temperature, respiratory rate, oxygen saturation, oxygen requirement, CBC with neutrophil counts, lymphocyte count, complete metabolic panel, liver function tests, CRP, chest x-ray, chest CT, location in hospital.
- Safety and efficacy: Day 0 (baseline), 1, 2, 3, 7, 14, and 28 and once monthly at 2-3 months.

- SARS-CoV-2 PCR from nasopharyngeal swabs: Day 0, 3, 7, 14 to assess viremia response. Other clinically-approved SARS-CoV-2 testing may be used if available (e.g. saliva, nares, blood).
- Biomarker tests performed in the research lab (e.g. antibody titer, cytokine levels) on day 0, 1, 3, 7, 14, additional days 21 and 28 may be included, as available.
- Post-therapy outcomes: increased O2 requirement (PaO2/FiO2 ratio or SpO2/FIo2), supplemental oxygen strategy (e.g. nasal cannula, high-flow nasal cannula, noninvasive ventilation, intubation and invasive mechanical ventilation, rescue ventilation i.e. neuromuscular blocking agents, prone positioning, corticosteroids, ECMO), vasopressors, renal support, ICU LOS, ICU mortality, Hospital LOS, Hospital mortality, 28 day mortality.

Study Agent:

- SARS-CoV-2 convalescent plasma (1 unit, on average ~300 mLs)

Primary Objective/Outcome:

1. Feasibility of performing study pathway consisting of consenting convalescent donors, harvesting convalescent plasma, application for FDA eIND and administering convalescent plasma to the patients
    a. Feasibility will be defined as 6-7 recipient subjects out of a total proposed number of 10 recipient subjects will complete the study infusion of plasma and be evaluable for follow-up with at least 24 hours' worth of data post transfusion. Post-transfusion data will include assessment of the study process, outcome endpoints and safety endpoints.
2. Type and duration of respiratory support (e.g. CPAP, BiPAP, high-flow nasal cannula, mechanical ventilation)

Primary Endpoint: Number of patients meeting inclusion criteria who received anti-SARS-CoV-2 convalescent plasma in the study period

Secondary endpoints:

1. Cardio-circulatory arrest (at any time)
2. Transfer to ICU
3. ICU mortality and LOS
4. Hospital mortality and LOS
5. Ventilator-free days
6. 28 day mortality

Primary Safety Objective: Evaluate the safety of an investigational treatment with anti-SARS-CoV-2 plasma in hospitalized patients with severe or life-threatening COVID-19

Primary Safety Endpoints:

1. Rapid deterioration of respiratory or clinical status during transfusion of anti-SARS-CoV-2 convalescent plasma
2. 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, new acute respiratory distress syndrome (ARDS).

Secondary Objectives:

1. Measure rates, levels and duration of SARS-CoV-2 RNA in nasopharyngeal swabs using RT-PCR among recipients. Other specimen types may be tested as available (*e.g.,* BAL fluid, tracheal secretions, sputum, etc.) or when RT-PCR assays are validated for additional sources (*i.e.,* stool, blood).
2. Biomarker tests performed in the research lab (e.g. antibody titers, cytokine levels) at days 0, 1, 3, 7 and 14 (additional days 21 and 28 may be included, as available) in the recipient.

Study population:

Plasma Donor Inclusion Criteria for Enrollment

- Age greater or equal to 18
- Able to donate blood per blood bank standard guidelines
- Prior diagnosis of COVID-19 documented by a laboratory test. Patients outside of the UCMC medical system will be asked to provide documentation of COVID-19 positive test
- Complete resolution of symptoms at least 28 days prior to donation
- Female donors who have never been pregnant, previously pregnant female donors negative for HLA antibodies (HLA screening), or male donors

Plasma Donor Subject Exclusion Criteria for Enrollment

- Does not provide consent
- Does not meet standard blood bank donation guidelines
- Unsuccessful blood donation

Convalescent plasma donor subjects are consenting for plasma donation towards hospitalized patients with severe or life-threatening COVID-19 disease. Convalescent plasma units in the UCM Blood Bank collected under this protocol will be used for the currently approved Expanded Access Protocol IRB20-0825.

Plasma Recipient Subject Inclusion Criteria for Enrollment

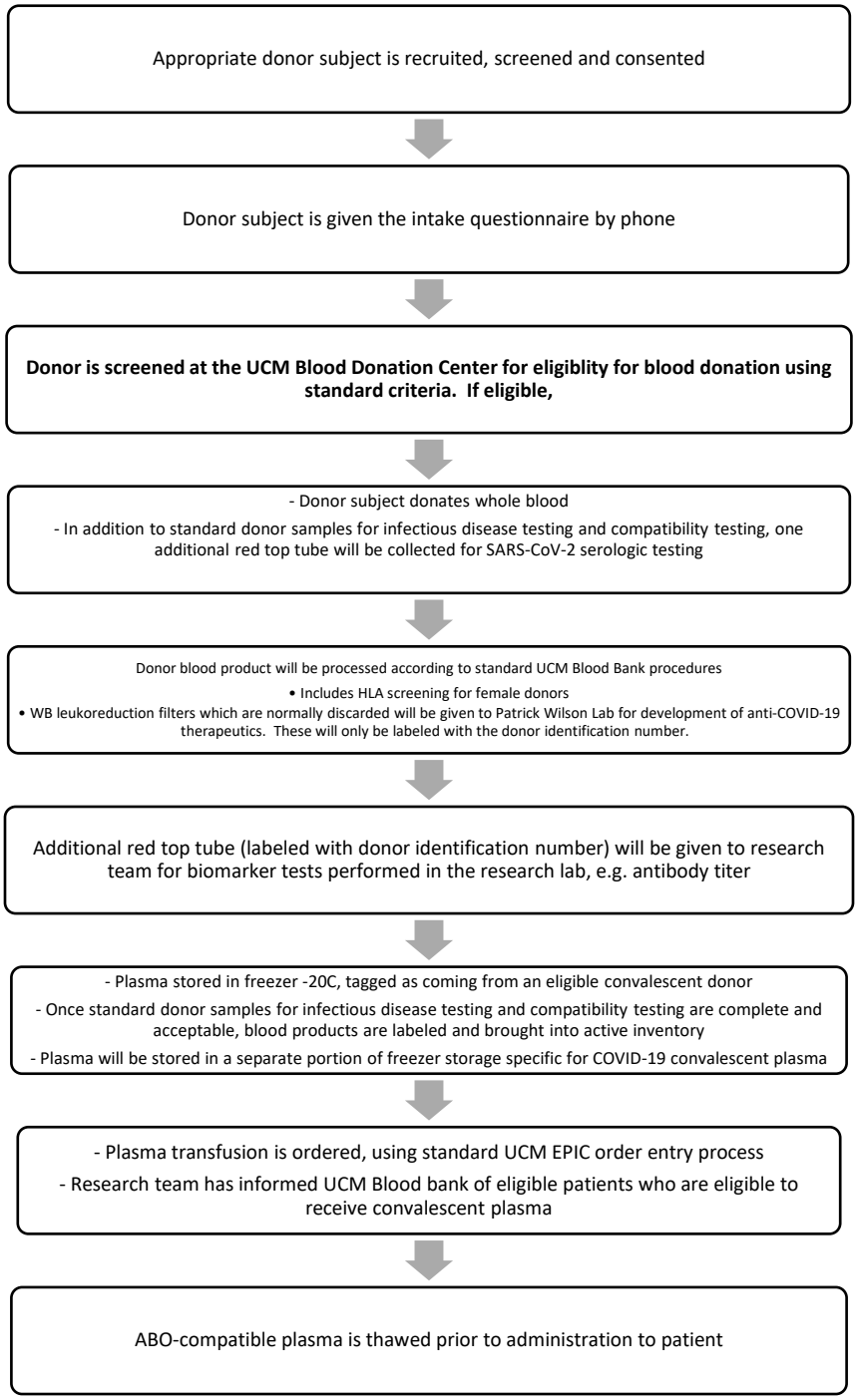
- Patients must be 18 years of age or older
- Must have laboratory-confirmed COVID-19
- Must have severe or immediately life-threatening COVID-19
    - Severe defined as dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or lung infiltrates > 50% within 24 to 48 hours
    - Life-threatening defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Lower priority should be given to patients with septic shock or multiple organ dysfunction or failure since their disease may have progressed to a point where they are not able to benefit from convalescent plasma therapy.

- Must be less than 21 days from the start of illness
- Patient is willing and able to provide written informed consent and comply with all protocol requirements. If the patient is not able to consent, we will obtain consent from the power of attorney or a health care proxy for the patient as determined by the Illinois Healthcare Surrogate Act
- Patient, power of attorney or health care proxy agrees to storage of specimens for future testing.
- Of note, eIND application for each recipient subject will need to be approved before administration of convalescent plasma

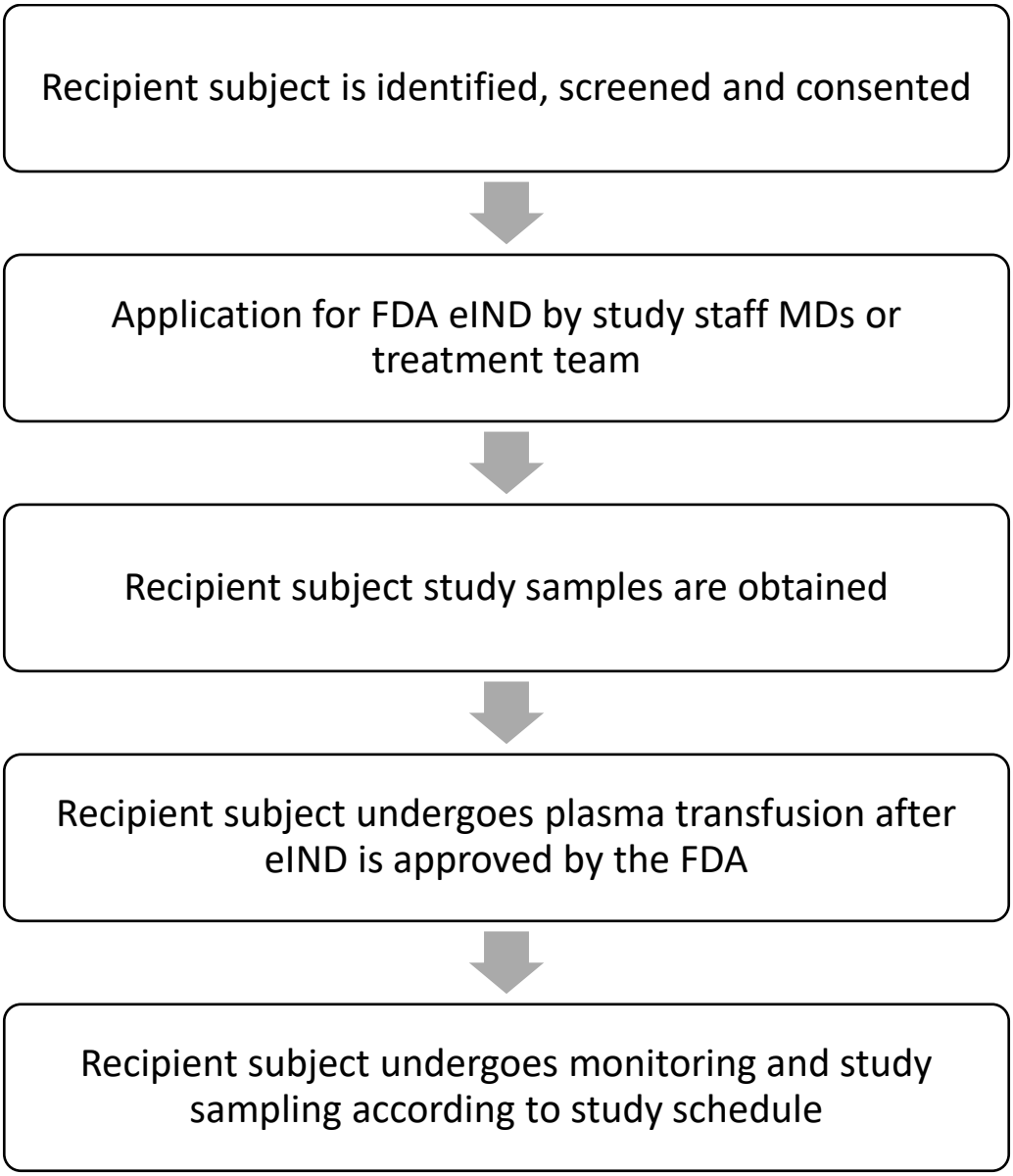
Plasma Recipient Subject Exclusion Criteria

- Female subjects with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period
- Receipt of pooled immunoglobulin in past 30 days
- Contraindication to transfusion or history of prior reactions to transfusion blood products
- Patients currently enrolled in other drug trials that preclude investigational treatment with anti-SARS-CoV-2 convalescent plasma

Anticipated study workflow pathway: donor subjects



Anticipated clinical workflow pathway: recipient subjects



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
eIND: Emergency Investigational New Drug Application
FDA: Food and Drug Administration
GCP: Good Clinical Practice
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
HLA: Human Leukocyte Antigen
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
PBMCs: peripheral blood mononuclear cells
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
UCMC: University of Chicago Medical Center
UP: Unanticipated Problem

UPnonAE: Unanticipated Problem that is not an Adverse Event
ZIKV: Zika virus

Background and scientific rationale

Beyond supportive care, there are currently no proven treatment options for 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 could be rapidly available when there are sufficient numbers of people who have recovered and can donate high titer neutralizing immunoglobulin-containing plasma.

Passive antibody therapy involves the administration of antibodies to a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent. In contrast, active vaccination requires the induction of an immune response that takes time to develop and varies depending on the vaccine recipient. Some immunocompromised patients fail to achieve an adequate immune response. Thus, passive antibody 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 grants immediate passive immunity to patients through the transfer of virus-neutralizing antibody derived from people who have recovered from infectious disease.

Passive antibody therapy has a storied history going back to the 1890s and was the only means of treating certain infectious diseases prior to the development of antimicrobial therapy in the 1940s (1,2). This strategy has been successfully used during SARS, MERS, influenza 1918, influenza A H1N1, and Ebola outbreaks, with demonstrable safety, efficacy and decrease in mortality as detailed below. Experience from prior outbreaks with other coronaviruses, such as SARS-CoV-1 shows that such convalescent plasma contains neutralizing antibodies to the relevant 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 for those treated with convalescent whole blood relative to those who received standard treatment (4).

The only antibody type that is currently available for immediate use is that found in human convalescent plasma. As more individuals contract COVID-19 and recover, the number of potential donors will continue to increase. A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease. Another

explanation is that antibody works by modifying the inflammatory response, which is also easier during the initial immune response, which may be asymptomatic (5).

For passive antibody therapy to be effective, a sufficient amount of antibody must be administered. When given to a susceptible person, this antibody will circulate in the blood, reach tissues and provide protection against infection. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin can last from weeks to months. In addition, administration of passive antibody therapy does not preclude a patient from receiving future monoclonal antibody therapy or vaccines which may be developed for COVID-19.

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, SARS1 in 2003 and MERS in 2012. In both outbreaks, the high mortality and absence of effective therapies led to the use of convalescent plasma. The largest study involved the treatment of 80 patients in Hong Kong with SARS (7). Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22. 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).

Among reports of **seriously ill individuals treated with convalescent plasma**, three patients with SARS in Taiwan were treated with 500 ml of convalescent plasma, resulting in a reduction in plasma virus titer and each survived (8). Three patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients had neutralizing antibody in their plasma (9). The latter study highlights a challenge in using convalescent plasma, namely, that some who recover from viral disease may not have high titers of neutralizing antibody (10). **Strikingly, a recent report from China where 10 patients with severe COVID-19 received human convalescent plasma (SARS-CoV-2 convalescent plasma) on day 10 to 20 of illness demonstrated improvement in clinical, radiographic and laboratory parameters such that patients were discharged to home and suffered no severe adverse effects** (https://www.medrxiv.org/content/10.1101/2020.03.16.20036145v1.full.pdf). These patients received plasma from donor blood collected from hospitalized patients three weeks after illness start and 4 days after discharge. The donors had to demonstrate criteria of recovery which were (a) normal temperature for at least 3 days; (b) resolution of respiratory tract symptoms; (c) 2 consecutively negative RT-PCR sputum results with one-day sampling interval. This was followed by a report by a separate group in China in JAMA on March 27, 2020 showing that 5 critically ill patients, including one on extra-corporeal membrane oxygenation (ECMO) support, who received low titer antibody serum with high virus neutralizing activity, were able to recover (Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma.

JAMA. Published online March 27, 2020. doi:10.1001/jama.2020.4783. 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 is safe.**

In these rapidly changing times, several groups across the United States have highlighted the importance of convalescent plasma in the anti-COVID-19 arsenal. These groups include National Academies of Sciences, Engineering, and Medicine (https://www.nationalacademies.org/news/2020/statement-from-the-presidents-of-the-nas-nae-and-nam-supporting-steps-necessary-to-assess-the-potential-for-human-convalescent-plasma-to-help-control-covid-19) and the AABB American Association of Blood Banking (http://www.aabb.org/advocacy/regulatorygovernment/Documents/COVID-19-Convalescent-Plasma-Resources.pdf).

In addition, the AABB with FDA support is currently working to establish a "master collection protocol under which blood centers would be able to quickly implement uniform practices to expedite the availability" of convalescent plasma. Because there are no currently available treatments for COVID-19, the FDA has approved the emergency investigational use of convalescent plasma to treat COVID-19 under the criteria of the single patient emergency investigational new drug application (eIND) (https://www.fda.gov/media/136470/download) (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds).

Known potential risks

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 proposed for MERS. Since the proposed use of convalescent plasma in the COVID-19 pandemic would rely on preparations with high titers of neutralizing antibody against the same virus, SARS2-CoV-2, ADE may be unlikely. The available evidence from the use of convalescent plasma in patients with SARS1 and MERS (13) and anecdotal evidence of its use in patients with COVID-19 (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm, https://www.medrxiv.org/content/10.1101/2020.03.16.20036145v1.full.pdf), suggest it is safe. However, because of these potential risks, we are limiting administration of SARS-CoV-2 convalescent plasma to patients with severe or life-threatening COVID-19 at this time. Caution and vigilance will be required for any evidence of enhanced infection.

Another theoretical risk is that antibody administration to those exposed to SARS-CoV-2 may avoid disease but modify the immune response such that those individuals mount

attenuated immune responses, which would leave them vulnerable to subsequent re-infection. In this regard, passive antibody administration before vaccination with respiratory syncytial virus was reported to attenuate humoral but not cellular immunity (14). If the concern proved real, these individuals could be vaccinated against COVID-19 when a vaccine becomes available. Furthermore, this issue will be investigated by measuring immune responses in those exposed and treated with convalescent plasma to prevent disease in an ongoing clinical trial. In addition, once serum antibody testing becomes readily available, immunity can be more reliably assessed, *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.*

Finally, 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, transfusion related acute lung injury (TRALI), and transfusion associated cardiac overload (TACO). Infectious risks are minimized by collecting only eligible donors and testing donors for all FDA-required infectious diseases as part of standard allogeneic donor blood collection. TRALI is mitigated by collecting male donors, female donors who have never been pregnant, or previously pregnant women who are negative for HLA antibodies. Donors will fulfill all donor requirements for whole blood donation. The standard volume of plasma (~300 mL) will be transfused over a longer time period (4 hours) and the patient will be monitored for signs of overload.

Known potential benefits

A key potential benefit is the potential treatment for established infection. Convalescent plasma would be administered to those with clinical disease in an effort to reduce their symptoms and mortality. Based on the recent evidence from China with antibody administration, it can be anticipated that *antibody administration in patients with severe COVID-19 could improve mortality, decrease ICU needs and reverse ventilator- or oxygen-dependence in carefully selected patients.*

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 disease outweigh the risks. However, for all cases where convalescent plasma administration is considered, a risk-benefit assessment must be conducted to assess individual variables.

Investigational plan

Study Objectives

Primary Objective:

1. Feasibility of performing clinical pathway for convalescent plasma therapy consisting of consenting convalescent donors, harvesting anti-SARS-CoV-2 convalescent plasma, application for single patient eIND to the FDA and administering anti-SARS-CoV-2 convalescent plasma to the patients meeting study criteria

2. Type and duration of respiratory support (e.g. CPAP, BiPAP, high-flow nasal cannula, mechanical ventilation)

Primary Safety Objective:

Evaluate the safety of investigational treatment with anti-SARS-CoV-2 plasma in hospitalized patients with severe or life-threatening COVID-19

Secondary Objectives:

Biomarker tests performed in the research lab (e.g. antibody titer, cytokine levels) at days 0, 1, 3, 7 and 14 (additional days 21 and 28 may be included, as available) in the recipient.

Measure rates, levels and duration of SARS-CoV-2 RNA in nasopharyngeal swabs using RT-PCR among recipients. Other specimen types may be tested as available (eg., BAL fluid, tracheal secretions, sputum, etc.) or when RT-PCR assays are validated for additional sources (i.e., stool, blood).

Definitions

- Enrolled: From time consented to participate until designated as a screen failure or have either been discontinued from the study or completed it.
- Screen Failures: signed informed consent, but then determined to be ineligible or withdraws
- Discontinued: withdrawn by investigator or withdraws consent
- Completed: Subjects are considered to have completed when they are followed through day 90 or have had an adverse event or death occurred prior to day 90.

Study population

Plasma Donor Subject Inclusion Criteria for Enrollment

- Age 18 or older
- Able to donate blood per blood bank standard guidelines
- Prior diagnosis of COVID-19 documented by a laboratory test. Patients outside of the UCMC medical system will be asked to provide documentation of COVID-19 positive test.
- Complete resolution of symptoms at least 28 days prior to donation
- Female donors who have never been pregnant, previously pregnant female donors negative for HLA antibodies (HLA screening), or male donors

Plasma Donor Subject Exclusion Criteria for Enrollment

- Unable to give consent
- Unable to donate blood per blood bank standard guidelines
- Unsuccessful blood donation

Plasma Recipient Subject Inclusion Criteria for Enrollment

- Patients must be 18 years of age or older
- Must have laboratory-confirmed COVID-19
- Must have severe or immediately life-threatening COVID-19
    - Severe defined as dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or lung infiltrates > 50% within 24 to 48 hours
    - Life-threatening defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Lower priority should be given to patients with septic shock or multiple organ dysfunction or failure since their disease may have progressed to a point where they are not able to benefit from convalescent plasma therapy.
- Must be less than 21 days from the start of illness
- Patient is willing and able to provide written informed consent and comply with all protocol requirements. If the patient is not able to consent, we will obtain consent from the power of attorney or a health care proxy for the patient as determined by the Illinois Healthcare Surrogate Act
- Patient, health care proxy or power of attorney agrees to storage of specimens for future testing.
- eIND application for each recipient subject will need to be approved before administration of convalescent plasma

Plasma Recipient Subject Exclusion Criteria

- Female subjects with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period
- Receipt of pooled immunoglobulin in past 30 days
- Contraindication to transfusion or history of prior reactions to transfusion blood products
- Patients currently enrolled in other drug trials that preclude treatment with anti-SARS-CoV-2 convalescent plasma.

Recruitment (Plasma Donors)

Plasma donor subjects in the groups listed below will be contacted to obtain electronic consent to donate blood.
Patients who are on the list of COVID-19 positive patients maintained by the infectious disease team at the University of Chicago Medical Center (UCMC) The primary care physician or attending of patients who are on the list of COVID-19 positive patients maintained by the infectious disease team at the University of Chicago Medical Center.

1. People who are undergoing COVID-19 testing at UCMC will be asked about donating blood. .
2. Advertisement of this study will take place in community bulletins, throughout the university with posters/fliers, on the internet, UCMC press release and in the local news.

We have a dedicated call center number and email address to field questions from people who are interested in the study or who may be potential plasma donors to reach us.

A secure email address at the University of Chicago has been made. . Emails to this address will generate an automatic reply (detailed in the attached recruitment materials). Emails will be viewed by the study staff who will be able to respond if potential participants want to learn more about this research study.

Schedule of Events

Schedule of Events for Plasma Donor Subjects

Table 1. Schedule of events for plasma donor subjects:

Study period	Screen	Enroll		Donation
Day	-90 to -28 days	-1 days or more		0
Test positive for COVID-19 Patients outside of the UCMC medical system will be asked to provide documentation of COVID-19 positive test	x			
Subject recruitment and screening		x		
Consent for participation in donor portion of study		X		
Donor intake questionnaire via redcap.		X		
Consent for blood donation using standard UCM Blood Donation processes and procedure				x
Donation at UCMC Blood Bank				x

Table 2: Schedule of Events for Plasma Recipient Subject

Study period	Screen	Baseline	Transfusion	Follow-up				
Day	-7 to 0	0	0	1	3	7	14	28[1]
Eligibility								
Informed consent	x							
Demographic and Medical history	x							
COVID-19 symptom screen	x							
Pregnancy test	x							
ABO	x							
Application for single patient eIND FDA compassionate use for convalescent plasma	x							
eIND is approved	x							
Study Plasma Administration								
Plasma infusion			X					
Study Procedures								
Vital signs	x	x	xxxx[2]	x	x	x	x	
Physical examination	x		x	x		x		
Symptom screen	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x					
Assessment with 7-point ordinal scale		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	
Chest x-ray or CT chest if available	x			x	x	x	x	
SARS-CoV-2 RT-PCR		x			x	x	x	
Blood samples for biomarker tests performed in the research lab		x		x	x	x	x	

Biomarker tests performed in the research lab include antibody titer, neutralizing antibody, cytokine levels, viremia

[1] The assessments performed on day 28 will be repeated on days 60 and 90.
[2] Vital sign testing: 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

Subject Withdrawal

- Subjects can terminate study participation and/or withdraw consent at any time without prejudice.
- Subjects who withdraw from the study will not be replaced.
- 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.
- Discontinuation of the study: The IRB has the right to terminate this study at any time

Investigational plasmaTreatment

- Recipient subjects will receive anti-SARS-CoV-2 convalescent plasma as a pilot study after approval of single patient eIND application.
- Recipient subjects will receive anti-SARS-CoV-2 convalescent plasma under IRB20-0825
- Investigational Product: The investigational product is anti-SARS-CoV-2 convalescent plasma obtained from donors identified as having recovered from COVID-19.
- Donors samples will have been screened for transfusion-transmitted infections (e.g. HIV, HBV, HCV, WNV, HTLV-I/II, *T.cruzi*, syphilis, ZIKV) both through the use of the UCM Blood Donation Center Blood Donation Record and FDA-mandated blood donor screening tests. Plasma will have been collected as whole blood derived units donations and in accordance with standard FDA and blood bank protocols. Plasma will be ABO-compatible and HLA-screened per standard FDA and blood bank protocols.
- Recipient subjects will receive 1 unit of convalescent plasma after eIND approval. When CLIA clinical testing for antibody is available, plasma will be transfused with an anti-SARS-CoV-2 titer of >1:320, though this titer may be adjusted as *in vitro* titer assays of virus neutralization are correlated with *in vivo* assessments of virus neutralization.
- Plasma will be labeled according to FDA and blood bank guidelines.

Research biomarkers and other studies

During standard whole blood donation, peripheral blood mononuclear cells (PBMCs) are collected by the leukoreduction filter. This filter is normally discarded. Instead of discarding this filter as per usual practice, the filter will be labeled with the donor identification number and will be given to Patrick Wilson's laboratory for the isolation of B cells reactive to recombinant proteins from SARS-CoV-2 for the synthesis of monoclonal antibodies. These antibody proteins will be characterized for binding to COVID-19 proteins and other protective activities against the virus. These antibodies will be valuable as possible therapeutic agents or for the production of high-sensitivity

and high-specificity diagnostic reagents. These antibodies will also guide and template the generation of vaccines to protect against COVID-19. A small aliquot of serum from the patient blood samples will also be analyzed for binding to the various COVID-19 proteins we have access to by ELISA to learn which COVID-19 proteins are the most immunogenic, further guiding vaccine design efforts.

Per FDA guidelines, convalescent serum containing neutralizing antibody with a titer optimally greater than 1:320 should be used when antibody titer tests are available. Antibody testing is currently only available in research labs (Patrick Wilson at the University of Chicago). When antibody testing is available in clinical labs, we will be able to use titer information to guide plasma transfusion, e.g. titer can be adjusted as *in vitro* titer assays of virus neutralization are correlated with *in vivo* assessments of virus neutralization. This will identify individuals who have anti-SARS-CoV-2 neutralizing antibody and identify the strength of the virus-neutralizing antibody in each titer concentration.

Rationale for doses

The dose of 1 unit; ~300 mL was chosen to minimize volume given to a patient with compromised pulmonary function/acute respiratory distress syndrome, which fits the profile of COVID-19 patients with severe disease.

Investigational treatment-plasma administration

- Plasma will be administered after enrollment and approval of single patient eIND by the FDA or under the expanded access protocol IRB20-0825
- Infusion rate will be ~300 mL over 4 hours (~50 mL per hour)
- Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given per investigator and clinical care team discretion.
- If an AE develops during infusion, the infusion may be slowed or stopped as per investigator's decision.
    - Most reactions to plasma are relatively minor and the infusion can generally be continued. Infusion site burning and non-allergic systemic effects can generally be managed with slowing of the infusion. Infusion can generally be continued in cases of itching or hives after pausing the transfusion, administering antihistamines, and observing the patient for worsening.
    - Severe allergic reactions such as, bronchospasm and hypotension, and may require discontinuation of the infusion.

Concomitant medications will be documented on the CRF

- Prescription medications
- Over the counter medications

- Herbal treatments/nutritional supplements
- Blood products

Statistical considerations

Statistical Analysis

This is a pilot study focused on determining the protocol feasibility with limited subject enrollment. Therefore, statistical analysis will include descriptive summaries of both the primary and secondary outcomes of interest. For continuous variables we will determine: median, minimum and maximum values. Categorical variables will be summarized by the frequency. Unless otherwise indicated, percentages in tables will be column percentages, using the total number of observations in the population (*n*=10), as the denominator. 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).

Analysis of AE data

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

Analysis of SARS-CoV-2 viremia

Analysis of SARS-CoV-2 viremia will primarily be descriptive, comparing the viremia levels at days 0,1,3,7 and 14 between the subject recipients.

Analysis of research biomarkers

Analysis of biomarker tests performed in the research lab such as antibody titers, cytokine levels will primarily be descriptive, comparing the titers at days 0,1,3,7 and 14 between subject recipients.

Endpoints

Primary Endpoint:

1. Feasibility of performing study pathway consisting of consenting convalescent donors, harvesting convalescent plasma, application for FDA eIND and administering convalescent plasma to the patients
2. Type and duration of respiratory support (e.g. CPAP, BiPAP, high-flow nasal cannula, mechanical ventilation)

Secondary endpoints:

1. Cardio-circulatory arrest (at any time)
2. Transfer to ICU
3. ICU mortality and LOS
4. Hospital mortality and LOS
5. Ventilator-free days
6. 60 day mortality

Primary Safety Endpoints:

1. Rapid deterioration of respiratory or clinical status on transfusion of anti-SARS-CoV-2 convalescent plasma
2. 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

Secondary Endpoints

1. Rates and duration of SARS-CoV-2 PCR positivity (RT-PCR) at days 0, 3, 7, and 14.

Study procedures for plasma donors

Study procedures for plasma donors who enter the study through the following mechanisms:

- Patients who are on the list of COVID-19 positive patients maintained by the infectious disease team at the University of Chicago Medical Center (UCMC)
- The primary care physician or a treatment team attending of patients who are on the list of COVID-19 positive patients maintained by the infectious disease team at the University of Chicago Medical Center.
- People who are undergoing COVID-19 testing at UCMC.
- Advertisement of this study will take place in community bulletins, throughout the university with posters/fliers, on the internet, UCMC press release and in the local news to ask whether anyone would like to donate blood and participate in this research study.

Day -28 to -90:

- Tested positive for COVID-19. People outside of the UCMC medical system will be asked to provide documentation of COVID-19 positive test.

Day -28 to -90:

- Complete resolution of all COVID-19 symptoms

Day -1 or more:

- Screening for plasma donor inclusion criteria
- Consent for participation in donor portion of study
- Donor questionnaire

Day 0:

- Consent for blood donation using standard UCM Blood Donation processes and procedure
- Blood donation at the UCM Blood Donation Center

Study procedures for investigational plasma recipient

Day -7 to 0:

1. Screening for patient inclusion criteria
2. Subject informed consent (obtained before performing study related activities).

3. Baseline Evaluation (at screening) (much of the information will be obtained from the medical record)
   - Demographics (Age, sex ethnicity, race)
   - Medical history (timing of exposure to COVID-19 source patient, acute and chronic medical condition, medications, allergies, any drug trial therapy. Any medical condition arising after consent should be recorded as AE
   - COVID-19 symptom screen (fevers, cough, shortness of breath), day of onset of symptoms
   - Vital signs
   - COVID-19 testing (RT-PCR) from nasopharyngeal, throat, blood or stool (optional) samples. Other clinically-approved SARS-CoV-2 testing may be used if available (e.g. saliva, nares, blood).
   - Blood typing, CBC, comprehensive metabolic panel
   - Urine or serum pregnancy test for females of childbearing potential. Results from laboratory tests obtained up to 7 days before enrollment may be used for the pregnancy test.
   - Stored samples for biomarker tests performed in the research lab (e.g. antibody titer, cytokines)
   - Determination of eligibility as per inclusion/exclusion criteria
4. Application and approval of eIND per FDA guidelines for single patient compassionate use of convalescent plasma

<u>DAY 0:</u>

1. Study Plasma Administration: 1 unit of plasma 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
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (7-point ordinal scale)
4. New medical conditions, concomitant medication, AE evaluation
5. physical examination
6. Blood typing, CBC, comprehensive metabolic panel, C-reactive protein
7. Stored samples for biomarker tests performed in the research lab (e.g. antibody titer, cytokines)

<u>Day 1-7 (or for duration of hospitalization)</u>

1. Vital signs daily
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (7-point ordinal scale)
4. New medical conditions, AE evaluation
5. physical examination
6. CBC, comprehensive metabolic panel, CRP daily
7. COVID-19 testing (RT-PCR) from nasopharyngeal, throat, blood or stool (optional) samples. Other clinically-approved SARS-CoV-2 testing may be used if available (e.g. saliva, nares, blood)

8. Stored samples for biomarker tests performed in the research lab (e.g. antibody titer, cytokines)

Day 28:

Key issues to consider follow up by phone, alive, at home, in hospital (ICU or not), on supplemental O2 or not, back to work, fully, partially, SNF, nursing home, LTAC

a. COVID-19 symptom screen (fevers, cough, shortness of breath)
b. Assessment of clinical status (7-point ordinal scale)
c. New medical conditions, AE evaluation

Day 60 and 90:

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (7-point ordinal scale)
3. New medical conditions, AE evaluation

Efficacy and virology measures

Clinical Efficacy (ordinal scale)

1. Death/Cardio-circulatory arrest at anytime
2. Transfer to ICU
3. Type and duration of respiratory support (and other ICU support)
4. ICU mortality and LOS
5. Hospital mortality and LOS
6. Ventilator-free days
7. 28 day mortality

Virologic measures

1. Rates, levels and duration of SARS-CoV-2 RNA in NP swabs by RT-PCR at days 0, 3, 7 and 14. Other specimen types may be tested as available (*eg.,* BAL fluid, tracheal secretions, sputum, etc.) or when RT-PCR assays are validated for additional sources (*i.e.,* stool, blood).

Risks and benefits

Potential Benefits of treatment:

The potential benefits of antiviral treatment with anti-SARS CoV-2 plasma in patients with severe or life-threatening COVID-19 disease are not known. However, it is anticipated that treatment will decrease disease progression,

decrease ICU or higher-level medical support and possibly reverse disease course.

Potential benefits of clinical monitoring and virologic testing:
Subjects enrolled in the study may reduce their chances of disease progression.

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

Alternatives:
The alternative to participation in this study is supportive care. There are several ongoing clinical trials at UCM for COVID-19 patients, such as anti-IL6 therapy, anti-viral therapy and hydrochloroquine therapy.

Safety measures

Monitoring procedures
The PI and co-investigators ensure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.

Study data are accessible at all times for the team to review, and to the Independent Safety Monitor upon request. The PIs and co-investigators review study conduct, particularly accrual, drop-outs, and protocol deviations on a quarterly basis. The team reviews adverse events (AEs) individually in real-time and in aggregate on a quarterly basis. The PIs review serious adverse events (SAEs) in real-time. The PIs ensure that all protocol deviations, AEs and SAEs are reported to the IRB according to the applicable regulatory requirements.

1. Safety Evaluations will assess for the safety of anti-SARS-CoV-2 plasma
2. Clinical evaluations: Vital signs and symptom screen on days 0-7, 14 and symptom screens on days 28, 60, and 90.
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, CRP, and comprehensive metabolic panel) will be performed at the local CLIA-certified clinical laboratory on days 0-7 and 14.

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

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

Unanticipated Problem (UP)

Unanticipated problems involving risks to subjects or others refer to a problem, event or information item that is not expected, given the nature of the research procedures and the subject population being studied; and which suggests that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known. The IRB considers unanticipated problems, in general, to include any incident, experience, or outcome that meets ALL of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol, investigator's brochure, drug or device product information, informed consent document, or other research materials; and (b) the characteristics of the subject population being studied, including underlying diseases, behaviors, or traits;

2. related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);and

3. suggests that the research places subjects or others at a risk of unknown harm or addition/increased frequency of harms (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated problems may be adverse events, protocol deviations, noncompliance or other types of problems, but MUST meet all of the criteria listed above. It is the expectation of the IRB that all approved protocol procedures are being followed without alteration unless the IRB has been informed of a protocol change or deviation.

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, this will be reported.

Collection and reporting of SAEs and AEs. Documentation of adverse events will be determined by the clinician and recorded on the Clinical Adverse Event Report form and will include the following infor-mation: Description of the condition, dates of condition, treatment of condition (medications, doses, dates), whether emergency treatment was required, treatment outcome, relationship of the adverse event to the study medication(s) and severity of the event. Additional information about the AE will be provided as needed so as to understand the scope of the event.

Management of SAEs. Serious adverse events are always managed, first and foremost, based on medical appropriateness so as to ensure subject safety. The PIs are notified as soon as pos-sible about an SAE and will work with the medical team to ensure the best resolution possible of the problem. In medical emergencies the PIs are permitted to provide all health-care providers with appropriate medical information at hand about the subject consistent with HIPAA regulations.

Serious adverse events will be forwarded by the PI to the Independent Safety Monitor and IRB immediately. Fatal or life-threatening unexpected SAEs will be reported to the

IRB immediately. Non-fatal, non-life-threatening unexpected SAEs will be reported to the Independent Safety Monitor within 72 hours.

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.

Safety Oversight

Monitoring Plan

1. All AE and SAW will be reviewed by protocol team in real time.
2. An Independent Safety Monitor (ISM) has be appointed. The ISM is Dr. O'Connor has in infectious diseases 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 Dr. Madariaga, the research team and the Office of Clinical research (OCR). Monitors will verify that
    a. There is documentation of the informed consent process and signed informed consent documents 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

In the event that any of the 6 events listed under “Halting Criteria for the Study” occur, the IRB will be immediately notified and the study placed on hold until such time as the IRB agreed that study activities could resume.

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. , TRALI, TACO

3. One subject with an SAE associated with study product.

4. Two subjects with a Grade 3 or higher lab toxicity for the same parameter associated with study product.

5. An overall pattern of symptomatic, clinical, or laboratory events that the medical monitor, ISM, or 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.

6. 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, the IRB 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 study drug 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

Ethics/Protection of human subjects

Ethical Standard

The University of Chicago is committed to the integrity and quality of the clinical studies it coordinates and implements. The University of Chicago will ensure that the legal and ethical obligations associated with the conduct of clinical research involving human subjects are met.

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

In addition, The University of Chicago has a Federal wide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP).

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

Institutional Review Board

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

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.

Informed Consent Process for Legally authorized representative (LAR) or appropriately identified surrogate

Informed consent will be discussed and obtained in the subject's private hospital room before any screening procedures take place.

For decisionally impaired individuals, the study staff will carry out the consent discussion by phone or over video chat with the LAR or appropriately identified surrogate.

Consent documents will be mailed/faxed or emailed to the (LAR) or appropriately identified surrogate initially. After the discussion and consent process take place, the consent documents which are signed and dated by the LAR or appropriately identified surrogate will be sent back to the study team. The consent document that is signed by the LAR or appropriately identified surrogate may be received in the following manners: faxed copy, scanned copy or email. The study team will then send the LAR or appropriately identified surrogate a fully executed copy of the consent to the LAR or appropriately identified surrogate for their records.

If needed, a walk-out and meet approach could be used for those LAR or appropriately identified surrogate s who do not have the capabilities to receive/send documentation electronically.

Consent discussion and execution will be done by Dr. Madariaga or a member of the research team.

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, investigators at the site involved with the study, and the IRB.

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.

No human genetic testing will be performed on the samples.

Five ml of blood samples will be collected at 5 time points (See Schedule of Events). Serum 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. 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.

Samples would not be shared with investigators other than investigators at the University of Chicago unless outside investigators had relevant assays or expertise not available to the study investigators. The specimens would remain linked and at University of Chicago for 5 years. Any use of these specimens not specified in the current protocol will be reviewed by the University of Chicago IRB.

Data management and monitoring

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.

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.

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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