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 (CONTAIN COVID-19)

Protocol Version: 3

Protocol Date: February 11, 2021

IND 20427

ClinicalTrials.gov Identifier: NCT 04364737

LIST OF ABBREVIATIONS

ADR: Adverse Drug Reaction
ADE: Antibody-mediated enhancement of infection
AE: Adverse Event/Adverse Experience
AFib: Atrial fibrillation
CBC: Complete Blood Count
CDC: United States Centers for Disease Control and Prevention
CFR: Code of Federal Regulations
CHF: Chronic heart failure
CLIA: Clinical Laboratory Improvement Amendment of 1988
COI: Conflict of Interest
COPD: Chronic obstructive pulmonary disease
COVID-19: Coronavirus Disease
CRF: Case Report Form
CRP: C-Reactive Protein
CP: Convalesced Plasma
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
ILD: Interstitial lung disease
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
NP: Nasopharyngeal
NYBC: New York Blood Center
SS: Saline Solution (defined as half-, quarter- or normal saline)
OHRP: Office of Human Research Protections
OP: Oropharyngeal
OSA: Obstructive sleep apnea
RT-PCR: Reverse Transcriptase Real-Time Polymerase Chain Reaction
PK: Pharmacokinetic
SAE: Serious Adverse Event
SAP: Statistical Analysis Plan
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 (CONTAIN COVID-19)

Clinical Phase: 2 Blinded

Sample Size: Enrollment will be adapted based on continuous Bayesian monitoring as detailed in the SAP. The estimated total sample size for the trial is >1000 subjects

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

Study Composition: NYU Langone Heath will serve as the Clinical and Data Coordinating Center for the study under IND 20427. Collaborating sites will contribute recruitment and conduct the study per the FDA approved protocol with oversight by their individual IRBs.

Study Duration: April 17, 2020 to January 31, 2023

Study Design: This trial design is built as a process with the possibility of multiple interventions being investigated. The trial is designed to be flexible, and these flexible aspects are designed and planned as part of the protocol. This trial may incorporate a flexible number of interventions, with the possibility of these numbers evolving as the science evolves. Each period of the study where intervention arms are added or dropped will be considered a separate study *Stage*, though the model will analyze all stages simultaneously.

Study Stages and Interventions: The first stage of the study has been determined. In Stage 1, there will be two intervention arms: (1) placebo control, Saline Solution (SS is defined as half-,quarter-, or normal saline), and (2) SARS-CoV-2 Convalescent Plasma (1 unit). Stage 2 has not yet been defined given that results from Stage 1 will guide how to structure the two arms for Stage 2 and subsequent Stages. Once each study Stage is completed and prior to initiating the subsequent study Stage, a protocol modification describing the specific arms and approach will be made to the IRB for review and approval.

Randomization: Randomization assignments are performed for patients at baseline. Randomization is performed separately by two strata, treatment site and risk of severe disease (high versus lower) as defined below. The randomization scheme will be determined by the study *Stage* and its associated group of intervention arms (For example, in Stages 1 and 2, subjects will be randomized to 1:1 ratio). Randomization should obviate the need for additional adjustment factors but if pre-specified demographic or clinical characteristics are unbalanced with respect to treatment group, we will consider adjustment; these characteristics include but are not limited to age, sex, race, ethnicity, BMI and COVID severity at baseline.

Risk for severe COVID-19 based on baseline characteristics:
- <u>High risk</u>: Subjects with age ≥60 years or, age <60 and at least one of the following:
  - Chronic pulmonary conditions (COPD, OSA, ILD, etc)
  - Chronic heart conditions (CHF with NYHA>= class 2, AFib, ischaemic heart disease, etc)
  - Hypertension
  - Chronic kidney disease with eGFR < 60 mL/min
  - Body Mass Index >=35
  - Diabetes mellitus

- Immunosuppression (CD4<200, on immunosuppressive medications for autoimmune conditions, cancers, solid or stem cell transplants, steroids such as prednisone >10mg/day or equivalent)

- <u>Lower risk</u>: Subjects with age <60 and without the presence of any high risk factors listed above.

Data Collection:
The following will be assessed in all subjects: (detailed schedule of assessments is found 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
4. Laboratory Data:
   o Hematologic Markers: CBC with differential (neutrophil, lymphocyte counts and platelet count explicitly recorded), PTT, LDH, D-dimer, fibrinogen, ferritin
   o Metabolic Markers: Complete metabolic panel, LFT
   o Cardiac Markers: Troponin, (pro-)BNP
   o Inflammatory Markers: CRP, procalcitonin
5. Chest imaging (CT or Chest x-ray), EKG, echocardiogram if done: Day 0, Day 3, and Day 14 or discharge whichever comes first and times obtained as part of standard care
6. Venous duplex of lower extremities as clinically indicated
7. Evaluation for pulmonary embolism as clinically indicated

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 selected Sites
1. Serum or plasma antibody titer[1] 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, 90

IV. Outcome measures:
Primary Outcome: Status at 14 days using the WHO 11-point ordinal scale for clinical improvement which ranges from 0 (uninfected) to 10 (death). Effect size will be measured as the cumulative odds ratio comparing treatment to placebo control, estimated using a cumulative proportional odds model that adjusts for initial status (indicator for status = 5 or status = 6).

Study Product:
- SARS-CoV-2 CP (1-2 units; ~250-500 mL with antibodies to SARS-CoV-2[1] per May 1, 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, obtained from New York Blood Center (NYBC) collected per their protocol (https://www.nybc.org/donate-blood/covid-19-and-blood-donation-copy/convalescent-plasma/).
- Equivalent volume of SS

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

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[1] Vetted for SARS-CoV-2 IgG by platform used by NYBC.

Primary Endpoint:

Primary Outcome: Status at 14 days using the WHO 11-point ordinal scale for clinical improvement which ranges from 0 (uninfected) to 10 (death). Effect size will be measured as the cumulative odds ratio comparing treatment to placebo control, estimated using a cumulative proportional odds model that adjusts for initial status (indicator for status = 5 or status = 6).

WHO ordinal scale for clinical improvement

Patient State	Score	Descriptor
Uninfected	0	Uninfected; no viral RNA detected
Ambulatory	1	Asymptomatic; viral RNA detected
	2	Symptomatic; Independent
	3	Symptomatic; assistance needed
Hospitalized: Mild disease	4	Hospitalized; no oxygen therapy
	5	Hospitalized; oxygen by mask or nasal prongs
Hospitalized: Severe disease	6	Hospitalized; oxygen by NIV or High flow
	7	Intubation & Mechanical ventilation; pO2/FIO2 >/= 150 or SpO2/FIO2 >/=200
	8	Mechanical ventilation pO2/FIO2 < 150 (SpO2/FIO2 <200) or vasopressors
	9	Mechanical ventilation pO2/FIO2 < 150 and vasopressors, dialysis or ECMO
Death	10	Dead

Secondary Objectives:

Secondary outcome; same as above at 28 days.

Exploratory objectives (To be performed on selected sites):
1. Serum or plasma anti-SARS-CoV-2 IgM, IgG, IgA on Days 0, 1, 7, 14, 28, 90
2. Serum or plasma SARS-CoV-2 neutralizing activity and antibody dependent cytotoxicity (ADCC) on Days 0, 1, 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, 90. Other specimen types may be tested as available (*e.g.,* BAL fluid, tracheal secretions, sputum, etc.).
4. Lymphocyte and neutrophil counts on days 0, 1, 3, 7, 14 or as obtained in care.
5. Hematological measurements (D-dimer, fibrinogen) on days 0, 1, 3, 7, 14 or as obtained in care.
6. Lymphocyte subsets and cytokine panel on days 0, 1, 7, 14, 28, 90

Safety objectives:
- Safety monitoring will be per DSMB

Study population:
Inclusion Criteria
1. Patients ≥18 years of age
2. Hospitalized with laboratory confirmed COVID-19
3. One or more of the following respiratory signs or symptoms: cough, chest pain, shortness of breath, fever, oxygen saturation ≤ 94%, abnormal CXR/CT imaging
4. Hospitalized for ≤ 72 hours OR within 7 days from first signs of illness
5. On supplemental oxygen, non-invasive ventilation or high-flow oxygen
6. 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 any Covid-19 vaccine or participation in a Covid-19 vaccine study as a subject.
2. Receipt of pooled immunoglobulin in past 30 days
3. Contraindication to transfusion or history of prior reactions to transfusion blood products
4. Invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
5. Volume overload secondary to congestive heart failure or renal failure
6. Unlikely to survive past 72 hours from screening based on the assessment of the investigator
7. Unlikely to follow-up or clinical assessment will be hindered by patient's poor functional status

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.

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

In the 21st century, there were two other epidemics with coronaviruses that were associated with high mortality, 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, 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: Evaluate the efficacy of convalescent plasma from people who have recovered from COVID-19 containing antibodies to SARS-CoV-2 versus control (SS) to prevent worsening respiratory status or death in hospitalized patients with COVID-19 who are within 3 days of presentation to the hospital or within 7 days of symptom onset.

Primary Endpoint:
Primary Outcome: Status at 14 days using the WHO 11-point ordinal scale for clinical improvement which ranges from 0 (uninfected) to 10 (death). Effect size will be measured as the cumulative odds ratio comparing treatment to placebo control, estimated using a cumulative proportional odds model that adjusts for initial status (indicator for status = 5 or status = 6).

WHO ordinal scale for clinical improvement

Patient State	Score	Descriptor
Uninfected	0	Uninfected; no viral RNA detected
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	7	Intubation & Mechanical ventilation; pO2/FIO2 >/= 150 or SpO2/FIO2 >/=200
	8	Mechanical ventilation pO2/FIO2 < 150 (SpO2/FIO2 <200) or vasopressors
	9	Mechanical ventilation pO2/FIO2 < 150 and vasopressors, dialysis or ECMO
Death	10	Dead

Secondary Objectives:
Secondary outcome; same as above at 28 days.

Exploratory objectives (To be performed at selected sites):
1. Serum or plasma anti-SARS-CoV-2 IgM, IgG, IgA on Days 0, 1, 7, 14, 28, 90
2. Serum or plasma SARS-CoV-2 neutralizing activity, antibody dependent cytotoxicity (ADCC) and phagocytosis (ADCP) on Days 0, 1, 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, 90. Other specimen types may be tested as available (*e.g.,* BAL fluid, tracheal secretions, sputum, etc.).
4. Lymphocyte and neutrophil counts on days 0, 1, 3, 7, 14 or as obtained in care.
5. Hematological measurements (D-dimer, fibrinogen) on days 0, 1, 3, 7, 14 or as obtained in care.
6. Lymphocyte subsets and cytokine panel on days 0, 1, 7, 14, 28, 90

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:
1. Patients ≥18 years of age
2. Hospitalized with laboratory confirmed COVID-19
3. One or more of the following respiratory signs or symptoms: cough, chest pain, shortness of breath, fever, oxygen saturation ≤ 94%, abnormal CXR/CT imaging
4. Hospitalized for ≤ 72 hours OR within 7 days from first signs of illness
5. On supplemental oxygen, non-invasive ventilation or high-flow oxygen
6. 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 any Covid-19 vaccine or participation in a Covid-19 vaccine study as a subject.
2. Receipt of pooled immunoglobulin in past 30 days
3. Contraindication to transfusion or history of prior reactions to transfusion blood products
4. Invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
5. Volume overload secondary to congestive heart failure or renal failure
6. Unlikely to survive past 72 hours from screening based on the assessment of the investigator
7. Unlikely to follow-up or clinical assessment will be hindered by patient's poor functional status

4. Subject Withdrawal

- Subjects can terminate study participation and/or withdraw consent at any time without prejudice.
- Randomized subjects who withdraw from the study will not be replaced.
- 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

Table 1: Schedule of Assessments

Study period	Screen	Baseline	Transfusion	Follow up[1]						
Day	-3 to 0	0	0	1	3	7	14	28	60	90
Eligibility										
Informed consent	x									

[1] Inpatient labs can be performed ±1 day from visit. If patient is discharged before day 14, the next visits will be days 14, 28, 90. Outpatient labs can be performed if able to be obtained in outpatient setting ±7 days from visit. Follow-up visits after discharge can be done ±5 days from the time-point.

Demographic and Medical history	x								
COVID-19 symptom screen	x								
SARS-CoV-2 RT-PCR for eligibility	x[2]								
Pregnancy test	x								
ABO for plasma compatibility[3]	x								
Chest imaging (CXR or CT scan)	x[4]								
Oxygenation Level	x								
(Pro-)BNP	x[6]								
Study Drug Administration									
Randomization		x							
Drug infusion			x						
Study Procedures									
Vital signs	x	x	xxxx[5]	x	x	x				
Physical examination	x		x	x	x	x	x[6]			
Symptom screen	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x				x	x	x	x	x
Assessment with 11-point ordinal scale		x		x	x[7]	x[7]	x[7]	x[7]	x	x
Chest imaging (CXR or CT scan)					x[6]		X[6]			
EKG	x[6]				x[6]		x[6]			
Echocardiogram and/or left heart catheterization data					x[6]					
Duplex US of extremities[8]				x[8]	x[8]	x[8]	x[8]			
INR monitoring[9]				x[9]	x[9]	x[9]	x[9]			
Adverse event monitoring		x	x	x	x	x	x	x	x	x

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[2] Performed within prior 7 days

[3] Prior active results may be used if available

[4] Chest imaging on admission or thereafter, before randomization. Optional repeat at day 14 or discharge, whichever comes first

[5] 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.

[6] If able to be obtained when not performed as part of standard clinical care

[7] To be done additionally at discharge day

[8] As dictated by clinical indications (suspicion of thromboembolism)

[9] As indicated clinically for patients on coumadin

Laboratory testing										
CBC with differential		x		x	x	x	x			
CMP (or BMP)		x		x	x	x	x			
LFT		x		x	x	x	x			
D-dimer[10]		x		x[10]	x[10]	x[10]	x[10]			
LDH[10]		x		x[10]	x[10]	x[10]	x[10]			
CRP[10]		x		x[10]	x[10]	x[10]	x[10]			
Ferritin[10]		x		x[10]	x[10]	x[10]	x[10]			
CPK		x[6]		x[6]	x[6]	x[6]	x[6]			
Fibrinogen		x[6]		x[6]	x[6]	x[6]	x[6]			
Procalcitonin		x[6]		x[6]	x[6]	x[6]	x[6]			
PTT		x[6]		x[6]	x[6]	x[6]	x[6]			
Troponin		x[6]		x[6]	x[6]	x[6]	x[6]			
(Pro-)BNP		x[6]			x[6]					
SARS-CoV-2 RT-PCR[11]						x[11]	x[1]	x[1]		x[1]
SARS-CoV-2 antibody[13]		x[13]	x[12,13]	x[13]		x[13]	x[1,13]	x[1,13]		x[1,13]
Lymphocyte subset[14]		x[6]		x[6]		x[6]	x[1,6]	x[1,6]		x[1,6]
Cytokine panel[15]		x[6]		x[6]		x[6]	x[1,6]	x[1,6]		x[1,6]
Blood for future testing (To be collected by selected sites)		x[6]		x[6]		x[6]	x[1,6]	x[1,6]		x[1,6]

5. Treatment

1. Subjects will be randomized in a 1:1 ratio to receive 1 unit of study product (CP) or placebo control (equivalent volume of SS) randomization will be stratified at each site by risk in Stage 1. In Stage 2, randomization will also be based on a 1:1 ratio but study arms have not yet been defined and will depend on the outcome in Stage 1.

2. 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) and NYBC protocol (https://www.nybc.org/donate-blood/covid-19-and-blood-donation-copy/convalescent-plasma/).
Donors will be assessed for eligibility by the NYBC: https://www.nybc.org/donate-blood/covid-19-and-blood-donation-copy/convalescent-plasma/

3. Potential donors and samples will be screened per FDA May 1, 2020 guidelines (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-

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[10] If unable to obtain at all visits, can collect at baseline and then at selected visits during hospitalization
[11] Repeat during discharge if able
[12] Blood bank collects and ships segment from plasma bag tail for antibody testing
[13] Samples to be shipped to Einstein/Montefiore Biorepository
[14] ARUP labs (https://www.aruplab.com/) - 95892
[15] ARUP labs (https://www.aruplab.com/) – 51394

process-cber/recommendations-investigational-covid-19-convalescent-plasma) and NYBC protocols (https://www.nybc.org/donate-blood/covid-19-and-blood-donation-copy/convalescent-plasma/).

4. Treatment arm will receive 1-2 units of CP antibodies to SARS-CoV-2, Stage 1.
5. Control arm will receive equivalent volume of SS, Stage 1.
6. CP will be in standard plasma unit bags, with a study specific International Society of Blood Transfusion (ISBT) label
7. Both study drugs will be blinded to minimize unblinding of the bedside nurse, research staff, and the patient.

Randomization assignments are performed for patients at baseline. Randomization is performed separately by two strata, treatment site and risk of severe disease (high versus lower) as defined below. The randomization scheme will be determined by the study *Stage* and its associated group of intervention arms (For example, in Stages 1 and 2, subjects will be randomized to 1:1 ratio). Randomization should obviate the need for additional adjustment factors but if pre-specified demographic or clinical characteristics are unbalanced with respect to treatment group, we will consider adjustment; these characteristics include but are not limited to age, sex, race, ethnicity, BMI and COVID severity at baseline. The collaborating sites will be using the interactive web response system (IWRS) developed for randomization.

6. Rationale for Dosing

One to two units of convalescent plasma (250-500mL) containing anti-SARS2-CoV-19 IgG, as determined by the NYBC protocol prior to dispensing the plasma as "convalescent plasma," will be used in the treatment group. The NYBC tests potential plasma for SARS-CoV-2 IgG prior to distributing it as "convalescent plasma." Given that the NYBC testing platform provides a qualitative SARS-CoV-2 determination, SARS-CoV-2 IgG and neutralizing titers will be determined retrospectively 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). At the discretion of the treating physician, two units (~500 mL) may be administered.

Based on previous use of CP therapy in SARS-1, 5 mL/kg of plasma at titer ≥ 1:160 was utilized (7), for a 70 Kg person. For CP therapy for COVID-19, plasma volume is estimated to be 2800mL (40 mL/kg x70 kg) with baseline anti-SARS-CoV-2 titer of 0; therefore, if protective titer was 1:25 and each unit had titer of 1:160, 500mL can achieve this ([500/(2800+500)] x 1:160>1:25). If titer is ≥1:320, 250mL can achieve this titer.

Convalescent plasma units come from single individuals with anti-SARS-CoV-2 IgG. It is not a pooled product. If a patient receives one unit it will have come from a single person. If two units are given, it will come from one person or two different people. This is not something we will know. We will know that the samples have anti-SARS-CoV-2 IgG.

The control group will receive an equivalent volume (250-500ml) of SS.

Attempts will be made to blind the appearance of the solution being administered, in order to minimize the risk of unblinding the treatment the patient, bedside nurse, and research staff.

7. Study product administration

1. Study product 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 in discussion with the blood bank.
   o 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.
   o Severe allergic reactions, such as bronchospasm and hypotension, require discontinuation of the infusion.
5. Post-treatment management of fluid overload (i.e. need for furosemide) as per supervising physician on a case-by-case basis.
6. 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. **Statistical Modeling**
   Inferences in this trial are based on a Bayesian statistical model, which estimates the posterior probability for each intervention based on the evidence that has accumulated during the trial in terms of the observed WHO ordinal outcome and assumed prior knowledge in the form of a prior distribution. The statistical model considers the variation in outcomes by site, strata, and phase of the trial.

   Details of the modeling, prior distribution assumptions, decision rules, and proposed secondary/exploratory analyses are provided in the Statistical Analysis Plan.

2. **Sample Size and Power Considerations**
   The planned total sample size for the trial is 1000 subjects, stratified by site and risk of severe disease (high versus lower), but target enrollment will be adapted based on continuous Bayesian monitoring as detailed in the SAP.

   We estimated an initial sample size for Stage 1 study design using simulations assuming a two-sided Type I error rate (alpha) of 0.05 and 80% power. We made the following additional assumptions:
   a. 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,
   b. 1.8 odds ratio (OR) of worsening respiratory status between the control group and the anti-SARS-CoV-2 convalescent plasma group, this approximately corresponds to an 13% absolute reduction in incidence of worsening respiratory status (5% death and 12% on invasive mechanical ventilation or ECMO, respectively) and 5% absolute increase of discharged alive using anti-SARS-CoV-2 convalescent plasma.
   c. 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 initially estimated that 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; therefore, the planned total sample size of 1000 subjects is more than sufficient. Stage 1 will complete according to

the monitoring rules described above, and may end with fewer patients due to futility, equivalence or superiority. Stage 2 of the study will proceed in a similar manner.

STUDY PROCEDURES

Study Protocol by Day:

Day -3 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, ethnicity

    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, chest pain
- History of illness: Onset of symptoms, source of contagion

    4. Vital signs
    5. COVID-19 testing (RT-PCR)
- Nasopharyngeal, oropharyngeal, tracheal aspirate, bronchoalveolar lavage. Results from laboratory tests obtained up to 7 days before enrollment may be used.

    6. Baseline Basic Lab Testing and imaging
- Blood typing (any prior active results may be used if available), (pro-)BNP (if part of standard of care)
- Chest imaging (CXRAY or CT scan), EKG (if part of standard of care)

    7. Urine or serum pregnancy test
- For females of childbearing potential or not menopausal
- Results from laboratory tests obtained up to 7 days before enrollment may be used for the pregnancy test

    8. Determination of eligibility
- Inclusion/exclusion criteria age
- Consent
- Documentation of positive for COVID-19 in the prior 7 days
- Symptoms of cough, shortness of breath, chest pain, fever, or oxygen saturation $\leq 94\%$, not already an ICU patient
- Oxygen supplementation
- Within 7 days from first sign of illness or within 72 hours of admission

Day 0:
1. Randomization of eligible subject in IWRS
2. Study Plasma Administration:
    a. 1-2 units of plasma will be transfused
    b. Time at start and end of infusion will be recorded

      c. 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

      d. Blood bank will collect plasma bag tail segment for SARS-CoV-2 antibody titers

3. COVID-19 symptom screen: fevers, cough, shortness of breath
4. Assessment of clinical status (WHO ordinal scale)
5. New medical conditions, concomitant medication, AE evaluation
6. Physical examination (standard of care/per protocol)
7. CBC, CMP or BMP, CRP, LFT, D-dimer, LDH, ferritin.
8. Serological testing: anti-SARS CoV-2 titers
9. If able to be obtained when not part of standard of care: (pro-)BNP, Fibrinogen, procalcitonin, CPK, PTT, troponin, Lymphocyte subsets, and Cytokine panel.
10. Stored samples for future studies at selected sites

Day 1-14 (as inpatient or for duration of hospitalization):

1. Vital signs daily
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (WHO ordinal scale)
4. New medical conditions, concomitant medications, AE evaluation
5. Physical examination (standard of care/per protocol)
6. CBC, CMP or BMP, LFT, CRP, LDH, ferritin, and D-Dimer
7. Serological testing: anti-SARS CoV-2 titers
8. Nasopharyngeal or throat: SARS-CoV-2 PCR
9. If able to be obtained when not part of standard of care: (pro-)BNP, Fibrinogen, procalcitonin, CPK, PTT, troponin, Lymphocyte subset, and Cytokine panel.
10. Stored samples for future studies at selected sites
11. CXR or CT (day 3 if part of standard care and day 14 or at discharge, whichever comes first)
12. EKG (day 3 and and 14 if patient is still hospitalized and clinically indicated)
13. Echocardiogram parameters and right and/or left heart cardiac catheterization data, if performed for clinical care
14. Duplex ultrasound of extremities if performed for clinical care

Day of Discharge:

1. Define disposition (home or other)
2. Assessment of clinical status (WHO ordinal scale)

Day 14 (as outpatient, phone call or in-person follow-up):

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (WHO ordinal scale)
3. New medical conditions, concomitant medications, AE evaluation
4. Serological testing: anti-SARS CoV-2 titers (if able to be obtained)
5. Nasopharyngeal or throat: SARS-CoV-2 PCR (if able to be obtained)
6. Lymphocyte subsets (if able to be obtained)
7. Cytokine panel (if able to be obtained)
8. Define disposition (home, hospital, status)
9. Pulmonary status (supplemental oxygen)
10. Stored samples for future studies at selected sites (if able to be obtained)

Day 28 (as outpatient, phone call or in-person follow-up):

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (WHO ordinal scale)

3. New medical conditions, concomitant medications, AE evaluation
4. Serological testing: anti-SARS CoV-2 titers (if able to be obtained)
5. Nasopharyngeal or throat: SARS-CoV-2 PCR (if able to be obtained)
6. Lymphocyte subsets (if able to be obtained)
7. Cytokine panel (if able to be obtained)
8. Define disposition (home, hospital, status)
9. Pulmonary status (supplemental oxygen)
10. Stored samples for future studies at selected sites (if able to be obtained)

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 (WHO ordinal scale)
3. New medical conditions, concomitant medications, AE evaluation
4. Define disposition (home, hospital, status)
5. Pulmonary status (supplemental oxygen)

Day 90 (as outpatient, phone call or in-person follow-up):
1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (WHO ordinal scale)
3. New medical conditions, concomitant medications, AE evaluation
4. Nasopharyngeal or throat: SARS-CoV-2 PCR (if able to be obtained)
5. Serological testing: anti-SARS CoV-2 titers (if able to be obtained)
6. Lymphocyte subsets (if able to be obtained)
7. Cytokine panel (if able to be obtained)
8. Define disposition (home, hospital, status)
9. Pulmonary status (supplemental oxygen)
10. Stored samples for future studies at selected sites (if able to be obtained)

HUMAN SUBJECTS PROTECTIONS

RISK/BENEFIT ASSESSMENT

1. **Known potential risks**

   A. The protocol involves blood sample collection (see Table). Blood is collected as part of the routine care of nearly all hospitalized patients. The risk of blood collection, or phlebotomy is bruising or fainting. Some samples required for this protocol are collected as part of the usual care of the patient and others will be specifically collected for the protocol (see Table). The latter will be collected at the same time as the former. A separate phelebotomy will only be required for post-discharge samples.

   B. 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

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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.

C. 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.

D. There are also 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.

E. COVID-19 can be complicated by coagulopathy, including disseminated intravascular coagulation (DIC), which has risk of venous thromboembolism. The incidence of venous thromboembolism among COVID-19 patients may be somewhat higher than in other disease conditions (20). One study found a 31% incidence of thrombotic complications in ICU patients with COVID-19 infections (21). Transfusion with fresh frozen plasma (FFP) can increase risk of thromboembolism, but it has also been shown to protect thrombosis in some patients. A retrospective study of trauma patients who received blood products for traumatic hemorrhage had an increased risk of venous thromboembolism if they received concomitant packed red blood cell (pRBC) transfusions with fresh frozen plasma (22) may have the potential to increase risk of thromboembolism. This is unproven and this was not described in reports of CP use in China or Korea (14, 16, 23). It may also reduce the risk of COVID-19-associated risk of thrombosis if it is effective therapy. INR will be monitored in patients on coumadin.

2. **Known potential benefits**

The most important potential benefit of CP is that it may reduce progression to respiratory failure in patients with COVID-19, particularly in patients with early symptoms of respiratory involvement, such as cough and shortness of breath and/or pulmonary infiltrates. The benefit of CP is expected to include 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). CP was safe, reduced symptoms, and improved oxygenation in a non-randomized open label study of patients with more advanced disease in Wuhan, China (13).

3. **Assessment of potential risks and benefits**

Given historical data showing CP 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. Neither the safety nor the risks of CP have been established in randomized, controlled trials. The potential benefits of CP amid a humanitarian crisis warrant urgent studies of the efficacy of CP. Effective therapies are desperately needed for COVID-19. At present, none exist. Thus, in view of the lack of any proven therapy, the benefits of CP outweigh its potential risks. However, for all patients in whom CP is considered, a risk-benefit assessment will be conducted to assess individual variables. This protocol will use a randomized controlled study design to assess the efficacy of CP. The placebo control poses minimal risk, that of additional volume. We note that a recent JAMA editorial by experts noted the importance of randomized clinical trials to demonstrate efficacy of this approach and change the course of the epidemic (20).

There are limited data on the potential risks and/or benefits of CP in pregnant woman and fetus. Pregnancy can cause changes in the coagulation and fibrinolytic systems and CP may potentially benefit some individuals by providing the coagulation factors. CP was given to pregnant women in studies of patients with Ebola (Van et al. Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea. 2016. *N Engl J Med* 374:33-42) and with COVID-19 in China (Zhang et al. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. 2020. *Chest* doi:10.1016/j.chest.2020.03.039.

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

SAFETY

1. Safety measures
1. Clinical evaluations: Vital signs and symptom screen on days 0-7, 14 if still hospitalized, and symptom screens on days 28, 60, and 90.
2. Laboratory evaluations to include chest radiography (chest x-rays and/or chest CT), EKG
Safety laboratory tests (ABO typing, urine or serum pregnancy testing, CBC, comprehensive metabolic panel, LFT, D-dimer, PTT, LDH, fibrinogen, ferritin, CRP, procalcitonin, troponin) will be performed at the local CLIA-certified clinical laboratory on days 0-7 and 14 as specified by above plan.
3. Monitoring for development of venous thromboembolism if related to plasma infusion.

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:
   a. Death
   b. Life-threatening (immediate risk of death)
   c. Prolongation of existing hospitalization
   d. Persistent or significant disability or incapacity
   e. 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

3. Safety Reporting Requirements

1. **Reporting Interval**
   All AEs and SAEs will be documented from enrollment. All AEs and SAEs that are unexpected and directly attributable to study drug transfusion will be followed until study end point (Day 90).

   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.

   All SAEs will be reported to the DSMB within 24hr if:
   - The event has a reasonable possibility of having been related to the study drug infusion
   - All unexpected deaths

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, research nurses, and nurse practitioners.

   For tests that are not reflective of progression of COVID-19 (e.g. liver function tests, electrolytes, neutrophil counts, bacterial cultures, BNP or pro-BNP), laboratory abnormalities will be reported as AEs if they are 5 times the upper limit of normal. Acute kidney injury will be reported if they are 1.5 times the upper limit of normal. Examples of laboratory abnormalities that pertain to progression of COVID-19 but do not need to be reported as AEs at any level unless requested by the DSMB are: lymphocyte counts and lymphocyte subset abnormalities, cytokines, D-dimer, platelet count, ferritin, fibrinogen, CRP.

   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 grade scale 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 or Medically Significant: Escalation of medical intervention/therapy required

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

5 = Death

3. **Assessment of Study Product Association**
   1. The association assessment categories that will be used for this study are:
      - **Definitely Related:** The event follows: (a) a reasonable, temporal sequence from study drug or a study procedure; and (b) cannot be explained by the known characteristics of the participant's clinical state or other therapies; and (c) evaluation of the participant's clinical state indicates to the investigator that the experience is definitely related to study procedures.
      - **Probably or Possibly Related:** The event should be assessed following the same criteria for "Definitely Related". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.
      - **Probably Not Related:** The event occurred while the participant was receiving study drug/intervention or undergoing study procedures but can reasonably be explained by the known characteristics of the participant's clinical state or other therapies.
      - **Definitely Not Related:** The event is definitely produced by the participant's clinical state or by other therapies administered to the participant.
      - **Uncertain Relationship:** The event does not meet any of the criteria previously outlined.

   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.

4. **Safety Oversight**
   Monitoring Plan
   1. All AEs and SAEs will be reviewed by protocol team regularly, or more often if needed.
   2. A data safety monitoring board (DSMB) composed of independent experts, without conflict of interests will be established. The DSMB reports will be disseminated to all other participating sites 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, and then regularly thereafter. The DSMB will review study data to evaluate the safety, enrollment, efficacy, study progress, and conduct of the study.

STUDY MODIFICATION

1. Halting Criteria for the Study: The DSMB charter and charter addendum specifies the halting criteria for this study. Termination may be suggested by the DSMB at any time.

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

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

Site specific 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. For each study Stage, a separate informed consent form will be developed for which participants will consent separately. The collaborating sites may use the electronic consent database developed for this study.

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.

For subjects who may not have capacity due to acuity of illness or other reasons the participant's legally authorized decision maker may be contacted. If the legally authorized decision maker is willing to consent for the participant to enter the trial and is able to provide the participant's medical history, such participants will be included in the study. Subjects will be regularly assessed throughout the study with discussions with the clinical

care team to determine whether or not they have regained or lost the capacity to consent. If subjects regain the capacity to consent during the study, they will be provided again with the full informed consent form to indicate that they are willing to continue in the study and allow the use of their data.

4. Subject Confidentiality

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

5. Other Studies

Patients will also be notified of the use of de-identified data in other studies, such as pooling analyses, sub-analyses, and/or meta-analyses.

A third party/honest broker (HB) (i.e. DSMB unblinded statistitian) who has access to the data as part of their role in compiling the study's data for the DSMB and is not involved as a listed researcher on the study will access the desired records and provide researchers of other studies with de-identified data or limited data sets (where applicable and approved by the IRB and Privacy Board). As requested HB will either strip the data of all identifiers and the data set is anonymized or will assign a code to the data. The researchers of the CONTAIN trial and any other researchers who will receive the data will not have access to the information linking the code to the identifiers of the research subjects. Using the code, researchers can request, through the HB, additional information corresponding to the research subject. When the honest broker provides coded data to the research but not the method to de-code the data, then the information provided will be considered de-identified or a limited data set depending upon the data elements included in the data set.

6. Future Use of de-Identified Patient Information and Stored Specimens

During the consent process, subjects will be asked for permission to use their data and samples for future research. The confidentiality of the subject will be maintained as per HIPAA regulations. Each participant will be assigned a unique identifier at the time of consent. The identifier links the information it contains about the patient and the specimen. De-identified patient information can be used for sub-group analyses after the conclusion of the trial and/or upon permission of the DSMB if the trial is still ongoing.

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). Blood samples from all trial participating sites will be sent to the Biorepository at Albert Einstein College of Medicine. Samples will be de-identified and coded upon receipt. Plasma will be separated from whole blood, aliquoted, frozen at -20ºF and stored in the Biorepository and stored until use for future research.

Samples will not be shared with investigators other than investigators included in this protocol. The specimens will remain linked and at Albert Einstein College of Medicine/Montefiore Medical Center for at least 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 IRB. There will be no plans to re-contact participants or to inform them of results.

7. **Data management and monitoring**
   a. Source Documents
   The primary source documents for this study will be the subjects' medical records. If the investigators maintain separate research records, both the medical record and the research records will be considered the source documents for the purposes of auditing the study. The investigator will retain a copy of source documents. The investigator will permit monitoring and auditing of these data, and will allow the 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 by the study team or by transfer of data from the electronic health record. 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. The collaborating sites will be using the electronic data capture (EDC) system developed by NYU for this study.

   d. 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.

		FIRST WEEK				SECOND WEEK			
	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]			

INCUBATION PERIOD and ONSET OF SYMPTOMS 3 DAYS AGO

LONG TERM INFO PENDING

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%)

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

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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