**PROTOCOL SUMMARY:**

**Long title:** Convalescent Plasma to Limit Coronavirus Associated Complications: A Randomized Double-Blind, Phase 2 Study Comparing the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 Plasma vs. Placebo in Emergency Room Patients

**Investigators: Siddhartha Jaiswal, Kevin Schulman, Hua Shan, Manisha Desai, James Quinn, Suchitra Pandey, Saurabh Gombar, Aruna Subramanian, Tho Pham**

**Protocol Number:** COVID-19-CP01

**Clinical Phase**: 2

**IND Sponsor**: Kevin Schulman, MD

**Conducted by:** Stanford Hospital

**Sample Size:** 206

**Study Population:** COVID-19+patients in the emergency room who need clinical evaluation but who do not require hospitalization

**Study Duration:** May 1, 2020 to December 31, 2022

**Study Design:** This randomized, placebo-controlled double-blind phase 2 trial will assess the efficacy and safety of anti-SARS-CoV-2 convalescent plasma

A total of 206 eligible subjects will be randomized in a 1:1 ratio to receive either high titer anti-SARS-CoV-2 plasma or control (standard thawed plasma)

The following will be assessed in all subjects:

1. Age, sex, comorbidities, date of symptoms, date of COVID test
2. Safety: Adverse reactions to transfused plasma (TACO, TRALI, transfusion-related infection, severe allergic response).
3. Efficacy- Clinical status using a 5 point COVID Outpatient Ordinal Outcomes Scale assessed daily to day 15.

**Study Agent:**

1. SARS-CoV-2 convalescent plasma (1-2 units; ~200-600 mL at antibody titer >1:80 if assays are available and validated)
2. Standard plasma collected prior to 31 December 2019 or that is negative for anti- SARS-CoV-2 antibodies

**Primary Efficacy Objective:** Evaluation of the efficacy of treatment with high-titer Anti- SARS-CoV-2 plasma versus control (standard plasma) in patients with COVID-19 respiratory symptoms.

**Primary Safety Endpoint:** Cumulative incidence of serious adverse events during the study period.

**Study population:**

**Inclusion Criteria for Enrollment**

1. Patients must be 18 years of age or older
2. Patients requiring clinical evaluation in the ED but who do not require hospital admission
3. Patients must be within 14 days since the onset of COVID-19 symptoms and with a documented positive test for SARS-CoV-2 by nucleic acid testing
4. Patient agrees to storage of specimens for future testing
5. If female must not be pregnant and/or breastfeeding

**Exclusion Criteria**

1. Female subjects with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period
2. Receipt of pooled immunoglobulin in past 30 days
3. Contraindication to transfusion or history of prior reactions to transfusion blood products

# STUDY POPULATION

### Inclusion Criteria for Enrollment

1. Patients must be 18 years of age or older
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# 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

NAT: Nucleic acid test

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

SBC: Stanford Blood Center

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

# BACKGROUND AND SCIENTIFIC RATIONALE

Beyond supportive care, there are currently no proven treatment options for coronavirus disease (COVID-19) and the related pneumonia, 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 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*). 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*). As an example, passive antibody therapy for pneumococcal pneumonia was most effective when administered shortly after the onset of symptoms and there was no benefit if antibody administration was delayed past the third day of disease (*6*).

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.

## Experience with the use of convalescent plasma against coronavirus diseases

***Pre-clinical studies:***

In the 21st century, there were two other epidemics with coronaviruses that were associated with high mortality, SARS in 2003 and MERS in 2012. In a mouse model of SARS infection, animals receiving immune serum from infected mice were protected against lower airway disease after intranasal challenge with virus (*7*). Several groups have also identified monoclonal neutralizing antibodies that have shown efficacy in animal models of SARS (*8*). In a mouse model of MERS infection, transfusion of sera from MERS-infected camels was efficacious for both prophylaxis and treatment (*9*). Similar results for convalescent sera were obtained in a marmoset model of MERS (*10*).

***Clinical studies:***

In both SARS and MERS outbreaks, the high mortality and absence of effective therapies led to the use of convalescent plasma in human studies. The largest study involved the treatment of 80 patients in Hong Kong with SARS (*11*). **Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective.** In addition, those who were RT-PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis. There is also some anecdotal information on the use of convalescent plasma in seriously ill individuals. Three patients with SARS in Taiwan were treated with 500 ml of convalescent plasma, resulting in a reduction in plasma virus titer and each survived (*12*). Three patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients had neutralizing antibody in their plasma (*13*). 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 (*14*). Consistent with this point, an analysis of 99 samples of convalescent sera from patients with MERS showed that 87 had neutralizing antibody with a geometric mean titer of 1:61. This suggests that antibody declines with time and/or that only some patients make high titer responses. It is also possible that other types of non-neutralizing antibodies are made that contribute to protection and recovery as described for other viral diseases (*15*).

There are also recent reports of improvement from SARS-CoV-2 infection in hospitalized patients given convalescent plasma (<http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm>). In another report, 5 critically ill patients with COVID-19 were given high-titer convalescent plasma (*16*). All patients had improved viral loads, 4 had resolution of ARDS, and 3 were weaned from mechanical ventilation within 2 weeks of treatment. There were no reported adverse events in the treated patients. However, this study was uncontrolled and all 5 patients also received other anti-viral treatments and corticosteroids, highlighting the need for a randomized controlled trial. In another case series, 10 patients with severe COVID-19 were administered convalescent plasma, and all improved clinically without any serious adverse events. In a historical control group matched to the 10 treated patients, only 1 out 10 patients showed similar improvements (*17*).

## Overview of 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 (*18*). Since the proposed use of convalescent plasma in the COVID-19 epidemic would rely on preparations with high titers of neutralizing antibody against the same virus, SARS2-CoV-2, ADE may be unlikely. The available evidence from the use of convalescent plasma in patients with SARS1 and MERS (*19*) and anecdotal evidence of its use in patients with COVID-19 (<http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm> and (*16*)), suggest it is safe. Nevertheless, 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 (*20*). 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.*

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), transfusion associated cardiac overload (TACO), and hemolysis should ABO incompatible plasma be administered. In order to minimize the risks of disease transmission, pathogen reduction techniques will be utilized to prepare the plasma. In addition, 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.

##  Known potential benefits

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

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

# INVESTIGATIONAL PLAN

## Study Objectives

**Primary Efficacy Objective:**

Evaluation of the efficacy of treatment with high-titer Anti- SARS-CoV-2 plasma versus control (standard plasma) in patients with COVID-19 respiratory symptoms.

## 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. Randomized: when a randomization number is assigned
3. Screen Failures: signed informed consent, but then determined to be ineligible or withdraws before being randomized
4. Discontinued: randomized, but then withdrawn by investigator or withdraws consent
5. Withdrawn: patient admitted to a hospital within 15 days after randomization will be withdrawn from this IND study.

# **Study Population**

### Inclusion Criteria for Enrollment

1. Patients must be 18 years of age or older
2. Patients requiring clinical evaluation in the ED but who do not require hospital admission.
3. Patients must be within 14 days since the onset of COVID-19 symptoms and also must be confirmed to have the disease via COVID-19 SARS-CoV-2 RT-PCR testing or rapid RNA assay.
4. Patient agrees to storage of specimens for future testing.
5. If female must not be pregnant and/or breastfeeding.

### Exclusion Criteria

1. Female subjects with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period
2. Receipt of pooled immunoglobulin in past 30 days
3. Contraindication to transfusion or history of prior reactions to transfusion blood products

### Subject Withdrawal

1. Subjects can terminate study participation and/or withdraw consent at any time without prejudice.
2. Randomized subjects who withdraw from the study will not be replaced.
3. The investigator will withdraw subjects if they are admitted to the hospital within 15 days after plasma infusion
4. Discontinuation of the study: The study sponsor, FDA and IRB all have the right to terminate this study at any time

### Intervention

1. Subjects will be randomized in a 1:1 ratio to receive study drug vs standard plasma
2. Study drug: The investigational product is anti-SARS-CoV-2 convalescent plasma obtained from patients identified as having recovered from COVID-19 with neutralizing antibody titers >1:160. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available. If antibody titers cannot be obtained in advance, a retention sample will be stored from the convalescent plasma donation for determining antibody titers at a later date.
3. Donors and samples will have been screened for transfusion-transmitted infections (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 have been collected using apheresis technology and in accordance with standard FDA and blood bank protocols.
4. Active arm will receive 1-2 units of plasma from donors that are recovered from COVID-19
5. Control arm will receive 1-2 units of standard plasma.
6. Both active and control drugs will be in standard plasma unit bags, with a study-specific ISBT label.

### Randomization

1. Subjects enrolled in the study will be randomized to receive study drug vs placebo at a 1:1 ratio.

## Study drug administration

* Drug will be administered within 24 hours of randomization
* Infusion rate ≤ 500 mL/hour
* Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given
* 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 is generally stopped in cases of itching or hives, participated treated and then infusion re-started.
* Allergic reactions such as, bronchospasm and hypotension, generally require discontinuation of the infusion.

### Study agent plasma

1. Testing from donor will demonstrate SARS-CoV-2 antibody titers of at least 1:160. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available. If antibody titers cannot be obtained in advance, a retention sample will be stored from the convalescent plasma donation for determining antibody titers at a later date.

### Control arm plasma

1. The control arm plasma follows identical collection and processing procedures, but will have been collected from community blood donors prior to documented SARS-CoV-2 in the United States (i.e., to be conservative all control arm plasma will be from collections prior to 31 December 2019). If plasma was collected after 31 December 2019 must be used for the control arm plasma, the plasma unit will not have demonstrable antibodies to SARS-CoV-2.

### Rationale for dosing

1. Convalescent or normal donor plasma will be given at a dose of 4-6 mL/kg of ideal body weight.
2. Dosing is based on experience with previous use of convalescent plasma therapy in SARS where 5 mL/kg of plasma at titer ≥ 1:160 was utilized (*11*). For someone with an ideal body weight of 50 kg, a dose of 200-300 mL may be given (approximately 1 unit). For someone with an ideal body weight of 80 kg, 320-480 mL may be given (approximately 2 units). Exact dosing will be determined by the ordering clinician (evaluation based on patient’s volume status), and availability of units (preference given to using whole units, so rounding to 1 or 2 units of product as needed).

### Concomitant medications will be documented on the CRF

1. Prescription medications
2. Over the counter medications
3. Herbal treatments/nutritional supplements
4. Blood products
5. Any approved or investigational drug with established activity against SARS-CoV-2

# STATISTICAL CONSIDERATIONS

## Endpoints

The primary endpoint is time to disease progression from COVID + illness for patients with acute COVID presentation. Patients are censored at day 15 after randomization. Daily clinical outcomes are described in a 5-point COVID Outpatient Ordinal Outcomes scale (adapted for outpatient use from Harrell 2020; http://hbiostat.org/proj/covid19/bayesplan.html). This scale is hierarchical where 1 is the highest severity (hospitalization) and 5 is the lowest severity.

COVID Outpatient Ordinal Outcomes Scale

1-patient requires care in the hospital

2-patient requires care in the ED or urgent care

3-patient at home with symptoms rates as moderate (defined as fever, shortness of breath, abdominal pain)

4-patient at home with symptoms rated as mild (defined as afebrile, constitutional symptoms (flu-like illness) without shortness of breath)

5-patient in their usual state of health

Progression of disease is defined as any patient admitted to the hospital (level 1), seen in the emergency room (level 2), a patient who reports increased symptoms of 2 levels on the scale over a 24 hour period, or a patient who reports increased symptoms of 1 level observed for a 48 hour period.

## Sample Size and Power Considerations

We need a total sample size of 206 patients to achieve our goals (103 per arm). Given this, we will have 80% power to detect a reasonable effect size - a hazard ratio of 0.52 (this corresponds to event rates of clinical worsening at Day 7 of 30% in the control vs 17% in the treatment arm). These calculations assume a one-month accrual period, 15 days follow-up period for each patient, and a drop out of 5% in the control arm under a two-sided log-rank test.

## Statistical Analysis

**5.3.1 Primary Efficacy Analysis**

For each patient, we will have their daily data on the COVID Outpatient Ordinal Outcomes Scale up to 15 days from randomization. We will define the date of clinical worsening as the study day on which any of the following is observed:

a) a patient who is admitted to the hospital (level 1) or seen in the emergency room (level 2), or

b) a patient who reports increased symptoms of 2 levels on the scale over a 24-hour period (in other words, clinical worsening is recorded as the study day when 24 hours of symptom worsening has been observed), or

c) a patient who reports increased symptoms of 1 level observed for a 48-hour period (in other words, progression is recorded as the study day when 48 hours of symptom worsening has been observed).

For our primary efficacy analysis, we will compare time until clinical worsening between the two treatment arms using a two-sided log-rank test. The test will be performed at the alpha = 0.05 level of significance. The distribution of clinical worsening will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment arm. Time to clinical worsening at the end of the study period along with 95% confidence intervals will be presented for each treatment arm. The hazard ratio for clinical worsening will be estimated, along with its 95% confidence interval, from a Cox proportional hazards model. If the proportional hazards assumption is not met, we will consider an extended Cox model that relaxes the proportional hazards assumption.

**5.3.2 Secondary efficacy analyses**

For our secondary efficacy analysis, we will use mixed-effect proportional ordinal logistic models to obtain the trajectory estimates of the overall treatment effect on our primary outcome (COVID Outpatient Ordinal Outcomes Scale) over time. Such models are typically utilized in the clinical studies and repeated measurements within patients when we expect to observe correlated observations. In this study, we expect patients with repeated measures over time to have similar or correlated outcomes. Our modelling will account for correlation of observations over time within a patient. In addition, the generalized linear mixed effects regression accounts for potential incomplete outcome data through modeling techniques that are robust to reasonable assumptions of missingness in the data. For the purpose of our analysis, we will construct a longitudinal dataset where the observation unit will be each follow-up visit via telephone or video call that will be implemented after randomization up to Day 15. To elaborate further, we will apply proportional odds logistic mixed-effect techniques by regressing our primary outcome on an indicator for treatment group (trt), days from randomization as a categorical variable (day) and interaction terms between treatment group and days from randomization (trt\*day). Also included in the model are a subject-specific random effect with normal distribution to account for the correlation of measurements over time within a subject/patient. We are interested in drawing inference around a set of exponentiated-transformed coefficients for the trt\*day term that represents the odds ratios(OR) for moving into the next ordinal group with higher rank (become less severe in symptoms) between the treatment and control at a given follow-up day, whereas OR>1 means positive impact of the treatment.

**5.3.3 Safety analyses**

The frequency of adverse events and serious adverse events will be tabulated by type and by treatment arm. AEs will be compared by arm using the Chi-squared test or Fisher’s exact test, as appropriate, in the safety analysis set.

**5.3.4 Interim Analyses**

An interim analysis for safety and futility will be performed once 50% of patients have 15 days of follow-up complete. Enrollment will pause once 50% of patients have received treatment and will remain paused until the DSMB makes their recommendation after their safety review. The DSMB will meet one or two days after enrollment is paused to review the safety data collected within the first 24 hours of follow-up on all enrolled patients. The DSMB will also review the efficacy data on all randomized participants at this meeting. The interim futility analysis will use the same methods as are planned for the final analysis using the ITT analysis. Based on the results of the interim analysis, the DSMB will either recommend to the sponsor to terminate the study for futility, terminate the study for safety concerns, modify the study, or continue the study as planned.

# STUDY PROCEDURES

Day 0:

1. Screening (must be completed before randomization)
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)
4. Demographics (Age, sex ethnicity, race)
5. Medical history (timing of exposure to COVID-19 source patient, acute and chronic medical condition, medications, allergies. Any medical condition arising after consent should be recorded as AE
6. Vital signs
7. COVID-19 testing from nasopharyngeal, throat, tracheal aspirate or broncho alveolar lavage
8. Blood typing, CBC, comprehensive metabolic panel
9. Serological testing: anti-SARS CoV-2 titers (or plasma saved for future testing)
10. 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
11. Determination of eligibility as per inclusion/exclusion criteria age, consent, positive for COVID-19
12. Randomization and study plasma administration: 1-2 units of convalescent or normal donor plasma will be transfused. Time at start and end of transfusion will be recorded and Vital signs will be measured immediately prior to transfusion, 10-20 minutes after start of infusion, at completion of transfusion and 30-60 minutes after the end of the transfusion
13. Stored samples for future studies

Daily to Day 15

1. COVID Outpatient Ordinal Assessment Scale (completed by phone)

**Table: Study Timeline**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study period | Screen | Baseline | Transfusion | Follow-up |
| Day | -1 to 0 | 0 | 0 | 1 to 15 |
| Eligibility |
| Informed consent | x |  |  |  |
| Demographic and Medical history | x |  |  |  |
| COVID-19 symptom screen | x |  |  |  |
| SARS-CoV-2 RT-PCR for eligibility | x |  |  |  |
| Pregnancy test | x |  |  |  |
| ABO type | x |  |  |  |
| Study Drug Administration |
| Randomization |  | x |  |  |
| Plasma infusion |  |  | X |  |
| Study Procedures |
| Vital signs | x | x | X |  |
| Baseline questionnaire | x |  |  |  |
| Daily Symptom/Location Assessment | x | x | X | x |
| Concomitant medications | x | x | x |  |
|  |  |  |  |  |
| Adverse event monitoring |  | x | x | x |
| Laboratory testing  |
| CBC and CMP |  | x |  |  |
| SARS-CoV-2 NAT1 |  | x |  |  |
| SARS-CoV-2 antibody |  | x |  |  |
| Blood for future testing  |  | x |  |  |

 RT-PCR assay or rapid RNA assay (Cepheid Xpert Xpress)

1. RISKS AND BENEFITS

**Potential Benefits of treatment:**

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

**Potential benefits of clinical monitoring and virologic testing:**

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

**Potential risks:**

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

**Alternatives:**

The alternative to participation in this study is routine care.

# SAFETY OVERSIGHT

## Monitoring Plan

A data safety monitoring board (DSMB), composed of independent experts without conflict of interests will be established. The Board will review the study before initiation and at least yearly thereafter. The Board will review study data to evaluate the safety, efficacy, study progress, and conduct of the study

## Serious Adverse Events (SAEs)

Data will be collected on the following SAEs which are associated with plasma transfusions:

1. Serious allergic reactions (anaphylaxis or bronchospasm requiring treatment)
2. Transfusion Associated Acute Lung Injury (TRALI), as defined by https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6850655/ (*21*). Given that these are patients with other risk factors for ARDS, a diagnosis of “possible TRALI” will require stable respiratory status in the 12 hours before transfusion. Because TRALI may mimic the natural progression of COVID-19, the demonstration of HLA antibodies in the donor product that matches the recipient’s HLA type will also be necessary to make the diagnosis of “possible TRALI”.
3. Transfusion Associated Circulatory Overload (TACO)
4. transmission of infectious agents

# ETHICS/PROTECTIONS FOR HUMAN SUBJECTS

## Ethical Standard

Stanford University is committed to the integrity and quality of the clinical studies it coordinates and implements. Stanford University 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, Stanford University will review these evolving standards in relation to the proposed activities and will advise the investigators on those that may apply.

In addition, Stanford University 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 Stanford University IRB will review this protocol and all protocol-related documents and procedures as required by OHRP and local requirements before subject enrollment. The Stanford University 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.

## Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor-investigator. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor-investigator. 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.

## 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. There 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.

Further testing, including genetic, and linkage to the medical record, may occur if patients are also consented for a separate biobanking protocol (PI: Angela Rogers).

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

## Data management and monitoring

### Source Documents

The primary source documents for this study will be the subjects’ medical records and the study research records. Both the medical record and the research records will be considered the source documents for the purposes of auditing the study. The sponsor-investigator will retain a copy of source documents. The sponsor-investigator will monitor and audit these data and will allow the IRB and regulatory authorities access to the original source documents.

The Sponsor-investigator is responsible for ensuring that the data collected are complete, accurate, and recorded in a timely manner. Data entered into the study database will be collected directly from subjects during study visits or will be abstracted from subjects’ medical records.

### Data Management Plan

Study data will be collected and entered into the study database. Patient follow-up and the administration of the COVID Outpatient Ordinal Outcomes Scale will be performed by Stanford. 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 sponsor-investigator 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.

**References**

1. A. Casadevall, M. D. Scharff, Return to the past: the case for antibody-based therapies in infectious diseases. *Clin Infect Dis* **21**, 150-161 (1995).

2. A. Casadevall, E. Dadachova, L. A. Pirofski, Passive antibody therapy for infectious diseases. *Nat Rev Microbiol* **2**, 695-703 (2004).

3. J. S. Zhang *et al.*, A serological survey on neutralizing antibody titer of SARS convalescent sera. *J Med Virol* **77**, 147-150 (2005).

4. F. Sahr *et al.*, Evaluation of convalescent whole blood for treating Ebola Virus Disease in Freetown, Sierra Leone. *J Infect* **74**, 302-309 (2017).

5. A. Casadevall, L. A. Pirofski, Antibody-mediated regulation of cellular immunity and the inflammatory response. *Trends Immunol* **24**, 474-478 (2003).

6. A. Casadevall, M. D. Scharff, Serum therapy revisited: animal models of infection and development of passive antibody therapy. *Antimicrob Agents Chemother* **38**, 1695-1702 (1994).

7. K. Subbarao *et al.*, Prior infection and passive transfer of neutralizing antibody prevent replication of severe acute respiratory syndrome coronavirus in the respiratory tract of mice. *J Virol* **78**, 3572-3577 (2004).

8. J. ter Meulen *et al.*, Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets. *Lancet* **363**, 2139-2141 (2004).

9. J. Zhao *et al.*, Passive immunotherapy with dromedary immune serum in an experimental animal model for Middle East respiratory syndrome coronavirus infection. *J Virol* **89**, 6117-6120 (2015).

10. N. van Doremalen *et al.*, Efficacy of antibody-based therapies against Middle East respiratory syndrome coronavirus (MERS-CoV) in common marmosets. *Antiviral Res* **143**, 30-37 (2017).

11. Y. Cheng *et al.*, Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* **24**, 44-46 (2005).

12. K. M. Yeh *et al.*, Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. *J Antimicrob Chemother* **56**, 919-922 (2005).

13. J. H. Ko *et al.*, Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. *Antivir Ther* **23**, 617-622 (2018).

14. Y. M. Arabi *et al.*, Feasibility of Using Convalescent Plasma Immunotherapy for MERS-CoV Infection, Saudi Arabia. *Emerg Infect Dis* **22**, 1554-1561 (2016).

15. E. A. van Erp, W. Luytjes, G. Ferwerda, P. B. van Kasteren, Fc-Mediated Antibody Effector Functions During Respiratory Syncytial Virus Infection and Disease. *Front Immunol* **10**, 548 (2019).

16. C. Shen *et al.*, Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA*, (2020).

17. K. Duan *et al.*, Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A*, (2020).

18. Y. Wan *et al.*, Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry. *J Virol* **94**, (2020).

19. J. Mair-Jenkins *et al.*, The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* **211**, 80-90 (2015).

20. J. E. Crowe, Jr., C. Y. Firestone, B. R. Murphy, Passively acquired antibodies suppress humoral but not cell-mediated immunity in mice immunized with live attenuated respiratory syncytial virus vaccines. *J Immunol* **167**, 3910-3918 (2001).

21. A. P. J. Vlaar *et al.*, A consensus redefinition of transfusion-related acute lung injury. *Transfusion* **59**, 2465-2476 (2019).