Study Protocol and Statistical Analysis Plan
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Study Proposal

Study Title: Open-label Treatment of severe Coronavirus Disease 2019 (COVID-19) with convalescent plasma collected from individuals with documented infection and recovery from COVID-19 (SARS-CoV-2)

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Study Hypothesis:
We hypothesize that use of convalescent plasma donated from individuals recovered from Coronavirus Disease 2019 (COVID-19) will help expedite recovery of individuals with active, severe COVID-19 infection.

Study Background:
Plasma obtained from convalesced (recovered from virus) individuals may be an effective treatment or prevention of viral disease through the transfer of passive immunity in the form of neutralizing antibodies[1].
Convalescent plasma therapy can be considered as a candidate intervention in the setting of an expanding viral epidemic of public health concern for which vaccines and approved antiviral drugs are unavailable[2]. It has been used to treat patients with Machupo virus (Bolivian hemorrhagic fever), Junin virus (Argentinian hemorrhagic fever), Lassa fever, and most recently, Ebola virus, West Nile encephalitis, SARS and Middle East respiratory syndrome (MERS)[3-8]. During the 2009 H1N1 (H1N1pdm09) virus epidemic, a prospective cohort study by Hung and colleagues showed a significant reduction in the relative risk of mortality (odds ratio 0·20 [95% CI 0·06–0·69], p=0·01) for patients treated with convalescent plasma[5]. During the Ebola epidemic in West Africa, investigational use of convalescent plasma demonstrated that it can be successfully collected from donors with recent infection, and used safely and effectively for treatment in affected individuals[7]. In 2014, World Health Organization (WHO) recommended the use of convalescent plasma collected from patients who had recovered from Ebola virus as an empirical treatment during the outbreak[8]. In 2015, a protocol for the use of convalescent plasma was utilized in the treatment of Middle East respiratory syndrome coronavirus[6].

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by WHO on 3/11/2020. On 3/27/20, there were almost 530,000 cases confirmed in the world, with over 23,700 deaths in 202 countries affected[9]. According to WHO, management of COVID-19 has mainly focused on infection prevention, case detection and monitoring, and supportive care[9]. However, no specific anti-SARS-CoV-2 treatment is recommended because of the absence of evidence. During the last week of March, the United States has reported more cases than any other country, thus becoming a new epicenter of the disease. Due to the gravity and urgency of the COVID-19 pandemic, formal multicenter clinical trials for feasibility and medical effectiveness for collection and use of convalescent plasma are not immediately feasible[10-11].
Now we have validated FDA Emergency Use Authorization (EUA) approved serological assays to specifically detect SARS-CoV-2 antibodies, however, the quantitative result is still in the investigational state and quantification of neutralizing antibodies are not available, yet. Until it becomes available, IgG Index may soon be more widely available and standardized.[12] We currently lack validated serological assays to specifically detect SARS-CoV-2 antibodies, however, technology is rapidly evolving and quantification of neutralizing antibodies may soon be more widely available and standardized[12]. Even in the absence of that technology in hand, convalescent plasma from recovered individuals may provide therapeutic benefit nonetheless, as neutralizing antibodies will inevitably be present in plasma. Indeed, there are a few centers around the world with investigational protocols for convalescent plasma infusion as a treatment for COVID-19 at the present time[13-15]. Therefore, under close supervision by the Food and Drug Administration (FDA) in the context of an Investigational New Drug application (IND) pathway[16], the collection and investigational use of convalescent plasma in accordance with the safety and quality criteria of established regulatory standards is proposed for Inova Health Systems.

Safety Considerations:

1) Clinical use of convalescent plasma in this setting is regarded as investigational as the safety and efficacy of convalescent plasma are unproven in the setting of this novel pandemic. Collection and clinical use of this product will be managed as an experimental therapy consistent with ethical safeguards (informed consent of donors and recipients, FDA approval through IND pathway, institutional approval, and special labeling).

2) Procedures will maximize safety of both plasma donors and recipients.
    a. Standard blood donation protocols and screening will be followed (Donor History Questionnaire, Appendix E)
    b. Potential donors will be assessed by physician or nurse practitioner to assure clinical stability and full recovery (confirmed by nucleic acid amplification technology (NAT)) prior to donation
    c. Plasma collections must be separated by ≥ 28 days, eligibility must be re-evaluated at each collection, and total volume collected will be based on estimated donor blood volume in accordance to guidelines for healthy donors
    d. As with other plasma therapies, ABO compatibility will be assured

    e. Potential risks to convalescent plasma recipients will be discussed in the informed consent process and monitored for closely in the hospital setting:
        i. risk of unintended transmission of relevant transfusion transmitted diseases from donor
        ii. risks of transfusion related reactions
        iii. theoretical risk of immune enhancement due to transferred antibodies that could exacerbate the disease

Plasma Collection and Storage: Collection, storage, and preparation of plasma will be performed by the Inova Blood Center Staff. The plasma product is to be handled like a regular or licensed FFP/FP24, with special labeling. Convalescent plasma will be stored at the Inova Blood Donor Services Facility, the largest hospital based donor center in the country. It is a well-established and regulated BSL2 facility which is CLIA/CAP certified in full compliance with regulatory guidelines including AABB, FDA, with use of good manufacturing practices.

The Inova Blood Center Staff are routinely engaged in automated plasma collection and preparation in accordance with American Association of Blood Banks (AABB) and FDA guidelines 21 CFR Part 640 Standard Operating Procedures[17]. For automated plasma collection instruments, the allowable volume of collection is predetermined based on a set of parameters as approved by FDA.

All established safeguards for prevention of relevant transfusion transmitted diseases for standard blood donation will be followed. Infectious disease testing includes EIA(enzyme immunoassay): HTLV 1 and 2; Syphilis; HIV 1, 2 and group O, Hepatitis B, Hepatitis C, Trypanosoma cruzi. Nucleic acid tests (NAT) are performed for: HIV 1 and 2, Hepatitis B, Hepatitis C, West Nile Virus and Zika. Other tests include antibody screen and ABO-Rh, all in accordance with FDA regulatory standards. In addition, Babesia was recently identified by FDA as a relevant transfusion transmitted disease. Therefore, Babesia testing will be implemented as soon as feasible no later than May 31, 2020 by Inova Blood Center.

Convalescent plasma will be collected from a single donor connected to an apheresis equipment (TRIMA by Terumo-BCT) using an anticoagulant: ACD-; frozen within 8 hours; volume: 200 – 600ml and may be separated into 200 ml aliquots and stored: < -18°C with a shelf-life of 365 days.

Plasma units will be labeled in the standard manner with ABO typing but will also include the following statement, "*Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a)).*

Structure of Study:

Phase 1:
Phase 1 will be recruitment and enrollment of plasma donors.

Phase 2:
Phase 2 will be continued recruitment and enrollment of plasma donors, with the addition of recruitment and enrollment of plasma recipients.

Study Participants:

PLASMA DONORS:

Inclusion Criteria for Convalescent Plasma Donors:
Outpatients 18 years old and older who have recovered from COVID-19:

- Have proof of Original Positive SARS-CoV-2 NAT nasopharyngeal (NP) test result
- Complete resolution of symptoms at least 14 days prior to donation
- Negative SARS-CoV-2 NAT nasopharyngeal (NP) specimen at screening visit
- Able to meet standard criteria for blood donation
- Clinically stable based on provider assessment

Recruitment Population: Self- referrals from community with local advertisement tools utilized. Patients captured in Inova COVID-19 Research Team database of patients diagnosed with COVID-19 in the Inova Health System (emergency department/hospital setting as well as outpatient clinics/urgent care facilities within Inova)
Target Donor Recruitment: 100-150 individuals

Exclusion criteria:
Inability to complete or contraindication to donation based on Donor History Questionnaire (DHQ), FDA approved standard blood donation form
Hb<13.0 g/dL for males
Hb<12.5 g/dL for females
History of 3 more pregnancies unless HLA antibody testing is performed and deemed acceptable by director of blood donor services (to reduce risks of transfusion Related Acute Lung Injury in recipients)
The presence of any transfusion transmitted diseases is based on history or test results from blood sample collected from the donor at time of plasma collection in accordance to standard practice.
Female subjects who are pregnant by self-report.
Receipt of pooled immunoglobulin in past 30 days

Schedule of Events for DONOR:

1) Phone call or email for pre-screening $\geq$ 14 days post confirmed COVID-19 infection to inquire about clinical status and interest in study participation; consent will be made available to patient electronically or mailed upon request for their review
2) Screening visit

In person screening visit can be waived if donors have documentation of a repeat SARS-CoV-2 NAT nasopharyngeal test from an outside source that is negative. In this situation, consent form can be reviewed over the phone and signed electronically.

Location: Inova Health System Facility
Infection control procedures will be utilized for the protection of both the donor and research staff.
Donor screening visit will occur in their private vehicles.
Staff will come to donor's vehicle dressed in personal protective equipment to include gown, gloves, goggles/face shield, and mask.
Study visit procedures include:

- Consent form reviewed and signed (electronic will be used unless not logistically feasible)
- Medical history and concomitant medications reviewed
- Donor temperature will be checked
- Visual inspection will be performed by physician or nurse practitioner
- SARS-CoV-2 NAT test performed (nasopharyngeal (NP) swab)
- Optional duplicate SARS-CoV-2 NAT test performed (NP swab) for assessment of presence of replicable virus
- If donors have documentation of a repeat SARS-CoV-2 NAT nasopharyngeal test from an outside source that is negative, this test result will be accepted in lieu of repeating the SARS-CoV-2 NAT nasopharyngeal test at screening visit
- If phlebotomy is feasible and safe:
    - Blood draw of two tubes (1 serum and 1 EDTA) of blood for SARS-CoV-2 antibody testing
    - Blood draw of up to four additional tubes for COVID-19 Inova Biobank specimen (optional) In cases of extreme urgency for recipient plasma infusion, there may be an option of drawing an additional four tubes for transfusion transmissible disease testing at screening visit to expedite readiness of plasma for use (normally this blood is drawn at time of plasma donation and may take an additional 1-2 days)

*If SARS-CoV-2 NAT nasopharyngeal test is positive at screening visit, potential donor will not be allowed to donate plasma and will be given the option to return for a repeat screening SARS-CoV-2 NAT nasopharyngeal test after 7 or more days.

- Once a negative SARS-CoV-2 NAT nasopharyngeal test has been confirmed, plasma donation appointment can be scheduled

** If timely antibody testing should become available at a future date that allows prospective evaluation of antibody profiles, donors may be asked to postpone plasma donation and return for repeat antibody testing prior to donation in order to enhance the presence of IgG in the plasma.
*** If SARS-CoV-2 antibody testing becomes more standardized in the future, may be able to forgo NAT nasal swab test if documented SARS-CoV-2 infection was >28 days prior to screening visit.

3) Plasma Donation
   - Location: Inova Blood Donor Services Facility May occur same day as screening visit after confirmed negative NAT test result, or on a subsequent day.
   - Completion of donor history questionnaire (in accordance to standard practice for blood donation). Plasma collection performed by blood donor services staff member according to standard protocol using automated apheresis machine (TRIMA by Terumo-BCT))
   - Plasma is collected in an aseptic manner into a closed sterile system
   - Duration of procedure is approximately 1.5 hours
   - Total collection volume dependent on individual donor characteristics and includes:
     - Whole blood sample collected into the sample diversion pouch and aliquoted into:
       - 3 purple top tubes and 1 red top tube for routine transfusion transmitted disease testing
       - Additional two tubes for SARS-CoV-2 antibody testing (if not already collected at screening visit or if initial screen failure with positive NAT nasal swab test in which case may be repeated)
       - Optional tubes for COVID-19 Inova Biobank specimen (if not already collected at screening visit) to permit retrospective determination of the characteristics of an effective product and dosage regimen
       - (if not already collected at screening visit)
     - Up to 1000mL of plasma may be collected in one donation as calculated by the automated collection machine based on patient characteristics (gender, weight, height, point of care complete blood count test results)
   - Due to secondary binding of calcium by citrate anticoagulant used in the extracorporeal circuit to prevent clotting during plasma collection, calcium carbonate 2000mg total (four Tums tablets) will be given to each patient per protocol.
   - Replacement fluid will be administered to donors during collection based on calculated volume by TRIMA instrument during automated plasma collection
   - Monitoring occurs per protocol for standard plasma donation

4) Follow-Up Phone Call or Email (1-7 days post-donation)

Script for Phone Call or Email to Donors:

1) How have you been feeling since your plasma donation?
2) Do you have any new health concerns?
3) Do you have any questions for the study team regarding your participation in the study?
4) Would you be interested in donating plasma again in 28 days if you are eligible?

Repeat plasma collections are optional and must be separated by ≥ 28 days. Eligibility must be re-evaluated at each collection, and total volume collected each time will be based on assessment at that time in accordance to guidelines for healthy donors.

COVID-19 Convalescent Plasma (CCP) collected as part of this clinical trial will be prioritized for use in recipients enrolled in this clinical trial. In the event that the need arises for CCP in patient(s) outside of the clinical trial and the Blood Bank has a donor match of CCP collected under the clinical trial, the Blood Bank will try to accommodate the request, in the best interest of patient care.

BIOBANKING:

Collection and retention of blood specimens from both donors and recipients (pre- and post-treatment) will be performed to permit retrospective determination of the characteristics of an effective product and dosage regimen, and the characteristics of patients most likely to benefit[18].
Data and blood specimen will be banked for future use pursuant to the IRB Approved Inova COVID-19 Biobanking Protocol. We will follow the guidelines and procedures for specimen storage and access as described in the IRB approved Inova COVID-19 Biobanking Protocol.
Specimens will be stored at the Office of Research at Inova Biobank with standard certifications in place.

PLASMA RECIPIENTS:

Inclusion Criteria for Recipients of COVID-19 Convalescent Plasma:

Patients in the Inova Health System with confirmed COVID-19 by PCR testing
Age ≥ 13 years
Currently hospitalized with COVID-19 infection with severe or life-threatening clinical syndrome[22] as follows:
Severe COVID-19: (three or more of the following)

- Dyspnea
- Respiratory rate ≥ 30/min
- Blood oxygen saturation (SpO2) ≤ 94% on room air
- Partial pressure of arterial oxygen to fraction of inspired oxygen (P:F) ratio < 300
- Pulmonary infiltrates > 50% of lung parenchyma within 24 to 48 hours

Life-threatening disease is defined as: (one of the following)

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

Patient must provide informed consent or have health care power of attorney/next of kin provide consent if he/she cannot.

Exclusion Criteria:
Contraindication to receive plasma as deemed by the treating physician
Severe hypercoagulable state (documented in medical chart or by treating physician assessment)
Absolute IgA deficiency
Prior history of Transfusion Related Acute Lung Injury (TRALI)
Inability to tolerate plasma volume due to severe systolic or diastolic heart failure despite slower infusion and diuretic administration
Positive pregnancy test (HCG)

Recipient Screening Labs
Blood Type
Total immunoglobulin (Ig) levels: IgG, IgA, IgM
Coagulation tests to include PT/INR and PTT
Complete blood count and differential

Pre-Treatment Testing:
Optional Blood draw for Inova COVID-19 Biobank (up to four tubes each) prior to each dose of plasma
Target Recipient Recruitment: 150-200 individuals

Primary Endpoints:

1) Change in clinical status as captured by 7-point ordinal scale score (being utilized in Gilead Sciences remdesivir trial[19, 20]) at time of plasma infusion (day 0) compared to day 7:

1. Death
2. Hospitalized, requiring mechanical ventilation or ECMO

3. Hospitalized, requiring non-invasive ventilation or high flow oxygen
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen--requiring ongoing medical care (COVID-19 related or otherwise)
6. Hospitalized, not requiring supplemental oxygen-not requiring ongoing medical care (COVID-19 related or otherwise).
7. Not Hospitalized

2) Adverse events related to plasma infusion (within 6 hours of infusion) to include[23]:

a) Transfusion-related events
   i. Transfusion Associated Circulatory Overload
   ii. Transfusion-Related Lung Injury
   iii. Allergic Reaction/Anaphylaxis
   iv. Transmission of transfusion transmitted diseases
   v. Febrile Transfusion Non-hemolytic Transfusion Reaction

Secondary Endpoints:

3) Change in 7-point ordinal scale score (being utilized in Gilead Sciences remdesivir trial) from time of plasma infusion (day 0-prior to first infusion) to days 14, 21, and 28[19,-20].
4) SOFA score at days 0, 7, 14, 21, 28[21]
5) Time to discontinuation of supplemental oxygen
6) Duration of hospitalization
7) Time to liberation from mechanical ventilation (for patients on a ventilator)
8) Need for mechanical ventilation (For those not on the ventilator)
9) All-cause Mortality [at 28 days]
   ○

***Organ System,* Measurement**	**SOFA Score**				
	0	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	Normal	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets $x10^3/mm^3$	Normal	<150	<100	<50	<20
Liver Bilirubin, mg/dL (µmol/l)	Normal	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (<204)
Cardiovascular Hypotension	Normal	MAP<70 mmHg	Dopamine ≤5 or dobutamine (any dose)**	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Score	Normal	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (µmol/l) or Urine output	Normal	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500 mL/day	>5.0 (>440) or <200 mL/day

* Source: Vincent et al., 1996.

10) All other adverse and serious adverse events will be recorded as well (see adverse events section to follow).
11) Change in standard of care inflammatory markers (ferritin, LDH, CRP, D-dimer) where available from day 0 to days 7, 14, 21, 28.

Exploratory Endpoints:

12) Association between antibody levels and donor characteristics/clinical course
13) Association between clinical response in recipients and antibody levels in the donors

Dosing:

- One dose of 200-300mL (standard collection bag volume) of convalescent plasma will be infused over approximately one hour intravenously with standard vital sign monitoring per unit protocol and standard of care for plasma infusion.
- Up to two additional doses of 200 mL of convalescent plasma may be administered within 14 days of initial dose at 1-7 day intervals according to disease severity and tolerance of the infusions. Where possible, plasma from distinct donors will be used for additional doses.
- To reduce probability of allergic reaction, pre-medication with diphenhydramine 25mg orally or intravenously will be given within 2 hours before each dose of plasma, unless there is a contraindication noted by treating physician.
- Slower infusion time of two hours with optional dose of 20mg intravenous furosemide after first hour can be considered for patients at risk for transfusion-associated circulatory overload
- Infusion can be slowed for patient comfort at any time.

Safety: Patients will be monitored closely during plasma infusion per Inova nursing policy titled "Transfusion/Infusion of Blood Components" Version 01.01.Patients will remain in the hospital for a minimum of 24 hours post-infusion with vital signs performed per standard of care with frequency based on the treating hospital unit. Patients will be discharged from hospital according to standard of care any time after completion of 24 hour observation period post-infusion dosing.

If oxygenation worsens post-infusion, treating physician will perform assessment as to the presence of a transfusion related reaction, increase oxygen delivery, and obtain portable chest film if deemed clinically appropriate. Treating physician will notify the study doctor and staff if there is an adverse reaction. Possible anticipated infusion related reactions could include:

1) Transfusion Associated Circulatory Overload – dose of intravenous furosemide may be considered
2) Transfusion-Related Lung Injury- supportive care as directed by treating physician
3) Allergic Reaction/Anaphylaxis – additional dose of diphenhydramine, dose of intravenous or oral corticosteroids or intramuscular epinephrine could be considered
4) Transmission of transfusion transmitted diseases – supportive care or targeted treatment if infection identified
5) Febrile Transfusion Non-hemolytic Transfusion Reaction – supportive care

These adverse events, if present, will be recorded by clinical research team.

Post-Treatment Blood Draws:

Optional blood draws (up to four tubes) may be drawn on days 7, 14, 21, and 28 (+/2 days) following each dose of convalescent plasma where feasible for Biobanking.

If patient is discharged prior to 7 days post-dosing, then follow-up phone call or email assessments will be made by study staff at 7 days, 14 days, 21, and 28 days (+/2 days) following the original dose.

Script for Phone Call(s) or Email(s) to Recipients (if applicable):

1) Are you in a home environment (your home or family member's home)?
2) If not, are you in a nursing or rehabilitation facility?
3) Are you using oxygen?
4) Have you required an urgent care or emergency room visit for any reason since your discharge?
5) Have you required re-hospitalization for any reason since your discharge?

Trial Methods

Convalescent plasma will be made available to patients hospitalized in the Inova Heath System.

Patient outcome monitoring and reporting will include indicators of safety and efficacy. Case Report Forms will be used to capture essential data.

Statistical Plan

Study parameters (e.g., clinical status scale, death, hospitalization, etc.) will be described using traditional descriptive statistics (median [IQR], frequency and percent). Data will be assessed for 'missingness' with parameters exceeding 10% missing explored for imputation (e.g., multiple imputation, last value carried forward, etc.). Departures from normality will be assessed via Shapiro-Wilkes test with data transformations explored as needed. All analyses will be conducted using SAS (version 9.4, Cary, NC) with $p<0.05$, two-tailed considered statistically significant.

Primary efficacy endpoints:

1. Gilead 7-point scale – For each time point (day 0 vs. 7), summary clinical status scores will be calculated. Changes in scores will be subsequently assessed via a generalized linear mixed model with clinical status assessed at day 0 vs. 7. A statistically significant increase of ± 2 points in β from day 0 to day 7 will be considered as evidence of efficacy. A mixed model allows for examination and inclusion of the variance-covariance matrix into the model as a result of expected within-subject serial correlation as a result of repeated assessments over time.
2. Plasma transfusion related adverse events will be scored as 1+ vs. 0 and will be assessed via Chi-Square test with a hypothesized distribution of expected AE (using the higher incidence estimate):
    i. Transfusion Associated Circulatory Overload: 1:1,566 to 1:68 plasma units transfused
    ii. Transfusion-Related Lung Injury: 1:1,200 to 1:190,000
    iii. Allergic Reaction/Anaphylaxis: 1-3%
    iv. Febrile Transfusion Non-hemolytic Transfusion Reaction: 0.1-1%

Secondary endpoints:

1. Change in 7-point ordinal scale score and SOFA score over time will be assessed via individual growth models (IGM). Times will be day0, 14, 21, and 28
2. Mortality will be assessed via Chi-Square test with a hypothesized current mortality rate of 1-5% (age adjusted).
3. Need for mechanical ventilation for those not ventilator at time of plasma infusion will be assessed via Chi-Square test with a currently available published estimates.

4. Time to discontinuation of supplemental oxygen, time to liberation from mechanical ventilation, duration of hospitalization will be summarized as median (IQR) or rates and compared to currently available published estimates.

ADVERSE EVENTS AND TOXICITY MANAGEMENT

Definitions of Adverse Events and Serious Adverse Events

Adverse Events (AE)

An AE is any untoward medical occurrence in a clinical study subject administered an investigational product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. AEs may also include pretreatment or posttreatment complications that occur as a result of protocol specified procedures or special situations.

Serious Adverse Events (SAE)

A SAE is defined as an event that, at any dose, results in the following:

1) Death
2) Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
3) In-patient hospitalization or prolongation of existing hospitalization
4) Persistent or significant disability/incapacity
5) A congenital anomaly/birth defect
6) A medically important event or reaction: such events may not be immediately
7) Life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

Data Storage and Records Retention Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data will be stored in a secure electronic database during and after the study and will not be shared with unauthorized persons. Subjects will be de-identified in the database. Each subject will have a unique identification number that will be maintained in a separate database. The principal investigator, co-investigators, and authorized clinical research personnel will have access to the data to perform the retrospective chart review to verify COVID-19 test result(s) and details of the index COVID-19 hospitalization (with regards to blood transfusion and blood type), if applicable. For the protection and privacy of the patients, no identifying information will be released.

Data will be retained and possibly used in the future for further analysis. All identifiers will be removed.

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