Use of Convalescent Plasma Collected From Donors Recovered From COVID-19 Virus Disease for Transfusion, as an Empirical and Preemptive Treatment during Viral Pandemic Outbreak

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Protocol Summary

Study Title: Use of Convalescent Plasma Transfusion, Collected From Donors Recovered From COVID-19 Virus Disease, as an Empirical and Preemptive Treatment during Pandemic Outbreak

Phase II

Expected Numbers of Patients:

Group 3: High risk patients n=159

Group 4: Health Care Providers n=152

Study Objectives:

1. To transfuse COVID-19 infected patients with convalescent plasma and to observe whether this will result in a significant improvement in clinical outcome in comparison to historical experience. Patients eligible include the following study groups:

Group 3: As preemptive therapy for High Risk Patients who present with mild or non-severe COVID-19 infection.
Group 4: As preemptive therapy for health care providers who have developed asymptomatic, mild or non-severe COVID-19 infection.

a. **Primary objective** is whether infusion of convalescent plasma will reduce the probability of progressing to severe or critical disease significantly lower than the reported case rate (for Group 3 and 4, respectively).

b. **Secondary objectives** are to determine if infusion of convalescent plasma will impact the patient's clinical course including days in hospital, days requiring ICU care, days on mechanical respirator/BIPAP, days on non-mechanical oxygen support, days with pneumonia, fever, and viral clearance.

Overview of Study Design

As of late 2019, the world population has been threatened by a life-threatening novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is abbreviated COVID-19. This virus is a new human pathogen with no known treatment available. Currently, there are no vaccines, monoclonal antibodies (mAb) or drugs available for COVID-19. While it is hoped that new drugs and vaccines will be developed and proven efficacious, these efforts will take many months to develop and test in clinical trials. Antimicrobial and immune modulating medications that are approved for other indications are being tested in clinical trials with the hope of abrogating the disease's progression to severe cardiopulmonary injury, but to date have not been shown to have definitive benefit. While there is no proven treatment available for COVID-19 virus disease, plasma collected from patients in the convalescent phase of infection has been used as an empirical treatment during viral pandemics for over one-hundred years with well documented benefit in reducing morbidity and mortality.[1,2] Most Individuals who recover from the viral infection develop humoral immunity with neutralizing antibodies that may persist for years. Collection of convalescent plasma and transfusion into an infected patient transfers immediate passive immunity, which was the only means to treat infections prior to the development of modern vaccine therapy. Not all patients benefit from convalescent plasma. Experience would indicate that the earlier in the course of illness convalescent plasma or immunoglobulin therapy was administered, the more likely benefit will be observed

with the highest benefit when used as prophylactic therapy.

In the past two decades there have been two epidemics with coronavirus that resulted in high mortality, SARS-1 in 2003 and Middle East respiratory syndrome (MERS) in 2012. The latter infections became an epidemic in the Middle East and triggered a secondary outbreak in South Korea. Due to the high mortality and lack of an effective therapy, convalescent plasma was utilized. The largest report involved 80 patients with severe SARS disease in Hong Kong.[9] For patient who received convalescent plasma transfusion prior to day 14 of the infection have an improved prognosis and an earlier hospital discharge prior to day 22 (58.3% vs 15.6%, *P*<.001). The mortality rates in the two groups were 6.3% and 21.9%, respectively. This observation is consistent with the prior historical observations that earlier administration in the course of the infection is more likely to be effective.

China has offered convalescent plasma therapy for 245 COVID-19 patients, and 91 cases have shown improvement in clinical indicators and symptoms, per press report.[3] Treatment of five critically ill patients in China with COVID-19 and acute respiratory distress syndrome (ARDS) with convalescent plasma was followed by resolution of ARDS in 4 patients within 9 days following transfusion.[4] Of the 5 patients 3 had been discharged and 2 were in stable condition at 37 days post-transfusion. In a third report, 10 patients with severe COVID-19 infection received one dose of convalescent plasma derived from recently recovered donors.[5] The primary endpoint was safety of plasma infusion and secondary endpoint was efficacy. Clinical symptoms improved along with improved oxygenation within 3 days of transfusion. The viral load was undetectable after transfusion in the seven of seven patients who had detection pretreatment at a median of 3 days (2-6 days). Cytokine surrogate marker, C-reactive protein, fell from a median before transfusion of 55.98 mg/L (nl range 0 – 6) to 18.13 following the treatment. No serious adverse reactions or safety events were recorded.

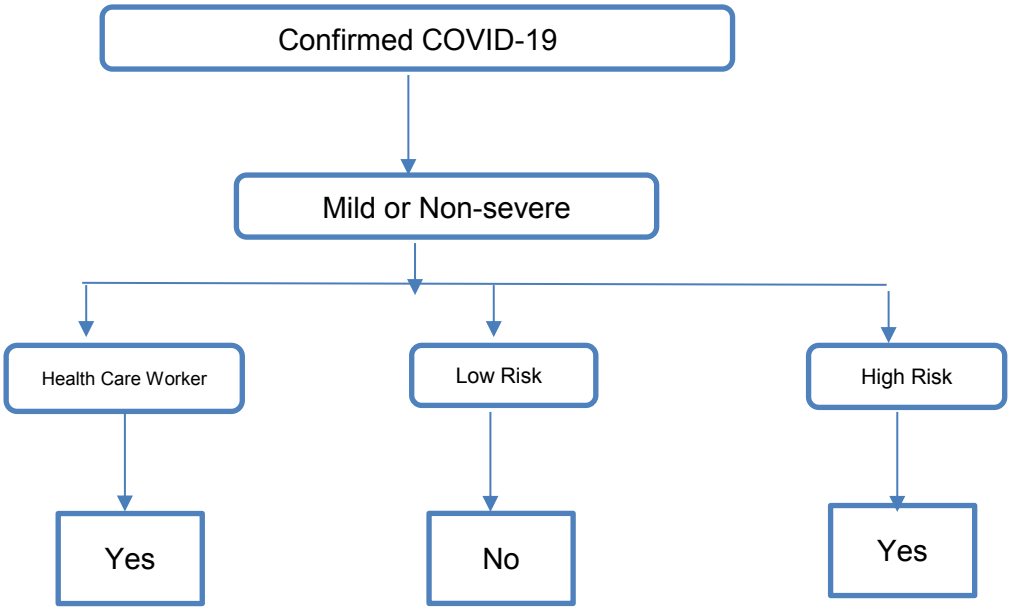
Group sequential design is employed for each hypothesis that analysis will be performed after enrolling and observing outcomes of one-third of maximum sample size. Our design includes two interim analyses and a final analysis for each hypothesis. The Pocock method is used to determine sample size and each study is sized to maintain the power of 80% and overall type I error 5%. To calculate the sample size, the large-sample Z test for a proportion is utilized for each analysis. The maximum number of enrollment for the four groups are: Group 1: 81, Group 2: 423, Group 3: 228 and Group 4: 219. Due to the likelihood that we may terminate a study for efficacy after an interim analysis, the expected numbers of enrollment for the four groups are 56, 296, 152 and 152, respectively.

Study Population: Eligible patients will be 18 years or older and must have a positive test result forCOVID-19 infection toand meetthe inclusion criteria described in Section 4.1

Duration of Study: 24 months

Participant Duration: 30 days or in the case of hospitalization, upon discharge; whichever is longer.

Schema: Convalescent Plasma Treatment for COVID-19 Infection



Definitions:
COVID-19 severity categories:

- Mild – No pneumonia but with typical symptoms such as fever, dry cough, fatigue, nausea, emesis or diarrhea.
- Non-severe – Radiographic changes compatible with viral PNA, but no signs of respiratory compromise or hypoxemia.
- Severe – Respiratory compromise with one of the following: Tachypnea with RR ≥30, O_2 Sat ≤93% at rest, $Pa0_2/Fi0_2$ index ≤ 300 mmHg
- Critical – One of the following: requiring mechanical ventilation, requiring pressor support, multi-organ failure.

Patient Risk Category:
High risk:

- Immunocompromised (e.g. neutropenia, h/o hematopoietic stem cell transplant (<3 months post-autologous transplant, <6 months post-allogeneic transplant), on systemic immunosuppression, h/o solid organ transplant, Cancer patient receiving active chemotherapy, insulin dependent diabetes mellitus, poorly controlled HIV, moderate or severe asthma history, serious heart condition, ESRD on hemodialysis, morbid obesity, moderately severe or greater COPD.
- Age ≥ 65 years

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1.0 Study Rationale

Convalescent plasma has been utilized for over one-hundred years for the empirical treatment of viral pandemics and has been reported to reduce duration of symptoms and mortality risk. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to clinical improvement.

1.1 Background and Rationale

1.1.1 Introduction

Since the early twentieth century convalescent plasma has been used during pandemics including the 1918 H1N1 Influenza virus pandemic (Spanish Flu),[vi] poliomyelitis[vii], measles,[viii,ix] mumps,[x] 2009-2010 H1N1 Influenza virus pandemic,[xi] SARS-1 in 2003[xii,xiii] and Middle East respiratory syndrome (MERS) in 2012.[xiv,xv] The most recent example is the West Africa Ebola epidemic, which was associated with a high mortality risk with no known drug or vaccine therapy. A small nonrandomized trial demonstrated significantly improved survival for those who received convalescent whole blood, and two patients urgently transferred to the United States and treated with a combination of convalescent plasma survived.[xvi,xvii,xviii]

While every viral disease and epidemic are different, immunological responses are similar and these historical precedents provide both reassuring and useful data in developing a treatment protocol using convalescent plasma for COVID-19 disease.

1.1.2 Rationale for using COVID-19 convalescent plasma

Experience with the use of convalescent plasma against coronavirus diseases

In the past two decades there have been two epidemics with coronavirus that resulted in high mortality, SARS-1 in 2003 and Middle East respiratory syndrome (MERS) in 2012. The latter infections became an endemic in the Middle East and triggered a secondary outbreak in South Korea. Due to the high mortality and lack of an effective therapy, convalescent plasma was utilized. The largest report involved 80 patients with severe SARS disease in Hong Kong.[9] For patient who received convalescent plasma transfusion prior to day 14 of the infection have an improved prognosis and an earlier hospital discharge prior to day 22 (58.3% vs 15.6%, $P<.001$). The mortality rates in the two groups were 6.3% and 21.9%, respectively. This observation is consistent with the prior historical observations that earlier administration in the course of the infection is more likely to be effective. Convalescent plasma given to three patients in Taiwan with severe SARS disease resulted in reduction the serum virus titer and each survived.[10]

China has offered convalescent plasma therapy for 245 COVID-19 patients, and 91 cases have shown improvement in clinical indicators and symptoms, per press report.[xix] Treatment of five critically ill patients in China with COVID-19 and acute respiratory distress syndrome (ARDS) with convalescent plasma was followed by resolution of ARDS in 4 patients within 9 days following transfusion.[xx] Of the 5 patients 3 had been discharged and 2 were in stable condition at 37 days post-transfusion. In a third report, 10 patients with severe COVID-19 infection received one dose of convalescent plasma derived from recently recovered donors.[xxi] The primary endpoint was safety of plasma infusion and secondary endpoint was efficacy. Clinical symptoms improved along with improved oxygenation within 3 days of transfusion. The viral load was undetectable after transfusion in the seven of seven patients who had detection pretreatment at a median of 3 days (2-6 days). Cytokine surrogate marker, C-reactive protein, fell from a median before transfusion of 55.98 mg/L (nl range 0 – 6) to 18.13 following the treatment. No serious adverse reactions or safety events were recorded.

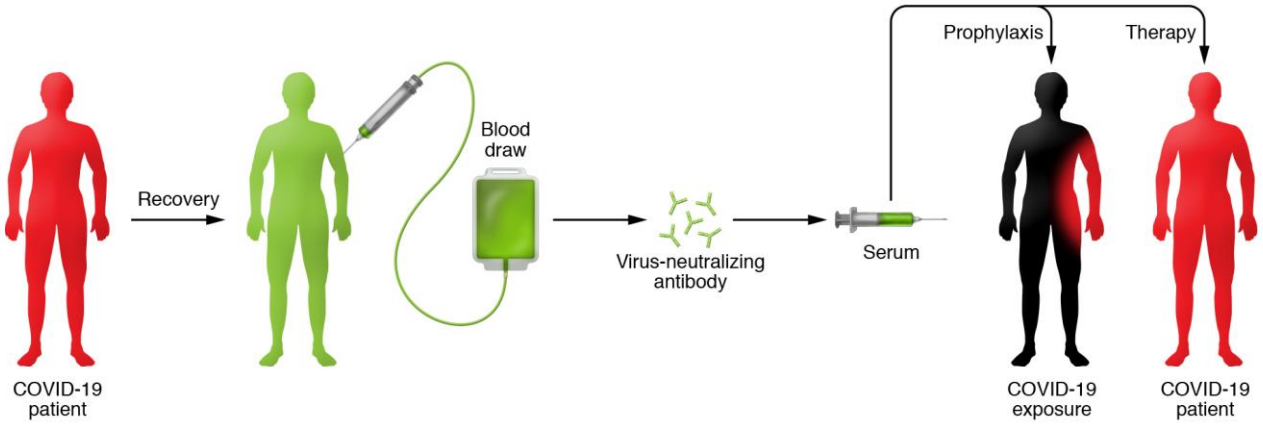

Figure 1. Schematic of the use of convalescent sera for COVID-19. An individual who is sick with COVID-19 and recovers has blood drawn and screened for virus-neutralizing antibodies. Following identification of those with high titers of neutralizing antibody, serum containing these virus-neutralizing antibodies can be administered in a prophylactic manner to prevent infection in high-risk cases, such as vulnerable individuals with underlying medical conditions, health care providers, and individuals with exposure to confirmed cases of COVID-19. Additionally, convalescent serum could potentially be used in individuals with clinical disease to reduce symptoms and mortality. The efficacy of these approaches is not known, but historical experience suggests that convalescent sera may be more effective in preventing disease than in the treatment of established disease.[2]

1.2 Clinical Characteristics of COVID-19 Disease

In the largest published review from Wuhan China, 1099 patients were followed with confirmed COVID-19 infection.[xxii] A primary composite end-point event occurred in 67 patients (6.1%), including 5% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died. The majority of patients (58%) received intravenous antibiotic therapy and oxygen was administered in 41.3% of patients. CT radiograph was performed on 975 patients and it showed ground-glass opacities in 56.4%, local patchy shadowing in 41.9% and bilateral patchy shadowing in 51.8% and interstitial abnormalities in 14.7%. Chest radiographs were performed in 274 patients and abnormalities were documented in 59.1% (20.1%, 28.1%, 36.5% and 4.4%; respectively). In severe cases, radiographic abnormalities were seen on CT study in 94.6% of patients. For hospitalized patients, fever was present in 88.1% of non-severe and 91.9% of severe patients.

A total of 173 patients were classified as having severe disease per the guidelines of the American Thoracic Society guidelines.[xxiii] For those 926 that presented with non-severe disease, 35.7% required oxygen, 2.4% required ICU admission and none required mechanical ventilation. For those with severe disease, 71.1% required oxygen therapy, 19.1% were admitted to the ICU and 38.7% required mechanical ventilation. The median length of hospital stay for the non-severe was 11 days (10-13) and for the severe 13 days (11.5-17). Death occurred in 0.1% of the patients with non-severe disease and 8.1% of patients with severe disease. For patients presenting with severe disease 71.1% required oxygen therapy, 15.6% developed acute respiratory distress syndrome, admission to the ICU was 19.1%, 38.7 percent required mechanical ventilation (14.5% invasive and 32.4% noninvasive) and median hospital duration was 13 days.

Correlate laboratory studies included C-reactive protein that was elevated above 10 mg/L in 81.5% of those with severe disease and in 56.4% with non-severe disease. Procalcitonin

greater than 0.5 ng/mL was seen in only 3.7% of those with non-severe disease and 13.7% with severe disease presentation.

In a larger report from Chinese Center for Disease Control and Prevention of 72,314 cases 14% presented with severe disease that was defined as dyspnea, respiratory frequency ≥ 30, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or lung infiltrates >50% within 24-48 hours.[xxiv] Critical disease developed in 5% that resulted in respiratory failure, septic shock and/or multi-organ failure. In this report the case fatality rate (CFR) was 8.0% in patients age 70-79, 14.8% in patients over age 80, and 49% in critical cases. CFR was elevated among those with preexisting comorbid conditions: 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension and 5.6% for cancer. A total of 1,716 infected were health care workers. Overall, 14.8% of health care workers developed severe or critical disease, and 5 deaths were observed.[xxv]

1.3 High Risk Clinical Characteristics of COVID-19 Disease

High risk groups for developing severe COVID-19 infection have been defined by the Center of Diseases and Control Prevention (CDC) and include:[xxvi]

- Persons 65 years and older
- Chronic Lung disease
- Moderate to Severe Asthma
- Serious Heart Conditions
- Immunocompromised patients (including undergoing cancer treatment, bone marrow or organ transplantation, immune deficiency diseases, poorly controlled HIV or AIDS, prolonged use of corticosteroids and other immune weakening medications (e.g. cyclosporine, tacrolimus, etc.)
- Severe obesity (BMI of 40 or higher)
- Diabetes
- Chronic Kidney disease and undergoing dialysis
- Liver Disease

On 3/26/2020, the FDA release selection criteria for COVID-19 disease to be eligible for donor convalescent plasma who met their definition for severe disease or immediately life-threatening status.

Severe disease is defined as:

- Dyspnea
- Respiratory frequency ≥ 30/min
- Blood oxygen saturation ≤ 93%
- Partial pressure oxygen to fraction of inspired oxygen ratio <300, and/or
- Lung infiltrates > 50% within 24 to 48 hours

Life-threatening disease is defined as:

- Respiratory failure
- Septic shock, and/or
- Multiple organ dysfunction or failure

1.4 Convalescent Plasma Information

Convalescent Plasma may be collected by either apheresis (often in combination with concurrent platelet apheresis collection) or via traditional phlebotomy followed by centrifuge

separation. For purposes of being able to safely expedite and optimize plasma donation for an otherwise healthy donor apheresis is the preferred procedure.

Donors must undergo screening as per guidelines set out by the FDA for collection of COVID-19 Convalescent Plasma.

We have previously initiated an IRB approved Convalescent Plasma Donor Program and are actively recruiting donors. Donors are being recruited in collaboration with the Georgia Department of Public Health, hospital epidemiology program and through public outreach. Donors are having sample(s) of their sera stored. Currently, quantitation of IgG Ab titers against COVID-19 is not available. Once testing is approved and commercially available potential donors will have their IgG Ab titers measured.

1.5 Risks and Benefits of Convalescent Plasma Therapy

It is anticipated that the risks associated with the infusion of convalescent donor plasma will be low, and of those events, most are expected to be of low grade (Grade 2 or less) severity.[xxvii,xxviii,xxix] The most common observed risk is allergic transfusion reaction (ATR) that has an estimated frequency of <1% - 3% of all transfusions.[xxx,xxxi] Most ATR are mild and limited to urticarial rash, pruritis, flushing and/or fever. These are generally reversible events. Rare side effects include anaphylactic allergic reactions characterized by bronchospasm, angioedema and/or hypotension; and have an estimated frequency range from 1:591 to 1:2,184 plasma units transfused. Antibodies to human IgA that are passively transfused in the plasma into IgA deficient patients can cause dramatic anaphylactic reactions mediated by complement activation to small amounts of plasma containing IgA proteins. The prevalence ranges from 1:100 to 1:1000 in Caucasian, African American and Middle Eastern populations.[xxxii]

Transfusion associated adverse effects include transfusion related acute lung injury (TRALI). and transfusion associated circulatory overload (TACO).[xxxiii,xxxiv] The incidence of TRALI is rare with an estimated incidence 1:12,000 transfusions since deferring female donors with HLA alloantibodies. TRALI is characterized by acute hypoxemia and noncardiogenic pulmonary edema within 6 hours of transfusion. Majority of patients recover within 72 hours, but there is a reported mortality rate of 5%-25%.[xxxv,xxxvi] TACO is similar to TRALI in that it is also characterized by acute respiratory distress, hypoxia and pulmonary edema; however, the edema is due to hydrostatic pressure changes that is associated with acute rise in BNP; and is not due to immune reaction and passive permeability edema.[xxxvii] The incidence of TACO ranges from <1% to 8%.[xxxviii,xxxix] Patients generally respond promptly to medication to promote diuresis, but the mortality risk has been reported to be 5%-15%.[xl] Risk factors include older and young patients, preexisting cardiac and/or renal dysfunction. BNP should be part of the investigation to ascertain whether TACO adverse effect has occurred.[xli] Because the majority of non-severe, severe and critical COVID-19 patients receiving convalescent donor plasma will have pulmonary infiltrates and require oxygen support, it will be difficult to ascertain whether an acute change in respiratory status is the result of the plasma infusion. As part of the study entry evaluation, BNP lab test is recommended pre-transfusion. If BNP is significantly elevated, then it may place the patient at higher risk for developing TACO. Clinical judgement regarding the use of concurrent diuretic therapy, whether to transfuse the plasma over a longer interval, or to defer the transfusion will need to be considered by the treating physician.

Other rare adverse events include acute hemolytic transfusion reaction and sepsis, the latter from bacteria growth in the product.[xlii] The latter is unusual in plasma products as they are either frozen or refrigerated shortly after collection. Hypotensive reactions may occur, and a specific risk has been associated with patients receiving angiotensin-converting enzyme inhibitors.[xliii,xliv] A patient with a suspected acute transfusion reaction should have the following performed: stop the transfusion and return bag for a transfusion reaction workup, confirmation

that the correct product was infused. Risk of infectious disease transmission is extremely low due to FDA required extensive donor medical screening and infectious disease testing. The estimated risk for acquiring HIV, HCV and HBV through transfusion is 1:1,467,000, 1:1,149,000 and 1:280,000 donations, respectively.

Hypothetical concerns regarding the use of convalescent plasma include the phenomenon of antibody-dependent enhancement of infection (ADE). For coronaviruses, several mechanisms for ADE have been described and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain.[xlv] Because convalescent plasma will have titers of neutralizing antibody against COVID-19, ADE is not anticipated to develop. The anecdotal report of the use of convalescent sera in patients with SARS1 and MERS, and evidence from its use in 245 patients with COVID-19 acute infection suggest it is safe and has not resulted in ADE. Another hypothetical concern is that the use of convalescent plasma may suppress the hosts humoral immune response, thereby, leaving the patient vulnerable to subsequent reinfection. There is no data to substantiate this concern in prior use of convalescent plasma for coronavirus diseases. There is also the risk that convalescent plasma for COVID-19 infection may be ineffective.

The potential benefits of administering convalescent plasma have been outlined in Section 1.1. The infusion of convalescent plasma will likely provide immediate passive neutralizing antibodies against the virus. Historical observations for other viral pandemic infections have demonstrated lower risk for morbidity and mortality. Investigators have shown correlation of rapid reversal of inflammatory response to the infection and cytokines following infusion of convalescent plasma for the SARS Coronavirus. In the recent report from China, 245 patients were given convalescent plasma and it was concluded that approximately 35% showed clinical benefit. It is hoped that the administration of convalescent plasma to the study patients will reduce the severity and duration of the infection, and the risk for death.

2.0 Study Objectives

2.1 To transfuse COVID-19 infected patients with convalescent plasma and to observe whether this will result in a significant improvement in clinical outcome in comparison to historical experience. Patients eligible include the following study groups:

Group 3: As preemptive therapy for high-risk patients who present early with mild or non-severe COVID-19 infection.

1.1.2.1 **Primary objective** is whether this will reduce the probability of progressing to severe or critical disease significantly lower than the reported case rate (for Group 3 and 4, respectively).

1.1.2.2 **Secondary objectives** are to determine if this will impact the patient's clinical course including days in hospital, days on non-mechanical oxygen support, days with pneumonia and/or fever, days requiring ICU care, days on mechanical respirator/BIPAP, and death. Corollary laboratory studies will include days to viral clearance.

Group 4: As preemptive therapy for health care providers who have developed asymptomatic, mild or non-severe COVID-19 infection.

1.1.2.3 **Primary objective** is whether this will result in a lower risk of developing severe COVID-19 disease.

1.1.2.4 **Secondary objectives** are to determine if this will impact the patient's clinical course including days in hospital, days requiring ICU care, days on mechanical respirator/BIPAP, days on non-mechanical oxygen support, days with pneumonia and fever. Corollary laboratory studies will include days to

viral clearance.

3.0 Study Design

3.1 Overview of Study

COVID-19 infected patients will be screened per selection criteria shown in the Objectives and Study Population Sections. All patients must have confirmed COVID-19 disease and meet the inclusion and exclusion criteria established. Eligible patients for study after completing consenting process will be stratified into 4 treatment groups.

3.1.1 Primary and Secondary Endpoints and Efficacy Assessments

The primary endpoint of the study will be:

1) progression to severe disease for those with high-risk disease that present with mild/non-severe disease, and
2) progression to severe disease for health care workers who present with asymptomatic, mild or non-severe disease.

Secondary endpoints will include:

1) Acute care facility/hospital length of stay
2) Number of days requiring oxygen support
3) Number of days in an intensive care unit
4) Number of days on mechanical ventilation (invasive, noninvasive and ECMO)
5) Incidence of viral disease associated cardiomyopathy
6) Incidence of multi-organ dysfunction/failure
7) Safety of transfusion—Incidence of severe adverse events

3.1.2 Study Entry: Time from COVID-19 Infection Onset

3.1.2.1 High Risk group: Entry within 14 days of COVID-19 infection documentation.

Patients in the High-Risk group must present with either mild or non-severe disease for to be eligible for study entry; thereby, being identified early in the infection. These patients are to be entered and consented within 14 days of symptomatic COVID-19 infection documentation. Mild symptoms could include typical symptoms such as fever, dry cough, fatigue, nausea, emesis or diarrhea

3.1.2.2 Health Care Providers group: Healthcare worker must present with asymptomatic and with a positive NP swab; or mild or non-severe disease for to be eligible for study entry; thereby, being identified early in the infection. Asymptomatic patients must be enrolled within 14 days of the positive COVID-19 test. Mild or non-severe must be enrolled within 14 days of symptomatic infection documentation.

3.1.3 Additional Considerations for Study Design

3.1.3.3 Repeat testing for COVID-19 via nasal pharyngeal swab will be performed at 7 days and 14 days following infusion of convalescent plasma in all patients.

3.1.3.4 When available, serology testing for COVID-19 neutralizing antibodies will be measured prior to transfusion of convalescent plasma and again between 21 to 30 days following study entry (if test not available, sera sample(s) will be collected and stored).

3.1.3.5 Data for secondary objective endpoints will be collected and analyzed, including Charlson comorbidity index, KPS, and concurrent immunosuppressive therapy.

3.2 Number of Patients

The number of patients expected per each of the 2 groups:

Group 3: High Risk: n=159
Group 4: Health Care Providers: n=152

3.3 Duration of Study

Enrollment is expected to last for at least 48 months. This may be less or longer depending upon the pandemic outbreak patterns for recurrent flares infection peaking within the community. The study may be curtailed early if an effective vaccine is developed and there has been wide spread immunization.

3.4 Participant Duration

Participation in this study will last 30 days. For patients in the hospital longer than 30 days, the date of discharge will be noted regardless of the time.

4.0 Study Population

4.1 Inclusion Criteria for the selection of COVID-19 Infected Patients for Convalescent Plasma Transfusion

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Age $\geq$ 18 years
2. Documented COVID-19 infection with nasal pharyngeal sampling test by real time reverse transcription polymerase chain reaction (rRT-PCR), or nucleic acid amplification technology (NAAT) molecular testing. A partial list of available tests can be accessed at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations
3. Have COVID-19 Disease criteria that meets one of the 2 following groups:

4.1.1 Group 3: High Risk Patients with Mild or Non-severe Disease

1. Mild Disease: upper respiratory symptoms, cough, gastrointestinal symptoms (emesis, diarrhea, abdominal pain) or fever; but no radiograph evidence for viral pneumonitis.
2. Non-severe Disease: Chest radiographic changes compatible with COVID-19 disease, but no signs of respiratory compromise or hypoxemia.
3. High Risk condition must include one of the following: Immunocompromised (e.g. neutropenia, active chemotherapy for cancer or hematological malignancy, less than 12 months after undergoing allogeneic hematopoietic stem cell transplant or 100 days from autologous hematopoietic stem cell transplant, on systemic immunosuppressive therapy, history of solid organ transplant and poorly controlled HIV disease (e.g. CD4, 250/uL, recurrent opportunistic infections), insulin dependent diabetes mellitus, moderate to severe asthma history, severe COPD (DLCO < 60), morbid obesity (BMI $\geq$ 40),age $\geq$ 65 years, hypertension, moderate or severe cardiac disease (eg. Cardiomyopathy, CHF, moderate or

severe valvular stenosis, ischemic heart disease), patients with severe renal disease (e.g. on dialysis), or liver disease

4. Informed consent signed within 14 days of symptoms developing for mild disease. For patients in the non-severe cohort, the time to consent must be within 14 days of positive chest x-ray or 14 days of first symptom whichever is longer (maximum 14 days to enrollment).

4.1.2 Group 4: Health Care Providers with asymptomatic, mild or non-severe disease

1. Health care providers who as part of their activities from time to time are at risk to exposure to COVID-19 infection. This includes administrative staff and ancillary support staff associated with hospitals or ambulatory clinic facilities.
2. Asymptomatic is defined as having diagnosis of COVID-19 without symptoms or clinical findings.
3. Mild or non-severe disease: Refer above for definitions.
4. Informed consent signed within 14 days positive COVID-19 test.

4.2 Exclusion Criteria for Selection of COVID-19 Patients

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Known history of IgA Deficiency
2. History of anaphylactic reaction to blood product transfusion including hypersensitivity to immunoglobulin therapy.

5.0 Treatment Plan and Convalescent Plasma

5.1 Treatment plan for patients consented to receive convalescent COVID-19 donor plasma

5.1.1 Lab and Clinical Studies Pre-Transfusion (<u>may be completed 72 hours before consent)</u> <u>(results are not required to be available prior to patient eligibility/administration of convalescent plasma but all tests must be completed before infusion)</u>

1. Confirmation of COVID-19 positive nasal pharyngeal sampling test – documentation of NP testing is required. Repeat testing is not required.
2. ABO Blood Typing and Cross & Match
3. CBC with platelets and differential
4. CMET including liver and renal function
5. COVID-19 neutralizing antibody titer (if test not available, to collect and store sera sample). Sample should be collected in an EDTA (lavender/purple or pink top tube)
6. Chest Radiographic study (CXR or CT-chest (preferred) within 72 hours of planned transfusion of Convalescent Plasma if clinically indicated.
7. Charlson Index Comorbidity Score (for all Groups)
8. Karnofsky Performance Score (for all Groups)
9. Baseline evaluation (see baseline treatment worksheet)
10. Recording of concurrent COVID-19 antiviral investigational therapy or other anti-viral therapies (e.g. IL-6 inhibitors (Tocilizumab), IL-1 inhibitors, hydroxychloroquine, ribavirin, lopinavir (for all Groups)
11. Recording of concurrent immunosuppressive medications (e.g. tacrolimus, cyclosporine, ruxolitinib, sirolimus, prednisone (steroids), Rituximab (within prior 12 months), chemotherapy treatment in prior 6 months, rheumatology therapy, Crohn's Disease or Ulcerative Colitis therapy) (for all Groups).
12. Documentation of days of symptoms preceding infusion of convalescent plasma (fever, cough, shortness of breath/dyspnea, emesis, diarrhea, abdominal pain, pharyngitis) (for all Groups)

5.1.2 Transfusion of COVID-19 Convalescent Plasma

1. Following verification of study eligibility and consenting of the subject, the Atlanta

Blood Center (or blood center providing the plasma) and the hospital blood bank will be notified to assign and release a Convalescent Donor Plasma Product. The intent is to release the product for transfusion within 24 hours following the consent being signed. On occasion a delay beyond 24 hours may occur if there is a scheduling delay for a courier to transport the product to an outlying hospital facility, or there is a delay due to waiting for a donor plasma product to complete release criteria as established by the FDA.

2. Directed Donor Convalescent Plasma Product(s) to have a two-person verification per institution protocol for identification of patient and product prior to transfusion of product(s).
3. Convalescent Plasma Product to be provided in 200-425 ml transfusion pack. The bag will be transfused (over at least 2 hours).
4. If patient demonstrates non-severe allergic transfusion reaction or any other mild adverse reaction to the plasma infusion, the infusion is to be held until resolution of signs and symptoms. Following evaluation and assessment by medical team that may include need for antihistamine, corticosteroid and/or diuretics administration, transfusion may be restarted at a slower infusion rate per directive of medical team.
5. If patient develops anaphylactic reaction or severe acute reaction, then the transfusion should be stopped. Institutional policy for managing severe transfusion reactions should be initiated in consultation with medical team.

5.1.3 Laboratory and Clinical Monitoring Post-COVID-19 Convalescent Plasma Infusion

5.1.3.1 Fever (maximum value) monitoring daily through D30. For patients who are discharged from the hospital, they will be provided the diary and asked to complete it from discharge until Day 30.

5.1.3.2 For patients in group 3 and 4, they will be asked to maintain a daily diary log for symptoms through day +30

5.1.3.3 Recording of inpatient hospital days, days in ICU, days on mechanical ventilator (invasive and noninvasive).

5.1.3.4 Chest radiograph (CT chest or CXR) on days 7 and 14: for patients in groups 3 and 4, if a baseline chest xray/radiograph was completed, follow up radiographic studies will be required on days 7 and 14.

5.1.3.5 COVID-19 sera neutralizing antibody titer (when test is available) to be obtained between days 21-30 following infusion of convalescent plasma. If test is not available sera will be collected and stored. This will be collected in an EDTA tube (lavender/purple or pink top)

5.1.3.6 COVID-19 NP swabs will be repeated all subjects on Days 7 & 14. .

5.2 Discontinuation of Study Intervention

The study involves one-time administration of ABO matched COVID-19 convalescent plasma.

5.3 Participant Discontinuation/Withdrawal from the Study

Study participant is free to withdraw consent from participation in further data collection at any time during the study. If a patient withdraws consent, survival data will still be collected. No additional data will be collected.

5.4 Lost to Follow-Up

The protocol follows the subjects only for a limited interval. It is not anticipated that study participants will be lost to follow-up.

6.0 Statistical and Quantitative Analysis

6.1 Determination of Sample Size and Statistical Analysis

Group sequential design is employed for each hypothesis that analysis will be performed after enrolling and observing outcomes of one-third of maximum sample size. Our design includes two interim analyses and a final analysis for each hypothesis. The Pocock method is used to determine sample size and each study is sized to maintain the power of 80% and overall type I error 5%. To calculate the sample size, the large-sample Z test for a proportion is utilized for each analysis.

	Enrollment at stage 1	Enrollment at stage 2	Enrollment at stage 3	Maximum enrollment	Expected enrollment for projected proportion
Study group 3	76	76	76	228	159
Study group 4	73	73	73	219	152

Group 3

For high-risk COVID-19 infected patients that present with early mild or non-severe disease the estimated percent who will develop severe disease is 27% for those over age 65. There is insufficient data on patients who have coexisting severe immune compromised status; however, for patients that presented with diabetes or heart disease/hypertension risk was 16% - 30%, respectively.[22] Assuming a reported risk of progression of 25%, it is postulated that the infusion of convalescent plasma will reduce the probability for progression to severe disease by a factor of 0.35 to 16.3% or lower. We will carry out 3-stage of enrollment and 76 patients are enrolled in each stage. The interim analysis will be performed after enrolling and observing outcomes of 76 patients. Our design leads to the maximum size of 219 patients after completing 3-stage of enrollment and the expected size is 159 patients.

Group 4

Among healthcare workers 14.8% of cases were classified as evolving to severe or critical per the Chinese epidemiological review.[24,25] It is postulated that the infusion of convalescent plasma will reduce the probability for progression from asymptomatic, mild or nonsevere disease to that of severe disease will be reduced by a factor of .5 to 7.5% or lower. We will carry out 3-stage of enrollment and 73 patients are enrolled in each stage. The interim analysis will be performed after enrolling and observing outcomes of 73 patients. Our design leads to the maximum size of 219 patients after completing 3-stage of enrollment and the expected size is 152 patients.

6.2 Secondary Endpoints

6.2.1

Secondary endpoints will be analyzed for potential efficacy and statistically compared to historical or matched controlled comparison population. For patients with severe disease, the expected rate of ICU admission is 19.%, with 38.7% requiring mechanical ventilation (14.5% invasive), 94.6% had radiographic abnormalities of the chest, 15.6% developing acute respiratory distress syndrome, and median hospital stay of 13 days. A total of 14% of patients with COVID-19 disease developed severe disease.

6.2.2

Impact of donor sera neutralizing antibody titer will be correlated to clinical outcome.

6.3 Statistical Analysis

We will perform intention-to-treat analysis to analyze outcomes of all enrolled patients. The primary analysis is to evaluate the CRF or disease progression rate against the null proportion. We plan to perform two interim analyses and one final analysis. The first interim analysis will be performed after enrolling and observing outcomes of one-third of maximum sample size. At an interim analysis, CRF or disease progression rate will be reported, together with a score confidence interval for the rate. The critical value used to evaluate the confidence interval is 2.289 based on the Pocock method. We will compare the upper limit of the confidence interval with the assumed null proportion. We will conclude efficacy of the treatment if the upper limit is less than the null proportion and terminate enrollment for the relevant study group. If the upper limit is greater than the null proportion, we will proceed to the second stage of enrollment and then perform the second interim analysis on the cumulative data. The same evaluation will be replicated in the second interim analysis, as well as in the final analysis should we proceed to this step.

After completing the trial, we will conduct secondary analysis to compare outcomes of this trial with published historical experience.[22,24] We will use the score test for comparing two proportions in each evaluation. We will report both p value and 95% score confidence interval for difference between two proportions.

It is acknowledged that COVID-19 viral pandemic outbreak remains dynamic. Epidemiological update reports from the CDC may result in reassessment for case fatality rates as well as case rates for disease progression used in our study design that may require adjustments in sample size determinations at the interim analysis as independently allowed by the biostatistician.

7.0 Adverse Event Reporting

7.1 Definitions

7.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a donor convalescent plasma product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the (investigational) product, whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

Only adverse events that are possibly, probably or definitely related to the infusion of convalescent plasma should be captured.

7.1.2 Serious Adverse Event Reporting

The investigator will comply with all safety reporting regulations as set forth in the Code of Federal Regulations. The investigator being the sponsor of the study has the sole responsibility for reporting all serious adverse events to the Northside Hospital Institutional Review Board (the IRB of record), and if serious and either likely, possibly, probably, or definitely related to study drug to the FDA via Form3500A. The investigator will communicate the occurrence of serious adverse events to the IRB of record within 24 hours of becoming aware of the event.

7.1.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. 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, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.
- Results in a development of drug dependency or drug abuse
- Is a serious adverse drug experience

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

7.2 Procedures for Reporting Serious Adverse Events

Reporting will only be required for serious adverse events judged by the treating physician to be potentially related to the administration of COVID-19 convalescent plasma. This will include determination plasma related allergic reaction, urticarial eruption, adverse change in cardiopulmonary status and other organ injury. The NIH grading criteria will be utilized. Special consideration will include the development of TACO or TRALI blood transfusion associated reaction, and anaphylactic reaction temporally related to the infusion of the donor product transfusion.

Serious adverse events judged by the treating physician to be potentially related to the administration of COVID-19 convalescent plasma should be reported to the principal investigator.

All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

8.0 ADMINISTRATIVE REQUIREMENTS

8.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should

be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

8.2 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator.

8.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation using the most current IRB approved consent form. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

8.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

8.5 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC.
Any departures from the protocol must be fully documented in the source documents.

8.6 Investigator and Site Responsibility for COVID-19 Donor Convalescent Plasma Accountability

Accountability for the administration of convalescent plasma at all study sites is the responsibility of the principal investigator. The investigator will ensure that the convalescent plasma product(s) is used only in accordance with this protocol. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

8.7 Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator there is sufficient reasonable cause.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete and/or unevaluable data
- Determination of efficacy based on interim analysis

8.8 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s).

8.9 COVID-19 Convalescent Plasma Products

Convalescent Plasma products will be provided by donor blood centers in accordance with FDA regulations and guidance. This will be transported to hospital blood bank for storage and subsequent distribution to the study patient, per FDA regulator guidelines for transportation, storage and distribution and transfusion of blood products.

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