Protocol Title: Antibody Enriched Plasma Donation for Future Treatment Opportunities

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Abstract:

Background:

Convalescent plasma (here on referred to as plasma) has been used in emergency life-threatening situations to treat infections for over 100 years. The plasma is often donated by an individual that has recovered from the very same infection that another person is infected with. This plasma is enriched in the antibodies that recognize and help the body's immune system to fight off the infection. When transfused from donor to recipient, those antibodies will aid the recipient in fighting off the infection. In recent history this has been used to fight Ebola.

Recently, the Federal Food and Drug Agency (FDA) made possible an expedited Investigational New Drug process for plasma use in the fight against COVID19 for emergency and lifesaving situations. We hypothesize that this method of treatment will help save lives in West Virginia and promote health in those infected with SARS-CoV-2.

Aim:

1) Contact patients (>27 days to 80 years) and their families (if children) for: a) possible plasma donation; or b) use of remaining samples that have already been collected for clinical purposes for future research on antibody structure; and
    a. Collect plasma from identified donors using standard of care practices to refer them to local/regional blood/plasma donation centers; and
    b. Capture remaining samples from patients who have recovered from COVID-19, are known to not have been exposed to COVID-19, or are

unable to produce antibodies to COVID-19. Those who do not meet eligibility criteria to provide a plasma donation for future treatment option or are unable to travel to a donation center to provide the donation, will also be eligible to donate samples (or have access from samples already collected from clinical procedures) to store in this portion and store for future research

2) Utilize donated plasma in accordance with the FDA IND requirements for COVID-19 positive patients.

Purpose and Hypothesis:
We are interested in the feasibility within the donation process. Potential donors come from various places and go to different types of facilities to provide their plasma. We hypothesize that local donation and distribution of blood/plasma is more feasible than national procedures (American Red Cross).

We also want to provide convalescent plasma to COVID-19 positive patients to assess impact of this treatment in terms of select outcomes. We hypothesize that the use of convalescent plasma enriched in COVID19 antibodies will help lower the mortality rate and promote health in those infected with SARS-CoV-2 in West Virginia.

Finally, we intend to collect plasma samples for future research on antibodies. These samples will be either from persons who are unable to donate to treat future patients (do not meet eligibility criteria for that portion) OR are extra (leftover) from samples collected from standard clinical procedures. There are no hypotheses noted for this as it is to be developed and reported to the IRB in separate protocols in the future.

Setting:
WVU Medicine 1 Campus Drive, Morgantown, WV 26056

Objectives:
Primary Objective for Donor plasma:

1) Determine which eligible donors are willing to donate
2) Determine who of the willing donors are allowed to donate plasma based on the American Red Cross or equivalent entities standards.

Secondary Objectives for Donor plasma:

1) Time

Primary Objectives for Plasma Recipients:

1) Time from plasma recipient consent to infusion
2) Survival

Secondary Objectives for Plasma Recipients:

1) Safety
2) Morbidity reduction
3) Reduced length of stay

4) Reduced length on advance respiratory support (any measure above low flow (2 Liters/minute) nasal canula oxygen)

Endpoints:

Donor plasma:

1) Primary endpoints:

a. Availability of convalescent plasma for local/regional use

b. Percentage of those that are COVID19 positive who are willing to donate
   - Percentage of those who are allowed to donate
   - Percentage of those who follow through with donation
   - Provision of plasma based on donation source (aggregate ARC or regional center)

2) Secondary endpoint:

a. Time from diagnosis to repeat testing negative

b. Time from diagnosis to donation

Plasma Recipients:

1) Primary endpoints:

a. Delays in infusion greater than 12 hours

b. Percentage of plasma shortages

c. Percentage of ABO compatible shortages

d. Reduction in mortality

e. Percentage of progression of illness to become CP eligible in the low risk arm

2) Secondary endpoints:

a. Delays in infusion great than 12 hours after 2 weeks from start of study

b. Percentage of shortages after 2 weeks from start of study

c. Percentage of ABO compatible shortages after 2 weeks from start of study

d. Survival until repeat COVID19 PCR test negative

e. Association with days of survival in those that have passed on

f. Length of stay/time:
   i. Hospitalized, in the intensive care unit, on ECMO, intubated, or other advanced respiratory support

g. Percentage of progression of illness
   i. After intention to treat with plasma and consent
   ii. After clinical concern for rapid progression plasma infusions
   iii. After infusions for severe or critical condition plasma infusions
   iv. 30-day readmission rate

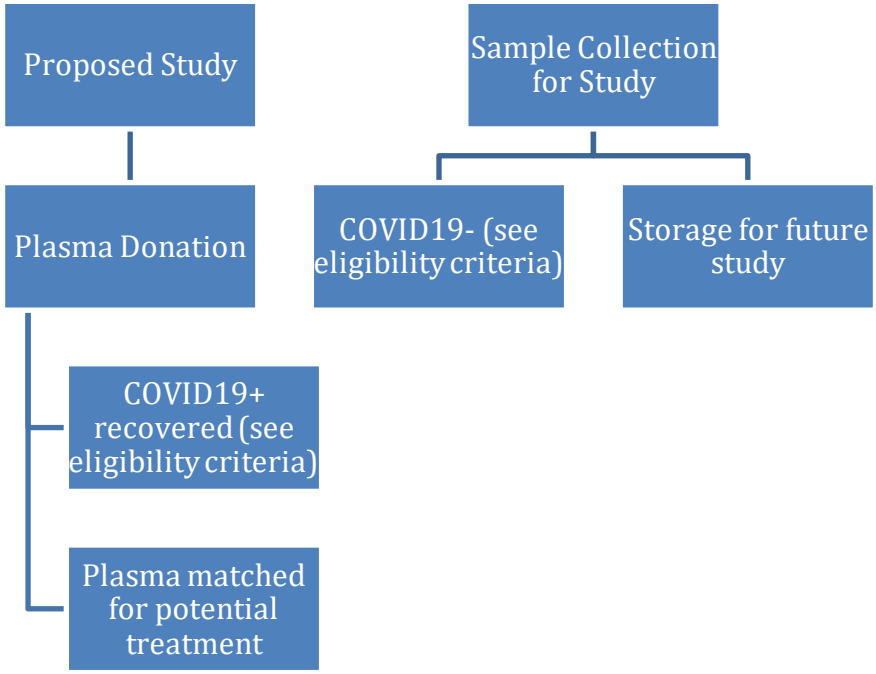
Design:

Donation:

The figure below provides an overview of the donation phase of this study. As noted earlier, there are two purposes in this phase. Individuals who have experienced COVID19 symptoms will be encouraged to make a plasma donation at a local center. This group

will not be consented as they will follow standard donation procedures to complete this request.

Individuals who are not eligible, or are unable to make the donation will be asked to provide a sample that will be stored for future study. Individuals who are COVID19 negative will be eligible for this second group. We will obtain consent for this second group to use the plasma sample for future research study.



Plasma Treatment

Donated plasma would be used for eligible recipient within the hospital setting and fits eligibility criteria. The plasma will be used to help fight off infections of those suffering from COVID19 in accordance to collection guidelines for plasma and FDA IND requirement. This study will include up to 240 participants potentially receiving convalescent plasma and an estimated 1000 potential donors.

Conclusion:

For over 100 years the use of convalescent plasma has been used to save lives suffering for novel and rare illnesses. The use of convalescent plasma enriched in COVID19 antibodies has the potential to help save lives in West Virginia and promote health in those infected with SARS-CoV-2.

Background and Significance

Convalescent plasma (here on referred to as plasma) has been used in emergency life-threatening situations to treat infections for over 100 years. The plasma is donated by an individual that has recovered from the very same infection that another person is infected with. This plasma is enriched in the antibodies that recognize and helped the body's immune system fight off the infection. When transfused from donor to recipient those antibodies will aid the recipient in fighting off the infection. In recent history this has been used to fight Ebola.[1] Recently, the Federal Food and Drug Agency (FDA) made possible expedited Investigational New Drug (IND) process for plasma use in the fight against COVID19 for emergency and lifesaving uses.[2]

There are several other investigational drugs for treatment of COVID19 such as: Remdesivir, and antiviral. The off-label use of Lopinavir/ritonavir, or Tocilizumab has been authorized. Convalescent plasma mechanism of action helps to promote health by working with one's own immune system and will not interfere with the other proposed medications. It also will not weaken the immune system as the investigational and off label medications have the potential to do. Convalescent plasma is time honored and although investigational for each use against novel or rare infections, it is the basis for IgG infusions in the immunodeficient populations. Currently the use of IgG infusions such as Intravenous IgG (IVIG) is assumed to not have the right antibodies from donors in the general public. This is secondary to the novel nature of the COVID19 and the fact that the IVIG available today was collected 6 to 12 months ago from plasma donors; prior to the COVID19's outbreak discovery in China.[3-6]

It is for that reason that IVIG is not recommended at this time and the FDA has made special fast-tracking announcements for plasma use for COVID19. Currently, plasma is the only treatment that has a previous history of success in these novel or rare viral outbreak situations. It has already been reported to have been associated with survival of 5 out of 5 participants in a pilot study in China.[4]

Preliminary results in West Virginia University Medicine's CP study has shown a greater percentage in survival ~75% in those that have received CP from those with the intention to treat but did not receive CP 25% secondary to shortages or the decision not to receive CP by the patient. The difference is not currently statistically significant due to the low "n". It has been noticed that many CP recipients will initially improve or stabilize with respect to respiratory symptoms and total lymphocyte counts. However, this initial benefit after two days appears to wane and the illness continues to progress.

With these results and the current national shortage on CP resolved, WVU Medicine is increasing the maximum CP through the participants hospitalization. This is being done secondary to the observations in the preliminary results as well as the inability to standardize the CP. Repeat sequential dosing will help to minimize this confounding factor.

Research Plan
Study Population. Plasma Donation

Inclusion Criteria		Exclusion Criteria
Prior diagnosis of COVID-19 documented by a laboratory test	Abbott RealTime SARS-CoV-2 real-time reverse transcription polymerase chain reaction (rRT-PCR) test on the Abbott m2000 System (Inpatient WVU testing)	Individuals that do not meet the requirement from the American Red Cross or Vitalant for plasma donation
	Other testing methods and vendors using FDA approved detection methods of SARS-CoV-2 under the Emergency Use Authorization (EUA)	Individuals plasma that has not passed safety screening procurement by the FDA standards for plasma donation
Complete resolution of symptoms at least 28 days prior to donation (with negative repeat testing when required)		
Complete resolution of symptoms for at least 14 days with negative repeat COVID-19 testing approved by the FDA EUA		
Female donors that have never been pregnant or negative for HLA antibodies		
Male donors[9]		
Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood.	A partial list of available tests can be accessed at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations.	
At least or greater than 50kg (110 lbs) of weight		
*For *in vitro* research purposes blood donations will be accepted as outlined below. This is to be separate from plasma donations for transfusion as listed above.		

Plasma Recipient

Inclusion Criteria		Exclusion Criteria
Individuals of any age above 27 days of life, sex, or pregnancy status who are hospitalized and experiencing respiratory failure from laboratory confirmed COVID19 and in critical condition meeting the FDA IND guidelines		Individuals with COVID19 who are not in clinical concern for rapid progression, severe or critical condition
Must have severe or immediately life-threatening COVID-19, for example:[3]	Severe disease is defined as: • Dyspnea, • respiratory frequency ≥ 30/min, • blood oxygen saturation ≤ 93%, • partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 • lung infiltrates > 50% within 24 to 48 hours Life-threatening disease is defined as: • respiratory failure, • septic shock, and/or • multiple organ dysfunction or failure	Individuals who are in critical condition that are not confirmed to have COVID19
Must provide informed consent		Individuals with known Selective IgA Deficiency, that has not been found to be absent of anti-IgA antibody
For the purpose of this study advanced respiratory support will include any measure of respiratory support above low flow nasal canula oxygen (2 Liters/minute flow rate).		Individuals on Comfort Measures Only (CMO).
For the purpose of this study dyspnea will be defined as any shortness of breath that is not completely relieved with the use of low flow nasal canula oxygen set to 2 Liters/minute flow rate and/or requiring breathing treatments such as but not limited to: bronchodilators more than every 4 hours to relieve symptoms.		Age less than 28 days of life (Neonate)

Subject Recruitment and Enrollment:

Plasma donors for potential treatment options for other patients:

Identification of potential donors will be done through the use of EMR, unsolicited potential donors reaching out directly to the study team and from WVU staff members that know of willing potential donors that have reached out to them through their own prompting. The investigative team will contact potential donors by telephone or, when possible, in person just prior to

discharge for inpatient services. In the case that a potential donor is inpatient but beyond 10 days after recovery they will be approached for potential donation while inpatient. Those in the outpatient setting that are in self-quarantine will be called on sooner than 10 days after sample collection to discuss the possibility of donation.

Inpatient potential participants will be tracked upon confirmed COVID19 testing and are eligible to enroll in the study. Enrollment allows for continued tracking and a type and screen to be drawn, but does not mean that they will receive plasma if they do not meet recipient criteria. In the event that the patient meets recipient criteria, the potential donor will be transferred to the potential recipient recruitment plan below. If the potential donor is recovering, they will be approached in their room to discuss plasma donation. Should they at any time say or expressed the notion of "no" the discussion will end with closing pleasantries and contact information should they change their mind. In the event that a potential donor does not pass transfusion screening, or chooses not to donate for transfusion but still meets transfusion criteria they will be given the option to donate locally to a WVU lab study (and review and consent to participate in the plasma collection portion).

Outpatient potential participants contact information will be obtained from medical records upon a confirmed COVID19 test. Should they be admitted they would follow the inpatient potential participants recruitment and enrollment in the above paragraph. Upon 10 days after sample collection they will be contacted by phone. A preapproved phone script will be used to begin the conversation, about potential donation. Any and all question will be answered to the best of our ability. Should they at any time say or expresses the notion of "no" the discussion will end with closing pleasantries and contact information should they change their mind.

All male and female's with negative HLA antibodies potential donor's plasma will be used for transfusions to help reduce risk of adverse reactions with recipients.[8]

Potential recipients' primary team will be approached if the potential donor becomes eligible to receive plasma. The primary care or consult team may also contact the study group if they are concerned or feel they have a patient that may benefit from the plasma infusion. The criteria to receive the plasma will be reviewed with the primary care team and the patients case reviewed. Upon agreement that the patient meets the criteria for plasma, the potential recipient and/or their medical decision proxy will be approached and consented/assented if they are not already consented/assented.

If the participant is already consented/assented (as outlined above for tracking and obtaining a type and screen), but was not eligible at the time of consent/assenting to receive plasma (mild severity, outlined below under "Initial Plasma Dosage Determinations)", they will be informed when and if they become eligible. At this time the primary care team will be informed prior to informing the patient to review the patient's status and any concerns. The participant will then be informed of their status, any concerns, modifications to the protocol based on their medical status. They will be given the opportunity to op-out prior to plasma transfusion at this time. The participant may option back into the study on their own accord, but will not be approached by the study team after opting out.

Plasma collected for future antibody research:

Individuals are eligible for this portion of the study if they have recovered from COVID-19, are known to not have been exposed to COVID-19, or are unable to produce antibodies to COVID-19. Those who do not meet eligibility criteria to provide a plasma donation for future treatment

option or are unable to travel to a donation center to provide the donation, will also be eligible to donate samples (or have access from samples already collected from clinical procedures) to store in this portion. Up to 15 mL of the total donation will be held for local storage, and analyses on antibodies and structure. Consent from the individual and/or a legal guardian will be required to use existing samples for this purpose or collect a sample specifically to store and examine in the future. The plasma collected will be de-identified, given a study ID number, and stored in -18 to -80C storage for testing at later date in the pathology lab (Main hospital 3C35).

Samples already collected for routine medical care within 24 hours of the transfusion will be used in preference to new blood draws if available. Sample after the transfusion will be collected no sooner than 2 hours post transfusion and no later than 24 hours port transfusion. Timing will be arranged to coincide with routine medical care blood collection when possible.

Plasma collected will be used to help develop antibody assays and neutralization testing.

All plasma stored at WVU Medicine will be stored in accordance with storage of plasma in either its fresh or frozen form. Expiration date will be assigned based on the standard shelf life of plasma based on the method of storage. All Plasma stored at WVU Medicine will be labeled with: “Caution: New Drug--Limited by Federal (or United States) law to investigational use." Per the FDA IND announcements specifications.

Plasma Treatment Recipients:

Patients (pediatric and adult) who meet eligibility criteria will be identified through hospital electronic medical records and approached to consider study participation.

Plan for Obtaining Consent/Assent

***Plasma Donor for Potential Treatment Consent*:**
We will use standard procedures for advising patients on where and how to provide plasma donations that will be used for future treatment options for other patients. These individuals will not need to be consented.

Plasma collected for future antibody research:
A team member will review the purpose of the plasma collection, particularly the collection steps and risks associated with it. They will also be shown a consent form (see attachment section). If by phone, the consent language will be reviewed and then consented by phone. A consent document will then be sent by mail for the individual to review and sign in person. Potential donors will be offered an interpreter should they not be fluent in English or need assistance. They will have up to 7 days to decide and contact the research team with any questions, concerns and decisions. During this time the research team will not initiate contact with the potential donor. After 7 days, if a decision has not been conveyed to the research team, the potential donor will be called by the research team to discuss donation. If they are not reached, a standard message will be left with the research teams contact information. If there is no return phone call within 2 days, they will be called once more and left a second and final standard message. Should the potential donor not return the call they will be presumed uninterested in donation and no further attempts to contact them will be initiated by the research team.

Consented participants will be given a date and time for coming to the WVU Medicine if outside of the outpatient or inpatient facilities during consent. Individuals who are still receiving care and meet eligibility criteria will be consented on-site prior to discharge.

Plasma Recipients:

Individuals will be consented/assented in person. In the special case that medical decision proxy is not in the hospital and will not be able to get to the hospital in time or recipient is located outside WVU Medicine at 1 Campus Drive, consent/assent will be obtained over the phone. Potential recipients or their medical decision proxy will be offered an interpreter should they not be fluent in English. A signed English consent/assent will be accepted in the event that proper translation of the consent/assent form cannot be done in time, provided that each section is reviewed with the aid of an interpreter. Written consent will be collected once able for files.

Potential plasma recipients, or their medical decision proxy, will be allowed as much time as they need, provided that the patient's status continues to meet study criteria. In the event that the potential plasma recipient's health does not meet FDA criteria for the IND (or their health improves and does not meet the FDA criteria for the IND), then the plasma will not be offered at that time. However, consent/assent will still be allowed for the purpose of collecting a type and screen and monitoring their progress. Should their health worsen or return to critical then they would again be eligible to receive plasma if it is available.

Initial Plasma Dosage Determinations

The respective characteristics shall be assigned to each severity. However, clinical judgement of the primary care team and research team will take precedent over any of the listed criteria below. Default to assignment of severity in case of disagreement will be awarded to the primary care teams' clinical judgement.

- Our approach to plasma delivery is based on availability of the plasma and the recipient's condition.

Mild: 1 plus 2 or 3. **No Plasma, will obtain type and screen in case of progression**

1) Responding to conventional treatments, or absence of sustained progression of illness for greater than 4 hours based on routine clinical judgement
2) On room air

or

3) On Low flow (LF) nasal cannula (NC) oxygen =/<2L with no shortness of breath (SOB) or higher for less than 4 hours at a time with no sob

Moderate: 1 and 2 must be met **Convalescent Plasma 1 Unit**

1) SOB on more than LFNC as specified under "Mild", but not on Mechanical Ventilation or High Flow Nasal Canula (HFNC)
2) Not responding (or unsure if responding) to conventional treatments, acute worsening of condition for greater than 4 hours based on routine clinical judgement

Severe or critical: 1 plus 2 or 3; or 1 plus 4 mechanical ventilation and/or clinical judgement; or 5 alone. **Convalescent Plasma 2 Units**

1) Dyspnea,
2) respiratory frequency ≥ 30/min,
3) blood oxygen saturation ≤ 93%,

a. partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
b. lung infiltrates > 50% within 24 to 48 hours

4) Mechanical Ventilation or High Flow Nasal Canula (HFNC)

5) Life-threatening disease is defined as:
a. respiratory failure,
b. septic shock, and/or
c. multiple organ dysfunction or failure

Note. All pediatric patients will receive 10 mL/kg (1 dose) if moderate with concern for rapid progression if up to 1 Unit; 10 mL/kg up to 2 units if severe or critical.

- Plasma recipients with moderate severity and concern for rapid progression will only be given one treatment of plasma as the standard approach. A unit will consist of about 200mL for both pediatric (up to 1 unit) and adult populations.
- Two units will be given to those that are deemed clinically severe or critical criteria in both pediatric (up to 2 unit) and adult populations.
- Each pediatric recipient will receive 10mL/kg up to 2 units of plasma is in severe or critical condition.[10,11]
- In the event that more than one recipient is identified and plasma is available in less than the total number of approved recipients, priority will be given to those approved by the FDA for the IND use of plasma for severe or critical condition above rapid progression. If there still exists a deficit of plasma, the priority will be given to those in following triage order and only proceeding the decision tier is a tie continues to exist: 1) Those that the remaining plasma would satisfy the full transfusion amount allowed for the participant 2) on advanced respiratory support with the most critical settings (if unclear then will be considered a tie) 3) active pressor treatments and lastly 4) lottery pull with potential remaining recipients as the final tie breaker.
- Those who are given 1 unit may receive the second unit (or the remainder of the maximum pediatric weight calculated amount of plasma up to 1 additional unit) if they progress to severe or critical condition or if already in severe or critical condition but only received 1 unit secondary to shortages.
- A recipient may also receive additional plasma above 2 units if the neutralizing titers of the plasma infusions are determined to be less than 1:360 or neutralizing titers are unable to be performed and at least 2 days has passed from last transfusion and the participant is still in rapidly progressing, severe or critical condition. Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., of at least 1:160[2], 1:360 up to 1:640 is preferred.[4,5] In shortage case 1:80 is acceptable[2])
- A recipient may also receive additional plasma above 2 units, if their condition clinical worsens or fails to improve (severity, but not dosage will be based on the criteria for initial plasma dosage determinations), they will be eligible to have up to 1 additional unit every 3 days for a maximum of 8 units (or weight-based equivalent treatments for pediatrics) of convalescent plasma, if doses are available. Directionality of clinical condition will be multifactorial and include, but not be limited to: Patient reports, vitals, FiO2 requirements, Flow rates, HFNC, BIPAP, CPAP, intubation, venous and or arterial blood gasses, total lymphocyte counts, inflammatory markers. Directionality of clinical condition will be discussed with the primary care team and final decision in disagreements will be awarded to the primary care team.
- Adult participants that undergo plasma electrophoresis, as part of their clinical care from their primary care team's management decisions, after their initial 2 units or maximum 8 units, they will be eligible for 2 additional units of convalescent plasma per electrophoresis treatment and up to 8 units total after electrophoresis series is completed, if doses are available.
- Plasma electrophoresis discarded waste plasma created as part of their clinical care from their primary care team's management decisions, will be collected and stored for testing

development as described below or discarded based on routine practices depending on plasma research test development needs.

- Up to 3mL of plasma will be collected from each convalescent plasma unit prior to transfusion for analysis and labeled with lot number.
- Up to 5mL of blood will be collected from each recipient prior to transfusion with focus on obtaining and saving a discarded sample the morning of infusion or the day prior to transfusion
- Up to 5mL of blood will be collected from each recipient within 24 hours after transfusion, but no sooner than 2 hours after transfusion for analysis.
- Blood and plasma samples will be used to test for antibody levels, neutralizations tests, quantitative viral load testing, inflammatory markers, chemokine, cytokines and interleukin testing, future biomarker testing. The number of tests and which tests to be run will be determined by the sample availability, samples age and the testing capabilities, some of which are still under development.

Plasma Availability

Because donors provide their plasma through the American Red Cross or Vitalant, there is no guarantee that plasma will be available for an enrolled recipient. Current plasma donation is coordinated nationally. Enrolled plasma recipients will be informed if the plasma may not be available for them and other reasons (e.g., no match) if the situation is applicable.

Privacy protection and Data Confidentiality:

All data will be stored on two separate H-drives. One H-drive will have participant PHI information and study ID. The second will have de-identified data assigned with the study ID for each participant. The H-drive for identification will only be accessible by those consenting the patients for either donation or for receiving plasma. All other study members will be blinded from participant PHI information. All plasma used will have identifiers recorded per the FDA guidelines.

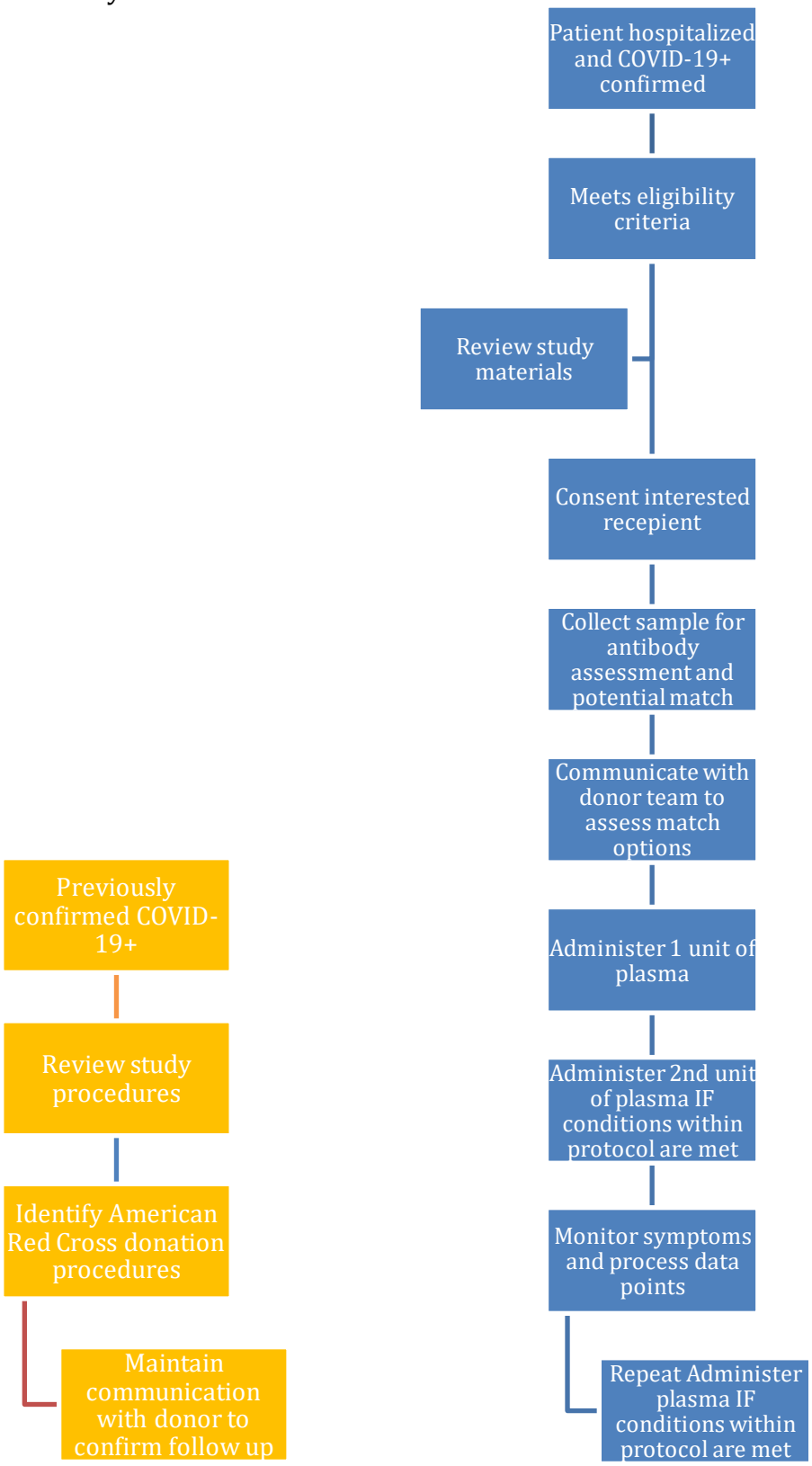
Study Procedures: The study team will actively recruit individuals who are interested in donating their plasma either for the potential treatment use or for future antibody studies (plasma storage component). They will also work with other physicians so that they can be informed when someone is eligible and has expressed an interest to donate for either purpose. This method plus reviewing electronic medical records for those who are eligible for either donation group will help identify individuals who may be eligible to contribute plasma.

Once identified, the study team will follow the consent procedures noted earlier for each group. Consent will not be needed for those who meet eligibility and are able to donate their plasma to the standard American Red Cross or other centers. The study team will consent individuals who are willing to have plasma stored for future studies and individuals who are in need of the plasma for treating COVID19 symptoms.

For those consented and donating plasma for future studies, their plasma will be collected and stored according to the details in this protocol. Patients in need of plasma will be treated with plasma, as available, according to the dosage determination section earlier in this protocol.

Figure 1 illustrates the study procedures.

Figure 1. Study Procedures Overview



Data Collection Points:

Participants data will be collected and stored on excel sheets in two different secure drives. One drive will contain participant identifiers and study ID assignments and the second one will study ID and additional data unique to donor and recipients.

The donor data file will contain date of COVID19 diagnosis, date of initial symptoms, date of recovery and date of donation or denial of being a potential donor. When testing for COVID19 antibodies is established, the titer values for each donation will be added to the data file.

The recipient data file will contain the date COVID19 diagnosis, date of initial symptoms, date of approval for being a recipient, date of being a recipient, days from approval to being a recipient, volume of plasma received, donor study ID or equivalent.[2] Outcomes, 30-day readmission, adverse events, total hospital length of stay, length of stay after transfusion, days of advanced respiratory support after plasma approval and transfusion, intubation/ECMO status pre and post plasma approval and transfusion, days and status of ICU versus general floor status pre and post plasma approval and transfusion. Medication prior to and after plasma transfusion will be recorded, along with at each interval of contact up to 30 days post transfusion.

Safety and Reporting:

- Life-threatening or serious and suspected life-threatening or serious adverse events that are potentially related to the administration of convalescent plasma will be reported in this study. The clinical suspicion of these related events will be made by the treating physician.
- Suspected adverse reactions will be recorded as part of the studies variables but not reported, unless it is unexpected.
- Unexpected adverse events, unexcepted suspected adverse reaction, and unanticipated concerns/issues should be reported to the Sponsor/principal investigator: Brian P. Peppers
- All serious, suspected and unexpected adverse events and/or reaction should be reported to the Sponsor/principal investigator: Brian P. Peppers
- The sponsor will provide sponsor report to the FDA after the first 30 days and then every 4 months afterwards except in the cases listed below.
- An IND safety report will be submitted within 15 days will be submitted as described mainly in 21 CFR 312.32 (a) under paragraphs: (c) (1), (i), (ii), (iii), and (iv) as well as in special circumstances listed in the remainder of 21 CFR 312.32 (a)

Statistical Methods

Data will be analyzed using a retrospective approach given the clinical nature of the use of the plasma for recipients. Due to the likelihood of a low “n”, no minimum number of donors or participates will be set for power in the study.

Gender/Minority/Pediatric Inclusion for Research

All vulnerable populations will be eligible to be recipients if they meet the criteria in the study. There are no gender or minority exclusion criteria for being a recipient of plasma in this study. Neonatal age group has been excluded from this protocol; all other ages are eligible. All vulnerable populations if they meet the criteria will be eligible to be donors.

Assessment of Resources:

WVU Medicine has the capacity for large volumes of ICU patients and has identified and is caring from those with COVID19 already. WVU Medicine is experienced in routine blood product transfusions.

WVU Medicine is not licensed to collect plasma. WVU medicine's blood bank and department of pathology is working with the American Red Cross and Vitalant for any and all Convalescent plasma collection for use in this study.

Risks and discomforts and how minimized

a. Both Plasma Donors and Recipients have the risk of beech of confidentiality and will be minimized by careful data handling.
b. Plasma Donors: Venous access has minimal risk involved for discomfort, fainting, bruising and infection. This will be minimized by using American Red Cross, Vitalant and FDA standards of plasma collection. These measures include the participant will be seated or lying down, the site will be sterilized after the vein with best chance of access is identified and sterile bandage will be applied. Refreshments are on site if needed as well as American Red Cross, Vitalant and FDA approved emergency medical equipment for plasma donation.
c. EMLA or similar numbing agent may be used if needed to decease discomfort of blood draws for lab research purposes.

Plasma Recipients:

i. Venous access has minimal risk involved for discomfort, fainting, bruising and infection. These risks will be minimized by using existing venous access when possible. When new access is required, the participant will be seated or lying down, the site will be sterilized after the vein with best chance of access is identified and sterile bandage will be applied. Venous Ultrasound is also available should it be needed to establish venous access.
ii. The participant will be receiving blood products and there is a risk of allergic and anaphylactic reactions. This will be minimized by excluding selective IgA deficient participants that have anti-IgA antibodies or unknown status of anti-IgA antibodies. With every transfusion, intramuscular epinephrine will be ordered and in the participants room to be administered should anaphylaxis occur. For allergic reactions that are less than anaphylaxis, such as flushing or hives, IV diphenhydramine or equivalent antihistamine will be given at standard dosing. In either event the transfusion will be stopped immediately and the decision to continue will be based on the primary care teams wish to continue, Allergy and Immunology consulted and the participant is still willing to continue. A desensitization to the plasma, if appropriate, will be supervised by Dr. Peppers in accordance with the standards for Allergy and Immunology practices.
iii. Infectious transmission risk and prion disease are rare but possible risks factors for recipients. This will be minimized by excluding anyone donor with known prion disease. The donor will also be screened by the ARC for viruses such as, but not limited to: hepatitis B and C, Human Immunodeficiency Virus, and have to meet the American Red Crosses criteria to be a Plasma donor.
iv. HLA-Mismatch with plasma is risk factor as well and will be minimized per the FDA recommendations and literature that shows decreased adverse reactions with the use of only using male donors compared to female donors whose HLA status is unknown or positive. Female donors whose HLA status is negative or unknown will be allowed to donate for transfusions Per the FDA IND announcements specifications.[2] HLA testing will be done by the plasma donation center to determine HLA status post plasma donation.

Compensation for injuries

There will be no compensation for injuries in this study. Any injury suffered as a result of this study will be treated according to routine medical practices. Donors will be treated on site at the American Red Cross or Vitalant and if needed transported to the nearest hospital or medical facility that can treat the participants injuries. Recipients will be treated at the hospital they are current admitted to. Plasma donor's or recipients and their respective health insurance will be billed for treatments of any adverse events.

Benefits to subjects

- Plasma donors will be helping to establish the global medical knowledge on the use of plasma for the use against COVID19
- Plasma recipients may directly benefit from the plasma infusion. They will also help to establish the global medical knowledge of the benefits of plasma use in the fight against COVID19.

Costs to subjects

There are no costs to plasma donors other than time for plasma collection. Plasma recipients will be charged routine hospital expenses while in the hospital. They will not be charged additional fees for being participants in the study.

Alternative to participation

Plasma Donors: The alternative for this is not to donate plasma either for treatment or future research purposes. Potential donors who would like to participate at a later time, can contact the study group for consideration.

Plasma Recipients: Patients do not have to consent to receive the plasma as a treatment option. The potential recipient will continue to receive care based on the standards accepted for the treatment of COVID19. Should they wish to participate at a later date and still meet criteria they will be allowed to participate.

Payment to subjects
There is no payment to the either donor or recipient in this study

Provisions for subjects from vulnerable populations
All vulnerable populations will be eligible to be recipients if they meet the criteria defined by the FDA IND. All vulnerable populations if they meet the criteria will be eligible to be donors.

Data and safety monitoring plan
As with any research, there is a potential risk of breach of confidentiality of data, which will be minimized by careful data handling. Dr's Peppers, Perrotta, Shmookler, Sharma, Mullet and Giblin Sutton will perform and meticulously maintain the data and safety monitoring. Additionally, Dr. Greg Schaefer, Associate Professor for the Trauma, Acute Care Surgery, and Surgical Critical Care at WVU has agree to serve as an outside member of the DSMB. The primary research team will supervise data collection and any potential adverse events will be reported to the IRB.

Safety of the participants will be monitored in accordance with the phase and stage of the study they are in (Table 1).

Plans for subjects at the end of the protocol
Plasma donors will be thanked for their participation and asked if it would be okay to contact them in future should additional plasma donations be needed. Plasma recipients will be monitored for 30 days post infusion for return hospitalization or complications. If outpatient at the end of 30 days, they will be contacted by phone for an update.

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