A randomized controlled adaptive study comparing COVID-19 convalescent plasma to non-immune plasma to limit coronavirus-associated complications in hospitalized patients.

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Protocol Chairs: **Annie Luetkemeyer & Priscilla Hsue**

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A randomized, controlled, adaptive study comparing COVID-19 convalescent plasma to non-immune plasma to limit coronavirus-associated complications in hospitalized patients.

SIGNATURE PAGE

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

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Signed: _____ Date: _____
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2 LIST OF ABBREVIATIONS

ADR: Adverse Drug Reaction
ADE: Antibody-mediated enhancement of infection
AE: Adverse Event/Adverse Experience
APACHE: Acute Physiological Measurement and Chronic Health Evaluation
CBC: Complete Blood Count
CCP: COVID-19 Convalescent Plasm
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
CRP: C-Reactive Protein
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
HFNC: High flow nasal cannula
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
LOS: Length of Stay
MERS: Middle East Respiratory Syndrome
mNGS: Metagenomic Next generation sequencing
MTN: Mid-turbinate nalal
NP: Nasopharyngeal
OHRP: Office of Human Research Protections
OP: Oropharyngeal
RT-PCR: Reverse Transcriptase Real-Time Polymerase Chain Reaction
PK: Pharmacokinetic
RDV: Remdesivir
SAE: Serious Adverse Event
SARS: Severe Acute Respiratory Syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
SOFA: Sequential Organ Failure Assessment
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

3 PROTOCOL SUMMARY

Long title: A randomized controlled adaptive study comparing COVID-19 convalescent plasma (CCP) to non-immune plasma to limit coronavirus-associated complications in hospitalized patients.

Sample Size: n=50

Study Population: Hospitalized COVID-19 patients aged ≥18 years with respiratory symptoms and hypoxia, who do not currently require mechanical ventilation, enrolled within 3 days of admission to the hospital OR within 14 days of initial onset of symptoms.

Study Duration: May 25, 2020 to April 30, 2021

Study Design: This randomized, pragmatically blinded, placebo-controlled, adaptive trial will assess the efficacy and safety of anti-SARS-CoV-2 convalescent plasma in hospitalized patients with acute respiratory symptoms up to 14 days after the onset of initial symptoms.

A total of 50 eligible subjects will be randomized in a 1:1 ratio to receive either convalescent fresh frozen plasma from blood donors who have recovered from COVID-19 containing antibodies to SARS-CoV-2 or control (standard fresh frozen plasma collected prior to 12/1/2019 or with documented negative SARS-CoV-2 antibody). Should additional anti-COVID agents (anti-viral and/or anti-inflammatory) become available for use as standard of care during implementation, the sample size will be recalculated and increased to account for the estimated impact that these agents may have on the reducing the progression to the primary endpoint of severe hypoxemia.

Clinical, Laboratory and Imaging Data

1. Date of symptom onset and history of presenting illness
2. Demographics: Age, sex, comorbidities, zip code + 4
3. Vital Signs: Temperature, respiratory rate, blood pressure, oxygen saturation, oxygen requirements, APACHE score, SOFA score.
4. Laboratory Data:

    - Hematologic Markers: CBC with differential (neutrophil, lymphocyte counts explicitly recorded), PT/PTT, D-dimer
    - Metabolic Markers: Creatinine, liver function tests
    - Inflammatory Markers: CRP, ferritin
    - Arterial blood gas values, if available
    - Measurement of isotype, total antibody, and neutralizing capacity of donor plasma antibodies to SARS-CoV-2
    - Serum or plasma antibody to SARS-CoV-2: Day 1, 5,8,15, 29, 120
    - SARS-CoV-2 PCR from nasopharyngeal swab (NP) or mid-turbinate nasal swab (MTN Day 1,2,5,8,15

5. Chest imaging (CT or Chest x-ray): obtained as part of standard care

Primary Objective: Evaluate the efficacy of convalescent fresh frozen plasma from blood donors who have recovered from Covid-19 containing antibodies to SARS-CoV-2 versus control (standard fresh frozen plasma) to prevent severe hypoxemia during the 14 days after administration in hospitalized patients with COVID-19 who are within 72 hours of hospital admission OR 14 days of symptom onset.
Primary Endpoint: Progression to mechanical ventilation/ECMO for hypoxia/hypercarbia, or death from any cause

Safety and Efficacy of the intervention will be assessed during multiple time points Day 1 (baseline), 2,5,8,15, 29 and once at month 4 (day 120) .

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary Objective	
Evaluate the efficacy of convalescent fresh frozen plasma from blood donors who have recovered from Covid-19 containing antibodies to SARS-CoV-2 versus control (standard fresh frozen plasma) to prevent mechanical intubation or death within 14 days of CPP administration in hospitalized patients with COVID-19 who are within 3 days of hospital admission or 14 days of symptom onset. .	Progression to mechanical ventilation or death within the first 14 days of enrollment. . A secondary endpoint will evaluate progression to endpoint within the first 28 days of enrollment.
Key Secondary Objectives	
To evaluate the clinical efficacy of CCP relative to the control arm in adults hospitalized with COVID-19 according to clinical status (8-point ordinal scale) at Day 29	• Death; • Hospitalized, on invasive mechanical ventilation or ECMO; • Hospitalized, on non-invasive ventilation or high flow oxygen devices; • Hospitalized, requiring supplemental oxygen; • Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); • Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; • Not hospitalized, limitation on activities and/or requiring home oxygen; • Not hospitalized, no limitations on activities.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Additional Secondary Objectives	
To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: **Clinical Severity Ordinal scale**: • Time to an improvement of one category and two categories from Day 0 (baseline) using an ordinal scale. • Subject clinical status using ordinal scale at Days 2,5,8,15, 29 • Mean change in the ordinal scale from Day 1 to Days 2,5,8,15, 29	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 15, 29 and 120 • Time to clinical recovery (defined as ordinal score 1-3)
National Early Warning Score (NEWS): • Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. • Change from Day 1 to Days 2,5,8,15, 29	• NEWS assessed daily while hospitalized
Oxygenation: • Oxygenation use up to Day 120. • Incidence and duration of new oxygen use during the study. • Oxygen requirement on day 1,2,5,8,15, 29	• Days of supplemental oxygen (if applicable) up to Day 29 • PaO2/FiO2 ratio or SpO2/FiO2 • O2 requirement at day 120
Non-invasive ventilation/high flow oxygen: • Non-invasive ventilation/high flow oxygen use up to Day 29. • Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.	• Days of non-invasive ventilation/high flow oxygen (if applicable) up to Day 29
Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO): • Ventilator / ECMO use up to Day 29. • Incidence and duration of new mechanical ventilation or ECMO use during the study.	• Days of invasive mechanical ventilation/ECMO (if applicable) up to Day 29.
Hospitalization • Duration of hospitalization (days).	• Days of hospitalization as of Day 29 and day 120
Mortality • 15-day mortality • 29-day mortality • 120-day mortality	• Date and cause of death (if applicable)
To evaluate the safety of CCP as compared to the control arm as assessed by:	• SAEs

• Cumulative incidence of SAEs through Day 29. • Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29. • Transfusion associated adverse events	• Grade 3 and 4 AEs • Grade 2 or higher AE's attributed to CCP
• Exploratory Objectives	
To evaluate the virologic efficacy of CCP as compared to the control arm as assessed by: • Percent of subjects with SARS-CoV-2 detectable in nasal sample at Days 1,5,8,15 • Quantitative SARS-CoV-2 virus in NP/MTN sample at Days 1,2,5,8,15	• Qualitative and quantitative polymerase chain reaction (PCR) for SARS-CoV-2 in NP/MTN swab on Day 1,2,5,8,15 (while hospitalized)

Study population

Inclusion Criteria for Enrollment:

1. Patients ≥18 years of age
2. Hospitalized with COVID-19
3. Enrolled within 72 hours of hospitalization OR within day 14 from first symptoms of illness
4. Pulmonary infiltrates on chest imaging
5. Oxygenation of <95% on room air
6. Laboratory confirmed COVID-19

Exclusion Criteria

1. Contraindication to transfusion due to inability to tolerate additional fluid, such as due to decompensated congestive heart failure
2. Baseline requirement for oxygen supplementation prior to COVID-19 infection or use of positive pressure therapy for sleep disordered breathing
3. Currently experiencing severe hypoxemic failure, as defined in study endpoints
4. Prior receipt of plasma products, IVIG, or hyperimmune globulin within past 3 months
5. Not currently enrolled another interventional clinical trial of COVID-19 treatment.

Note: If taking medications with potential anti-COVID activity for the purpose of COVID-19 treatment that do not yet have data to support efficacy, such as IL-6 antagonists these medications must be stopped prior to enrollment. Receipt of current standard of care COVID-19 treatment, including remdesivir and dexmethasone is permitted and should be recorded as concomitant medications.

4 RATIONALE/BACKGROUND:

4.1 Background and scientific rationale

Human convalescent plasma is a treatment option for COVID-19 and could be rapidly available when there are enough people who have recovered and donate plasma containing high titer (anti- SARS-CoV-2) neutralizing immunoglobulins. As more individuals contract COVID-19 and recover, the number of potential donors will continue to increase, to allow greater use.

Use of convalescent plasma is a form of passive antibody therapy that involves the administration of antibodies to a given agent to a susceptible individual for the purpose of preventing or treating the infectious disease it causes. In contrast, active vaccination requires the induction of an immune response that takes time to develop and varies in efficacy depending on the vaccine recipient. Some immunocompromised patients fail to achieve an adequate immune response to active vaccination and at present, there are no vaccines to prevent COVID-19. When given to a susceptible person, antibody used for therapy will circulate in the blood, reach tissues and hopefully mediate a beneficial effect by anti-microbial and anti-inflammatory activity [2]. Depending on antibody amount and composition, protection conferred by transferred immunoglobulin can last from weeks to months.

Passive antibody administration is the only means of providing immediate immunity to susceptible persons and immunity of any measurable kind for susceptible, including immunocompromised patients with Covid-19. This kind of 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 [3, 4]. Experience from prior outbreaks with other coronaviruses, such as SARS-CoV-1 shows that such convalescent plasma contains neutralizing antibodies to the relevant virus [5]. 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 [6].

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 [7]. For 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 [3]. Clinical outcomes after convalescent antibody therapy were better when it was administered to ill patients SARS-CoV-1 within 14 days after onset of symptoms (discussed below) [8]. Our goal is to treat patients who are sick enough to warrant hospitalization but do not have severe respiratory disease and/or ARDS.

4.1.1 **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 [8]. Consistent with historical data that earlier administration of antibody is more likely to be effective, 30 patients treated a mean of 11.7 (+/- 2.3) days after symptom onset had improved prognosis defined by discharge from hospital before day 22, whereas 47 patients who received plasma a mean of 16 days after symptom onset died before day 22 or had a late discharge. The mortality rates in the two groups were 6.3% and 21.9%, respectively (*P*=0.08), and those who were nasal swab 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 SARS1 in Taiwan were treated with 500 ml of convalescent plasma, resulting in a reduction in plasma virus titer and each survived [9]. Three patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients developed neutralizing antibody one week after infusion [10]. The latter study highlights a challenge in using convalescent plasma; some who recover may not have high titers of neutralizing antibody [11]. In addition, only 2 of 4 donor plasma infusions showed neutralizing antibody activity. This is consistent with an analysis of 99 samples of convalescent sera from patients with MERS which showed that 87 had neutralizing antibody with a geometric mean titer of 1:64. This suggests that antibody declines with time and/or only a few patients make high titer responses. Our study addresses this issue by screening plasma for antibody to SARS-CoV-2 and will only use plasma with SARS-CoV-2 antibodies detected. However, it is possible non-neutralizing antibodies may also contribute to protection as described for other viral diseases [12, 13]. In addition, to ensure that the control arm plasma does not have SARS-CoV-2 antibodies present, control fresh frozen plasma will be used from prior to December,2019 or testing for SARS-CoV-2 antibodies in the control plasma will be performed immediately prior to administration.

A recently performed pilot study in Wuhan, China collected convalescent liquid plasma from COVID-19 positive patients 3 weeks following the onset of illness and 4 days post-discharge and treated patients diagnosed with 'severe COVID-19' as defined by WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 National Health Commission of China [14]. Ten patients were treated with one dose of convalescent plasma (200ml, >1:640 titer by neutralization assay) at a median of 16.5 days (11-19.3 days) post-onset of symptoms. A COVID-19 positive control cohort was retrospectively identified and matched by demographics, comorbidities, and severity of illness. There were no serious adverse reactions or safety events recorded with convalescent plasma, including no reported transfusion related reactions, transfusion-related acute lung injury, or antibody-mediated enhancement of infection. In the treatment group, there were 0 deaths, 3 discharges and 7 patients improved, whereas there were 3 deaths and 7 patients who improved in the control group ($p < 0.001$). In addition, 2 of 3 patients in the treatment on mechanical ventilation were weaned to high flow nasal cannula, which was discontinued in one patient. There was a reduction in blood RNA viral load in 7 of 10 patients on day 6 post-convalescent plasma therapy as well as improvement in laboratory markers. There were also varying degrees of improvement in pulmonary lesions on chest CT after convalescent plasma therapy. In another case series from China, five severely ill patients with COVID-19, all on mechanical ventilation received convalescent plasma within 22 days of admission [15]. Temperatures normalized in 4 of 5 patients within 3 days, SOFA scores decreased, and there was improvement in oxygenation and ARDS resolution. All survived, with 3 discharged home and 2 in stable condition. These reports suggest convalescent plasma may hold promise for ameliorating the severity of Covid-19 and deserves immediate investigation for this indication.

4.1.2 **Known potential risks**

A theoretical risk of administration of convalescent plasma is the phenomenon of antibody-mediated enhancement of infection (ADE). ADE can occur in viral diseases, such as dengue and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms of ADE have been described, including the theoretical concern that antibodies to one type of coronavirus could enhance infection to another strain [16]. It may be possible to predict the risk of ADE in SARS-CoV-2 experimentally, as proposed for MERS [16]. Since the proposed use of convalescent plasma in the COVID-19 epidemic would rely on preparations with high titers of antibody against the same virus, SARS2-CoV-2, ADE may be unlikely. Available evidence from the use of convalescent plasma in patients with SARS1 and MERS [17] demonstrated it is safe and there were no adverse effects in a pilot study of patients with COVID-19 [14]. Nevertheless, caution and vigilance will be exercised to use clinical and laboratory measures to detect evidence of enhanced infection.

Another theoretical risk is that CCP to those exposed to SARS-CoV-2 may prevent disease but modify the immune response such that those who are treated may mount attenuated immune responses. This may leave them vulnerable to subsequent re-infection. Passive antibody administration before vaccination with respiratory syncytial virus attenuated humoral but not cellular immunity [18]. This will be investigated as part of this clinical trial by comparing immune responses in those who receive standard plasma and convalescent plasma. If responses differ, those with attenuated levels could be vaccinated against COVID-19 when a vaccine becomes available. Nonetheless, these concerns are modest compared to the possible benefit of reducing the risk of respiratory failure and avoiding mechanical ventilation.

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 mistakenly administered. To minimize the risks of disease transmission, all plasma donors will be required to meet full allogeneic blood donation requirements as determined by FDA and the collection center. Donors are screened for behavioral risk factors for bloodborne infections using the standard blood donor history questionnaire (DHQ) and extensive testing for blood borne pathogens using FDA-licensed tests for blood product testing. In addition, donors will fulfill all FDA convalescent donor requirements which require a history of COVID19 illness (documented by positive COVID-19 test at time of illness OR positive COVID-19 serology) and complete resolution of symptoms at least 28 days prior to donation, or complete resolution of symptoms at least 14 days prior to donation with negative COVID-19 nasopharyngeal swab or molecular diagnostic test from blood[19].

A recent observational series described the safety of CCP administered to over 5000 hospitalized patients with COVID-19 infection. The incidence of adverse events in the day after plasma infusion was < 1% with only 2 of 36 events attributed to CCP by the treating clinician, suggesting a favorable initial safety signal and no clear evidence of ADE. [20]

4.1.3 **Known potential benefits**

The most important potential benefit is that convalescent plasma may reduce progression to respiratory failure in patients with COVID-19 and early respiratory symptoms, such as shortness of breath, cough, chest pain, and pulmonary infiltrates. The benefit of plasma is expected to be an improvement in symptoms, oxygenation, the need for mechanical ventilation and possibly reduced mortality. Based on historical experience with antibody administration, antibody administration is expected to be effective relatively early in disease [2]. Convalescent plasma was safe, reduced symptoms, and improved oxygenation in a non-randomized open label study of patients with more advanced disease in Wuhan, China [14].

Given historical data showing convalescent plasma was safe and possibly effective in patients with SARS1 [8, 17], and emerging data from China suggest it is safe and possibly effective in patients with severe COVID-19, the benefits of its use in those at high risk for severe disease outweigh the risks. However, for all patients in whom convalescent plasma administration is considered, a risk-benefit assessment will be conducted to assess individual variables. This protocol proposes a randomized controlled pragmatically blinded trial to assess the efficacy of convalescent plasma in preventing severe hypoxemia in patients with COVID-19. A JAMA editorial by experts note the importance of randomized clinical trials to demonstrate efficacy of this approach and change the course of the epidemic [21].

4.1.4 **Target population**

This study will enroll hypoxic hospitalized COVID-19 patients, a group that is at elevated risk for poor outcomes and progressive respiratory failure. To date, approximately 30-50% of hospitalized San Francisco COVID-19 patients have required intensive care level treatment, the majority due to respiratory failure[1]. This high progression to ICU level care due to respiratory failure has been seen across the US. This study targets patients who are still early in the course of disease, when CCP may be most effective, the “green zone” described in Figure 2. Once severe respiratory decompensation and ARDS occur and patients have progressed to the “red zone”, CCP may be less effective, as was the case with use of CCP in SARS-1 -[8]. The study has been amended to include those on high flow nasal oxygenation, as well as those on nasal cannula. In the ACTT-1 study, 25% of participants on HFNC (ordinal group 6) progressed to mechanical ventilation or death [22] These individuals are at elevated risk of progression to intubation and it is important to understand if CCP can reduce deterioration of respiratory status .

This study will permit enrollment of pregnant women, breastfeeding women and women of childbearing potential. CCP should not pose a pregnancy specific risk, other than the known risks associated with blood product infusions in general. However, for pregnant or breastfeeding women, additional counseling will be provide as to the lack of data for CCP use in COVID-19 infection during pregnancy and lactation and that an adverse event that impacts the participant could also affect an unborn child by affecting maternal health. Pregnant women who chose to enroll will have the pregnancy outcome recorded.

Figure 1: San Francisco COVID Data Tracker: Total COVID acute care beds and subset of ICU beds [1].

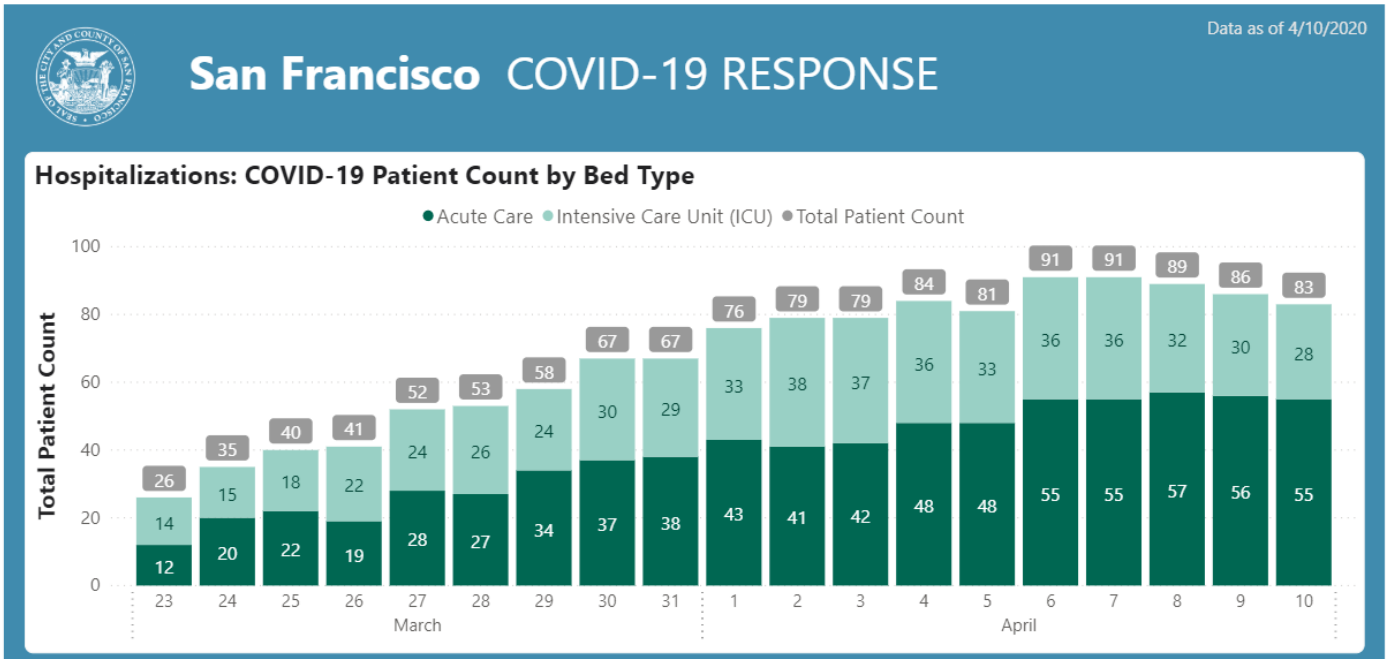
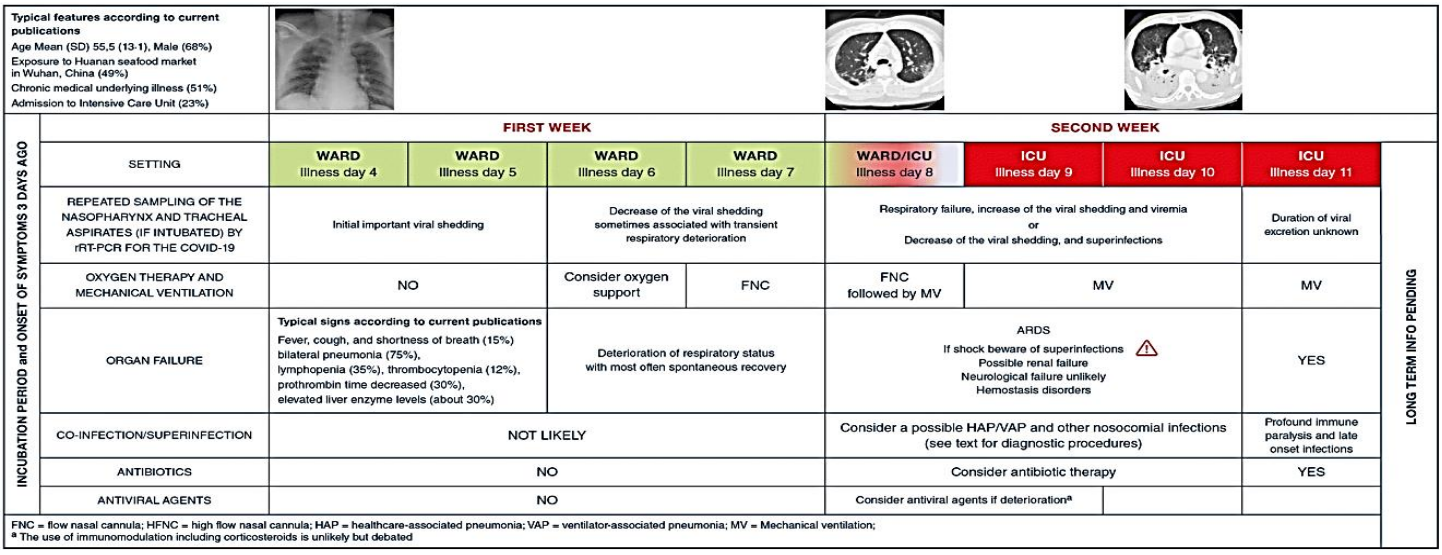


Figure 2. Natural history of COVID-19 infection with a biphasic initial mild disease (green zone) and subsequent severe respiratory failure (red zone)[23]



Typical features according to current publications Age Mean (SD) 55,5 (13-1), Male (68%) Exposure to Huanan seafood market in Wuhan, China (49%) Chronic medical underlying illness (51%) Admission to Intensive Care Unit (23%)									
INCUBATION PERIOD and ONSET OF SYMPTOMS 3 DAYS AGO		FIRST WEEK				SECOND WEEK			LONG TERM INFO PENDING
	SETTING	WARD Illness day 4	WARD Illness day 5	WARD Illness day 6	WARD Illness day 7	WARD/ICU Illness day 8	ICU Illness day 9	ICU Illness day 10	ICU Illness day 11
	REPEATED SAMPLING OF THE NASOPHARYNX AND TRACHEAL ASPIRATES (IF INTUBATED) BY rRT-PCR FOR THE COVID-19	Initial important viral shedding		Decrease of the viral shedding sometimes associated with transient respiratory deterioration		Respiratory failure, increase of the viral shedding and viremia or Decrease of the viral shedding, and superinfections			Duration of viral excretion unknown
	OXYGEN THERAPY AND MECHANICAL VENTILATION	NO		Consider oxygen support	FNC	FNC followed by MV	MV		MV
	ORGAN FAILURE	Typical signs according to current publications Fever, cough, and shortness of breath (15%) bilateral pneumonia (75%), lymphopenia (35%), thrombocytopenia (12%), prothrombin time decreased (30%), elevated liver enzyme levels (about 30%)		Deterioration of respiratory status with most often spontaneous recovery		ARDS If shock beware of superinfections ⚠ Possible renal failure Neurological failure unlikely Hemostasis disorders			YES
	CO-INFECTION/SUPERINFECTION	NOT LIKELY				Consider a possible HAP/VAP and other nosocomial infections (see text for diagnostic procedures)			Profound immune paralysis and late onset infections
	ANTIBIOTICS	NO				Consider antibiotic therapy			YES
	ANTIVIRAL AGENTS	NO				Consider antiviral agents if deterioration[a]			

FNC = flow nasal cannula; HFNC = high flow nasal cannula; HAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia; MV = Mechanical ventilation;
[a] The use of immunomodulation including corticosteroids is unlikely but debated

4.1.6 **Antibody evaluation of CCP units**

To ensure that CCP units have a sufficient quantity of anti-SARS-CoV-2 antibodies, all CCP units will be tested for antibodies. The mean plus 4 standard deviations over antibodies levels from the pre-COVID-19 era will be used as the cut-off for CCP units. This is based on data indicating 100% specificity when evaluating 71 samples collected from febrile patients with upper respiratory symptoms that were either SARS-CoV-2 RT-PCR negative or positive for other respiratory viruses using this cutoff (Lynch et al, *unpublished)*

4.1.7 **Viral load testing**

Serial nasopharyngeal testing will be conducted to evaluate SARS-CoV-2 viral decline in each arm. Metagenomic next generation sequencing (mNGS) will be conducted on PCR specimens. mNGS enables simultaneous profiling of host gene expression and viral load, and assessment of the SARS-CoV-2 viral genome. This approach will enable broad detection of host transcriptional biomarkers that may correlate with treatment outcomes, and may reveal biological mechanisms underpinning CCP antiviral activity. mNGS will additionally provide an opportunity to assess whether SARS-CoV-2 viral load and genotype correlate with clinical outcomes and treatment response.

4.1.8 **Adaptive trial design**

This trial is designed as a randomized controlled trial of CCP versus a control arm of plasma without SARS-CoV-2 antibodies. At this time, the antiviral remdesivir (RDV) will be permitted, as has demonstrated a 31% faster time to recovery with RDV vs. placebo in preliminary data from a randomized controlled trial of hospitalization in COVID-19 patients [24]. The preliminary mortality rate of 8% in the RDV arm indicates that hospital-based RDV administration alone was not sufficient to mitigate morbidity/mortality associated with severe COVID-19 disease. Should the data from the ACTT studies or other RDV study indicate a substantial reduction in progression to severe hypoxemia in the target population of hospitalized hypoxic COVID-19 patients, the sample size will be recalculated with a potential increase if necessary.

Preliminary findings from the open label, randomized RECOVERY study have demonstrated a mortality reduction with dexamethasone use compared to standard of care, 29% vs 41.1% respectively, rate ratio of 0.64 [95% CI 0.0.51 to 0.81] [26]. A smaller mortality reduction was reported in hypoxic patients of 23.3% vs 26.2%, rate ratio of 0.82 [95% CI 0.07 to 0.94] with no data are available on those on lower vs higher level of oxygen support. Given the modest benefit in non-ICU patients, this protocol will exclude use of dexamethasone for COVID treatment at the time of enrollment. Participants with progressive disease who reach the study hypoxemia endpoint can receive dexamethasone, at the discretion of the treating provider. Of note, our institutional practice does not treat all hospitalized patients with dexamethasone as standard of care.

Other investigational or off label interventions will not be permitted during the first 15 days unless the study subject meets the primary endpoint of progression to mechanical intubation. Should evidence become available during the study to support the use of anti-COVID-19 therapeutics, including antivirals and/or immune modulators that improve clinical outcomes and/or significantly reduce viral load, the study will incorporate these therapies into the study design, with a recalculation of the sample size. Given the

substantial risk for decompensation, hospitalized hypoxic COVID-19 may benefit from CCP in addition to other effective treatment, which may further reduce the risk of respiratory decompensation.

4.1.9 Collaboration with longitudinal cohorts and data pooling efforts

Participants will be encouraged to enroll in a longitudinal observational cohort conducted by collaborating investigators with aligned specimens collections to facilitate translational evaluations and long term follow-up of immunologic and clinical outcomes.

Data from this protocol will be pooled with other similar studies of CCP in hospitalized hypoxic individuals enrolled in randomized controlled trials of CCP vs. control. Data shared will be de-identified and contain no protected health information (PHI).

4.1.10 Future direction

This proof-of-concept clinical trial will lay the foundation for a future study that may incorporate hyperimmune IgG and/or monoclonal antibodies, when available, along with anti-COVID agents (either anti-viral and/or anti-inflammatory strategies) as emerging data are available to support use as standard of care. This initial study will provide much needed infrastructure and preliminary data to support larger, multicenter trials using either convalescent plasma or hyperimmune IgG across the greater SF Bay Area.

5 INVESTIGATIONAL PLAN:

5.1 Study objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary Objective	
Evaluate the efficacy of convalescent fresh frozen plasma from blood donors who have recovered from Covid-19 containing antibodies to SARS-CoV-2 versus control (standard fresh frozen plasma) to prevent mechanical intubation within 14 days of CPP administration in hospitalized patients with COVID-19 who are within 3 days of hospital admission or 14 days of symptom onset. .	Progression to mechanical intubation or death within the first 14 days of enrollment. . A secondary endpoint will evaluate progression to endpoint within the first 28 days of enrollment.
Key Secondary Objectives	
To evaluate the clinical efficacy of CCP relative to the control arm in adults hospitalized with COVID-19 according to clinical status (8-point ordinal scale) at Day 29	• Death; • Hospitalized, on invasive mechanical ventilation or ECMO; • Hospitalized, on non-invasive ventilation or high flow oxygen devices; • Hospitalized, requiring supplemental oxygen; • Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); • Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; • Not hospitalized, limitation on activities and/or requiring home oxygen; • Not hospitalized, no limitations on activities.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Additional Secondary Objectives	
To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: **Clinical Severity Ordinal scale**: • Time to an improvement of one category and two categories from Day 0 (baseline) using an ordinal scale. • Subject clinical status using ordinal scale at Days 2,5,8,15, 29 • Mean change in the ordinal scale from Day 1 to Days 2,5,8,15, 29	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 15, 29 and 120 • Time to clinical recovery (defined as ordinal score 1-3)
National Early Warning Score (NEWS): • Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. • Change from Day 1 to Days 2,5,8,15, 29	• NEWS assessed daily while hospitalized
Oxygenation: • Oxygenation use up to Day 90. • Incidence and duration of new oxygen use during the study. • Oxygen requirement on day 1,2,5,8,15, 29	• Days of supplemental oxygen (if applicable) up to Day 29 • PaO2/FiO2 ratio or SpO2/FiO2 • O2 requirement at day 120
Non-invasive ventilation/high flow oxygen: • Non-invasive ventilation/high flow oxygen use up to Day 29. • Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.	• Days of non-invasive ventilation/high flow oxygen (if applicable) up to Day 29
Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO): • Ventilator / ECMO use up to Day 29. • Incidence and duration of new mechanical ventilation or ECMO use during the study.	• Days of invasive mechanical ventilation/ECMO (if applicable) up to Day 29.
Hospitalization • Duration of hospitalization (days).	• Days of hospitalization as of Day 29 and day 120
Mortality • 15-day mortality • 29-day mortality • 120-day mortality	• Date and cause of death (if applicable)
To evaluate the safety of CCP as compared to the control arm as assessed by:	• SAEs

• Cumulative incidence of SAEs through Day 29. • Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29. • Transfusion associated adverse events	• Grade 3 and 4 AEs • Grade 2 or higher AE's attributed to CCP
• Exploratory Objectives	
To evaluate the virologic efficacy of CCP as compared to the control arm as assessed by: • Percent of subjects with SARS-CoV-2 detectable in NP/MTN sample at Days 1,5,8,15 • Quantitative SARS-CoV-2 virus in NP/MTN sample at Days 1,2, 5,8,15	• Qualitative and quantitative polymerase chain reaction (PCR) for SARS-CoV-2 in NP/MTN swab on Day 1,2,5,8,15 (while hospitalized)

5.2 Study Definitions

- *Enrolled*: From time consented to participate until designated as (i) ineligible based on the inclusion/exclusion criteria or withdraws, (ii) been discontinued from the study or (iii) completed the study.
- *Randomized*: when a randomization number is assigned.
- *Screen Failures*: signed informed consent, but then determined to be ineligible or withdraws before being randomized.
- *Discontinued*: randomized, but then withdrawn by investigator or subject withdraws consent
- *Completed:* Subjects are considered completed when they are followed through to day 29, had an adverse event or death occurred prior to day 29. Patients will be asked to have day29 and day 120 study visits as well.

5.3 Study Population

5.3.1 Inclusion Criteria for Enrollment:

1. Patients ≥18 years of age
2. Hospitalized with COVID-19
3. Enrolled within 72 hours of hospitalization OR within day 14 from first signs of illness
4. Pulmonary infiltrates on chest imaging
5. Oxygenation of <95% on room air
6. Laboratory confirmed COVID-19

5.3.2 Exclusion Criteria

1. Contraindication to transfusion due to inability to tolerate additional fluid, such as due to decompensated congestive heart failure
2. Baseline requirement for oxygen supplementation prior to COVID-19 infection or use of positive pressure therapy for sleep disordered breathing
3. Currently experiencing severe hypoxemic failure, as defined in study endpoints
4. Prior receipt of plasma products, IVIG, or hyperimmune globulin within past 3 months
5. Currently enrolled another interventional clinical trial of COVID-19 treatment.

Note: If taking medications with potential anti-COVID activity that do not have data to support efficacy, such as IL-6 antagonists, these medications must be stopped prior to enrollment. Receipt of current standard of care COVID-19 treatment, including remdesivir is permitted and should be recorded as a concomitant medication.

Note: Pregnancy is not exclusionary but will merit additional discussion of risks & benefits in the context of ongoing pregnancy

5.3.3 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 be replaced
3. The investigator may withdraw subjects if they are 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 study sponsor, FDA and IRB all have the right to terminate this study at any time

5.3.4 Treatment

1. Subjects will be randomized in a 1:1 ratio to receive study drug (convalescent fresh frozen plasma) versus standard plasma, one unit of FFP, approximately 250 ml. A single dose of CCP will be provided
2. Study drug: The investigational product is anti-SARS-CoV-2 convalescent fresh frozen plasma, ABO compatible with the patient. Convalescent plasma for this trial will be obtained from Vitalant (or American Red Cross if necessary.) Donor screening and plasma collection are not conducted as study specific procedures and will be conducted by the collaborating blood bank according to their current SOP. Patients identified as having recovered from COVID-19 will serve as potential donors. Potential donors will be screened using an anti-SARS-CoV-2 serologic assay and antibody levels will be determined. Donors will be screened for standard transfusion-transmitted infections (e.g. HIV, HBV, HCV, West Nile Virus, HTLV-I/II, *T. cruzi*, Zika virus) both with the uniform donor history questionnaire (DHQ) and FDA licensed blood donor screening tests as required by FDA. Plasma will be collected using apheresis technology or via separate from a whole blood donation.
3. Control plasma will be obtained from Vitalant (or American Red Cross if necessary) and will be either collected prior to 12/1/2019 or tested and confirmed to be negative for anti-SARS-CoV-2.
4. Convalescent plasma will undergo testing to evaluate for anti-SARS-CoV-2 antibodies;
5. A sample of the convalescent plasma will be stored for future study to investigate total antibody quantitation, neutralizing antibody activity, and future evaluation of other correlates of immunity and COVID-19 related analyses.
6. Both treatment and control plasma will be in standard plasma bags, with International Society of Blood Transfusion (ISBT) labels. The convalescent plasma will be additionally labelled as “COVID 19 Convalescent Plasma” and will have a tie tag indicating “New Drug – Limited by Law to Investigational Use.”
7. Study investigators analyzing the data and participants will be blinded to the randomization. It may not be feasible to blind nursing staff to the treatment assignment to ensure proper ABO checking of the plasma unit at bedside per standard transfusion procedures, but every effort will be made to preserve blinding of the investigators, participant, and primary team providing care. An unblinded research assistant who is not involved in other aspects of the study will randomize the participant once enrolled. Randomization will be provided to an unblinded provider who is not part of the care team who will place the order for the plasma (CCP vs. control plasma) using a paper order that will not be part of the electronic medical record.

5.3.5 Randomization:

1. Subjects enrolled in the study will be randomized using a web based randomization procedure to receive convalescent plasma versus non-immune plasma at a 1:1 ratio.

5.3.6 Study drug administration

0. Drug will be administered within 24 hours of randomization

1. Infusion rate ≤ 500 mL/hour
2. Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given at the discretion of the clinical care team.
3. 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, generally require discontinuation of the infusion.

5.3.7 **Concomitant medications**

Concomitant medications will be documented on the Case Report Form (CRF) up to day 15.

- Antibiotics
- Anticoagulation
- Any COVID-19 related treatment, including RDV
- Corticosteroids (> 10 mg prednisone equivalent)
- Blood products

After this time, only medications related to COVID-19 treatment will be documented for days 16-120

5.3.8 **Prohibited medications**

For study day 1-15, use of medications, including off-label, expanded access, or investigational agents, with potential anti-COVID-19 activity should not be administered. These include the following:

- Hydroxychloroquine or chloroquine
- Lopinavir/ritonavir (unless already prescribed for HIV infection)
- IL-6 receptor antagonists
- High dose corticosteroids initiated for COVID-19 treatment, and not for another indication

If there is uncertainty about possible anti-COVID-19 activity, the medication being used should be discussed with the team. This list will be revised as new data to support or refute efficacy become available.

Note: Azithromycin administered for treatment of presumed or confirmed infection will be permitted.

After study day 15 or in participants who have reached the study endpoint of severe hypoxemia, use of additional anti-COVID-19 treatments such as dexamethasone for those with persistent severe COVID-19 are permitted but should be recorded.

5.4 Study procedures

Table 1: Schedule of Evaluations

Study period	Screen	Enrollment	Transfusion (within 24 hours of randomization)	Follow up					
Day	Within 3d prior to enrollment	1 (values within 24 hours prior to enrollment)	1	2	5	8	15	29	120
Visit window				+/-1 day				+/- 7d	+/- 14d
Eligibility									
Informed consent	x								
Demographic and Medical history	x								
COVID-19 symptom screen	x								
SARS-CoV-2 RT-PCR for eligibility	within 14 days								
Pregnancy test									
ABO for plasma compatibility	x								
Chest imaging (CXR or CT scan)	x								
Oxygenation Status	x	x							
Study Drug Administration									
Randomization		x							
Drug infusion			x						
Study Procedures									
Vital signs		x	xxx[1]	daily days 2-8[2]			x[2]		
Oxygenation status		x		daily 2-8[2]			x	x	x

Symptom screen	x	x	x	x	x	x	x	x	x
Day	Within 3d prior to enrollment	Enrollment (values within 24 hours prior to enrollment)	Plasma transfusion	2	5	8	15	29	120
Visit window				+/-1 day				+/- 5d	+/- 14d
Concomitant medications		x		x	x	x	x (only COVID treatment related)		
Assessment with 8-point ordinal scale		x		x	x	x	x	x	x
Assessment with WHO 11 point ordinal scale							x	x	
Chest imaging (CXR or CT scan) [4]					x		x		
Laboratory testing									
CBC (with absolute lymphocyte count)		x		$x^{2,5}$	$x^{2,5}$	$x^{2,5}$	$x^{2,5}$	x^{6}	x
Renal function, liver function test		x		$x^{2,5}$	$x^{2,5}$	$x^{2,5}$	$x^{2,5}$		
PT, PTT, D-dimer, hsCRP, ferritin		x		x^{2}	x^{2}	x^{2}	x^{2}	x^{6}	x
SARS-CoV-2 RT-PCR(NP/MTN swab) [7]		x		x	$x^{2,7}$	$x^{2,7}$	$x^{2,7}$		
Blood for future testing (includes SARS-CoV-2 Ab)[7]		x			$x^{2,7}$	$x^{2,7}$	$x^{2,7}$	x^{6}	x^{6}

[1] 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, ideally bundled with other required clinical care.
[2] If still hospitalized.
[4] Record most recent preceding chest imaging, if available and conducted per standard of care
[5] Record lab values if collected as part of standard of care. Will encourage clinical teams to collect but will not be required.
[6] Blood drawn if in-person visit is feasible
[7]Prioritize day 1 research blood collection and nasal swab . Collect on day 5, 8, 15 if feasible

STUDY PROCEDURES

1. Study Protocol by Day:

Day -2 to 1:

A. Screening (must be completed before randomization)
B. Informed consent (obtained before performing study related activities)
C. Baseline Evaluation (at screening) (much of the information will be obtained from the medical record)

1. Demographics: Age, sex, race
2. Medical history:
    - Timing of exposure to COVID-19 source patient
    - Acute and chronic medical conditions that a risk factors for COVID
    - Medications, allergies
    - Any medical condition arising after consent to be recorded as AE.
3. COVID-19 symptom screen: Fevers, cough, shortness of breath.
4. History of illness: Onset of symptoms
5. Vital signs
6. Oxygenation status: current FiO2 or liters of O2, route of oxygen support, and oxygen saturation or Pa02 (if available)
7. COVID-19 testing (RT-PCR) Per standard of care. Positive test PCR required within 14 days of screening
8. Baseline Basic Lab Testing
    - ABO Blood typing, CBC with absolute lymphocyte count, comprehensive metabolic panel, inflammatory and coagulation markers (d-dimer, hsCRP, PT/INR, PTT)
9. For females of childbearing potential, urine or serum pregnancy test
    - Results from laboratory tests obtained up to 14 days before enrollment may be used for the pregnancy test

D. Determination of eligibility

- Inclusion/exclusion criteria age
- Consent
- Positive for COVID-19 within past 14 days
- not already an ICU patient
- Within 14 days of first sign of illness or within 72 hours of admission

Day 1:

1. Randomization of eligible subject
2. Study Plasma Administration:
    - 1 unit of plasma will be transfused within 24 hours of enrollment
    - Time at start and end of infusion will be recorded
    - 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
4. Assessment of clinical status (8-point ordinal scale)
5. New medical conditions, concomitant medication, AE evaluation
7. Oxygenation status: current FiO2 or liters of O2, route of oxygen, and oxygen saturation or Pa02 (if available)
8. COVID-19 testing (RT-PCR): nasopharyngeal samples
10. Stored samples for future studies (3 EDT tubes and 1 SST). This will include serological testing for SARS CoV-2 antibodies

Day 2-15 (if remain hospitalized)

1. Vitals signs (day 2-8)
3. Assessment of clinical status (8-point ordinal scale) (days 2,5,8)
4. New medical conditions, concomitant medications, AE evaluation (days 2,5,8)
6. Oxygenation status: current FiO2 or liters of O2, route of oxygen, and oxygen saturation or Pa02 (if available) (days 1-8)
7. Nasopharyngeal or mid-turbinate nasal swabs, if feasible (days 2,5,8)
8. Stored samples for future studies(3 EDT tubes and 1 SST) (day 5, 8 only) if feasible. This testing includes SARS-CoV-2 antibody testing
10. CXR (or CT with increased oxygen requirement): day 5,(record most recent imaging prior to day 5, conducted per standard of care)

Day 15 (phone contact if no longer hospitalized or if in person visit is not feasible)

1.COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (8-point ordinal scale) & WHO 11 point scale[27] (added to facilitate data analysis across data sets)
3. New medical conditions, AE evaluation, concomitant medications
4.Oxygenation status: current FiO2 or liters of O2, route of oxygen, and oxygen saturation or Pa02 (if available)
5. CBC, comprehensive metabolic panel, inflammatory markers (if seen in person)
6. Serological testing: anti-SARS CoV-2 antibody levels if hospitalized
7. Nasopharyngeal or mid-turbinate nasal swabs with OP swab if possible (if seen in person)
8. CXR (or CT with increased oxygen requirement): day 15,(record most recent imaging prior to day 15, conducted per standard of care)
9. Stored samples for future studies(3 EDTA, 1 SST) (if seen in person)

Day 29: (in person visit if feasible, phone contact if not)

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (8-point ordinal scale) & WHO 11 point scale[27] (added to facilitate data analysis across data sets)
3. Oxygenation status: current FiO2 or liters of O2, route of oxygen, and oxygen saturation or Pa02 (if available)
4. New medical conditions, AE evaluation, concomitant medications (only recorded if treatment given for COVID-19 after day 15)
5. CBC, inflammatory markers (if seen in person)
6. Blood for stored testing, if feasible (3 EDTA, 1 SST)This will include serological testing for SARS CoV-2 antibodies

Day 120 In-person (if feasible)

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (8-point ordinal scale)
3. New medical conditions, AE evaluation
4. Serological testing: anti-SARS CoV-2 antibody levels
5. Blood for stored testing, if feasible (3 EDTA, 1 SST). This will include serological testing for SARS CoV-2 antibodies

8 point WHO ordinal Scale of clinical status[28]

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

11 point WHO ordinal Scale[27]

0: Uninfected, no viral RNA detected

1. Asymptomatic, viral RNA detected
2. Symptomatic, independent
3. Symptomatic, assistance needed
4. Hospitalized, no oxygen therapy
5. Hospitalized, oxygen by mask or nasal prongs
6. Hospitalized, oxygen by non-invasive ventilation or high flow
7. Intubation & Mechanical ventilation, $pO2/FIO2 \geq 150$ or $SpO2/FIO2 \geq 200$
8. Mechanical ventilation, $pO2/FIO2 < 150$ ($SpO2/FIO2 < 200$) or vasopressors
9. Mechanical ventilation, $pO2/FIO2 < 150$ and vasopressors, dialysis or ECMO
10. Dead

6 STATISTICAL PLAN

6.1 Sample Size and Power Considerations

All power calculations were performed using Stata "power" package assuming a two-tailed α=0.05. The planned sample size for the trial is 50 subjects, randomized in a 1:1 ratio to anti-SARS-CoV-2 convalescent plasma versus control plasma. The primary analysis will compare the combined endpoint of mechanical ventilation or death in the anti-SARS-CoV-2 convalescent plasma and control groups.

We base our sample size projection on the ACTT-1 data [22]They reported the progression within 15 days separately for COVID-19 hospitalized requiring supplemental oxygen and those requiring high flow oxygen or non-invasive ventilation. The proportion progressing were 20% and 34%, respectively in the standard of care group and 8% and 25% in the remdesivir group progression. For our assumption we assume a 32% progression rate on the standard of care (no convalescent plasma) In the absence of treatment with convalescent plasma, we anticipate that between 10 to 30% will experience the primary outcome of mechanical ventilation or death . Using the Fisher exact test: we will reject the null hypothesis under the data scenario in the Table below.

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Rejection Region for the Fisher Exact Test

No. Mechanical ventilation/Death (%)	Control arm (%)	Active arm (%)
	5/25 (20%)	0/25 (0%)
	6/25 (24%)	<= 1/25 (4%)
	7/25 (28%)	<= 1/25 (4%)
	8/25 (32%)	<= 1/25 (4%)
	9/25 (36%)	<= 2/25 (8%)
	10/25 (40%)	<= 3/25 (12%)

We will use an 8-point ordinal scale to assess clinical status, based on WHO clinical trial guidance. We assume the same distribution of outcomes for the control arm (i.e., in the absence of treatment with

convalescent plasma) as in ACTT, as tabulated below. Assuming 25 participants are treated with convalescent plasma and 25 participants are untreated, we would have 80% power to detect a difference between treatment arms as follows:

Category	Control arm (%)	Active arm (%)
Death	12%	0
Hospitalized, on invasive mechanical ventilation plus additional organ support (pressors, RRT, ECMO)	0	0
Hospitalized, intubated and mechanical ventilation	20.0%	0
Hospitalized, on non-invasive ventilation or high flow oxygen devices;	12%	8%
Hospitalized, requiring supplemental oxygen fy mask or nasal prong	0	20%
Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise);	24%	12%
Not hospitalized, limitation on activities	16%	28%
Not hospitalized, no limitations on activities.	16%	32%

6.2 Statistical Analysis

6.2.1 Primary endpoint

Our primary hypothesis is that by providing anti-SARS-CoV-2 plasma, the rate of progression to mechanical ventilation or death will be decreased as compared to the rate in in the group receiving control plasma. We will apply a Fisher exact test to compare the combined endpoint of mechanical ventilation/death respiratory failure rates between the two groups occurring by day 15. 29. All analyses

will be conducted with a modified intention-to-treat approach, which excludes randomized subjects who do not initiate an infusion of the study plasma. As secondary analysis, we will also analyze the reduced oxygenation rate, requirement for supplemental oxygen rate, length of hospitalization, time to recovery (ordinal score 1-3) and mechanical ventilation rate, respectively, as well as occurrence of the primary endpoint by day 29 Statistical inference will be based on a two-sided Type 1 error rate of 0.05 and 95% confidence intervals.

Participants who are intubated for reasons other than hypercarbia/hypoxia, such as for a procedure or airway obstruction, will have ventilation settings evaluated to determine if need for ventilation due to hypoxia is meet. This will be determined by >12 hours of requirement for a mandatory mode of ventilation (volume control or pressure control) or Fi02 of > 40%. External adjudication of intubation for non-hypoxic/hypercarbic indication will be conducted.

6.2.2 **Secondary endpoint (clinical status):**

We will evaluate the clinical efficacy of CCP relative to the control arm in adults hospitalized with COVID-19 according to clinical status (8-point WHO ordinal scale) using a proportional odds model. Because clinical status is evaluated on multiple days, we will use a generalized estimating equations (GEE) approach to account for repeated measures within each patient. Changes in ordinal scale at each timepoint will be summarized by proportions.

6.2.3 **Other secondary endpoints:**

Differences in time-to-event endpoints (e.g., death, hospital discharge) will be summarized by treatment arm using Kaplan-Meier curves and 95% confidence bounds. Duration of events (e.g., days of hospitalization, supplemental oxygen, ventilation) will be summarized by treatment arm by median days with quartiles. Binary data (e.g., incidence of new oxygen use) will be summarized by treatment arm as percentages with 95% confidence intervals. Categorical data (e.g., 29-day mortality, ordinal scale by day) will be summarized by treatment arm as proportions by category and using odds ratios with 95% confidence intervals.

6.2.4 **Analysis of AE data**

Analysis of AE data will primarily be descriptive based on DAIDS toxicity table coding of events. Rates of AE will be compared between randomized arms using Fisher's Exact Test.

6.2.5 **Analysis of the anti-SARS-CoV-2 levels and inflammatory markers.**

Analysis of antibody levels will primarily be descriptive, comparing the geometric mean antibody levels at days 1,2,5,8,15, 29, and 120 between the randomized arms. Furthermore, it is of interest to describe the entire distributions of anti-SARS-CoV-2 antibody levels by randomized arms and contrast these distributions. Therefore, we will use quantile regression in order to describe whether there is a shift or change in the titer distribution between randomized arms. Given that repeated measures of antibody levels will be obtained, we will account for the correlation in measures within individuals using a cluster bootstrap

in order to properly estimate the p-value and 95% confidence intervals. Similar analysis will also be applied to lymphocyte counts on days 1,2,5,8,15, 29 hematological measurements (D-dimer, ferritin, hsCRP) on days 1,2,5,8,15, 29, 29, and other lab measures showing right-skewed distributions. Exploratory analyses of antibody isotypes,neutralizing antibody activity, antibody affinity, glycosylation and T-cell responses will be conducted to compare between arms and over time.

6.2.6 Analysis the rates, levels and duration of SARS-CoV-2 RNA in NP/MTN swabs

This secondary analysis will be primarily descriptive. The proportion positive at days 1,2,5,8, and 15 and whether individuals lose positivity status at a subsequent visit among those who were initially positive will be examined. To determine the proportion that are positive at each visit, we will do a pooled complementary log-log model in order to describe the cumulative incidence of SARS-CoV-2 positivity over time. The pooled complementary log-log model is a discrete time-to-event-analysis that estimates the log hazard rate at each discrete time point. Similar to the analysis of anti-SARS-CoV-2 antibody levels, the goal of this secondary aim is to describe the distribution of SARS-CoV-2 RNA between randomized arms. Therefore, we will use the same approach as that for the anti-SARS-CoV-2 antibody levels. Because the exact day that an individual becomes negative is not known, a minimum and maximum amount of positive time will be used to describe the positive duration of each individual. If the sample is adequate, we will describe the duration of positivity using a non-parametric approach for time-to-event analysis.

6.2.7 Analysis of ICU rate, in-hospital mortality and 29 day mortality

The goal is to compare ICU rate and mortality between randomized arms. We will use the same approach as above for the primary outcome (respiratory failure rate).

6.3 Adaptive trial design

During the conduct of this trial, new data may emerge to support the clinical and/or antiviral efficacy of an anti-COVID therapy such that this therapy becomes a standard of care. Should this occur, the sample size will be recalculated taking into account the anticipated effect size of the new therapy and any data to inform the anticipated additive or synergistic effect of the therapy when coadministered with CCP. This therapy will be incorporated into the study as soon as possible as the background standard of care, with an expanded sample size as appropriate.

7 HUMAN SUBJECTS PROTECTIONS

7.1 Risks and Benefits

Potential Benefits of Treatment: The potential benefits of antiviral treatment with anti-SARS CoV-2 plasma in patients with COVID-19 and respiratory symptoms consistent at high risk for respiratory decompensation are not known. We hypothesize that treatment will decrease the risk of disease progression requiring supplemental oxygen, ICU admission and aggressive respiratory support including possible mechanical ventilation (and other ICU support).

Potential Benefits of Clinical monitoring and Virologic Testing: Monitoring and testing are required to assess the effect of convalescent plasma on the course of COVID-19 respiratory disease.

7.1.1 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, coughing

Alternatives: The alternative to participation in this study is routine care.

7.1.2 Safety measures

1. Safety Evaluations will assess for clinical and laboratory indices of reactions to high antibody level anti-SARS-CoV-2 plasma and determine if they are higher, lower or the same as standard plasma
2. Clinical evaluations: Vital signs and symptom screen on days 1-8, 15 and symptom screens on days 29, and 120.
3. Laboratory evaluations to include chest radiography (chest x-rays and/or chest CT and/or ultrasound)

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 1-8 and 15 as specified by above plan.

7.2 Definitions

1. **Adverse 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.

2**. Serious Adverse Event (SAE):** 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.

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

4. **Serious and Unexpected Suspected Adverse Reaction (SUSAR):** An adverse reaction, the nature of which is not consistent with the investigator's brochure with severity as defined by SAE above.

5**. Unanticipated Problem (UP):** Unanticipated Problem that is not an Adverse Event (e.g. breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug).

6. **Protocol Deviation:** Deviation from the IRB-approved study procedures. Designated serious and non-serious

7. **Serious Protocol Deviation:** Protocol deviation that is also an SAE and/or compromises the safety, welfare or rights of subjects or others

7.3 Safety Reporting Requirements

7.3.1 Reporting Interval

All grade 3 and 4 AE's, grade 2 AE attributed to study product and SAEs will be documented from the first administration of study product. These AEs and SAEs will be followed until resolution even if AEs extend 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.

7.3.2 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 standard deviation increase above baseline.

7.3.3 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 graded using the DAIDS toxicity table
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

7.3.4 **Assessment of Association**

1. 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.

2. 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.

7.4 Safety Oversight

7.4.1 **Monitoring Plan**

1. AE requiring reporting as per above and SAE will be reviewed by protocol team weekly, or more often if needed.

2. A Safety Monitoring Committee (SMC) composed of independent experts without conflict of interests will be established. The SMC will review the study before initiation, after enrollment of patient 5 and patient 15, and monthly thereafter until enrollment completed. The SMC will review study data, including unblinded data, to evaluate the safety, efficacy, study progress, and conduct of the study.

7.5 Study compliance with clinical trial requirements

1. Study will be conducted in accordance with GCP and ICH. Specifically, regular QC will be conducted to document the following:

   a. There is documentation of the informed consent process and signed informed consent documents for each participant

   b. There is compliance with recording requirements for data points

   c. All SAEs are reported as required

   d. Individual participant study records and source documents align

   e. Investigators are in compliance with the protocol

   d. Regulatory requirements as per Office for Human Research Protections (OHRP), FDA, and applicable guidelines (ICH-GCP) are being followed.

8 STUDY MODIFICATION

8.1 Halting Criteria for the Study

The study enrollment and dosing will be stopped and an ad hoc review by the SMC will be performed if any of the specific following events occur or, if in the judgment of the study physician, participant 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 participant with an SAE associated with study product.

4. Two participants with a Grade 3 or higher lab toxicity for the same parameter associated with study product. (Grading will be assessed using DAIDS Toxicity Table https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf)

5. An overall pattern of symptomatic, clinical, or laboratory events that the SMC considers 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.

8.2 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 > 130 beats per minute; 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

9 ETHICS/PROTECTION OF HUMAN SUBJECTS

9.1 Ethical Standard

UCSF is committed to the integrity and quality of the clinical studies it coordinates and implements. UCSF will ensure that the legal and ethical obligations associated with the conduct of clinical research involving human subjects are met. The information provided in this section relates to all UCSF sites participating in this research study

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.

9.2 Institutional Review Board

This study will be reviewed by Advarra, under an intent to relay agreement via the UCSF IRB

9.3 Informed Consent Process

The informed consent process will be initiated before a volunteer agrees to participate in the study and should continue throughout the individual's study participation. Informed consent will be obtained in accordance with site SOP for COVID consenting and in compliance with current FDA guidance for consenting in setting of COVID pandemic https://www.fda.gov/media/136238/download. 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.

9.4 Subject Confidentiality

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

only by authorized personnel directly involved with the study and will be coded. Subjects' records will be available to the FDA, Vitalant, investigators at the site involved with the study, and the IRB.

9.5 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. No human genetic testing will be performed on the samples. 3 EDTA tubes and 1 SST tube will be collected (see Schedule of Events).. 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 included in this protocol unless outside investigators had relevant assays or expertise not available to the study investigators. The specimens would remain linked and at UCSF or with study collaborator Vitalant for 5 years. Any use of these specimens not specified in the current protocol will be reviewed by the Einstein IRB.

9.6 Data management and monitoring

9.6.1 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 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.

9.6.2 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.

9.6.3 **Data Capture Methods**

Clinical data will be entered into a 21 CFR 11-compliant Internet Data Entry System (IDES). The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

9.6.4 **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.

No study document should be destroyed. 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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