TITLE:
ANTIBODY-LEVEL BASED ANALYSIS OF COVID-19 CONVALESCENT SERUM (ABACCuS)

NCT04432272

Approval date: 08/26/2020

Protocol and Statistical Analysis Plan

PROTOCOL SUMMARY:

Long title: **A**ntibody-level **B**ased **A**nalysis of **C**OVID **C**onvalescent **S**erum

Short title: **ABACCuS**

Protocol Date: August 13, 2020

Clinical Phase: Phase 2

Blinding and Randomization: Double-Blinded to Antibody Content of Convalescent Plasma, Not Formally Randomized

IND Sponsor: Beaumont Health

Conducted by: Beaumont Health
Beaumont Hospital, Royal Oak
Beaumont Hospital, Troy
Beaumont Hospital, Grosse Pointe
Beaumont Hospital, Dearborn
Beaumont Hospital, Taylor
Beaumont Hospital, Trenton
Beaumont Hospital, Wayne
Beaumont Hospital, Farmington Hills

Trial Oversight
Matthew Sims, MD PhD, Principal Investigator
Craig Fletcher, MD, Sub-Investigator
Gabriel Maine, MD, Sub-Investigator
Peter Milward, MD, Sub-Investigator
Christopher Carpenter, MD MHSA, Sub-Investigator
Paul Chittick, MD, Sub-Investigator
Richard Kennedy, PhD, Sub-Investigator
Robert Podolsky, PhD, Biostatistician
Deborah Hasenau, RN, MS, Research Director

Beaumont Hospital, Royal Oak – Florian Bukovec, MD, Sub-Investigator
Beaumont Hospital, Troy – Sachi Gowda, MD, Sub-Investigator
Beaumont Hospital, Grosse Pointe – Joel Fishbain, MD, Sub-Investigator
Beaumont Hospital, Dearborn – Cecilia Big, MD, Sub-Investigator
Beaumont Hospital, Taylor – Neeraja Varanasi, MD, Sub-Investigator
Beaumont Hospital, Trenton – Faisal Musa, MD, Sub-Investigator
Beaumont Hospital, Wayne – Mustafa Bohra, MD, Sub-Investigator
Beaumont Hospital, Farmington Hills – Wiley Fan, DO, Sub-Investigator

LIST OF ABBREVIATIONS

ADR: Adverse Drug Reaction
ADE: Antibody Dependent Enhancement of infection
AE: Adverse Event/Adverse Experience
CDC: United States Centers for Disease Control and Prevention
CFR: Code of Federal Regulations
CLIA: Clinical Laboratory Improvement Amendment of 1988
COI: Conflict of Interest
COVID-19: Coronavirus Disease
CRF: Case Report Form
DSMB: Data and Safety Monitoring Board
EMR: Electronic Medical Record
EUA: Emergency Use Authorization
FDA: Food and Drug Administration
GCP: Good Clinical Practice
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
HTLV: Human T-cell lymphotropic virus
IB: Investigator's Brochure
ICF: Informed Consent (Informed Consent Form)
ICH: International Conference on Harmonization
ICU: Intensive Care Unit
IND: Investigational New Drug Application
IRB: Institutional review board
ISBT: International Society of Blood Transfusion
MERS: Middle East Respiratory Syndrome
NP: Nasopharyngeal
PI: Principal Investigator
PPE: Personal Protective Equipment
RT-PCR: Reverse Transcriptase Real-Time Polymerase chain reaction
SAE: Serious adverse event
SARS: Severe Acute Respiratory Syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
TACO: Transfusion-associated circulatory overload
TRALI: Transfusion-related acute lung injury
UP: Unanticipated Problem

Sample Size: 500 (300 serious but non-intubated patients, 200 intubated patients)

Study Population:
Group A: Hospitalized COVID-19 patients ages ≥18 years with respiratory symptoms, requiring >6L of oxygen to maintain O_2 saturation >92%. Patient may not require intubation, and may be admitted for no longer than 14 days.

Group B: Hospitalized COVID-19 patients ages ≥18 years requiring intubation.

Study Duration: May 15, 2020 to December 31, 2022

Study Design: This phase 2 trial will evaluate the efficacy and safety of SARS-CoV-2 convalescent plasma as treatment for confirmed COVID-19 respiratory disease (as defined in the inclusion criteria). Adults 18 years of age and older may participate. Patients may be enrolled in group A within 14 days of admission to the hospital and may be enrolled in group B at any time after intubation. A total of 300 eligible subjects with significant oxygen requirements and 200 eligible subjects who require intubation will be included in the study. They will receive convalescent plasma from either a patient who has recovered from COVID-19 or from an asymptomatic carrier with confirmed IgG against SARS-CoV-2. Subjects will not be randomized but the amount of anti-SARS-CoV-2 IgG and IgA in any unit of plasma will not be known when the unit is assigned to the patient. This will allow us to examine the relationship between the amount of anti-SARS-CoV-2 antibody and outcomes. Analysis will be based on measurement of optical density of the IgG level in the unit of plasma the patient is randomly supplied by the blood bank. While investigators and patients will be aware the patient is receiving a unit of COVID-19 convalescent plasma, both the investigators and the patients will be blinded to the antibody content of that unit.

Assessment in all subjects: Given the issues with the pandemic such as limitations on PPE, and the need for strict isolation, patient data will be limited to that which is acquired from the EPIC EMR (in use at our institution) but not from face to face interview with the patient. The data will be supplemented as possible with phone interview with the patient or their LAR. Consenting will be e-consent based using RedCap with the consent form e-mailed to the patient or the LAR for review prior to the actual consent process. Consent will be obtained over the phone and with a witness: the consent provider and the witness will both document the consent process within the patient's chart in the EPIC EMR.

Study Product: COVID-19 convalescent plasma (1 unit; ~300 mL) The product will be produced by Verseti Blood Bank (or other acceptable, blood bank licensed to produce plasma) using standard screening and safety procedures. The product may be procured from patients who have: 1) been symptom free for 14 days and screen negative via NP swab or 2) symptom free for at least 28 days or 3) individuals who have never had symptoms of COVID-19 but were found to have elevated anti-SARS-CoV-2 IgG by a serology test deemed to be of acceptable quality and fitting the current guidance by the FDA. Current protocols from Verseti do not screen for antibody level in COVID convalescent plasma, but Verseti retains a residual sample for later testing. Any emerging FDA guidance will be followed. From each unit, immediately after thawing, 2 mL will be removed, 1 mL for SARS-CoV-2 IgA and IgG tests and 1 mL to be held at -80°C for future neutralizing antibody testing.

1. Background

1.1 COVID-19: A Major Pandemic Currently Affecting the Entire World

In late 2019 the first cases of what has come to be named COVID-19 were noted in Wuhan China[1]. COVID-19 is caused by a novel coronavirus now designated SARS coronavirus-2 (SARS-CoV-2). As of 5/3/2020, the total number of diagnosed cases of COVID-19 worldwide is 3,566,487 with 248,302 deaths and 1,154,550 have been documented to have recovered, and in the United States there are 1,188,122 cases, 68,598 deaths, and 178,263 recovered[2]. Michigan as a state has been disproportionately impacted, at one point ranked third highest number of cases, though due to stay at home orders and other mitigation strategies it has more recently fallen to seventh. It remains third highest for deaths due to COVID-19, and it has the highest percentage of cases leading to mortality in the US. As of 5/3/1010 in Michigan there are currently 43,754 cases, 4,049 deaths, and recovered is not currently available[2]. The first death in Michigan was reported from Beaumont, Wayne[3]. Eighty percent of the cases in Michigan fall within the tri-county Detroit metropolitan area which Beaumont Health serves.

The most common presenting symptoms of COVID-19 are fever, cough, and shortness of breath[4] and the disease presentation ranges from asymptomatic to mild to an overwhelming inflammatory response leading to acute respiratory distress syndrome (ARDS) and cytokine release syndrome and ultimately death. The actual mortality of the disease is currently unknown but estimates from China suggest a mortality rate of 3.6% (95% CI 3.5–3.7)[5]. In the United States mortality estimates to date indicate that fatality was highest in persons aged ≥85, ranging from 10% to 27%, followed by 3% to 11% among persons aged 65–84 years, 1% to 3% among persons aged 55-64 years, <1% among persons aged 20–54 years, and no fatalities among persons aged ≤19 years[6]. The overall mortality rate ~1.5% which varies day to day (0.8%-2.6% depending on the day it is calculated)[7]. Importantly current mortality numbers for the United States are based on a time when the health care system was not overwhelmed. When analyzing the mortality of COVID-19 in Italy, a country whose health care system can no longer handle the patient load caused by this disease, the mortality is currently estimated at 9.3%[2].

Those at high risk for progression to severe illness include people over the age of 65, people who live in a long term care facility, people with chronic lung disease, people with heart disease, immunocompromised patients, people who are obese (BMI≥40), and people with other chronic medical conditions such as diabetes, renal failure, and liver disease[8]. At Beaumont Health we have noted a trend that severe cases tend to be male, African American, with diabetes and hypertension (unpublished data).

1.2 Current Treatment of COVID-19

There is currently a single treatment approved by the FDA under emergency use authorization, remdesivir[9]. Remdesivir is an experimental medication developed for the treatment of Ebola virus and active against RNA viruses including COVID[10]. Remdesivir was studied in an NIH sponsored clinical trial in COVID-19 and did not show a statistically significant reduction in mortality, but did show a decrease in length of the disease by 31%[11]. At this time availability of remdesivir remains low and exactly where it best fits in the therapy of COVID-19 remains unclear.

There have been numerous other approaches to therapy tried including hydroxychloroquine and azithromycin based in part on the study of Gautret et al[12] which revealed promising outcomes that were unable to be duplicated by Molina et al[13]. Other studies of hydroxychloroquine in more severely ill COVID-19 patients failed to show a significant benefit [14-16] though it remains to be seen if it is useful early in the course of the disease to prevent progression or as prophylaxis. Lopinavir-ritonavir is a repurposed HIV protease inhibitor which showed good activity against SARS[17] but has failed to show activity against COVID-19[18]. There are numerous other compounds in research studies, but none have yet shown any benefit[19].

1.3 Convalescent Plasma as a Therapy for Infectious Diseases

It is not clear how long convalescent plasma therapy has been used to treat infectious diseases but the first protocolized use was in the 1890s as a means to treat Diphtheria[20]. The use continued in the 20th century as a means to treat Scarlet Fever and Pertussis and was the only means of treating certain infectious diseases prior to the widespread availability of antimicrobial therapy in the 1940s[21]. The use of convalescent plasma to treat viral diseases, including severe respiratory diseases is widespread[22] but unfortunately the studies are generally poorly controlled for bias[23]. Notably convalescent plasma therapy was used to treat influenza during the Spanish Flu Pandemic of 1918-1920 with a suggestion of success multiple studies, a meta-analysis of the use of convalescent plasma for the Spanish Flu was published in 2006[24]. More recently convalescent plasma was used as a potential treatment in the 2013 African Ebola epidemic. A small non-randomized study in Sierra Leone revealed a significant increase in survival for those treated with convalescent whole blood relative to those who received standard treatment[25] while other studies were not as positive[26].

1.4 Convalescent Plasma as a Therapy for Coronaviruses

SARS-CoV-2 is the most recent coronavirus to impact humans, while there are literally hundreds, perhaps even thousands of coronaviruses only 7 have been shown to affect humans. There are 4 coronaviruses which are causes of the common cold; 229E, NL63, OC43, and HKU1. There are 2 other coronaviruses that have been associated with epidemics and high mortality, SARS-CoV, the etiologic agent of SARS, and MERS-CoV, the etiologic agent of MERS. For both of these epidemics the high mortality and lack of effective treatments led to use of convalescent plasma in an attempt to save lives.

A number of case series of patients treated with convalescent plasma for SARS have been published[27-32] and were reviewed in a meta-analysis in 2015 by Mair-Jenkins et al[33]. Three of the reports included a single patient each[27-29], one report was a series of 3 health care workers who received plasma[30].

The first study with a reasonable number of patients reported 19 patients who received plasma after steroids vs 21 patients who only received steroids[31]. This study reported that no one in the plasma arm died where 5 in the steroid arm died. However the study had multiple issues, it was not randomized, the steroid group had significantly higher comorbidities, and 9 members of the steroid group crossed over and received plasma. They concluded that plasma was associated with a significant decrease in mortality (p=0.049) and that receiving plasma after day 16 was associated with a poor clinical response (based on the crossover group). The also recognized that this may simply have been due to the control group receiving steroids which was later shown to be

contra-indicated in SARS.

The largest case series was 80 patients in Hong Kong who received convalescent plasma[32]. Of the 80 patients, 33 had a good outcome, which was defined as discharge by day 22 from onset of the disease, 47 had a poor outcome which was defined as death by day 22 from onset of the disease or continued need for hospitalization after day 22. In this study the overall mortality rate among the 80 patients was 12.5% whereas the overall mortality rate in Hong Kong was 17%. Sub-analysis of the patients who received convalescent plasma also noted that those who received convalescent plasma before 14 days did better than those who received it after 14 days.

Both studies involving a larger number of patients noted that there were no adverse events associated with receiving convalescent plasma and both studies noted that there were better outcomes when plasma was given before 14 or 16 days. The choice to limit Group A in this study to patients admitted no longer than 14 days is based on these observations.

While there were clearly attempts to use convalescent plasma for MERS[34], there are no published cases series and only a single case report documenting a patient treated with convalescent plasma who developed TRALI[35]. Unlike SARS and COVID-19, MERS has a very low rate of person to person spread. An analysis of MERS antibody levels in patients with MERS or suspected MERS, healthcare workers with confirmed exposure to MERS, and household contacts of patients with MERS was performed in 2015[36]. The study had numerous issues, including the fact that very few participants had laboratory confirmed MERS and the timing of serology testing after infection or exposure was highly variable, however it showed very few had developed significant antibody levels making the use of convalescent plasma in MERS questionable and raising the concern that simply using plasma from patients who recovered from a coronavirus infection may not have adequate antibodies for a therapeutic effect.

1.5 Convalescent Plasma as a Therapy for COVID-19

To date there have been 6 case series published using COVID-19 convalescent plasma as a treatment[37-42]. In addition, there was a meta-analysis performed of the initial 5 case series[43]. The various case series treated anywhere from 2 to 6 patients and in 5 of the reports all patients survived. However, when the patient populations in these studies are looked at, even when described as severe, cases often were not actually severe at the time they received convalescent plasma all but had been severe earlier in their admission[38]. In fact, one patient in a series was already discharged from the hospital but called back in and given a dose of convalescent plasma because they had a positive PCR for SARS-CoV-2 despite clinical improvement[39].

In the last case series 21 patients were eligible for plasma but only 6 received it due to the limited availability of convalescent plasma and ABO compatibility. The mortality in the treatment group was 5/6 and in the control group was 14/15. The patients who received convalescent plasma had a higher clearance of the virus (p=0.005) and a longer survival period (p=0.029) but no improvement in mortality[42].

It is important to note that in the various case series, with few exceptions there was no measurement of anti-SARS-CoV-2 antibody in the convalescent plasma and no specific protocol under which it was given. The patients were highly heterogeneous, the

definition of a unit of plasma by volume varied, and the volume of plasma given varied from 200 ml to 2400 ml with no clear reason behind dosing additional units other than lack of patient improvement[40].

1.6 Mechanism of Action

Convalescent antibody therapy involves the administration of plasma from persons recovered from an infection to a susceptible or ill individual. It is assumed, the plasma contains antibodies against the infectious agent but this has frequently not been confirmed in prior studies.

It is intuitively obvious that if convalescent plasma is efficacious for the treatment of an infection that the mechanism of action would be passive antibody therapy where antibodies against the pathogen lead to neutralization of the pathogen[44]. However, other mechanisms may be possible, such as antibody dependent cellular cytotoxicity and/or phagocytosis[45]. It has also been suggested that there are multiple ways in which convalescent plasma can lead to antibody regulated immunomodulation which in turn leads to down regulation of the hyper-inflammatory reaction associated with COVID-19[46].

One study examining the convalescent plasma from SARS patients found increased levels of multiple inflammation inhibitors in the plasma that were completely unrelated to the antibodies present[47].

Given that many of the patients who recovered from COVID-19 in the published case series were intubated long past the time when it was likely active virus was still present to be neutralized[48] and long past the time when they should have developed their own neutralizing antibodies[49], there may be an as yet undefined mechanism to the activity of convalescent plasma.

2. Research Design

2.1 Objectives

Group A Primary Efficacy Objective: Evaluate the association between efficacy of treatment with COVID-19 convalescent plasma and the amount of Anti-SARS-CoV-2-spike protein IgG as assayed by the EUROIMMUN Anti-SARS-CoV-2 assay.

Group A Primary Efficacy Endpoint: Avoidance of intubation at 28 days.

Group A Secondary Efficacy Endpoints:

1. Final outcome on a 7-point ordinal scale
2. Cardio-circulatory arrest (at any time)
3. Renal failure, as measured by RIFLE criteria
4. Liver failure, as measured by elevation of ALT and AST to 5x the upper limit of normal or significant worsening of current liver failure with rise in transaminases of >25%
5. Evidence of cytokine storm based on measurement of inflammatory markers
6. Type and duration of respiratory support
7. Requirement of pressor support
8. ICU mortality
9. ICU length of stay
10. In hospital mortality
11. 28-day mortality
12. Length of stay
13. Ventilator-free days
14. Readmission rate
15. Patient level of anti-SARS-CoV-2 IgG at the following times: prior to transfusion, 1-hour post-transfusion, 24 hours post-transfusion, 72 hours post-transfusion, 7 days post-transfusion, every 7 days until discharge, day of discharge.
16. Evaluate the rates, levels (based on CT values) and duration of SARS-CoV-2 RNA in nasopharyngeal swabs using RT-PCR amongst the anti-SARS-CoV-2 convalescent plasma at the following times: prior to transfusion, 24 hours post-transfusion, 72 hours post-transfusion, 7 days post-transfusion, and 14 days post-transfusion.

Group A Investigational Efficacy Objectives:

1. Evaluate the efficacy of treatment with COVID-19 convalescent plasma in relation to the amount of Anti-SARS-CoV-2-spike protein IgA as assayed by the EUROIMMUN Anti-SARS-CoV-2 assay.
2. Evaluate the efficacy of treatment with COVID-19 convalescent plasma in relation to the amount of both Anti-SARS-CoV-2-spike protein IgG and IgA as assayed by the EUROIMMUN Anti-SARS-CoV-2 assay.

All primary and secondary efficacy endpoints for the study will be re-evaluated based on levels of IgA for investigational objective #1 and based on combined levels of IgG and IgA for investigational objective #2

Group B Primary Efficacy Objective: Evaluate the association between efficacy of treatment with COVID-19 convalescent plasma in relation to the amount of Anti-SARS-CoV-2-spike protein IgG as assayed by the EUROIMMUN Anti-SARS-CoV-2 assay.

Group B Primary Efficacy Endpoint: Mortality at 28 days.

Group B Secondary Efficacy Endpoints:

1. Final outcome on a 7-point ordinal scale
2. Cardio-circulatory arrest (at any time)
3. Renal failure, as measured by RIFLE criteria
4. Liver failure, as measured by elevation of ALT and AST to 5x the upper limit of normal or significant worsening of current liver failure with rise in transaminases of >25%
5. Evidence of cytokine storm based on measurement of inflammatory markers
6. Type and duration of respiratory support
7. Requirement of pressor support
8. ICU mortality
9. ICU length of stay
10. In hospital mortality
11. Length of stay
12. Days from transfusion till end of ventilator support in survivors
13. Ventilator-free days
14. Readmission rate
15. Patient level of anti-SARS-CoV-2 IgG at the following times: prior to transfusion, 1-hour post-transfusion, 24 hours post-transfusion, 72 hours post-transfusion, 7 days post-transfusion, every 7 days until discharge, day of discharge.
16. Evaluate the rates, levels (based on CT values) and duration of SARS-CoV-2 RNA in nasopharyngeal swabs using RT-PCR amongst the anti-SARS-CoV-2 convalescent plasma at the following times: prior to transfusion, 24 hours post-transfusion, 72 hours post-transfusion, 7 days post-transfusion, and 14 days post-transfusion.

Group B Investigational Efficacy Objectives:

1. Evaluate the efficacy of treatment with COVID-19 convalescent plasma in relation to the amount of Anti-SARS-CoV-2-spike protein IgA as assayed by the EUROIMMUN Anti-SARS-CoV-2 assay.
2. Evaluate the efficacy of treatment with COVID-19 convalescent plasma in relation to the amount of both Anti-SARS-CoV-2-spike protein IgG and IgA as assayed by the EUROIMMUN Anti-SARS-CoV-2 assay.

All primary and secondary efficacy endpoints for Group B will be re-evaluated based on levels of IgA for investigational objective #1 and based on combined levels of IgG and IgA for investigational objective #2

Primary Safety Objective for Group A and B: Evaluate the safety of treatment with COVID-19 convalescent plasma in relation to the amount of Anti-SARS-CoV-2-spike protein IgG as assayed by the EUROIMMUN Anti-SARS-CoV-2 assay.

Primary Safety Endpoints:

1. Rapid deterioration of respiratory or clinical status on transfusion of COVID-19 convalescent plasma
2. Development of increased cytokine storm activity within 48 hours of receiving a unit of COVID convalescent plasma.

Secondary Objectives:

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

Investigational Safety Objectives:

1. Evaluate the safety of treatment with COVID-19 convalescent plasma in relation to the amount of Anti-SARS-CoV-2-spike protein IgA as assayed by the EUROIMMUN Anti-SARS-CoV-2 assay.
2. Evaluate the safety of treatment with COVID-19 convalescent plasma in relation to the amount of Anti-SARS-CoV-2-spike protein IgG and IgA as assayed by the EUROIMMUN Anti-SARS-CoV-2 assay.

All primary and secondary safety endpoints for the study will be re-evaluated based on levels of IgA for investigational objective #1 and based on combined levels of IgG and IgA for investigational objective #2

2.2 Data collection

The following data points will be gathered for all patients in the study while inpatient. Patients discharged prior to 28 days will receive a phone call to determine their 28 day outcome and patients enrolled in the study will be monitored for 90 days from discharge to determine if there is a readmission and the reason for the readmission.

COVID-19 Presentation: Collected on enrollment, see form on page 30.
Demographics: Collected on enrollment, see form on page 31.
Medical History: Collected on enrollment, see form on page 31.
Concomitant Medications: Collected on enrollment, see form on page 31.
Vital Signs: Collected daily from enrollment to discharge, see form on pages 30 and 32.
Laboratory Values: Collected daily from enrollment to discharge, patient is required to have a CBC with differential, a CMP, a ferritin and a CRP. On enrollment and weekly the patient must have an IL-6, D-Dimer, procalcitonin, LDH, fibrinogen, ESR, and CK. IL-6 and LDH, other laboratory values will be recorded when obtained through standard of care. See form on page 32.
Clinical Status: Collected daily from enrollment to discharge, see form on page 32.
Medications: Collected daily from enrollment to discharge, see form on page 33.
Serology Values: Collected per schedule, see form on pages 34 and 35.
PCR Values: Collected per schedule, see form on page 36
Safety Data: Collected for first 24 hours after transfusion, see form on page 37.
Outcomes: Collected at discharge or death, see form on pages 38 and 39.

2.3 Study population

Inclusion Criteria for Enrollment

1. Subjects must be 18 years of age or older.
2. Hospitalized with confirmed COVID-19 infection via COVID-19 SARS-CoV-2 RT-PCR testing.
3. Symptoms consistent with COVID-19 infection (fever, acute onset cough, shortness of breath) at time of screening.
4. Patient requires >6L NC O_2 (Group A) or intubated (Group B).
5. Patient (or their representative) is willing and able to provide written informed consent and comply with all protocol requirements.

Exclusion Criteria

1. Female subjects with positive pregnancy test, breastfeeding, or planning to become pregnant or breastfeed during the study period.
2. Receipt of pooled immunoglobulin in past 30 days.
3. Contraindication to transfusion or history of prior reactions to transfusion blood products.
4. Patients currently undergoing cancer treatment or those who are presently immunocompromised.
5. Patient who in the opinion of the investigator will not be a good study candidate.

2.4 Schedule of events

Study Period	Screening	Baseline	Treatment	Follow Up[a]						
Day	-1 to 0	0	0	D	1	3	7	14	21	28
Eligibility										
Inclusion/Exclusion	X									
Informed consent	X									
Demographics and medical history form	X									
Initial data collection form	X									
Type and Screen	X									
Pregnancy Test	X									
Study Procedures										
Plasma transfusion			X							
Vital signs			X[b]							
Physical exam[c]	X		X[d]		X		X			
Daily vital signs, clinical and laboratory values form				X						
Daily medications form				X						
Adverse event monitoring		X	X	X						
Serology collection form		X	X		X	X	X	X	X	X[e]
Outcome form										X[f]
Laboratory Tests[g]										
CBC with differential		X		X						
CMP		X		X						
Ferritin		X		X						
Fibrinogen		X					X	X	X	X
CRP		X		X			X	X	X	X
ESR		X					X	X	X	X
Creatine Kinase		X					X	X	X	X
D-Dimer		X					X	X	X	X
LDH		X					X	X	X	X
Interleukin-6		X					X	X	X	X
Triglycerides		X					X	X	X	X
Procalcitonin		X					X	X	X	X
Anti-SARS-CoV-2 IgA			X[h]		X	X	X	X	X	X[i]
Anti-SARS-CoV-2 IgG			X[h]		X	X	X	X	X	X[i]
SARS-CoV-2 RT PCR			X[j]		X	X	X	X		

a – Column D are obtained daily, day 1 and 3 are obtained 24 hours (+/- 1 hour) from transfusion end, day 7, 14, 21, and 28 are obtained any time on that calendar day.
b – Standard vital signs for transfusion of blood products will be performed.
c – Given the issues with isolation and PPE, the exam of the attending physician's team or the pulmonary critical care team can be used.
d – Only if needed due to acute reaction.
e – After 28 days will be collected every 7 days +/- 1 day till discharge.
f – Outcome form to be filled out on final day of admission if prior to 28 days or at 28 days, after 28 days a second outcome form to be filled out on final day of admission, readmission will be tracked for 90 days.
g – All laboratory tests from this list which are obtained as standard of care will be tracked, baseline labs within 24 hours are acceptable and do not need to be reordered.
h – To be drawn within 1 hour prior to transfusion and 1 hour post-transfusion completion (no earlier than 1 hour but up to 75 min post transfusion).
i – After day 28 this will be drawn every 7 days +/- 1 day while participant remains hospitalized.
j – To be obtained within 1 hour prior to transfusion.

2.5 Treatment

All study participants will receive 1 unit of the study product. There is no re-dosing of the product within this study. There is no formal randomization, but both the patient and the study team will be blinded to the amount of anti-SARS-CoV-2 antibodies found in the unit of plasma assigned to the participant. The blind will be maintained until study closure and formal data analysis.

2.6 Rationale for Dose

Review of the literature using COVID-19 convalescent plasma reveals that there is currently no standard dose or schedule for giving convalescent plasma. In addition there is currently no standard assay for antibody level performed on plasma in the United States and there is no way to guarantee access to more than one unit of plasma at a time or guarantee that if more than one unit were available they would be comparable in antibody content. As such the dose was chosen via the pragmatic approach of using a single unit of plasma and stratifying the results by the serological assay of that unit.

2.7 Study drug administration

1. Plasma will be administered at an infusion rate ≤ 500 mL/hour per standards determined by the blood bank.
2. Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given per investigator and clinical care team discretion.
3. If an AE develops during infusion, the infusion may be slowed or stopped as per investigator's decision.
4. Most reactions to plasma are relatively minor and the infusion can generally be continued. Infusion site burning and non-allergic systemic effects can generally be managed with slowing of the infusion. Infusion can generally be continued in case of itching or hives after pausing the transfusion, administering antihistamines, and observing the patient for worsening.
5. Severe allergic reactions, such as bronchospasm and hypotension, may require discontinuation of the infusion.

2.8 Subject Withdrawal

Taking part in this research study is completely voluntary. A participant may choose not to take part or to stop being in the study (withdraw) at any time without penalty or loss of benefits to which they are otherwise entitled, and without jeopardizing their medical care.

If a participant (or their LAR) decides to withdraw from the study they will need to notify the study PI, in writing, of their decision to stop taking part in the study. Detailed directions regarding this will be included in the consent and authorization form for the study.

Participation in this study may be stopped by the study PI or the site PI without the participant's consent for an appropriate reason, which will be explained to the participant or their LAR. Examples include:

- The study medication or procedures appear to be medically harmful to the participant.
- The participant fails to follow directions for the study.

- It is discovered the participant does not meet the study requirements.
- The study is canceled.
- It is determined to be in the participant's best interest.

Subjects who withdraw or are removed from the study will not be replaced.
Discontinuation of the study: The IND holder, Beaumont Health, the FDA, the IRB, and the DSMB all have the right to terminate this study at any time.

3. Statistics

3.1 Data Analysis

We will summarize all baseline data using means, standard deviations, medians and interquartile range for all continuous variables. All data will be examined graphically prior to any modeling.

Primary Outcomes: All analyses of primary outcomes will use a 5% significance level. This study will have two primary outcomes: (1) whether a patient needed intubation for Group B patients, and (2) 28-day survival for Group B patients. For both outcomes, we will use logistic regression models with IgG levels as the primary independent variable. We expect that the relationship between outcome and IgG levels will be non-linear since there should be a quick increased probability of a "good" outcome once IgG levels are sufficiently large, and with this probability of a "good" outcome not increasing much if Ig levels become very high. As such, the relationship with IgG levels will be modeled using splines. We will use both the Akaike informatic criterion (AIC) and the Schwartz Bayesian information criterion (BIC) to select the number of knots to include. Age, gender, and race will also be included as covariates. We will conduct a sensitivity analysis focused on the estimate and confidence interval for the relative risk in a linear model for IgG levels. This sensitivity analysis will add comorbidities singly as covariates.

While log-binomial models would be preferred to logistic regression models for obtaining estimates of relative risk based on model parameters, log-binomial regression models are often difficult to fit, especially when including splines. As such, we will estimate local relative risks based on the fitted model using numerical derivatives for a given IgG level. We will also be able to estimate relative risk of two IgG levels using the same approach.

We will also consider using a piecewise log-binomial model,

$$\log(p) = \beta_0 + \beta_1 I(x > s),$$

where p is the probability of the outcome, β_0 is the intercept (baseline-probability of the outcome), and β_1 is the coefficient describing the log of the relative risk for having large amounts of antibody, the knot s determines the cutoff for characterizing large amounts of antibody. We will use Bayesian inference with a binomial likelihood, a beta(0.5,0.5) prior for $\exp(\beta_0)$, a weak normal prior for β_1, and a uniform(0,maximum(IgG/IgA level)) prior for the knot, s.

Secondary Outcomes: Analyses of all secondary outcomes will use a 0.3% significance level based on the Bonferroni correction for 16 tests. Final outcome measured on a 7-point ordinal scale will be analyzed using standard linear regression,

although we will also consider proportional odds models should the range of the scale actually used be small (i.e., only 3-4 categories appear in the data). We will not use splines for the standard linear regression, but will use splines if a proportional odds model is fit to the data. We will use the same logistic regression approach as for the primary outcomes for all binary secondary outcomes (cardio-circulatory arrest, renal failure, liver failure, evidence of cytokine storm, pressor support required, and readmission).

We anticipate a small number of total number of mortality events for Group A. Should mortality for Group A be small, we will use Fisher's exact test based on categorizing the unit received by each patient as either low vs. high for amount of Anti-SARS-CoV-2-spike protein IgG. The cutoff for categorizing units will be based on either median amount or based on the cutoff determined by the Bayesian log-binomial piecewise model. For Group B, all secondary mortality outcomes will be analyzed the same as for the primary outcome. Should the number of events for any specific type of mortality (e.g., ICU mortality) prove small, we will use the approach used for analyses of Group A.

We will use a generalized linear model with splines to analyze all duration types of variables (duration of respiratory support, ICU length of stay, total length of stay). We will consider using normal, log-normal, and gamma distributions, along with appropriate links.

Type of respiratory support will be analyzed using a multinomial regression with splines for antibody amount, although we will also consider using Fisher's exact test by categorizing the unit received by each patient as either low vs. high for amount of Anti-SARS-CoV-2-spike protein IgG.

We will use either standard linear regression or Poisson regression for ventilator-free days, including splines.

We will use generalized linear mixed models to characterize changes in patient level of anti-SARS-CoV-2 IgG, and the rates, levels (based on CT values) and duration of SARS-CoV-2 RNA in nasopharyngeal swabs. These models will include time as a fixed effect, and will also include the random intercept for subject. We will also consider adding other random coefficients based on both AIC and BIC.

Investigational Outcomes: We will examine the relationship between primary and appropriate secondary outcomes with IgA levels as an investigational analysis using the same types of models being fit as for IgG levels.

3.2 Power and sample size

We determined sample size based on a logistic regression model with a linear relationship between outcome and IgG level, and we used simulations to evaluate power for different sample sizes since we expect some sort of non-linear relationship. We assumed a piecewise model in which the probability of a good outcome increased once IgG levels were greater a threshold. Most of our power calculations used a threshold of 5 since a larger threshold resulted in slightly greater power. We expect this simulation approach to provide an estimate of the minimal power since we use a linear

relationship when the relationship is actually not linear. We assumed the baseline probability was 25% for 28-day survival and 38% for intubation rate. We selected a sample size of 200 for 28-day survival since this sample size provides excellent power (87.8%) for detecting an increase in 28-day survival to 50% (Table 1). We selected a sample size of 300 for intubation rate since this sample size provides excellent power (87.9%) to detect a decrease in intubation rate to 18% (Table 2).

Table 1. Power for detecting an increase in 28-day survival when the baseline probability is 0.25 and the sample size is 200.

28-day Survival for high levels of IgG	**Power**
0.45	74.4%
0.50	87.8%
0.55	97.6%

Table 2. Power for detecting a decrease in intubation rate when the baseline probability is 0.38 and the sample size is 300.

Intubation Rate for high levels of IgG	**Power**
0.23	60.6%
0.18	87.9%
0.13	98.3%

4. Protection of Human Subjects

The entirety of this study will be approved and monitored by the Beaumont Health Institutional Review Board of Record (FWA0002516).

This research will be conducted as a clinical investigation requiring an IND as per title 21 of the Code of Federal Regulations, part 312 (21 CFR part 312) and the guidance from the FDA given on May 1, 2020 found at https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

4.1 Risks to the Subjects

Human Participant Involvement and Characteristics

Antibody-level **B**ased **A**nalysis of **C**OVID **C**onvalescent **S**erum, **ABACCuS,** will be a prospective, single-center, double-blinded, study of the effectiveness of COVID-19 convalescent plasma for the treatment of COVID-19.

We plan to enroll 500 inpatients from the eight Beaumont Hospitals, 300 of which are requiring >6L of oxygen to maintain O_2 saturation >92% but are not requiring intubation and 200 of which are requiring intubation. All enrolled patients, or their legally authorized representative (LAR) must sign an Informed Consent Form (ICF).

All patients will receive a unit of COVID-19 convalescent plasma but the antibody content of the unit will not be known and there will be a double-blind such that neither the patient nor the study personnel will know the anti-SARS-CoV-2 antibody levels within the plasma.

During the study, various clinical and demographic data on each patient will be collected as detailed in the Research Design section.

A schedule of events for all patients in the study is included above (**Section 2.4**).
Inclusion and exclusion criteria for the study are included above (**Section 2.3**).

No vulnerable populations of children or pregnant women will be recruited to the study. Children are exempted due to differing impact of SARS-CoV-2 on the pediatric population as compared to that of adults. Pregnant women are exempted due to unknown risks to the fetus. Cognitively impaired patients are allowed but will need to be consented using an LAR.

Sources of Materials

Participants will provide the required blood samples at the indicated time points, as described in the Research Strategy, and outlined in the above schedule of events (**Section 2.4**). Additional participant data will be obtained through a chart review within Beaumont's EMR (EPIC) and supplemented where appropriate by patient completion of interviews.

All patients enrolled in the study will be followed daily while inpatient by research coordinators who will gather all required data.

Potential Risks

Historical and current anecdotal data on use of convalescent plasma suggest its use to treat COVID-19 is generally safe. The large number of exposed individuals, in combination with the high mortality of COVID-19, particularly in vulnerable persons, strongly suggests that the potential benefits of convalescent serum outweigh its possible risks in SARS-CoV-2 infected individuals with significant oxygen requirements.

Known Risks of Plasma Transfusion

Risks of any transfusion of plasma include: fever, chills, rash, headache, serious allergic reactions, TRALI, TACO, transmission of infectious agents.
The chances of any of these occurring are as follows:

Acute hemolytic reaction: 1 in 40,000 units transfused
Febrile transfusion reaction: 1 in 100 to 1 in 1000 units transfused
Urticarial reaction (hives): 1 in 100 units transfused
Anaphylaxis: 1 in 20,000 to 1 in 50,000 units transfused
Transfusion related acute lung injury (TRALI): 1 in 1,200 to 1 in 190,000 units transfused
Transfusion related circulatory overload (TACO): less than 1 in 100 units transfused
Transmission of Hepatitis B: less than 1 in 250,000 units transfused
Transmission of Hepatitis C: less than 1 in 1,000,000 units transfused
Transmission of HIV: less than 1 in 1,000,000 units transfused

Hypothetical Risks of Plasma Transfusion

There is a theoretical risk of antibody-mediated enhancement of infection (ADE). ADE has been shown to occur for several viral diseases, most notably flaviviruses including Dengue and Zika[50], and involves an enhancement of disease in the presence of non-neutralizing or poorly neutralizing antibodies. The concern has been raised that the highly variable presentation of COVID-19 may in part be due to an ADE phenomenon[51-52] due to partially cross-reacting antibodies from other human coronaviruses, most likely OC43 or HKU1 as they, like SARS-CoV-2 are members of the Beta-coronavirus family and are more likely to be cross reactive. Such ADE phenomena have been seen in both SARS[53-54] and MERS[55-56] in animal studies so are definitely of concern in COVID-19.

While it would be expected that COVID-19 convalescent plasma would have high titers

of neutralizing antibody against SARS2-CoV-2, this is not always the case and antibody levels can vary[57]. When plasma from donors who only test positive by serology are added into the pool of available COVID convalescent plasma the concern rises further.

Just as low neutralizing antibody levels can potentially cause issue due to ADE, high levels of anti-Spike IgG were found to be directly responsible for increased acute lung injury in a Chinese macaque model of SARS infection[58]. We must be concerned of the danger of both too low and too high a level of neutralizing antibodies in convalescent plasma. The use of COVID convalescent plasma must be carefully studied over a range of antibody levels to be sure it is safe to use at any level. This study is designed to detect any evidence of worsening respiratory status based on actual antibody level in the plasma transfused.

Another theoretical risk is that administering antibody to those with an active SARS-CoV-2 infection may treat the disease but modify the native immune response such that treated individuals mount an attenuated humoral immune response. This would leave them vulnerable to subsequent re-infection. Such a phenomenon has been seen in respiratory syncytial virus where passive antibody treatment before vaccination with respiratory syncytial virus was shown to attenuate humoral but not cellular immunity[59]. This has not been demonstrated in coronaviruses to this point.

Risks of Laboratory Testing

For all patients there will be multiple blood draws. For female patients of childbearing years, a serum pregnancy test will be sent before a unit of plasma is ordered, and if positive they will be removed from the study, whenever possible this test will be added on to previously drawn blood or done at the same time as another blood draw. A blood draw carries the common risks of bleeding, bruising, and pain, and the rare risks of blood clot, infection, light-headedness, dizziness, and fainting.

For all patients there will multiple nasopharyngeal swabs. The risks of a nasopharyngeal swab: local discomfort, vomiting.

Confidentiality

Risks for this study include breach of confidentiality. To minimize this risk all case forms will use a code consisting of a unique number. A list will be kept that links the patient's name and health system medical record number to the code. This list will be kept in a securely in the RedCap database which will be used to store patient date. Only study personnel will have access to the list and the case report forms. A list of the patients involved in the study will be kept within the EPIC EMR in order to facilitate access to the patient's records for purposes of the study and to prevent recruitment of patients who are already in the study. The list will be private, maintained by the study principal investigator at each site with their lead coordinator, and accessible only to appropriate study personnel.

4.2 Potential Benefits

The potential benefits of treatment with COVID-19 convalescent plasma in patients with respiratory symptoms, requiring oxygens, and at high risk for requiring ICU admission are not known. However, it is anticipated that treatment will decrease the risk of disease progression requiring ICU admission and progression to mechanical ventilation.

The potential benefits of treatment with COVID-19 convalescent plasma in patients

already requiring mechanical ventilation are even less clear. It is anticipated that treatment will reduce the overall mortality and increase the chance of the patient no longer requiring mechanical ventilation.

4.3Adequacy of Protection Against Risks

Risk-Benefit Ratio

The dangers of plasma transfusion in general are well known and well described. The probability of their occurrence in predictable. The likelihood of the hypothetical risks of COVID-19 convalescent plasma transfusion are unknown but, in those studies currently available the overall use appears safe.

Therefore, the risks to subjects are reasonable in relation to potential to directly benefit the participant by reducing the morbidity and mortality of COVID-19 as well as the importance of the knowledge that is expected to result.

At all times, the risk-benefit ratio will be considered when recruiting a patient to the study.

Recruitment and Informed Consent

- A waiver of consent for screening will be sought for this trial in order to identify potential patients via the EMR.
- Patients may be identified via an automated search of the Electronic Medical Record (EMR), which has already been built and is currently used to identify potential patients for clinical trials.
- The search in the EMR will automatically narrow the search to patients in the appropriate age range (both female and male patients), who have tested positive for SARS-CoV-2. The search also identifies the amount of oxygen given to the patient and whether they are on a ventilator.
- Patients may also be referred directly from the patient's attending physician and/or the local site investigator
- The inclusion and exclusion criteria for the study are listed in Section 2.3. Review and determination of eligibility will be conducted by the study coordinator with additional review of any subjects by the site principal investigator or other appropriate physician investigator for this study when the site principal investigator is not available.
- After initial screening for inclusion and exclusion criteria, and with approval of the patient's attending physician, the patient or his LAR will be approached to participate in the study by highly experienced study coordinators and/or a physician member of the study team. The background, purpose, basic requirements for participation, benefits, and risks of the study will be explained to the patient. The consent provider will explain that the cost of the study drug and any study procedures will be covered by the study with no expense to the patient. Patients will have adequate time to read the informed consent form and be given the opportunity to ask questions of the coordinator or investigator and have their questions answered to their satisfaction.
- All discussions with the patient will be conducted remotely as per established emergency policies developed by the Beaumont IRB and Research Administration for consenting during this pandemic in order to maximize the safety of all involved and reduce the utilization of needed personal protective

equipment. All consenting will be witnessed by a third part from Beaumont and both the consent provider and the witness will document the consent in a research note in the patient's clinical record in the EMR.

- No pressure will be placed on patients to participate in the trial and they will be assured that their medical care will continue without any negative impact whether they participate in the study or not.
- Written informed consent will be obtained from all study participants.
- No parental consent will be necessary for this study as no patients under age 18 will be enrolled.
- Consent by an LAR may be utilized for this study as the participants may not be able to consent themselves and the treatment is considered potentially lifesaving at this time.
- Oversight and study management will be provided by the PI and the Beaumont Urology Research Director. Monitoring will be provided by the Beaumont Research Coordinating Center.
- All consent provider training and consent audits will be managed by the Beaumont Research Manager or her delegate.
- No work will begin on this project until approval is granted by the Beaumont Health IRB.

Protection against Risk

All known risks will be specified in the informed consent form so participants are aware of the potential for adverse events and what those might be.

Maintenance of Confidentiality:

All appropriate measures will be taken to protect the identity of subjects and the confidentiality of collected data.

Data will be collected using study-specific source documents which are included in this document. The data will be stored in the RedCap database, a secure hospital-based computer system with password protection. The author of an entry is easily identifiable, and the system is such that editing of documents and the person who edited it is tracked. The study personnel responsible for data collection will be trained to ensure reliability and quality of the data and the data will be monitored by the Beaumont Research Coordinating Center. All patient identifiers will be removed from the collected data to ensure HIPAA compliance and patient confidentiality. Patient data will be identified using initials and a patient study number. Any communication relating to the study, study documents, and electronic databases will identify patients by initials and their assigned number only.

A patient identification log will be kept permitting easy identification of each patient during and after the study. The patient identification log will be confidential and will be kept in a secure location in the study office. To ensure confidentiality, no copy will be made. The log will link the patient's name and medical record number to the unique study identification number. An electronic list of patients in the study, only available to study personnel, will be kept within the EPIC EMR of our health care system for use in rapidly accessing the patient's health information for purposes of the study and to assure that no patient is recruited to the study more than once. When the study and all

review is complete, the list linking the study code to identifiers will be destroyed and the patient list within the EMR will be deleted.

In accordance with ICH/GCP (International Conference on Harmonization/Good Clinical Practice) guidelines, the study team will maintain all source documents that support the data collected from each patient, as well as all study documents specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by appropriate regulatory requirements. All documents related to the study will be kept in a secure location in the study office and will be preserved for a minimum of eleven years as required by internal policy either within the study office or another approved location for long-term secure storage.

Adverse Events:
An adverse event (AE) can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

The occurrence of an AE may come to the attention of study personnel during at any point in the study. The period of observation for which AEs are to be collected will begin after the subject has signed the ICF and will continue throughout their participation in the study. All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's research chart.

Information to be collected includes event description, time of onset, investigator's assessment of severity, investigator's assessment of relationship to study drug, and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of their relationship to the study treatment. AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the condition deteriorates at any time during the study, it will be recorded as an AE. Any laboratory abnormality not considered to be clinically significant by the investigator will not be considered an AE. All AEs will be graded for intensity and relationship to the study treatment.

One of the investigators will determine the relationship between the study treatment and the occurrence of an AE as defined below:

- Definitely related events are those that the investigator determines are definitely related to the intervention, and for which the investigator believes no alternative etiology exists.
- Probably related events are those for which the investigator believes there is a reasonable likelihood the AE may have been caused by the intervention involved in the research.
- Probably not related events are those for which the investigator believes there is a reasonable likelihood the AE may have been caused by other factors and not caused by the intervention involved in the research.

- Unrelated events are those that the investigator determines are not related to the intervention either due to timing or a confirmed alternative cause.
- Unable to Determine: The investigator is unable to determine the likelihood that the AE and the study treatment have a causal relationship.

Serious Adverse Events
An adverse event or suspected adverse event is considered serious if, in the view of the investigator, the medical monitor, or the 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.

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

Important medical events that do not meet the criteria of resulting in death, being life-threatening, or requiring hospitalization may still be considered serious when, based upon appropriate medical judgment, they might jeopardize the subject's life and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. An example of this would be an early allergic reaction that does not reach the level of life-threatening due to early medical intervention with steroids and bronchodialators.

Unanticipated Problems
Unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Data and Safety Monitoring Plan
This study protocol will employ rigorous methods to ensure data safety. Human subject safeguards will include at a minimum, completion of Human Subjects Protection Training. In the event that any study participant has a significant adverse reaction related to the study, standard of care treatment to address the SAE for the participant

will be followed. The attending team for each participant will be directly involved and know to inform the site principal investigator, or the research coordinator should there be a significant worsening of the patient's clinical status.

Adverse Event Reporting

If an untoward event occurs, it will be reported by the principal investigator in accordance with the Department of Health and Human Services (DHHS) code of federal regulations (Title 45, Part 46).

There are two categories of AEs: 1) Serious Adverse Events and 2) Adverse Events. Serious adverse events are required to be reported within 48 hours of knowledge of the event. Adverse events not in the "serious" category but judged to be "severe" or "life-threatening" are also subject to the 48 hours reporting requirement. Copies of reports of all SAEs will be forwarded to the IRB and the DSMB. The PI will be responsible for generating a summary report for the IRB and DSMB. The report will document that a review of data and outcomes took place on a given date, when the event occurred, and when the PI became aware of it. Adverse events are reported to the IRB during the regular progress reports and will be reported to the DSMB at the same time.

Unanticipated problems that are serious adverse events will be reported to the IRB and the DSMB within 48 hours of the investigator becoming aware of the event.

Any other unanticipated problem which is not also an SAE will be reported to the IRB within 1 week of the investigator becoming aware of the problem.

Compliance with Policy/Regulation

Protection of Human Patients

Compliance with Informed Consent Regulations (U.S. 21 CFR Part 50) will be strictly maintained. Informed consent audits will be conducted by the Infectious Diseases Clinical Research Manager and kept on file, per Research Institute policy.

Compliance with Electronic Records; Electronic Signatures Regulations

This study will be conducted in compliance with the regulations on electronic records and electronic signatures and will comply with the Guidance on Computerized Systems used in Clinical Trials.

Patient Confidentiality

A report of the results of this study may be published but patients' names will not be disclosed in these documents. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Data Safety Monitoring Board

A formal data safety monitoring board will be established for this study per NIH guidelines. The membership will consist of independent experts without conflicts of interest and without direct involvement in this study. The membership shall consist of 4 physicians including an Infectious Diseases specialist and a Hematologist. The fifth member of the DSMB will be a biostatistician. The DSMB will meet within 1 week of the first patient being enrolled at least monthly to review the data thereafter. The exact schedule may be modified depending on the level of enrollment with faster enrollment leading to more frequent meetings and slower enrollment leading to less frequent meetings though the meetings will never be less then quarterly. At any time the halting

criteria for the study are met the DSMB will meet to review what occurred and make a decision on whether the study can resume.

Halting Criteria for the Study

The study enrollment and dosing will be stopped and an ad hoc review by the DSMB will be performed if any of the specific following events occur or, if in the judgment of the study physician, subject safety is at risk of being compromised:

1. Death within one hour of plasma infusion
2. Occurrence of more than a single life-threatening allergic/hypersensitivity reaction (anaphylaxis), manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation.
3. An overall pattern of symptomatic, clinical, or laboratory events that the investigator feels is associated with the study product and that may appear minor in terms of individual events but that collectively may represent a serious potential concern for safety.
4. Any unanticipated problem which is felt to alter the overall risk-benefit ratio of the study.

Upon completion of this ad hoc review the DSMB will determine if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol.

Halting Criteria/Rules for Subject Infusion

The rules for halting plasma transfusion are established by policy at Beaumont Health and will be followed by nursing staff who are supervising the transfusion. Decision to discontinue or resume the transfusion with or without medication treatment will be made by the study investigator based on the pre-established policies. See Beaumont Health Policy 7876626.

At the discretion of the study investigator or the clinical care team pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given to a participant

If an adverse reaction develops during infusion, the infusion may be slowed or stopped at the investigator's discretion.

Most reactions to plasma are relatively minor and the infusion can generally be continued. Infusion site burning and non-allergic systemic effects can generally be managed with slowing of the infusion. Infusion can generally be continued in cases of itching or hives after pausing the transfusion, administering antihistamines, and observing the patient for worsening.

Severe reactions such as, anaphylaxis, bronchospasm, respiratory compromise and hypotension, will require discontinuation of the infusion.

REFERENCES:

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15; 395(10223):507-513. doi: 10.1016/S0140-6736(20)30211-7. Epub 2020 Jan 30.
2. Johns Hopkins Coronavirus Resource Center, ttps://coronavirus.jhu.edu/map.html, accessed 5/4/2020 at 1:34 AM.
3. https://www.clickondetroit.com/news/local/2020/03/18/man-at-wayne-county-hospital-is-michigans-first-confirmed-coronavirus-death , accessed 3/23/2020 at 6:50 PM
4. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html, accessed 3/23/2020 at 1:16 AM
5. Baud D, Qi X, Nielsen-Saines K, et al. Real estimates of mortality following COVID-19 infection. Lancet InfDis (published online 3/12/2020)
6. Bialek S, Boundy E, Bowen V, et al (CDC COVID-19 Response Team). Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep. ePub: 18 March 2020
7. McCarthy A. U.S. COVID-19 Fatality Rate Steady: About 1 Percent. National Review ePub: 20 March 2020.
8. https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/people-at-higher-risk.html, accessed 3/23/2020 at 1:17 AM
9. https://www.fda.gov/media/137564/download accessed at 9:04 AM 5/4/2020
10. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020 Mar;30(3):269-271.Casadevall A, Scharff MD. Return to the past: the case for antibody-based therapies in infectious diseases. Clinical infectious diseases. 1995;21(1):150–161.
11. https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19 accessed 8:30 AM 5/4/2020
12. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrobial Agents. ePub March 2020.
13. Molina JM, Delaugerre C, Le Goff Jet al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Médecine et Maladies Infectieuses. ePub March 30, 2020
14. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. medRxiv preprint doi: ttps://doi.org/10.1101/2020.04.16.20065920.

15. Mahévas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial. medRxiv preprint doi: https://doi.org/10.1101/2020.04.10.20060699.

16. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. medRxiv preprint doi: https://doi.org/10.1101/2020.04.10.20060558.

17. Chu CM, Cheng VCC, Hung IFN, et al on behalf of the HKU/UCH SARS Study Group. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59:252–256

18. Cao B, Wang Y, Wen D, et al A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 Mar 18. doi: 0.1056/NEJMoa2001282. [Epub ahead of print]

19. https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=&type=Intr&rslt=&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=

20. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, Grazzini G. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus. 2016 Mar; 14(2): 152–157.

21. Luke TC, Casadevall A, Watowich SJ, et al. Hark back: passive immunotherapy for influenza and other serious infections. Crit Care Med. 2010 Apr;38(4 Suppl):e66-73.

22. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis. 2015;211:80-90.

23. Tiberghien P, de Lamballerie X, Morel P, et al. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how? Vox Sang. 2020 Apr 2. doi: 10.1111/vox.12926. [Epub ahead of print]

24. Luke TC, Kilbane EM, Jackson JL, et al. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med. 2006;145:599-609.

25. Sahr F, Ansumana R, Massaquoi T, Idriss B, Sesay F, Lamin J, et al. Evaluation of convalescent whole blood for treating Ebola Virus Disease in Freetown, Sierra Leone. Journal of Infection. 2017;74(3):302–309.

26. van Griensven J, Edwards T, de Lamballerie X, et al. Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea. NEJM. 2016;374(1):33-42

27. Zhou XZ, Zhao M, Wang FS, et al. Epidemiologic features, clinical diagnosis, and therapy of first cluster of patients with severe acute respiratory syndrome in Beijing area. Zhonghua Yi Xue Za Zhi. 2003;83: 1018-22 (Chinese Language)

28. Wong VWS, Dai D, Wu AKL, Sung JJY. Treatment of severe acute respiratory syndrome with convalescent plasma. Hong Kong Med J. 2003;9(3): 199-201
29. Kong L, Letter to the Editor. Transfus and Apher Sci. 2003;29: 101
30. Yeh K-M, Chiueh T-S, Siu L, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. Journal of Antimicrobial Chemotherapy. 2005;56(5): 919–922.
31. Soo YOY, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol and Infect. 2004;10(7): 676-78
32. Cheng Y, Wong R, Soo Y, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. European Journal of Clinical Microbiology and Infectious Diseases. 2005;24(1): 44–46.
33. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. The Journal of infectious diseases. 2015;211(1):80–90.
34. Ko JH, Seok H, Cho SY, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single center experience. Antiviral therapy. 2018;23(7): 617–622.
35. Chun S, Chung CR, Ha YE, et al. Possible transfusion-related acute lung injury following convalescent plasma transfusion in a patient with Middle East respiratory syndrome. Ann Lab Med. 2016;36: 393-95.
36. Arabi YM, Hajeer AH, Luke T, et al. Feasibility of using convalescent plasma immunotherapy for MERS-CoV infection, Saudi Arabia. Emerging infectious diseases. 2016;22(9): 1554-61.
37. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020;323(16): 15-82-1589.
38. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. PNAS. 2020;117(17): 9490-96.
39. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol. 2020; doi: 10.1002/jmv.25882. [Epub ahead of print]
40. Zhang B, Liu S, Tan T. et al. Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection. Chest. 2020; [E-Pub ahead of print]. doi.org/10.1016/j.chest.2020.03.039
41. Ahn JY, Sohn Y, Lee SH et al. Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea. J Korean Med Sci. 2020;35(14): e149

42. Zeng QL, Yu ZJ, Gou JJ, et al. Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients. J Infect Dis. 2020 Apr 29. pii: jiaa228. doi: 10.1093/infdis/jiaa228. [Epub ahead of print]

43. Rajendran K, Narayanasamy K, Rangarajan J, et al. Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. J Med Virol. 2020. doi: 10.1002/jmv.25961. [Epub ahead of print]

44. Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. J Clin Invest. 2020; 120(4): 1545-1648.

45. Casadevall A, Pirofski L. Antibody-mediated regulation of cellular immunity and the inflammatory response. TRENDS in Immunology. 2003;24(9):474–478.

46. Rojas M ,Rodriguez Y, Monsalve DM, et al. Convalescent plasma in Covid-19: Possible mechanisms of action, Autoimmunity Rev. 2020; doi: 10.1016/j.autrev.2020.102554. [Epub ahead of print]

47. Wan J, Sun W, Li X, et al. Inflammation inhibitors were remarkably up-regulated in plasma of severe acute respiratory syndrome patients at progressive phase. Proteomics. 2006;6(9): 2886-94

48. Wölfel R, Corman VM, Guggemos W, et al. (2020). Virological assessment of hospitalized patients with COVID-2019. Nature. doi:10.1038/s41586-020-2196-x

49. Zhang G, Nie S, Zhang Z, Zhang Z. Longitudinal Change of SARS-Cov2 Antibodies in Patients with COVID-19. J Infect Dis. 2020 May 2. pii: jiaa229. doi: 10.1093/infdis/jiaa229. [Epub ahead of print]

50. Khandia R, Munjal A, Dhama K, et al. Modulation of Dengue/Zika Virus Pathogenicity by Antibody-Dependent Enhancement and Strategies to Protect Against Enhancement in Zika Virus Infection. Front Immunol. 2018;9: 597.

51. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes and Infection. 2020;22: 72-73

52. Iwasaki A and Yang Y. The potential danger of suboptimal antibody responses in COVID-19. Nat Rev Immunol. 2020. doi: 10.1038/s41577-020-0321-6. [Epub ahead of print]

53. Yip MS, Cheung CY, Li PH et al. Investigation of Antibody-Dependent Enhancement (ADE) of SARS coronavirus infection and its role in pathogenesis of SARS.BMC Proceedings. 2011; 5(Suppl 1): P80.

54. Houser KV, Broadbent AJ, Gretebeck L, et al. Enhanced inflammation in New Zealand white rabbits when MERS-CoV reinfection occurs in the absence of neutralizing antibody. PLoS Pathog 13(8): e1006565

55. Houser KV, Broadbent AJ, Gretebeck L, et al. Enhanced inflammation in New Zealand white rabbits when MERS-CoV reinfection occurs in the absence of neutralizing antibody. PLoS Pathog. 2017 Aug 17;13(8):e1006565.

56. Wan Y, Shang J, Sun S, Tai W, Chen J, Geng Q, et al. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. Journal of Virology. 2020;94(5).

57. Zhang L, Pang R, Xue X, et al. Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19. Aging. 2020;12(8): 6536-6542.

58. Liu L, Wei Q, Lin Q, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI Insight. 2019;4(4). pii: 123158

59. Crowe JE, Firestone C-Y, Murphy BR. Passively acquired antibodies suppress humoral but not cell-mediated immunity in mice immunized with live attenuated respiratory syncytial virus vaccines. The Journal of Immunology. 2001;167(7):3910–3918.

ABACCuS Initial Data Collection Form

Patient Initials/Study ID: _____ Date of Enrollment: _____

Date of admission: _____
Date of initial symptoms: _____ Date of first +COVID PCR: _____

Hospitalization Status: Standard floor/COVID Unit/MPCU/ICU

Symptoms onset date:

_____ Cough	_____ SOB
_____ Fever	_____ Lack of taste
_____ Nausea	_____ Lack of smell
_____ Vomiting	_____ Muscle aches
_____ Diarrhea	_____ Headache

Vital signs in last 24 hours (Current reflects measurement immediately prior to transfusion)

Maximum temperature: _____ Minimum temperature: _____ Current temperature: _____
Maximum heart rate: _____ Minimum heart rate: _____ Current heart rate: _____
Maximum blood pressure (based on mean arterial pressure): _____ MAP: _____
Minimum blood pressure (based on mean arterial pressure): _____ MAP: _____
Current blood pressure: _____ MAP: _____
Maximum O_2 patient was on and the method of delivery: _____
Minimum O_2 patient is on and the method of delivery: _____
Minimum O_2 saturation, O_2 delivered, and the method of delivery: _____
Maximum O_2 saturation, O_2 delivered and the method of delivery: _____
Current O_2 saturation, O_2 delivered, and the method of delivery: _____
Maximum respiratory rate: _____ Minimum respiratory rate: _____ Current respiratory rate: _____

SOFA Score: _____ APACHE II Score: _____ H-Score: _____

Include with source documentation the report from EPIC EMR of the most recent of the following lab results prior to transfusion of IP if available:

CBC with differential (if a more recent CBC without differential is available include as well)
CMP (if more recent components of the CMP are available include as well)
Triglycerides, Ferritin, Fibrinogen, CRP, ESR, LDH, D Dimer, IL-6, CK, COVID PCR
Pregnancy test (for women of childbearing potential), Type and Screen

Include with source documentation the following reports during the admission for COVID if available:

Initial chest CT, most recent chest CT, initial chest X-ray, most recent chest X-ray, initial echocardiogram, most recent echocardiogram

_____
Signature of coordinator Date

_____
Signature of Investigator reviewing data Date

ABACCuS Demographics/Medical History Data Collection Form:

Patient Initials/Study ID: _____ Date of Enrollment: _____

Demographics

Age: _____ Sex: _____ Race: _____

Date of birth: _____ Profession: _____

Zip Code of Residence: _____

Medical History

- Diabetes mellitus: Y / N
- Cardiovascular disease: Y / N
- Chronic lung disease: Y / N
- Chronic kidney disease: Y / N
- Hypertension: Y / N
- Immunocompromised: Y / N
    - Transplant [SOT] : Y / N
    - Hematologic malignancy: Y / N
    - Active chemotherapy: Y / N
    - Chronic steroids >0.5 mg/kg/day prednisone equivalent: Y / N
    - Congenital or acquired immunodeficiency: Y / N
    - Splenectomy: Y / N
    - Biologic agents for immunosuppression: Y / N
    - Other: Y / N _____

Other Major Medical Conditions:

_____

_____

_____

Current Medications:

Append current medication list from EPIC EMR,
Append **ACE inhibitors and ARBs** received during current admission,
Append **all steroids** received during current admission,
Append **all antibiotics** received during current admission,
Append **all anti-coagulation** received during current admission,
Append **all vasopressors** received during current admission,
Append **all treatments given specifically for COVID** during current admission

Chronic Medications: Append outpatient medication list from EPIC EMR

_____

Signature of coordinator Date

_____

Signature of Investigator reviewing data Date

ABACCuS Daily Vital Signs, Clinical and Laboratory Values Data Collection Form:

Patient Initials/Study ID: _____ Date of Enrollment: _____

Study day #:_____ Date of record: _____

Hospital day #: _____ Date data recorded: _____

For the calendar day indicated above:

Maximum temperature: _____ Minimum temperature: _____

Maximum heart rate: _____ Minimum heart rate: _____

Maximum blood pressure (based on mean arterial pressure): _____ MAP: _____

Minimum blood pressure (based on mean arterial pressure): _____ MAP: _____

Maximum O_2 patient was on and the method of delivery: _____

Minimum O_2 patient is on and the method of delivery: _____

Minimum O_2 saturation, O_2 delivered, and the method of delivery: _____

Maximum O_2 saturation, O_2 delivered and the method of delivery: _____

Maximum respiratory rate: _____ Minimum respiratory rate: _____

Was the patient: On Ventilator: Y/N Proned: Y/N On Nitrox: Y/N On ECMO: Y/N

Laboratory Values

Markers of Inflammation and Other	Value
Ferritin	
Fibrinogen	
CRP	
ESR	
CK	
D-Dimer	
LDH	
Interleukin-6	
Triglycerides	
Procalcitonin	

Complete Blood Count With Differential	Value
WBC	
Hemoglobin	
Hematocrit	
Platelets	
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	

Metabolic Markers	Value
Sodium	
Potassium	
Chloride	
CO_2	
BUN	
Creatinine	
Glucose	
Total Protein	
Albumin	
Globulin	
Alk Phos	
ALT	
AST	
Total Bilirubin	

Append any chest imaging, EKG, or echocardiogram for this date of hospitalization

Append any positive microbiology results for this date of hospitalization

Append any blood gasses for this date of hospitalization

_____

Signature of coordinator Date

_____

Signature of Investigator reviewing data Date

ABACCuS Daily Medications Data Collection Form:

Patient Initials/Study ID: _____ Date of Enrollment: _____

Study day #:_____ Date of record: _____
Hospital day #: _____ Date data recorded: _____

For the calendar day indicated above:

Was the Patient Sedated: Y/N Sedation Used: _____

Was the Patient Paralyzed: Y/N Paralytic Used: _____

Was the Patient on Pressors: Y/N Pressors Used: _____

Medications Initiated on This Calendar Day:

Medication	Dose	Route of Administration	Frequency	Time Started

Medications Discontinued or Completed on This Calendar Day:

Medication	Medication	Medication

Medications with Dose Modifications on This Calendar Day:

Medication	Dose Change	Frequency Change	Time of Change

Append the medication administration record and any blood products for the above calendar date

_____
Signature of coordinator Date

_____
Signature of Investigator reviewing data Date

ABACCuS Serology Data Collection Form:

Patient Initials/Study ID: _____ Date of Enrollment: _____

Plasma Unit Used: _____ Date and Time of Transfusion: _____

Patient Baseline Serology:

IgA OD: _____ IgG OD: _____ Date and Time of Specimen: _____

Patient Serology 1 Hour Post-Transfusion (+/- 5 min)

IgA OD: _____ IgG OD: _____ Date and Time of Specimen: _____

Patient Serology 24 Hours Post-Transfusion (+/- 1 hour)

IgA OD: _____ IgG OD: _____ Date and Time of Specimen: _____

Patient Serology 72 Hours Post-Transfusion (+/- 3 hours)

IgA OD: _____ IgG OD: _____ Date and Time of Specimen: _____

Patient Serology 1 Week Post-Transfusion (+/- 1 day)

IgA OD: _____ IgG OD: _____ Date and Time of Specimen: _____

Patient Serology 2 Weeks Post-Transfusion (+/- 1 day)

IgA OD: _____ IgG OD: _____ Date and Time of Specimen: _____

Patient Serology 3 Weeks Post-Transfusion (+/- 1 day)

IgA OD: _____ IgG OD: _____ Date and Time of Specimen: _____

Patient Serology 4 Weeks Post-Transfusion (+/- 1 day)

IgA OD: _____ IgG OD: _____ Date and Time of Specimen: _____

Patient Serology Day of Discharge

IgA OD: _____ IgG OD: _____ Date and Time of Specimen: _____

_____

Signature of coordinator Date

_____

Signature of Investigator reviewing data Date

ABACCuS Supplemental Serology Data Collection Form:

Patient Initials/Study ID: _____________ Date of Enrollment: _____________

Plasma Unit Used: _____________________ Date and Time of Transfusion: ______________

Patient Serology _____ Weeks Post-Transfusion (+/- 1 day)

IgA OD: __________ IgG OD: __________ Date and Time of Specimen: _______________

Patient Serology _____ Weeks Post-Transfusion (+/- 1 day)

IgA OD: __________ IgG OD: __________ Date and Time of Specimen: _______________

Patient Serology _____ Weeks Post-Transfusion (+/- 1 day)

IgA OD: __________ IgG OD: __________ Date and Time of Specimen: _______________

Patient Serology _____ Weeks Post-Transfusion (+/- 1 day)

IgA OD: __________ IgG OD: __________ Date and Time of Specimen: _______________

Patient Serology _____ Weeks Post-Transfusion (+/- 1 day)

IgA OD: __________ IgG OD: __________ Date and Time of Specimen: _______________

Patient Serology _____ Weeks Post-Transfusion (+/- 1 day)

IgA OD: __________ IgG OD: __________ Date and Time of Specimen: _______________

Patient Serology _____ Weeks Post-Transfusion (+/- 1 day)

IgA OD: __________ IgG OD: __________ Date and Time of Specimen: _______________

Patient Serology _____ Weeks Post-Transfusion (+/- 1 day)

IgA OD: __________ IgG OD: __________ Date and Time of Specimen: _______________

Patient Serology _____ Weeks Post-Transfusion (+/- 1 day)

IgA OD: __________ IgG OD: __________ Date and Time of Specimen: _______________

____

Signature of coordinator Date

____

Signature of Investigator reviewing data Date

ABACCuS SARS-CoV-2 RT PCR Data Collection Form:

Patient Initials/Study ID: _____ Date of Enrollment: _____

Plasma Unit Used: _____ Date and Time of Transfusion: _____

Patient Qualifying RT PCR:

Result: _____ CT Value: _____ Date and Time of Specimen: _____

Patient Pre-Transfusion RT PCR:

Result: _____ CT Value: _____ Date and Time of Specimen: _____

Patient 24 hour Post-Transfusion RT PCR:

Result: _____ CT Value: _____ Date and Time of Specimen: _____

Patient 72 hour Post-Transfusion RT PCR:

Result: _____ CT Value: _____ Date and Time of Specimen: _____

Patient 7 Days Post-Transfusion RT PCR:

Result: _____ CT Value: _____ Date and Time of Specimen: _____

Patient 14 Days Post-Transfusion RT PCR:

Result: _____ CT Value: _____ Date and Time of Specimen: _____

_____

Signature of coordinator Date

_____

Signature of Investigator reviewing data Date

ABACCuS 28 Safety Form:

Patient Initials/Study ID: _____ Date of Enrollment: _____

Plasma Unit Used: _____ Date and Time of Transfusion: _____

In the 2 hours after the transfusion:
Did the patient have a rapid decline in respiratory status: Y/N

If yes: Date and Time: _____ Severity: _____

If yes: Description of the event: _____

Did the patient have a rapid decline in clinical status: Y/N

If yes: Date and Time: _____ Severity: _____

If yes: Description of the event: _____

In the 4 hours after the transfusion:
Did the patient have a fever of >38°C: Y/N T_{max}: _____ If yes: Date and Time: _____

Did the patient have an allergic reaction: Y/N If yes: Date and Time: _____

Conjunctival Edema: Y/N Edema of Oral Area: Y/N Periorbital Erythema/Edema: Y/N
Generalized Flushing: Y/N Hypotension: Y/N Localized Angioedema: Y/N
Maculopapular Rash: Y/N Pruritus (itching): Y/N Bronchospasm: Y/N
Urticaria (hives): Y/N Severity: _____

In the 6 hours after the transfusion:
Was the patient diagnosed with Transfusion Associated Circulatory Overload (TACO): Y/N

If yes: Date and Time: _____ Severity: _____

Was the patient diagnosed with Transfusion Related Acute Lung Injury (TRALI): Y/N

If yes: Date and Time: _____ Severity: _____

In the 24 hours after the transfusion:
Did the patient have evidence of cytokine storm: Y/N

If yes: Date and Time: _____ Severity: _____

If yes: Description of the event: _____

_____
Signature of coordinator Date

_____
Signature of Investigator reviewing data Date

ABACCuS 28 Day Outcome Form Group A:

Patient Initials/Study ID: _____ Date of Enrollment: _____

Plasma Unit Used: _____ Date and Time of Transfusion: _____

Primary Outcome:

Was the patient intubated within 28 days of the transfusion: Y/N

If intubated: Date of intubation: _____ Study Day #: _____

Secondary Outcomes:

Outcome on a 7-point ordinal scale:

❍ Not hospitalized, ❍ (1) No limitations on activities ❍ (2) Limitation on activities

❍ Hospitalized, ❍ (3) Not requiring supplemental O_2 ❍ (4) Requiring supplemental O_2

❍ (5) On non-invasive ventilation or high flow O_2 devices

❍ (6) On invasive mechanical ventilation or ECMO

❍ Death ❍ (7) Deceased

Cardio-circulatory arrest within 28 days of transfusion: Y/N If so date: _____

Renal failure by RIFLE criteria within 28 days of transfusion: Y/N If so date: _____

Liver failure within 28 days of transfusion: Y/N If so date: _____

New rise in ALT or AST >5x the upper limit of normal Y/N

Significant worsening of preexisting liver failure rise in ALT or AST of >25%: Y/N

Evidence of cytokine storm based on inflammatory markers: Y/N If so date: _____

Days on ventilator: _____ Days off ventilator: _____ Days on coldflow: _____

Days on CPAP: _____ Days on BIPAP: _____ Days on non-rebreather: _____

Days on NC: _____ Days on Hiflo NC: _____ Discharge on new home O_2: Y/N

Requirement of pressor support: Y/N

Pressors used and dates of use: _____ _____ _____

_____ _____ _____ _____

In hospital mortality: Y/N Within 28 days: Y/N In ICU: Y/N If so date: _____

Length of Stay: _____ ICU Length of Stay: _____

Readmission: Y/N If so diagnosis: _____ If so date: _____

_____

Signature of coordinator Date

_____

Signature of Investigator reviewing data Date

ABACCuS Final Outcome Form Group A:

Patient Initials/Study ID: _____ Date of Enrollment: _____

Plasma Unit Used: _____ Date and Time of Transfusion: _____

Primary Outcome:

Was the patient intubated after the transfusion: Y/N

If intubated: Date of intubation: _____ Study Day #: _____

Secondary Outcomes:

Final outcome on a 7-point ordinal scale:

❍ Not hospitalized, ❍ (1) No limitations on activities ❍ (2) Limitation on activities

❍ Hospitalized, ❍ (3) Not requiring supplemental O_2 ❍ (4) Requiring supplemental O_2

❍ (5) On non-invasive ventilation or high flow O_2 devices

❍ (6) On invasive mechanical ventilation or ECMO

❍ Death ❍ (7) Deceased

Cardio-circulatory arrest after transfusion: Y/N If so date: _____

Renal failure by RIFLE criteria after transfusion: Y/N If so date: _____

Liver failure after transfusion: Y/N If so date: _____

New rise in ALT or AST >5x the upper limit of normal Y/N

Significant worsening of preexisting liver failure rise in ALT or AST of >25%: Y/N

Evidence of cytokine storm based on inflammatory markers: Y/N If so date: _____

Days on ventilator: _____ Days off ventilator: _____ Days on coldflow: _____

Days on CPAP: _____ Days on BIPAP: _____ Days on non-rebreather: _____

Days on NC: _____ Days on Hiflo NC: _____ Discharge on new home O_2: Y/N

Requirement of pressor support: Y/N

Pressors used and dates of use: _____ _____ _____

_____ _____ _____ _____

In hospital mortality: Y/N In ICU: Y/N If so date: _____

Length of Stay: _____ ICU Length of Stay: _____

Readmission: Y/N If so diagnosis: _____ If so date: _____

_____

Signature of coordinator Date

_____

Signature of Investigator reviewing data Date