Convalescent Plasma in the Early Treatment of High Risk Patients with SARS-CoV-2 (COVID-19) Infection Protocol

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Convalescent Plasma in the Early Treatment of High-Risk Patients with SARS-CoV-2 (COVID-19) Infection

PROTOCOL Amendment 1.0 (Version 31 AUG 2020)

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Therapy:	COVID-19 Convalescent Plasma Infusion

SCHEMA

Treatment Plan

High Risk Patient Selection

Must have the Following • Diagnosis of SARS-CoV-2 infection via RT-PCR or FDA approved testing. Patients must also have the following indications for enrollment: • D-Dimer > 500 ng/ml FEU **OR** • IL-6> 5 pg/mL With any of the following • Lymphocytes < 0.8 10^3/ul **OR** • LDH > 700 U/L **OR** • CK > 170 U/L **OR** • CRP > 1.0 mg/dl **OR** • Ferritin > 1000 ng/ml **AND** one of the following: Age over 60 years Underlying Active Malignancy Cardiovascular Disease Active Tobacco Use History of Pulmonary Volume Reduction Surgery Hypertension	1 unit (Approximately 200 mL) of Convalescent Plasma over 60 minutes

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1.0 OBJECTIVES

1.1 Primary Objectives:

To determine the therapeutic efficacy (response rate) of convalescent plasma infusion in patients at high risk for mortality when infected by SARS-CoV-2 (COVID-19). The primary endpoint will be determined as prevention of progression to severe or life threatening COVID-19 during the current hospitalization. The primary endpoint will be assessed at discharge and by evaluating if the patient experienced the following data elements: respiratory rate >30/min, Blood oxygen saturation <93%, partial pressure of arterial oxygen to fraction of inspired oxygen ration <300, or received a medical diagnosis of respiratory failure, septic shock or multiple organ dysfunction/failure. This will be captured from the daily physical exam/clinical assessment done as part of routine care. See table 1.

1.2 Secondary Objectives

1.2.1 To determine the immunologic effects of convalescent plasma infusion as measured by serial SARS-CoV-2 Ag levels through RT-PCR. This will be measured by CoV PCR collected at enrollment, day 7 and discharge.

1.2.2 To measure normalization of laboratory parameters for risk as referenced in Appendix 2. Lab values outlined in appendix 2 will be documented every 3 days while the patient is hospitalized and we will evaluate labs from the time of convalescent plasma infusion to the time that lab value returns to within the institution's normal range.

2.0 BACKGROUND AND RATIONALE

The morbidity and mortality of the SARS-CoV-2 (COVID-19) pandemic has been well established. Approaches to COVID-19 has focused on preventing mass spread and treating those with critical disease, while providing supportive care to mild, moderate or severe disease. The FDA has provided guidelines for the treatment of patients with convalescent plasma and this has been restricted to patients with severe or critical disease. As our understanding of the epidemiology of this syndrome continues to expand, it has become clearer that given the extremely poor outcome for those requiring mechanical ventilation and those within a few discreet categories, a therapeutic approach focused around prevention of the transition to critical status is a key to ameliorate the poor outcomes experienced to date.

2.1 SARS-CoV-2 Infection (COVID-19)

The impact of the severe acute respiratory syndrome coronavirus - 2 (SARS-CoV-2) pandemic and more specifically the associated syndrome [COVID-19], has been rapid and extreme. As of June 1, 2020 estimates for worldwide spread suggests almost 6.3 million confirmed cases, 375,000 deaths and 1.8 million confirmed cases in the United States (GISANDDATA.maps.arcgis.com). Data continues to suggest that those at greatest risk for poor outcome include the elderly and those with comorbid illness((1)(2)(3)). In fact, Zhou reports in a retrospective multivariate analysis the odds of dying in the hospital related to COVID-19 was highest with increased age, Sequential Organ Failure Assessment (SOFA) score and concomitant markers of inflammation.(4) A report of 72,314 patients in China reports

the case fatality rate (CFR) of those over 80 years of age is 14.8%, as compared to the overall CFR of 2.3%. (5) In fact, 61.5% of those with critical disease died. (6)

There is an increasing understanding of the temporal seroconversion rate in patients infected by SARS-CoV-2 virus. Zhao and colleagues reported that among 173 patients tested median seroconversion time for IgM and IgG occurred on day 12 and day 14 respectively.(7) The relationship of this conversion timeline and the best timing of plasma procurement is still to be determined. Though this data allows that between day 14 and 21 seem optimal for plasma procurement, much of the timeliness is sure to be clarified in large multicenter trials.

Most recently, the United States Food and Drug Administration has published guidelines on the emergent use of convalescent plasma in the treatment of the COVID-19 patient.(8) It was made clear that patients with severe disease as measured by a laboratory confirmed COVID-19 infection, severe or immediately life threatening COVID-19 clinical presentation, with severe being consistent with presence of dyspnea, tachypnea (respiratory frequency $\geq$30/min), blood oxygen saturation $\leq$ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or lung infiltrates > 50% within 24 to 48 hours may be eligible to receive convalescent plasma through an emergent IND protocol. In this definition, life threatening disease is defined as the presence of respiratory failure, septic shock or multiple organ dysfunction.(8)

2.2 Rationale for Convalescent Plasma Infusion in COVID-19

Currently, there are no specific therapeutic agents for COVID-19 and the principal approach to the infected patient is supportive in nature. Several therapies are under investigation including Hydroxychloroquine, Remdesivir and others, but the efficacy of these agents are not fully understood.(9–11) Over the last several years, convalescent plasma has been utilized in the treatment of severe acute respiratory illness related to an array of viral infections, including corona viruses. (12)(13–17) This "passive antibody" therapy incorporates the infusion of antibodies against specific antigen, in this case, the SARS-CoV-2 virus through the use of convalescent plasma. To date, this is the only means to provide immediate immunity to infected individuals and differs from the impact of vaccination. (17)(18) The use of convalescent plasma was first considered as possible treatment during outbreaks for SARS, Avian influenza and Ebola virus in the early part of this century.(13,19) In a study of 80 patients with SARS, the use of convalescent plasma was associated with a higher rate of hospital discharge as compared with patients who did not receive convalescent plasma.(14) Accordingly, these findings encouraged the theory that the use of convalescent plasma transfusion could be beneficial in patients infected with SARS-CoV-2.(20) Recently, there has been preliminary data in the use of convalescent plasma in the treatment of 5 critically ill patients infected with SARS-CoV-2.(21) Shen and colleagues report that all 5 patients were moribund and receiving mechanical ventilation. Further, 3 of the 5 patients were ultimately able to be discharged and 2 patients remained clinically stabilized. All patients had laboratory-confirmed covid-19 and displayed acute respiratory distress syndrome (ARDS and exhibited significant end organ dysfunction in the form of rapid clinical deterioration and the requirement for high levels of medical and ventilator support.(21)(22) In the work by Shen, the ABO blood types of the patients were determined as is standard for compatibility of donor. Each recipient received two consecutive transfusions of 200 to 250 mL of ABO-compatible convalescent plasma for a total of 400 mL. This occurred on the same day it was obtained from the donor. The Chinese team of Duan and colleagues have also published data on the use of convalescent plasma therapy in patients with COVID-19. (23) (24) They described the benefits in their study group of 10 patients where several

parameters such as c-reactive protein, lymphocyte count and viral load all showed improvement within seven days of infusion of plasma. Importantly, they reported no severe adverse effects. These results from 10 severely ill patients demonstrated that one dose of 200 mL convalescent plasma was very well tolerated and led to disappearance of clinical symptoms in 3 days and viremia in 7 days. Further, the authors suggest that treatment earlier in the disease course seemed to result in improved responsiveness.

Given this historical data of significant improvement in respiratory failure secondary to viral infection, coupled with the new case series of COVID-19 patients benefitting from convalescent plasma infusions the idea of utilization of this modality earlier in the clinical course is compelling and warrants further expansion of this safe and readily available therapy.

2.3 Patient Characteristics for High Risk of Mortality

There are a number of reports of the constellation of clinical parameters that are associated with worse outcome when individuals are infected with SARS-CoV-2. (1) As noted by Ruan and colleagues, age has a profound impact on risk of death ($P<0.001$) as does presence of comorbid illness ($p=0.0069$).(25) This was confirmed by several authors.(26) (27)(1)(6) This is especially true of cardiovascular diseases which are associated with significantly increased risk of death when they are infected with SARS-CoV-2 ($p < 0.001$) and cancer which makes sense when one considers the underlying lymphopenic milieu seen in a number of hematological malignancies and their associated therapies.(2,28)(1)(29) In the Washington experience, Comorbidities were identified in 18 cases with chronic kidney disease and congestive heart failure being the most common diseases suggesting a poor outcome.(30)

Broadly, there are several markers of inflammation that portend to a worse prognosis as well. These include presence of lymphopenia, cardiac troponin, C-reactive protein, Interleukin-6 (IL-6) and thrombocytopenia.(25)(4,26,31,32) Markers of inflammation tended to demonstrate significantly higher levels in those with severe disease or those who go on to severe disease than in those with mild disease. Gao etal reported several key findings. C-reactive protein (CRP), D-Dimer, IL-6 were all significantly higher in the severe patient populations than in those with mild disease. Specifically, they showed the level of CRP was significantly higher in the severe group than in the mild group, D-Dimer level was higher in the severe group versus the mild group and IL-6 tended to be elevated in the severe group. In fact, testing the combination of IL-6 and D-Dimer added to the sensitivity and specificity for predicting severity of disease. When combining IL-6 with D-Dimer by parallel testing, the sensitivity and specificity were 66.7% and 96.4%, respectively. The specificity was reported at 96.4% when IL-6 and D-Dimer were combined by tandem testing. (33) Others confirmed these findings, yet it is still unclear whether these solely represent the physiological response to disease or may serve as a target for treatment.(4)

Much has been proposed in relation to outcomes of COVID-19 infections in patients with cancer. There continues to be some conflicting results. Liu and colleagues found no increased mortality in 78 patients studied with cancer and SARS-CoV-2 infections.(31) Though in reporting on 1590 patients, Liang concludes that those with an underlying malignancy had a worse outcome. In fact, patients who underwent chemotherapy or surgery in the month prior had a higher risk of clinically severe events than did those not receiving chemotherapy or surgery.(34) A case fatality rate of 5.6% in patients with cancer was reported by Wu and colleagues.(1)

A common feature of COVID-19 is the presence of absolute lymphopenia. (35) This tends to predominate within the T cell subsets of both CD4 and CD8. Often, one may find a corresponding increase in the B cell subpopulation. Lymphopenia has been clearly shown to be associated with a worse outcome.(26) In fact, CD4+T and CD8+T cells decreased in nearly all the patients studied and were especially low in severe cases (177.5 and 89.0 × 106/L) compared with moderate cases (381.5 and 254.0 × 106/L). Bhatraju etal described lymphopenia occurring in around 75% of patients on admission to the ICU in the Seattle experience, where median lymphocyte count was 720 per cubic millimeter.(10) Dr. Tan and colleagues conclude that "lymphopenia is an effective and reliable indicator of the severity and hospitalization in COVID-19 patients".(36) They go on to provide several theories as to the origin of lymphopenia, including proinflammatory effect, direct impact on lymphatic organs and presence of ACE2, a target of SARS-CoV-2, on the lymphocytes.

As noted, there are several studies that assign increased mortality related to COVID-19 amongst those who present with comorbid illnesses. However, the most poignant data seems to suggest the presence of heart disease is particularly associated with poor outcome. (37) One meta-analysis described patients with previous cardiovascular diseases were at greater risk of developing into advanced disease.(38) Personal history of hypertension in several studies seem particularly associated with worse outcomes.(4)(1) SARS-CoV-2 is thought to directly impact cardiac tissue via attachment to ACE2 receptors in the myocardium which results in cellular damage. ACE2 presence in the lungs and myocardium likely results in those two organ systems being disproportionately impacted resulting in untoward results. (39) Further, those with underlying cardiovascular disease have less reserve and this constellation results in SARS-CoV-2 infection with underlying cardiovascular disease at profound risk of mortality. Recognizing this risk and establishing clinical approach to protect this particularly vulnerable group is prudent.

It is quite interesting that patients who are active tobacco users tended to fare worse as well. (40) There are several theories but Emami suggests it is related to regulation of the ACE2 in patients who smoke tobacco compared to those who do not.

COVID-19 has had a catastrophic impact on patients and society as a whole. While herculean efforts have been undertaken to mitigate the spread of the infection, it seems that asymptomatic and mildly symptomatic patients have added to the impact globally. It is clear that patients who present in a critical state do quite poorly and many or most will die. The purpose of this study is to employ a safe therapeutic modality that can readily be accessed and use it earlier in the clinical course in high risk patients and those whose clinical picture portends to worse outcome. If able to stop this progression to critical status, it will likely provide us with the best opportunity to truly impact the morbidity and mortality of COVID-19.

3.0 RATIONALE FOR STUDY SCHEDULE

Duan and colleagues have reported excellent outcomes with the use of 200 mL convalescent plasma in the treatment of COVID-19.(24) This is administered as one unit of plasma (approximately 200 mL) over 30 to 60 minutes.

4.0 PATIENT SELECTION

4.1 Eligibility Criteria

4.1.1 Diagnosis of SARS-CoV-2 infection via RT-PCR or FDA approved testing.

4.1.2 Patients must also have the following indications for enrollment:

i. D-Dimer > 500 ng/ml FEU **OR**
ii. IL-6> 5 pg/mL

With any of the following

iii. Lymphocytes < 0.8 10^3/ul **OR**
iv. LDH > 700 U/L **OR**
v. CK > 170 U/L **OR**
vi. CRP > 1.0 mg/dl **OR**
vii. Ferritin > 1000 ng/ml

AND one of the following:

viii. Age over 60 years
ix. Underlying Active Malignancy
x. Cardiovascular Disease
xi. Active Tobacco Use
xii. History of Pulmonary Volume Reduction Surgery
xiii. Hypertension

4.1.3 Prior Treatment: Patients are still eligible for this trial if active antimicrobial agents are in use. Patients are also eligible if they had been treated on COVID-19 clinical trial in the course of their disease.

4.1.4 Age ≥ 18 years.

4.1.5 The effects of allogeneic plasma infusion on the developing fetus is unknown. For this reason women who are pregnant are not eligible to participate.

4.1.6 Agrees to required laboratory data collected which will include the baseline organ function and regular ongoing assessments done as part of routine care.

4.1.7 Ability to understand and the willingness to sign a written informed consent document or ability to have consent provided by Legally Authorized Representative.

4.2 Exclusion Criteria:

4.2.1 Patients who do not meet above inclusion criteria are not eligible**.**
4.2.2 Patients may not be receiving any other investigational agents.
4.2.3 History of allergic reactions attributed to previous transfusion history.
4.2.4 Respiratory rate >30/min
4.2.5 Blood oxygen saturation <93%
4.2.6 Partial pressure of arterial oxygen to fraction of inspired oxygen ration <300
4.2.7 Diagnosis of respiratory failure, septic shock or multiple organ dysfunction/failure

4.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

5.0 DONOR INFORMATION

5.1 Eligible donors must have evidence of COVID-19 documented by

5.1.1. A laboratory test either by diagnostic test at the time of illness OR a positive serological test for SARS-CoV-2 antibodies after recovery, if diagnostic testing was not performed at the time COVID-19 was suspected. AND

5.1.2. Complete resolution of symptoms at least 14 days prior to donation.

5.2 Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.

5.3 Those who are identified as a potential donor will be referred to Kentucky Blood Center, a FDA registered (#1070402) and licensed blood establishment, and must adhere to standards as described for all potential donors per federal regulations. Convalescent plasma is collected, processed, and provided in accordance with Kentucky Blood Center SOP 11-02-005 Convalescent Plasma (Appendix 1).

5.4 ABO compatible with the patient.

5.5 If SARS-CoV-2 neutralizing antibody titers are available:

5.4.1 Neutralizing antibody titers of at least 1:160 is preferred.

5.4.2 A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.

5.4.3 If a measurement of neutralizing antibody titers is not available, a retention sample from the convalescent plasma donation will be retained for determining antibody titers at a later date.

6.0 Treatment Plan

6.1 Convalescent Plasma Therapy

6.1.1. Convalescent Plasma Infusion Workflow

- Eligibility criteria reviewed and patient is eligible.
- Informed Consent from Patient or Legally Authorized Representative obtained
- Patient Registered with Kentucky Blood Center per protocol.
- Patient is Typed and Crossed per Institution protocols.

Convalescent plasma will be labeled as per FDA guidance for the use of convalescent plasma in the treatment of COVID-19 patients. One unit (approximately 200mL) of convalescent plasma will be infused over 1 hour per standard institution protocols for the safe administration of blood products. Acetaminophen and Diphenhydramine are allowed as premedications consistent with institution standard practices.

Patients will be monitored in accordance with pre-established institutional guidelines.

6.2 Supportive Care for Clinical Deterioration While on This Study

Due to the possibility of clinical worsening in the interim after infusion, full supportive measures should be undertaken. This includes ventilator support, adequate volume expansion and pressure support. Antimicrobials are allowed in accordance with institution standard procedures.

6.3 Other Supportive Care

- Acetaminophen prior to plasma infusion is allowed.
- Diphenhydramine prior to or after plasma infusion is allowed in accordance with institutional procedural standards.
- Patients should receive *full supportive care*, including further transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate.

6.4 Duration of Therapy

Patients should be considered enrolled in this clinical trial until discharge from the hospital or the following:

- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 6.4 apply. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6.6 Correlative Studies

6.6.1 Baseline and longitudinal laboratory assessment (Appendix 2). Appendix 2 contains data elements that will be collected at both baseline and every three days while the patient is hospitalized.

7.0 PROCEDURES FOR PATIENT ENTRY ON STUDY

7.1 Informed Consent

The patient or legal surrogate must be aware of the nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required.

Whenever possible, the clinician or other delegated staff will obtain informed consent in person. In the event PPE preservation is needed, we will use the process outlined below.

Consent Process for Hospitalized COVID-19 Positive Patients in Isolation

- Once a potential subject is identified, the PI will speak with the treating clinician. The clinician will tell the patient that they may be eligible for a trial and that someone from the research team would be calling them.
- Someone from the study team will speak with the patient to introduce the study and assess their initial interest (via phone call/facetime/zoom if the patient has access).
- If patient is interested in learning more about the study, the study team would email the consent form to the patients' nurse to print out and take to the patient to read the next time she/he enters the room.
- Research staff (delegated to conduct consent) will have another discussion with the patient via phone (or facetime/zoom) to review the consent form, answer the patient's questions and obtain verbal consent.
- If the patient has a phone with a camera in their hospital room, they can print their name, sign and date the subject lines of the consent document, take a picture of the signed page and email it to the research staff.
- If the patient does not have a phone camera in their room to take a picture of the signed consent document, a witness (unit nurse ideally) would need to be present in the room or on a three way phone call to attest that the consent was reviewed with the patient, the patient had an opportunity to ask questions and they agree to consent to participate in the study.
- Due to isolation precautions, the consent will remain with the patient and not be removed from the room. Upon patient discharge the consent form will be destroyed.
- The witness will sign a copy that has not been taken in the room, take a picture or scan a copy of the signature page and send via email to the research staff.
- The independent witness will document in EPIC his/her participation in the consent process.
- The research team should document the consent process in EPIC, sign as the person obtaining consent and upload a copy of the signed consent under the media tab.
- The research team should document the entire consent discussion in EPIC including questions that the patient asked and how understanding was assessed.
- When the patient is discharged, the research staff can mail a partially signed ICF document to the home of the patient when they are discharged home.

Consent process for hospitalized COVID-19 positive patients in isolation – When LAR is needed

- If a patient is on the ventilator and unable to provide consent, the patients' LAR can consent on their behalf following the LAR consenting process.

- If the LAR is not able to meet with the research team for the consent discussion due to their own quarantine or visitors being prohibited. The research team will have the option to email the consent to the LAR for their review.
- The research team will review the document with the LAR over the phone, answer all questions and assess understanding prior to obtaining signature.
- The LAR can sign and return the signed page by taking a photo or scanning and then emailing to the research team. Due to isolation precautions, the consent will remain with the LAR and not be returned. If, due to technology limitations, it is not possible for the LAR to receive the consent via email, print, sign electronically, or take an image of the consent form, the LAR may provide consent with a witness signing the consent.
- The research team will then sign as the person conducting consent send a signed copy to the LAR.
- The research staff will document the entire LAR consent process in EPIC
- The site will request a waiver of authorization from the IRB until the patient is able to sign the consent and authorization for themselves.

7.2 Eligibility Checklist

The Investigator and study personnel are required to complete the eligibility checklist and ensure that there is adequate source documentation regarding eligibility. In the event that there is no written confirmation that a patient meets a criterion, the Investigator must document eligibility in patient's chart.

8.0 DOSE MODIFICATION FOR OBESE PATIENTS

There is standard dose of 1 unit (approximately 200 mL) convalescent plasma for all patients.

9.0 CRITERIA FOR RESPONSE ASSESSMENT

All patients will be evaluated for response based on clinical outcomes and laboratory improvement.

Clinical assessment is done daily. Laboratory evaluation is done every three days.

10.0 MONITORING OF PATIENTS

Baseline evaluations are to be conducted the day of planned plasma infusion. At the discretion of the treating team, convalescent plasma may be held.

The recipient will be monitored for transfusion reaction in accordance with Norton Healthcare's policy which includes:

- Take vital signs (temp, pulse, blood pressure) prior to, 15 minutes after initiating and at the completion of the transfusion.
- RN, LPN, APRN, PA must remain with the patient unit the 15 min vital signs are performed and asses the patient periodically during the transfusion.

- Follow Norton Healthcare policy for Transfusion Reaction Protocol. Transfusion reactions will be reported per institutional policy.

Physical examination/clinical assessment will be done each day while on study.

Imaging will be completed at the discretion of the treatment team in response to clinical needs.

Laboratory testing as listed in Appendix 1 should be repeated every three days as part of clinical care. The frequency of overall testing should be at the discretion of the treating team.

Physical examination and laboratory recording should continue until patient no longer actively followed per section **6.4** and **6.5.**

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design / Endpoints

This study uses a standard descriptive statistics for outcomes.

To determine the therapeutic efficacy (response rate) of convalescent plasma infusion in patients at high risk for mortality when infected by SARS-CoV-2 (COVID-19). The primary endpoint will be determined as prevention of progression to severe or life threatening COVID-19 during the current hospitalization. The primary endpoint will be assessed at discharge and by evaluating if the patient experienced the following data elements: respiratory rate >30/min, Blood oxygen saturation <93%, partial pressure of arterial oxygen to fraction of inspired oxygen ration <300, or received a medical diagnosis of respiratory failure, septic shock or multiple organ dysfunction/failure. This will be captured from the daily physical exam/clinical assessment done as part of routine care. See table 1.
The secondary objectives are to:

- Determine the immunologic effects of convalescent plasma infusion as measured by serial SARS-CoV-2 Ag levels through RT-PCR. This will be measured by CoV PCR collected at enrollment, day 7 and discharge.
- To measure normalization of laboratory parameters for risk as referenced in Appendix 2. Lab values outlined in appendix 2 will be documented every 3 days while the patient is hospitalized and we will evaluate labs from the time of convalescent plasma infusion to the time that lab value returns to within the institution's normal range.

11.2 Sample Size and Accrual Rate

The maximum projected accrual is 100 patients. Patients who succumb to COVID-19 or associated comorbid illness will be clearly identified. Patients who die as a result of the convalescent plasma infusion, though likely rare, will result in mandatory study suspension until review undertaken.

Summary statistics will be calculated: mean and standard deviation for continuous variables; frequency for categorical variables. No inferential statistical tests of hypotheses are planned. For exploratory purposes, standard statistical method will be used. For repeated measures over time, individual as well as group profile plots will be generated to visualize the data.

12.0 DATA REPORTING / REGULATORY REQUIREMENTS

All IRB and FDA reporting requirements will be followed per applicable FDA regulations.

Adverse events will be reported by the treating physician or other research team members to the principal investigator. The sponsor/principal investigator is responsible for filing reports to the FDA and IRB as required.

All adverse events will be reviewed by the medical monitor at Norton Healthcare.

This study will be registered on clinicaltrials.gov.

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor investigator as described in the protocol and ordinarily would not be reported under paragraph 21 CFR 312.32(c).

13.0 ADVERSE EVENTS AND REPORTING REQUIREMENTS

Serious Adverse Events and Transfusion Reactions will be collected from the time of informed consent until the subject is discharged or dies.

The following information about the event will be documented: event, start and resolution date (and time if known), treatments received, and outcome.

The event will be reviewed by the Sponsor/Principal Investigator to determine severity and causality to the convalescent plasma infusion.

SAEs will be reported to the FDA and IRB as required. SAEs include those events that result in death, life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or other important medical event that may jeopardize the subject or may require intervention to prevent one of the outcomes included in this definition.

ADVERSE EVENT DEFINITIONS

The following definitions regarding adverse events, as defined by 21 CFR 312.32(a), will be used for this protocol.

Adverse event - Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction - An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction - An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or 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, or the development of drug dependency or drug abuse.

Suspected adverse reaction - Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction - An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Unexpected fatal or life-threatening suspected adverse reaction reports - The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

REVIEW OF SAFETY INFORMATION

The sponsor investigator must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor investigator from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

IND SAFETY REPORTS

The sponsor investigator must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor investigator is providing drug under in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor investigator determines that the information qualifies for reporting under paragraph 21 CFR 312.32 (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor investigator must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

REPORTING REQUIREMENTS

Serious and unexpected suspected adverse reaction - The sponsor investigator must report any suspected adverse reaction that is both serious and unexpected. The sponsor investigator must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under 312.32(c)(1)(i) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

Findings from other studies - The sponsor investigator must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph 21 CFR 312.32(c)(1)(i) of this section), whether or not conducted

under an IND, and whether or not conducted by the sponsor investigator, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

Findings from animal or in vitro testing - The sponsor investigator must report any findings from animal or in vitro testing, whether or not conducted by the sponsor investigator, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

Increased rate of occurrence of serious suspected adverse reactions - The sponsor investigator must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

Submission of IND safety reports - The sponsor investigator must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor investigator must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

FOLLOW-UP

- The sponsor investigator must promptly investigate all safety information it receives.
- Relevant follow up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Followup IND Safety Report."
- If the results of a sponsor investigator's investigation show that an adverse event not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor investigator must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

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15.0 TABLE 1: DEFINING CHARACTERISTICS OF SEVERE COVID-19 DISEASE

Respiratory Frequency >30/min

Blood Oxygen Saturation < 93%

Partial Pressure of Arterial Oxygen to Fraction of Inspired Oxygen Ratio <300

Respiratory Failure

Septic Shock

Multiple Organ Dysfunction /Failure

16.0 APPENDICES

15.1 Kentucky Blood Center SOP 11-02-005 Convalescent Plasma
15.2 RedCap Data Collection Form

APPENDIX 1

kentucky blood center	**SOP 11-02-005** **CONVALESCENT PLASMA**	**KENTUCKY BLOOD CENTER** Lexington, Kentucky (859) 276-2534

I. PURPOSE

To provide directions for the handling of convalescent plasma.

II. SPECIAL NOTES

A. **Convalescent Plasma (CP)** is plasma from patients who have recovered from an infection and used as a therapy to treat those with the same infection. Although it may be promising, convalescent plasma has not been shown to be effective in every disease studied.

B. **COVID-19 Convalescent Plasma (CCP)** is a treatment option for COVID-19 while additional treatment options are evolving. It is possible convalescent plasma may contain antibodies to SARS-CoV-2, the virus that causes COVID-19, and may be effective against the infection.

C. During an infectious disease outbreak or pandemic, the FDA may allow collection and transfusion of convalescent plasma due to the public health emergency.

1. The FDA through a single patient or traditional emergency Investigational New Drug Applications (eINDs) usually authorize this process. It is also possible for the FDA to utilize additional pathways, including the expanded access pathway (EAP) for the eIND, to allow increased participation by health care facilities.
2. COVID-19 Convalescent Plasma (CCP) is used for patients with serious or immediately life-threatening COVID-19 infections.

D. Hospitals should ensure the following prior to requesting convalescent plasma:

1. Obtain approval for treating patients with convalescent plasma. This usually entails obtaining an emergency Investigational New Drug Application (eIND) completed by the treating licensed physician through the FDA prior to transfusion. The eIND does not need to be yet accepted but the hospital will be given an eIND reference number.
2. Ensure the patient meets the requirements for transfusion with the convalescent plasma (and/or the eIND). At a minimum:
   a. Must have a laboratory confirmed positive test result (e.g. COVID-19)
   b. Must have severe or immediately life-threatening disease (or other criteria) as defined by the FDA.

E. KBC is not required to verify that the receiving hospital has an IND. The receiving hospital is responsible for ensuring that approval for treating patients with Convalescent Plasma is obtained.

F. Collection of CP does not require any approvals.

1. Kentucky Blood Center may collect donors for storage of COVID-19 convalescent plasma.
2. An IND is only required for transfusion of the component.

III. MATERIALS REQUIRED - N/A

IV. EQUIPMENT REQUIRED - N/A

V. DOCUMENTS REQUIRED

A. Attached in MasterControl - N/A

B. Linked in MasterControl

1. SOP 60-01-015 - Release of Untested Products

2. SOP 62-10-001 - Receiving Unprocessed Units Collected by KBC
3. SOP 62-10-005 - Preparation of Blood Components
4. SOP 62-22-001 - Fresh Frozen Plasma Preparation
5. SOP 70-21-031 - Emergency Release of Product - Hospital Services

C. Other - N/A

VI. PROCEDURE

A. BLOOD COLLECTIONS

1. Collection of the product must be coordinated with KBC's Medical Director.
2. Potential donors should be identified and screened. The following is required for the recovered potential donor:
   a. Documented positive laboratory test result (e.g. Positive COVID-19 test result).
   b. Resolution of symptoms for the required timeframe post-recovery.
      1) For COVID-19 the timeframe requirement for resolution of symptoms is 14 days post recovery in order to donate.
   c. Documented negative laboratory test result post-infection, if within required timeframe.
      1) For COVID-19 the requirement is a negative test result if less than 28 days post-recovery. If the timeframe is greater than 28 days post-recovery then no test is required.
   d. Eligible to donate blood. Female donors should be negative for HLA antibodies or never pregnant.
      NOTE: If the Medical Director approved the collection of plasma from a female donor who has been pregnant but her HLA status has not been determined, then initiate a KBC-025 and send with the test tube samples with the normal shipment.
   e. ABO compatible with the patient.
   f. Prior infectious disease testing is performed, if desired.
   g. Defined neutralizing antibody titers, if testing can be conducted (e.g. SARS-CoV-2 neutralizing antibody titers). This may be performed at a later date.
3. Collection will be performed at one of KBC's fixed collection sites by plasma pheresis (PA).
   NOTE: Most of the donors selected may not have donated blood before and most likely never have donated plasmapheresis. Provide explanations as needed of the collection process. Encourage the donor to drink offered fluids (after temperature has been taken) and snacks during the collection procedure.
   a. If during the screening process the donor reveals an unexpected answer that would disqualify them, contact the KBC Medical Director (<u>not</u> the on call physician) before proceeding with the deferral.

b. If the donor is deferred (or no product is collected), then notify the Covid-19 Plasma email group.

4. The BC Manager or designee will ensure the configurations of the Trima (collections are performed off-line from Vista) are set as follows:

NOTE: The Platelet/Plasma/RBC tubing set is capable of a jumbo plasma collection if the MultiPlasma tubing set is not available. Donors do receive saline as a replacement fluid if the MultiPlasma tubing set is used while the Platelet/Plasma/RBC tubing set does not provide an access to the use of saline as a replacement fluid.

a. The 5 digit catalog number of the MultiPlasma tubing set, 80700 or 82700 (as applicable) is entered in the Machine screen, as needed.

b. The upper limit for As Much As Possible (AMAP) is set to 825 mL on the Plasma screen.

c. To allow all qualified donors do the following:

1) For Trima version 6, change the donors allowed on the Plasma screen from MALES to ALL.

2) For Trima version 7, on the Procedure Priority screen add an AMAP procedure and change the donors allowed to ALL.

d. See the steps to follow based on the tubing set used to collect the plasma product:

1) If using the MultiPlasma tubing set, then collect the plasma product in two bags if the total volume is expected to be over 600mL.

2) If using the Platelet/Plasma/RBC tubing set then collect the plasma product in one bag.

5. Apply the appropriate face label for the collection. For collection of COVID-19 Convalescent Plasma see Appendix A for an example of the E9747 face label to be applied to the PA donation.

6. Collect 4 red top and 3 purple top test tube samples.

7. Blood Collections or designee will notify involved KBC departments when the donation has been completed. Blood Collections will immediately send the product and collection test tubes to Components Laboratory for processing.

8. Once CLAB has completed processing, notify QA via email to perform the donation review, if the product is to be emergency released for patient specific transfusion.

B. TECHNICAL SERVICES: COMPONENTS LABORATORY (CLAB) [PART I]

1. Receive the product and collection test tubes from Blood Collections, and process per SOP 62-10-001 Receiving Unprocessed Units Collected by KBC and SOP 62-10-005 Preparation of Blood Components. The process is similar to Fresh Frozen Plasma (FFP).

a. The product code for COVID-19 plasma collected by apheresis will be E9747 (Apheresis CONVALESCENT PLASMA|ACD-A/XX/<=-18C|COVID-19).
NOTE: If this product code is thawed the product code will then be E9752 (Thawed Apheresis CONVALESCENT PLASMA|ACD-A/XX/refg|COVID-19) and the expiration will be in 24 hours.
b. If needed, Apheresis plasma products are split for COVID-19 convalescent plasma. At a minimum, the products should be 200mL each and not less.
c. Save two segments of plasma for the donation product. Send the two segments to Testing Lab (TLAB) for freezing.

2. If the product is for emergency release, follow the emergency release process. Refer to SOP 60-01-015, Release of Untested Products.
a. Ensure the product has a tag designating the product as convalescent plasma for a patient. The tag should state the following:
1) Patient's first and last name
2) Date of Birth (DOB)
3) Hospital Name
4) Hospital ID

3. Send the plasma product, before freezing, and collection test tubes, the segments from the product, to Testing Laboratory (TLAB) for processing, including manually labeling the product, if for emergency release.
NOTE: Seven (7) test tubes will be delivered with the product from Blood Collections and should go to TLAB.

4. Receive the products from Testing Laboratory once manually ABO/Rh labeled and continue manufacturing through the freezing process per SOP 62-22-001 Fresh Frozen Plasma Preparation.
a. See step VI.D for additional CLAB manufacturing information.
b. Product should have a 1 year expiration date and be stored at -18ºC or colder.

C. TECHNICAL SERVICES: TESTING LABORATORY (TLAB)

1. Receive the product from Components Laboratory and process per SOP 60-01-015 Release of Untested Products, including manually labeling the product. TLAB will only receive the product if it will be emergency released.
a. Reference Lab will perform a manual ABO type and antibody screen.
b. TLAB and RLAB will manually ABO label the product(s).

2. Receive the collection test tubes from Components Laboratory. Save and freeze any plasma/serum from the test tubes as needed.
a. For COVID-19, seven (7) tubes should be delivered with the product. Serum from two (2) red top tubes should be frozen and saved for possible future testing. If serum tubes are not available, plasma from EDTA tubes may be used if necessary.

3. Send the product back to Components Laboratory to finish manufacturing.

4. Send tubes to designated testing laboratory for infectious disease testing.

D. TECHNICAL SERVICES: COMPONENTS LABORATORY (CLAB) [PART II]

1. Component Laboratory will freeze the product.
   a. If for emergency release, once freezing is completed, send product(s) to HS for shipment.
   b. If for storage, store products in the walk in freezer in a designated bin using the STOR process in BBCS.
      1) Once test results have posted, perform label verification in BBCS to label the convalescent plasma.
2. Send the product to Hospital Services once the freezing of the plasma product is complete if for emergency release for patient specific transfusion.

E. TECHNICAL SERVICES: HOSPITAL SERVICES (HS)

1. Visually inspect the product upon receipt. The container label must contain the following: "Caution: New-Drug - Limited by Federal (United States) law to investigational use".
2. Ensure there are no blanks on the label, including the volume and anticoagulant section.
3. If for emergency release, ship the product per SOP 70-21-031 Emergency Release of Product - Hospital Services. A manual shipping document will need to be completed. Otherwise, ship per normal shipping procedure.
   NOTE: The product cannot be shipped until QA performs a review of the donor record. QA will notify when the review has been completed.

VII. REFERENCE VALUES – N/A

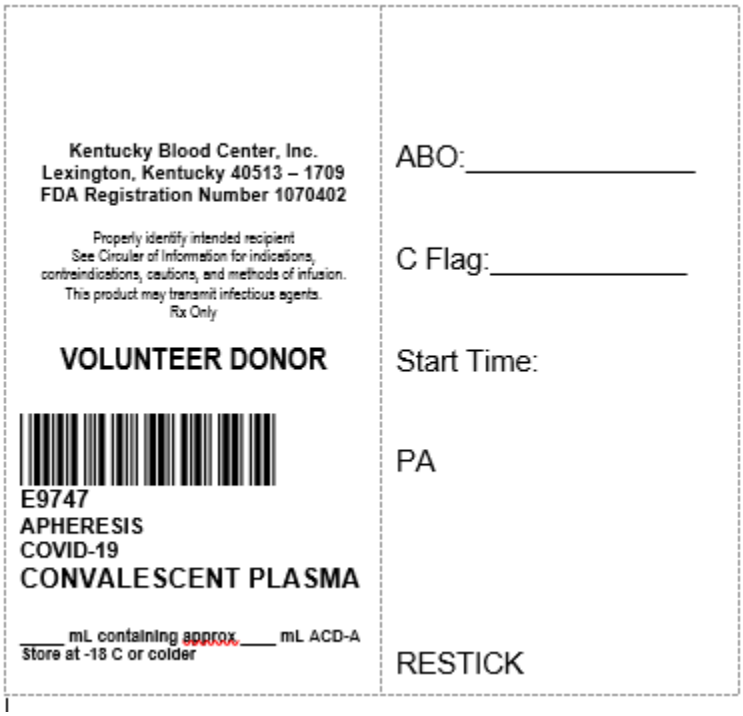
VIII. REFERENCES

A. Food and Drug Administration (FDA) emergency Investigational New Drug (IND) guidelines

B.

IX. APPENDIX

A. Appendix A: E9747 Label - COVID-19



APPENDIX 2

Convalescent Plasma in Early Treatment of High-Risk Patients with SARS-CoV-2 (COVID-19) Infection
RedCap Data Collection Form

LAB VALUES

Lab Name	Result	Units
White blood cell count		10*3/uL
Hemoglobin		g/dL
Platelet count		10*3/uL
Absolute neutrophil count		10*3/uL
Absolute lymphocyte count		10*3/uL
Absolute eosinophil count		10*3/uL
Sodium		mmol/L
Potassium		mmol/L
Chloride		mmol/L
Bicarbonate		mmol/L
BUN		mg/dL
Creatinine		mg/dL
ALT		U/L
AST		U/L
Alkaline Phosphatase		U/L
Total Bilirubin		mg/dL
PT/INR last tested		sec
CK		U/L
LDH		U/L
CRP		mg/dl
D-Dimer		ng/ml FEU
IL–6		
Other Pertinent Lab results, ABGs, Culture Results		
Ferritin		ng/mL

APPENDIX 2

Convalescent Plasma in Early Treatment of High-Risk Patients with SARS-CoV-2 (COVID-19) Infection
RedCap Data Collection Form

CoV PCR (indicate site and date of collection*)*	Done prior to enrollment, at day 7, and on discharge	

Plasma

- Date of plasma infusion
- Plasma infusion start time
- Plasma infusion end time
- Total volume infused
- Plasma unit number infused

Radiological Results

- Radiological procedure completed: (must be able to enter multiple)
- Date Completed
- Normal/Abnormal
    - If abnormal, describe

Physical Exam (must be able to enter daily)
Date Completed

- HEENT – (column for body systems, Normal/Abnormal -- If abnormal, describe)
- Neurological
- Cardiac
- Pulmonary
- Abdominal
- Skin
- Extremities

Oxygen Use (will need to be able to have multiple entries):

- Route of Oxygen administration
- Amount of O2
- Start Date
- Stop Date

Respiratory Status (enter daily)

- Highest respiratory rate in 24 hour period
- Lowest blood oxygen saturation in a 24 period
- Partial Pressure of Arterial Oxygen to Fraction of Inspired Oxygen Ratio, if available

APPENDIX 2

Convalescent Plasma in Early Treatment of High-Risk Patients with SARS-CoV-2 (COVID-19) Infection
RedCap Data Collection Form

Concomitant medications (must be able to enter multiple)

- Name
- Dose
- Frequency
- Route
- Indication
- Start Date
- End Date

Adverse Events (must be able to enter multiple)

- Event
- Start Date
- End Date
- Serious Yes/No
- Severity
- Relationship to investigational product

Ventilator

Was Ventilator support ever needed during this hospitalization? Yes/No

If yes, date placed on vent, date off vent

Outcomes

- Date of symptom resolution
- Date of hospital discharge or death
- Did the subject complete the protocol?
    - Date of completion or withdrawal
    - If withdrawal, describe reason

Additional Diagnosis after Convalescent Plasma Treatment with Date of Diagnosis

- Respiratory Failure _____
- Septic Shock _____
- Multiple Organ Dysfunction /Failure _____