**CONVALESCENT PLASMA TO LIMIT CORONAVIRUS ASSOCIATED COMPLICATIONS: A RANDOMIZED BLINDED PHASE 2 STUDY COMPARING THE EFFICACY AND SAFETY OF ANTI-SARS-COV-2 PLASMA TO PLACEBO IN COVID-19 HOSPITALIZED PATIENTS**

**Protocol Version:** 1.0

**Protocol Date:** April 13, 2020

**LIST OF ABBREVIATIONS**

ADR: Adverse Drug Reaction

ADE: Antibody-mediated enhancement of infection

AE: Adverse Event/Adverse Experience

CBC: Complete Blood Count

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

NEWS 2- National Early Warning Score

NP: Nasopharyngeal

OHRP: Office of Human Research Protections

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

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

**PROTOCOL SUMMARY**

**Long title:** Convalescent Plasma to Limit Coronavirus Associated Complications: A Randomized Blinded Phase 2 Study Comparing the Efficacy and Safety of Anti-SARS-CoV-2 Plasma to Placebo in COVID-19 hospitalized patients

**Clinical Phase**: 2 Blinded

**Sample Size:** 300

**Study Population:** Hospitalized COVID-19 patients aged ≥18 years of age with respiratory symptoms within 3 to 7 days from the onset of illness OR within 3 days of hospitalization.

**Study Duration:** May 1, 2020 to January 31, 2023

**Study Design**: This randomized, blinded phase 2 trial will assess the efficacy and safety of anti-SARS-CoV-2 convalescent plasma in hospitalized patients with acute respiratory symptoms between 3 and 7 days after the onset of symptoms OR within 3 days of hospitalization. A total of 300 eligible subjects will be randomized in a 1:1 ratio to receive either convalescent plasma from people who have recovered from COVID-19 containing antibodies to SARS-CoV-2 or control (standard thawed plasma).

Stratified randomization by site and risk (high versus average risk).

Underlying risk based on pre-COVID 19 infection baseline characteristics:

* High risk: Any of the following: ≥60 years or age, immune compromised (immunosuppressive drugs, solid tumor, solid organ transplant, hematologic malignancies, hematologic stem cell transplantation, rheumatological disease on immunosuppressants, inflammatory bowel disease on immunosuppressants, asthma or COPD on chronic steroid therapy), diabetes mellitus, cardiovascular or pulmonary co-morbidities, HIV (CD4<200)
* Average risk: <60 years of age AND absence of immune compromise, diabetes mellitus, cardiovascular, pulmonary comorbidities, HIV (CD4>200)

**Data Collection:**

The following will be assessed in all subjects: (frequency noted in Table 1)

I. Clinical, Laboratory and Imaging Data

1. Date of Symptom Onset and history of presenting illness
2. Demographics: Age, sex, comorbidities, zip code, race/ethnicity, BMI
3. Vital Signs: Temperature, respiratory rate, blood pressure, oxygen saturation, oxygen requirements, NEWS score
4. Laboratory Data:
   * Hematologic Markers: CBC with differential (neutrophil, lymphocyte counts and platelet count explicitly recorded), PTT, LDH, D-dimer, fibrinogen, ferritin
   * Metabolic Markers: Creatinine, arterial blood gas, LFTs
   * Cardiac Markers: Troponin
   * Inflammatory Markers: CRP, procalcitonin
5. Chest imaging (CT or Chest x-ray), EKG and/or ultrasound: Day 0, and day14 or discharge whichever comes first and times obtained as part of standard care

II. Safety and Efficacy

1. Day 0 (baseline), 1, 2, 3, 7, 14, and 28 and once at 2-3 months.

III. SARS-CoV-2 Viral and Antibody Response – to be done at Montefiore Medical Center Sites

1. Serum or plasma antibody titer[[1]](#footnote-2) to SARS-CoV-2: Day 0, 1, 7, 14, 28, 90
2. SARS-CoV-2 PCR from nasopharyngeal swab, quantitative if available: Day 0, 7, 14, 28

IV. Outcome measures:

Primary Outcome: Status at 14 days (1 through 5). Effect size will be measured as the cumulative odds ratio comparing treatment to control, estimated using a cumulative proportional odds model that adjusts for initial status (indicator for status = 3 or status = 4).

**Study Agent:**

SARS-CoV-2 convalescent plasma (1-2 units; ~250-500 mL with antibodies to SARS-CoV-21 per April 8, 2020 directive <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>, pathogen reduced) obtained from New York Blood Center or American Red Cross

* Standard plasma[[2]](#footnote-3)

**Primary Objective:** Evaluate the efficacy of convalescent plasma from people who have recovered from COVID-19 containing antibodies to SARS-CoV-2 versus control (standard plasma) to prevent worsening respiratory status or death in hospitalized patients with COVID-19 who are within 3 days of presentation to the hospital or 3-7 days of symptom onset.

**Primary Endpoint**:

Primary Outcome: Status at 14 days (1 through 5, defined below). Effect size will be measured as the cumulative odds ratio comparing treatment to control, estimated using a cumulative proportional odds model that adjusts for initial status (indicator for status = 3 or status = 4).

Clinical Status Scale

1. Death;

2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);

3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

4. Hospitalized, requiring supplemental oxygen;

5. Discharged alive

Score 3 or 4 describes eligibility and a score of 1-5 defines the outcome status at 14 days:

**Secondary Objectives:**

Secondary outcome; same as above at 28 days.

**Exploratory objectives:**

1. Serum or plasma anti-SARS-CoV-2 IgM, IgG, IgA on Days 0, 7, 14, 28, 90
2. Serum or plasma SARS-CoV-2 neutralizing activity and antibody dependent cytotoxicity (ADCC) on Days Day 0, 7, 14, 28, 90
3. Rates, levels and duration of SARS-CoV-2 RNA in NP swabs using RT-PCR on days 0, 7, 14, 28. Other specimen types may be tested as available (*e.g.,* BAL fluid, tracheal secretions, sputum, etc.).
4. Lymphocyte and neutrophil counts on days 0, 3, 7, 14 or as obtained in care.
5. Hematological measurements (D-dimer, fibrinogen) on days 0, 3, 7, 14 or as obtained in care.
6. T and B cell subsets on days 0, 7, 28

**Safety**

1. Cumulative incidence of adverse events during the study period: transfusion reaction (fever, rash), transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion related infection.

**Study population**

**Inclusion Criteria for Enrollment:**

1. Patients ≥18 years of age
2. Hospitalized for COVID-19 respiratory symptoms
3. Hospitalized for less than 72 hours OR within day 3 to 7 from first signs of illness
4. Laboratory confirmed COVID-19
5. On supplemental oxygen, non-invasive ventilation or high-flow oxygen (clinical status 3 or 4)
6. N.B. It is assumed patients may be on other randomized controlled trials of pharmaceuticals for COVID -19 and patients who meet eligibility criteria will not be excluded on this basis.

**Exclusion Criteria**

1. Receipt of pooled immunoglobulin in past 30 days
2. Contraindication to transfusion or history of prior reactions to transfusion blood products
3. Invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
4. Volume overload secondary to congestive heart failure or renal failure

**RATIONALE/BACKGROUND:**

1. **Background and scientific rationale**

There are currently no proven treatment options for coronavirus disease (COVID-19) and the related pneumonia, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) beyond supportive care. 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 high titer (anti- SARS-CoV-2) neutralizing immunoglobulin-containing plasma. 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 anti-inflammatory activity (1). 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 (2, 3). Experience from prior outbreaks with other coronaviruses, such as SARS-CoV-1 shows that such convalescent plasma contains neutralizing antibodies to the relevant virus (4). 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 (5).

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 (6). 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 (2). 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) (7). Our goal is to treat patients who are sick enough to warrant hospitalization but do not have severe respiratory disease and/or ARDS.

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 (7). 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 SARS in Taiwan were treated with 500 ml of convalescent plasma, resulting in a reduction in plasma virus titer and each survived (8). Three patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients had neutralizing antibody in their plasma (9). The latter study highlights a challenge in using convalescent plasma; some who recover may not have high titers of neutralizing antibody (10). An analysis of 99 samples of convalescent sera from patients with MERS showed 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 titers to SARS-CoV-2 and using high titer antibody for treatment. Although the optimal titer for treatment of SARS-CoV-2 is not established, plasma with a neutralizing titer of at least 1:64 should be administered. However, it is possible non-neutralizing antibodies may also contribute to protection as described for other viral diseases (11, 12).

A recently performed pilot study in Wuhan, China collected convalescent 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 (13). 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 canula, 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 (14). Temperatures normalized in 4 of 5 patients within 3 days, NEWS 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.

There are limited data on use of convalescent plasma in pregnancy. A non-randomized comparative study that evaluated use of convalescent plasma for Ebola Virus Disease reported that eight out of 84 participants were pregnant and that mortality was 25% among pregnant women and 32% among non-pregnant individuals after receiving plasma treatment (15). A case series of 4 Chinese patients, among whom one was pregnant, received convalescent plasma and had recovered from SARS-CoV-2 infection (16). We do not have robust data of using convalescent plasma in pregnancy as most trials have excluded pregnant patients. IVIG therapy however is safe to give during pregnancy and is often used in those with inflammatory disorder and/or autoimmune conditions.

**INVESTIGATIONAL PLAN:**

**1. Study Objectives**

**Primary Objective:**

1. Evaluate the efficacy of high-titer anti-SARS-CoV-2 plasma versus control (standard plasma) to prevent worsening respiratory failure or death in hospitalized patients with COVID-19 who are within 3 days of presentation to the hospital or 3-7 days of symptom onset.

**Secondary Objectives:**

Secondary outcome; same as above at 28 days.

**Exploratory objectives:**

1. Compare the study (anti-SARS-CoV-2 convalescent plasma) and control (standard plasma) groups anti-SARS-CoV-2 titers at Days 0, 7, 14, 28, 90.
2. Compare the rates, levels and duration of SARS-CoV-2 RNA in NP swabs using RT-PCR between the study (anti-SARS-CoV-2 convalescent plasma) and control (standard plasma) groups at days 0, 7 14, 28. Other specimen types may be tested as available (*e.g.,* BAL fluid, tracheal secretions, sputum, etc.) or when RT-PCR assays are validated for additional sources (*i.e.,* stool, blood).
3. Mortality, in-hospital and Day 28; rates of ICU admission
4. Lymphocyte and neutrophil counts on days 0, 3, 7, 14 or as obtained in care; Hematological measurements (D-dimer, fibrinogen) on days 0, 3, 7, 14 or as obtained in care; and T and B cell subsets on days 0, 7, 28.

**Safety**

Cumulative incidence of serious adverse events during the study period: transfusion reaction (fever, rash), transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion related infection.

**2. 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 28, had an adverse event or death occurred prior to day 28. Patients will be asked to have day 60 and day 90 study visits as well.

**3. Study Population**

**Inclusion Criteria for Enrollment:**

1. Patients ≥18 years of age
2. Hospitalized for COVID-19 respiratory symptoms
3. Hospitalized for less than 72 hours OR within day 3 to 7 from first signs of illness
4. Laboratory confirmed COVID-19
5. On supplemental oxygen, non-invasive ventilation or high-flow oxygen (clinical status 3 or 4)
6. N.B. It is assumed patients may be on other randomized controlled trials of pharmaceuticals for COVID -19 and patients who meet eligibility criteria will not be excluded on this basis.

**Exclusion Criteria**

1. Receipt of pooled immunoglobulin in past 30 days
2. Contraindication to transfusion or history of prior reactions to transfusion blood products
3. Invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
4. Volume overload secondary to congestive heart failure or renal failure

**4. 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 may withdraw subjects if the investigator determines that continued participation in the study would be harmful to the subject or the integrity of the study data
4. Discontinuation of the study: The study sponsor, FDA and IRB all have the right to terminate this study at any time

**Table 1: Schedule of Evaluations**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study period** | **Screen** | **Baseline** | **Transfusion** | **Follow up** | | | | | |  |
| Day | -1 to 0 | 0 | 0 | 1 | 3 | 7 | 14 | 28 | 60 | 90 |
| Procedure |  |  |  |  |  |  |  |  |  |  |
| 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 for plasma compatibility | x |  |  |  |  |  |  |  |  |  |
| Chest imaging (CXRAY or CT scan), EKG | x1 |  |  |  |  |  | x1 |  |  |  |
| Oxygenation Level | x |  |  |  |  |  |  |  |  |  |
| Study Drug Administration | | | | | | | | | |  |
| Randomization |  | x |  |  |  |  |  |  |  |  |
| Drug infusion |  |  | x |  |  |  |  |  |  |  |
| Study Procedures |  |  |  |  |  |  |  |  |  |  |
| Vital signs | x | x | xxxx[[3]](#footnote-4) | x | x | x | x | x | x | x |
| Physical examination | x |  | x | x | x | x | x | x | x | x |
| Symptom screen | x | x | x | x | x | x | x | x | x | x |
| Concomitant medications | x | x | x |  |  |  |  |  |  |  |
| Assessment with 5-point ordinal scale |  | x |  | x | x | x | x | x | x | x |
| Chest imaging (CXR or CT scan), |  |  |  |  | x |  |  |  |  |  |
| Adverse event monitoring |  | x | x | x | x | x | x | x | x | x |
| Laboratory testing | | | | | | | | | |  |
| CBC and CMP |  | x |  | x | x | x | x |  |  |  |
| PTT, LDH, fibrinogen, CRP, procalcitonin, ferritin |  | x |  | x | x | x | x |  |  |  |
| Troponin |  | x |  | x | x | x | x |  |  |  |
| SARS-CoV-2 RT-PCR[[4]](#footnote-5) |  | x |  |  |  | x | x | x |  |  |
| SARS-CoV-2 antibody |  | x | x2 | x |  | x | x | x |  | x |
| Blood for future testing (including IL-6, cytokines) |  | x |  | x |  | x | x | x |  | x |

1EKG, Chest imaging on admission or thereafter, before randomization. Repeat at 14 days or discharge, whichever comes first.

2 Blood bank collects from plasma tail bag for antibody testing

1. **Treatment**
2. Subjects will be randomized in a 1:1 ratio to receive study drug (convalescent plasma) versus standard plasma; randomization will be stratified by site and risk.
3. Study drug: The investigational product is anti-SARS-CoV-2 convalescent plasma. Patients identified as having recovered from COVID-19 will serve as potential donors as per FDA guidelines (<https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>).

As blood banks and/or the FDA revised guidelines for convalescent plasma donation – *the following criteria may be implemented*:

SARS-CoV-2 convalescent plasma donors must meet the following critera:

1. Diagnosed with COVID as documented by a physician with symptoms that included:
   1. Fever
   2. Cough
   3. OR a positive COVID RT-PCR assay
   4. OR evidence of antibodies to SARS-CoV-2
   5. AND complete resolution of symptoms at least 14 days prior to donation
2. Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.
3. Potential donors and samples will be screened per New York Blood Center guidelines.
4. Treatment arm will receive 1-2 units of plasma with antibodies to SARS-CoV-2 per April 8, 2020 guidelines (<https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>).
5. Control arm will receive 1 unit of standard plasma
6. Both treatment and control plasma will be in standard plasma unit bags, with a study specific International Society of Blood Transfusion (ISBT) label

6. **Randomization:**

1. Subjects enrolled in the study will be randomized using an interactive web response system (IWRS) to receive study drug versus placebo at a 1:1 ratio with stratification by site and risk (high versus average).
2. **Rationale for Dosing**

Two units of plasma (approximately 250-500mL) containing anti-SARS2-CoV-19 antibodies and aim for a titer ≥1:160 per April 8, 2020 guidelines (<https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>).

We will utilize 2 units (~ 500 mL) of plasma with antibodies to SARS-CoV-as per April 8, 2020 FDA guidelines: <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>. Dosing is based on experience with previous use of convalescent plasma therapy in SARS1 where 5 mL/kg of plasma at titer  1:160 was utilized (7). For a 70 Kg person plasma volume is estimated at 2800 mL (40 mL/kg x70 kg) with baseline anti-SARS-CoV-2 titer of 0. For example, if protective titer was 1:25 and each unit had titer of 1:160, ~300 mL can achieve this ([250/(2800+250)] x 1:160*>*1:25).

At the discretion of the treating physician, one unit may be administered if the patient is deemed to be at high risk of circulatory overload.

8. **Study drug administration**

1. Drug will be administered within 24 hours of randomization
2. Infusion rate ≤ 500 mL/hour
3. Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given. Individual institutional guidelines/SOPs for the administration of plasma should be followed, including the use of any premeditations, such as acetaminophen and diphenhydramine.
4. 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. Concomitant medications will be documented on the Case Report Form (CRF)

* Prescription medications
* Over the counter medications
* Herbal treatments/nutritional supplements
* Blood products
* Any medications with established activity against SARS-CoV-2 that subject is receiving

**STATISTICAL PLAN**

1. **Sample Size and Power Considerations**

The planned sample size for the trial is 300 subjects, randomized in a 1:1 ratio stratified by site and risk (high versus average) to receive anti-SARS-CoV-2 convalescent plasma versus control plasma. The primary analysis will compare the efficacy of anti-SARS-CoV-2 convalescent plasma using a proportional odds model. We estimated the sample size of the proportional odds model by simulations assuming a two-sided Type I error rate (alpha) of 0.1 and 80% power. We made the following additional assumptions:

* + 1. 30% incidence of worsening respiratory status (10% death and 20% on invasive mechanical ventilation or ECMO, respectively) and 10% of discharged alive in the control group estimated by current data from our hospital,
    2. 1.7 odds ratio (OR) of worsening respiratory status between the control group and the anti-SARS-CoV-2 convalescent plasma group, this corresponds to an 11% absolute reduction in incidence of worsening respiratory status (6% death and 13% on invasive mechanical ventilation or ECMO, respectively) and 8% absolute increase of discharged alive using anti-SARS-CoV-2 convalescent plasma.
    3. Very few subjects will be randomized and fail to receive study plasma infusion or will be lost to follow-up and have missing data for the primary endpoint.

We estimated a sample size of 300 patients (150 in each arm) would be sufficient to detect the specified difference in clinical status between the two arms with a power of at least 0.8.

1. **Statistical Analysis**
   1. **Primary endpoint:**

Our primary hypothesis is that by providing anti-SARS-CoV-2 plasma, the proportional odds of worsening respiratory failure or death will be decreased as compared to the rate in the group receiving control plasma. We will apply a cumulative proportional odds model adjusting for initial status, site, and underlying risk. The general form of the cumulative proportional odds model will be: , j=1,…,4, in which Y is the status, X is the treatment, C is a covariate, and are the regression coefficients for the treatment and covariate. The is the corresponding OR ratio of treatment. 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. In secondary analysis, we will use inverse probability of selection weights to account for the individuals who did not initiate their assigned treatment. As secondary analysis, we will also analyze the reduced oxygenation rate, requirement for supplemental oxygen rate, and mechanical ventilation rate, respectively. Statistical inference will be based on a two-sided Type 1 error rate of 0.05 and 95% confidence intervals.

1. **Analysis of AE data**

Analysis of AE data will primarily be descriptive based on MedDRA coding of events. AE will be compared between randomized arms using Fisher’s Exact Test.

1. **EXPLORATORY ANALYSIS**
   1. **Analysis of the anti-SARS-CoV-2 titers**

Analysis of titers will primarily be descriptive, comparing the geometric mean titers at days 0, 7, 14, 28, 60 between the randomized arms. It is also of interest to describe the entire distributions of anti-SARS-CoV-2 titers by randomized arms and contrast these distributions. Therefore, we will use quantile regression to describe whether there is a shift or change in the titer distribution between randomized arms. Given that repeated measures of titers 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 and neutrophil counts on days 0, 3, 7, 14 or as obtained in care, hematological measurements (D-dimer, fibrinogen) on days 0, 3, 7, 14 or as obtained in care, and T and B cell subsets on days 0, 7, 28.

* 1. **Analysis the rates, levels and duration of SARS-CoV-2 RNA in NP swabs**

This exploratory analysis will be primarily descriptive. The proportion positive at days 0, 1, 7, 28 and whether individuals lose positive status at a subsequent time. To determine the proportion that are positive, 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. Like the analysis of anti-SARS-CoV-2 titers, 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 for the anti-SARS-CoV-2 titers. 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.

3.3 Mortality, in-hospital and Day 28; rates of ICU admission

Standard chi-square test will be applied to compare the two groups. Logistic regression will also be applied to adjust for the randomization stratification factors (age, immune compromised status, and comorbidity status) and any baseline variables that appear to be imbalanced across treatment arms despite randomization.

3.4 Lymphocyte and neutrophil counts on days 0, 3, 7, 14 or as obtained in care; Hematological measurements (D-dimer, fibrinogen) on days 0, 3, 7, 14 or as obtained in care; and T and B cell subsets on days 0, 7, 28, 90. We will use the same approach as above.

**STUDY PROCEDURES**

**1. Study Protocol by Day:**

**Day -1 to 0:**

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
      * Medications, allergies
      * Any medical condition arising after consent to be recorded as AE.

3. COVID-19 symptom screen:

* + - * Symptoms: Fevers, cough, shortness of breath.
      * History of illness: Onset of symptoms, source of contagion

4. Vital signs

5. COVID-19 testing (RT-PCR)

* + - * Nasopharyngeal, oropharyngeal, tracheal aspirate, bronchoalveolar lavage and/or stool (optional) samples

6. Baseline Basic Lab Testing and imaging

* + - * Blood typing, CBC, comprehensive metabolic panel
      * Chest imaging (CXRAY or CT scan), EKG

7. Serological testing: anti-SARS CoV-2 titers

8. Stored samples for future studies

9. Urine or serum pregnancy test

* + - * For females of childbearing potential ≤54 years (standard of care)
      * Results from laboratory tests obtained up to 7 days before enrollment may be used for the pregnancy test

10. Determination of eligibility

* + - * Inclusion/exclusion criteria age
      * Consent
      * Positive for COVID-19
      * Respiratory symptoms, not already an ICU patient
      * Between day 3 and 7 of first sign of illness or within 72 hours of admission

**Day 0:**

1. Randomization of eligible subject in IWRS
2. Study Plasma Administration:
   * 1. 1-2 units of plasma will be transfused
     2. Time at start and end of infusion will be recorded
     3. 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. Blood bank will collect plasma bag tail segment for SARS-CoV-2 and antibody titers
3. COVID-19 symptom screen:fevers, cough, shortness of breath
4. Assessment of clinical status (5-point ordinal scale)
5. New medical conditions, concomitant medication, AE evaluation
6. Physical examination (standard of care/per protocol)
7. COVID-19 testing (RT-PCR): nasopharyngeal samples
8. Blood typing, CBC, comprehensive metabolic panel, C-reactive protein, PTT, LDH, fibrinogen, procalcitonin, troponin, NT pro-BNP, D-dimer and CPK.
9. Serological testing: anti-SARS CoV-2 titers
10. Stored samples for future studies (IL-6, cytokines, CD4-CD8, HLA-DR)

**Day 1-7 (or for duration of hospitalization):**

1. Vital signs daily
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (5-point ordinal scale)
4. New medical conditions, AE evaluation
5. Physical examination (standard of care/per protocol)
6. CBC, comprehensive metabolic panel, CRP daily, PTT, LDH, fibrinogen, procalcitonin, troponin, CPK, D-Dimer, NT pro-BNP
7. Serological testing: anti-SARS CoV-2 titers
8. Stored samples for future studies
9. CXR (day 3) (or CT with increased oxygen requirement)
10. EKG (day 3 and 7 post plasma infusion)
11. Echocardiogram parameters and right and/or left heart cardiac catheterization data, if performed for clinical care

**Day 14 (if still hospitalized):**

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (5-point ordinal scale)
3. New medical conditions, AE evaluation
4. Physical examination (standard of care/per protocol)
5. CBC, comprehensive metabolic panel, CRP, PTT, LDH, fibrinogen, procalcitonin, troponin, CPK, D-dimer and NT pro-BNP
6. Serological testing: anti-SARS CoV-2 titers
7. Blood Direct PCR: SARS CoV-2
8. Stored samples for future studies

**Day 28 (if still hospitalized or as outpatient):**

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (5-point ordinal scale)
3. New medical conditions, AE evaluation
4. Serological testing: anti-SARS CoV-2 titers
5. Blood Direct PCR: SARS CoV-2
6. Define disposition (home, hospital, status)
7. Pulmonary status (supplemental oxygen)
8. Stored samples for future studies

**Day 60 (as outpatient, phone call or in-person follow-up):**

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (5-point ordinal scale)
3. New medical conditions, AE evaluation
4. Define disposition (home, hospital, status)
5. Pulmonary status (supplemental oxygen)

**Day 90 (as outpatient):**

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (5-point ordinal scale)
3. New medical conditions, AE evaluation
4. Serological testing: anti-SARS CoV-2 titers
5. Blood Direct PCR: SARS CoV-2
6. Define disposition (home, hospital, status)
7. Pulmonary status (supplemental oxygen)
8. Stored samples for future studies

**2. Efficacy, Virology, Serology and PK Measures:**

**Clinical Efficacy (ordinal scale):**

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

**SARS-CoV-2 Viral and Antibody Response**

1. Rates, levels and duration of SARS-CoV-2 RNA in NP swabs by RT-PCR

* + - Day 0, 7, 14, 28
    - Other specimen types may be tested as available (*e.g.,* BAL fluid, tracheal secretions, sputum, etc.) or when RT-PCR assays are validated for additional sources (*i.e.,* stool, blood).

2. Serologic positivity and neutralization antibody titers for anti-SARS-CoV-2

* + - Day 0, 7, 14, 28, 90

**HUMAN SUBJECTS PROTECTIONS**

**1. RISK/BENEFIT ASSESSMENT**

**Known potential risks**

* 1. 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 (17). It may be possible to predict the risk of ADE in SARS-CoV-2 experimentally, as proposed for MERS (17). 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 (18) demonstrated it is safe and there were no adverse effects in a pilot study of patients with COVID-19 (13). Nevertheless, caution and vigilance will be exercised to use clinical and laboratory measures to detect evidence of enhanced infection.
  2. Another theoretical risk is that antibody administration 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 (19). 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*.*
  3. 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. To minimize the risks of disease transmission, all plasma will be screened for blood borne pathogens, and pathogen reduction techniques will be utilized to prepare the plasma using standardly accepted FDA guidelines that oversee plasma collection. In addition, donors will fulfill donor requirements which require a history of COVID-19 illness, a positive COVID-19 test, a two-week period of being asymptomatic post infection and a negative nasopharyngeal swab for SARS-CoV2 by PCR. These patients will be screened for high titers against SARS-CoV2 and referred to NYC Blood Bank or American Red Cross for apheresis (plasma donation).

**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 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 (1). 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 (13).

**Assessment of potential risks and benefits**

Given historical data showing convalescent plasma was safe and possibly effective in patients with SARS1 (7, 18), and emerging data from China suggest it is safe and possibly effective in patients with severe COVID-19 along with the relative lack of other readily available therapeutic options for severe or life-threatening disease, 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 trial to assess the efficacy of convalescent plasma in preventing respiratory progression in patients with COVID-19. A recent JAMA editorial by experts note the importance of randomized clinical trials to demonstrate efficacy of this approach and change the course of the epidemic (20).

In pregnant woman and fetus there are limited data on potential risks and/or benefits. Pregnancy can cause changes in the coagulation and fibrinolytic systems and convalescent plasma may potentially benefit individuals but providing the coagulation factors.

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

**2. Safety measures**

1. Safety Evaluations will assess for clinical and laboratory indices of reactions to high titer 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 0-7, 14 and symptom screens on days 28, 60, and 90.
3. Laboratory evaluations to include chest radiography (chest x-rays and/or chest CT and/or ultrasound)

Safety laboratory tests (ABO typing, urine or serum pregnancy testing, CBC, comprehensive metabolic panel, PTT, LDH, fibrinogen, CRP, procalcitonin, troponin and CPK) will be performed at the local CLIA-certified clinical laboratory on days 0-7 and 14 as specified by above plan.

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

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

* **Serious and Unexpected Suspected Adverse Reaction (SUSAR):** An adverse reaction, the nature of which is not consistent with the investigator’s brochure with severity as defined by SAE above.
* **Unanticipated Problem (UP):** Unanticipated Problem that is not an Adverse Event (e.g. breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug).
* **Protocol Deviation:** Deviation from the IRB-approved study procedures. Designated serious and non-serious

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

**4. Safety Reporting Requirements**

**Reporting Interval**

All AEs and SAEs will be documented from the first administration of study product. All 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.

**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.

**Assessment of Seriousness**

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

2. Assessment of Severity

**Event severity will be assigned according to the scale below**

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

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

*3 = Severe:* Escalation of medical intervention/therapy required

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

*5 = Death*

**Assessment of Association**

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.

1. 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.

**5. Safety Oversight**

**Monitoring Plan**

1. All AE and SAE will be reviewed by protocol team weekly, or more often if needed.
2. A medical monitor will be appointed by the study team for safety oversight of the clinical study.
3. A data safety monitoring board (DSMB) composed of independent experts, including infectious diseases and hematology specialists, without conflict of interests will be established. The DSMB reports will be disseminated to all other participating site at least annually. If there is any information that suggests the changed risk of the study or lack of benefit, the report will be distributed to other sites within 2 days. The DSMB will review the study before initiation, after enrollment of patient 10, patient 20, then at the midpoint of enrollment and at least yearly thereafter. The DSMB will review study data to evaluate the safety, enrollment, efficacy, study progress, and conduct of the study.
4. An Independent Safety Monitor (ISM) will be appointed. The ISM is a physician with expertise in infectious diseases and whose primary responsibility is to provide timely independent safety monitoring. An ISM is in close proximity to the study site and has the authority to readily access study participant records. The ISM reviews any SAE that occurs at the study site in real time and provides a written assessment to DMID.

**6. Study monitoring**

1. As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored. The study team will verify that
   * + 1. There is documentation of the informed consent process and signed informed consent documents for each participant
       2. There is compliance with recording requirements for data points
       3. All SAEs are reported as required
       4. Individual participant study records and source documents align
       5. Investigators are in compliance with the protocol
       6. Regulatory requirements as per Office for Human Research Protections (OHRP), FDA, and applicable guidelines (ICH-GCP) are being followed.

**STUDY MODIFICATION**

**1. Halting Criteria for the Study:** The study enrollment and dosing will be stopped and an ad hoc review will be performed if any of the specific following events occur or, if in the judgment of the study physician, 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 Common Terminology Criteria for Adverse Events (CTCAE) grading scale developed by NCI, NIH , https://evs.nci.nih.gov/ftp1/CTCAE/About.html)
      5. An overall pattern of symptomatic, clinical, or laboratory events that the medical monitor, or DSMB consider associated with study product and that may appear minor in terms of individual events but that collectively may represent a serious potential concern for safety.
      6. Any other event(s) which is considered to be a serious adverse event in the good clinical judgment of the responsible physician. This will be appropriately documented.

**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

**ETHICS/PROTECTION OF HUMAN SUBJECTS**

1. **Ethical Standard**

All sites conducting this study are committed to the integrity and quality of the clinical studies it coordinates and implements according with local institutional and regulatory requirements.

All sites participating in this research have a Federal wide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP).

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

**2. Institutional Review Board**

The Albert Einstein College of Medicine IRB will review this protocol and all protocol-related documents and procedures as required by OHRP and local requirements before subject enrollment.

3. **Informed Consent Process**

Each site will follow institution specific policy and process for consenting participants of legally authorized representatives for the study. A site specific protocol addendum will be provided by each site to the respective IRB.

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.

**3. Subject Confidentiality**

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

**4. 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. Each specimen will be assigned a unique identifier at the time of collection. The identifier links the information it contains to the labeled specimen. The risk of collection of the sample will be the small risk of bruising or fainting associated with phlebotomy however these samples will be taken at the same time as other protocol required samples. No human genetic testing will be performed on the samples. Five ml of blood samples will be collected at 5 time points (See Schedule of Events). Serum and PBMCs will be frozen in aliquots and stored in Dr. Pirofski’s laboratory freezer at Albert Einstein College of Medicine as de-identified, coded samples. Studies on these samples will answer important questions on the antibody response to SARS-CoV-2 that will inform future therapeutic development, interventions, and vaccine development. For example, it is unknown which type of antibody will provide protection. Studies on these patients’ antibodies and immune responses may help determine the best viral antigen to target, provide insights into the role of neutralizing versus non neutralizing antibody; identify minimum required titers and functional attributes of antibodies needed to achieve a clinical response. Similarly, COVID-19 protective cellular responses are unknown. The analysis of these samples will allow immunophenotyping studies to characterize the functional state of cellular responses associated with clinical outcomes and antibody responses. The goal of these studies is to fill information gaps to inform the design of future therapeutics such as vaccines, monoclonal antibodies and immune modulators. These immune assays can also be used in the future for more granular prognostic indicators. 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 will not be shared with investigators other than investigators included in this protocol. The specimens will remain linked and at Montefiore Medical Center for 5 years. Storage beyond the study length will be an option. Any use of these specimens not specified in the current protocol will be reviewed by the Einstein IRB.

**5. Data management and monitoring**

* 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.

b. 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.

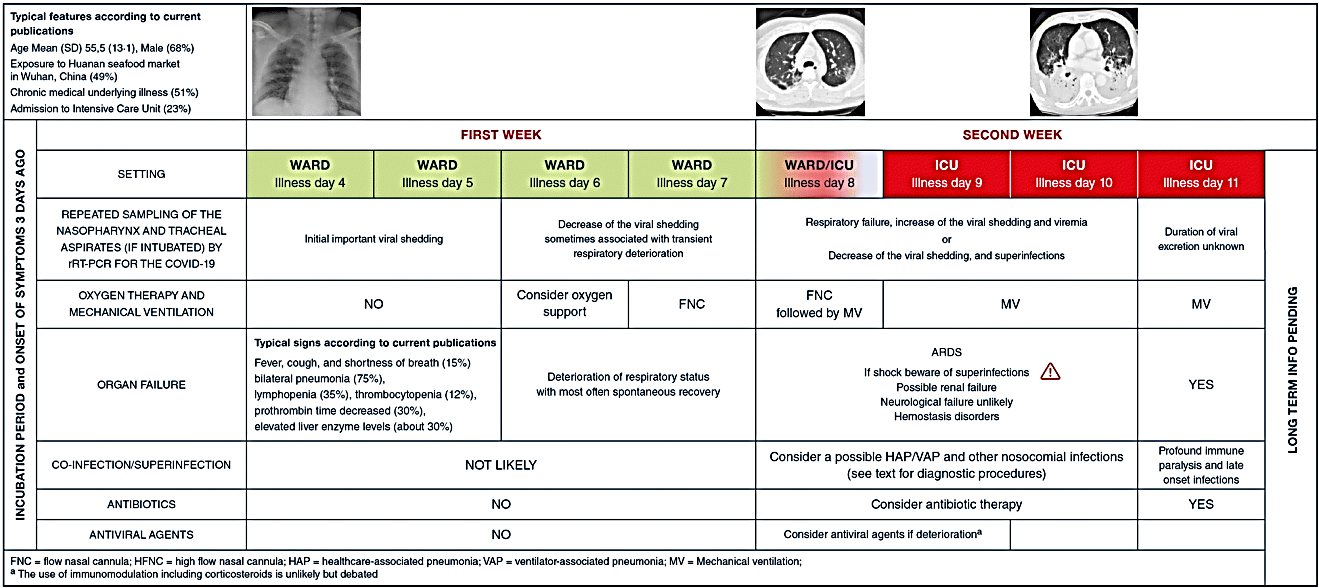
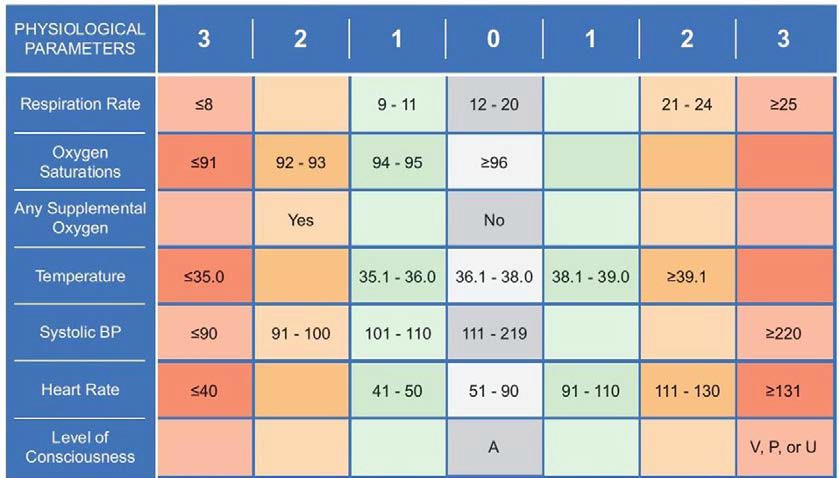
c. Data Capture Methods

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.

1. 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.

**Figure 2** NEWS score

**Figure 1** Describes what is known about the potential course of patients with COVID-19 pneumonia. The goal of this protocol is to administer convalescent plasma in the “green” area to evaluate its ability to improve the clinical respiratory status of the patient and avoid the need for respiratory support, mechanical ventilation and/or ICU admission. (from Bouadma et al Int Care Med 2020)

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1. Measured via initial anti-SARS-CoV-2 ELISA. [↑](#footnote-ref-2)
2. Solvent detergent treated pooled plasma [↑](#footnote-ref-3)
3. 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 [↑](#footnote-ref-4)
4. Sites could include nasopharyngeal and throat. [↑](#footnote-ref-5)