Convalescent Plasma to Limit Coronavirus Associated Complications: A Randomized, Double-Blind, Controlled, Phase 2 Study Comparing the Efficacy and Safety of Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 non-immune) Plasma Among Outpatients with Symptomatic COVID-19.

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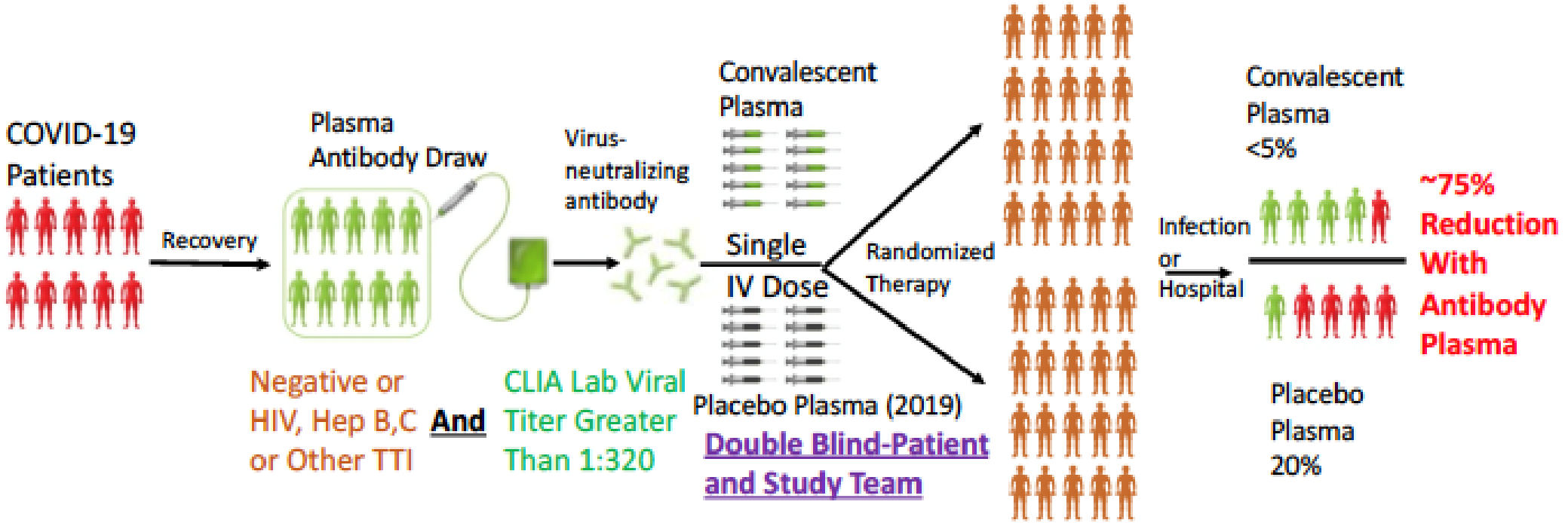
Protocol dated 27 December 2020 (version 8)

Early Outpatient COVID-19 Antibodies Reduce Infections and Hospitalizations



Convalescent Plasma Efficacy

- **Polio 1950s:**gamma globulin 80% protection from acquiring polio virus for 5 weeks
- **Argentine hemorrhagic fever:** Case fatality rate 1% (n=91) with convalescent Plasma and 16% (n=97) without
- **Spanish flu 1918:**Case fatality rate of 16% (n=336) with convalescent plasma and 37% (n=1219) without.
- **SARS-CoV-12003**: Case fatality rate of 12% (n=80) with convalescent plasma and 17%(n=1755) without (historic controls).
- **H1N1 influenza 2009:** Severe disease-Case fatality rate of 20% (n=20)with convalescent plasma and 54% (n=73) without.

Objectives

Primary Efficacy Objective

- Evaluate the efficacy of treatment with HCIP in reducing hospitalization and death among outpatient adults who have molecular detection test-confirmed COVID-19 AND have developed any symptoms of COVID-19 including but not limited to fever, cough, or other COVID associated symptoms like anosmia. In version 8 of the protocol, the following were put into the clinical events scale as hospitalization equivalents: 1) a stay of >24 hours for observation in an emergency department, field hospital, or other healthcare unit; 2) any receipt of O2 for >24 hours, outside of a hospital

Primary Safety Objective

- Evaluate the safety of treatment with HCIP and control plasma in symptomatic outpatient subjects presenting with a positive SARS-CoV-2 molecular test.

Efficacy Endpoints

Primary Efficacy Endpoint

- Cumulative incidence of COVID-19 related hospitalizations or deaths prior to hospitalization in treatment versus control groups by Day 28

Secondary Efficacy Endpoints

- Compare serum SARS-CoV-2 antibody titers between active and control groups at Days (-1 or 0), 14, 28 and 90.

- Compare the rates and duration of SARS-CoV-2 RNA positivity (by RT-PCR) of nasopharyngeal or oropharyngeal fluid between active and control groups at days (-1 or 0), 14 and 28.

Efficacy Endpoints (cont'd)

Tertiary Efficacy Endpoints

- Compare the levels of SARS-CoV-2 RNA between active and control groups at days (-1 or 0), 14 and 28
- Compare time to hospital disease severity measured by ICU admission, invasive mechanical ventilation or time to death in hospital.
- Assess rate of participant-reported secondary infection of household contacts
- Compare blood oxygen saturation levels as measured by pulse oximetry (where available) between active and control groups through Day 28
- Assess time to resolution of COVID-19 symptoms based on temperature logs and symptom score sheets
- Assess treatment effect heterogeneity by age (as continuous variable).
- Compare donor antibody titer to primary, secondary and tertiary endpoints

Safety Overview

The available evidence from the use of convalescent plasma in patients with SARS and MERS and anecdotal evidence of its use in patients with COVID-19 suggest convalescent plasma is safe.

Primary Safety Endpoints:

- Cumulative incidence of treatment-related serious adverse events categorized separately as either severe infusion reactions or Acute Respiratory Distress Syndrome (ARDS) during the study period
- Cumulative incidence of treatment-related grade 3 and 4 adverse events during the study period

Potential Safety Issues:

- Transfusion reaction (fever, rash)
- Transfusion related acute lung injury (TRALI), Transfusion associated circulatory overload (TACO)
- Transfusion related infection
- Antibody-mediated enhancement of infection (ADE)

Expected Adverse Events (general blood plasma transfusion)

Standard risks of human plasma	Steps to reduce risk
Transfusion Reaction: (<5 in 100 people) • Fever and/or chills/rigors • Itching and hives • Passive hemolysis • Low blood pressure, bronchospasm, difficulty breathing, and organ injury are more serious but also much less common. These are called transfusion-related acute lung injury (TRALI)	• Transfusion according to standard blood banking procedures and practices • Standard monitoring during- and shortly after transfusion, • Ready access to medications to treat individual transfusion reactions if needed (e.g., antihistamines, acetaminophen, corticosteroids, epinephrine) • Standard ,measures to reduce TRALI include limiting certain people from donating (such as women who have had many pregnancies)

Expected Adverse Events (general blood plasma transfusion)

Standard risks of human plasma	Steps to reduce risk
Transfusion associated circulatory overload (TACO): (less than 1 in 1000 people) • Pulmonary edema (excess fluid in the lung) can develop in individuals with underlying heart or kidney disease	• Risk is limited by transfusing only minimum volume necessary • Attention to fluid volumes in patients with severe heart or kidney disease predisposing to TACO
Infection: (less than 1 in 1000) • Bacteria, Viruses, Parasites, Prions	• Screening of donors and testing of all blood products per standard blood banking procedures

Study Population

Inclusion Criteria for Enrollment:

- ≥ 18 years of age
- Competent and capable to provide informed consent
- Positive molecular test for presence of SARS-CoV-2 in fluid collected by saliva for antigen, oropharyngeal or nasopharyngeal swab
- Experiencing any symptoms of COVID-19 including but not limited to fever (T> 100.5º F), cough, or other COVID associated symptoms like anosmia.
- ≤ 8 days since the first symptoms of COVID-19
- ≤ 8 days since first positive SARS-CoV-2 molecular test
- Able and willing to comply with protocol requirements listed in the informed consent.
- SARS-CoV-2 vaccine status can be either no vaccine receipt or vaccine receipt from day 0 to 90 before onset of symptoms with a positive molecular test. (receipt of COVID-19 vaccine does not exclude a participant with < 8 days of symptoms and a positive test.

Study Population

Exclusion Criteria:

- Hospitalized or expected to be hospitalized within 24 hours of enrollment
- Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator would affect subject safety and/or compliance
- History of prior reactions to transfusion blood products
- Inability to complete therapy with the study product within 24 hours after enrollment
- Receiving any treatment drug for COVID-19 within 14 days prior to screening evaluation (monoclonal antibodies, off label, compassionate use or study trial-related). Steroid treatment at any time does not affect study eligibility.

Randomization and Intervention

- Subjects will be recruited for enrollment into two age groups (<65 vs ≥ 65 years of age) of approximately equal number.

- Subjects within each age group will be randomized using an interactive web response system (IWRS) in a 1:1 ratio to receive HCIP or control plasma.

Investigational Product

- HCIP, is anti-SARS-CoV-2 convalescent plasma. HCIP will be collected by apheresis from healthy adults identified as having recovered from COVID-19.
- Healthy adult donors with SARS-CoV-2 antibody titers ≥ 1:320 by an FDA approved test will donate plasma to be used in the trial.
- The antibody testing will be performed in a CLIA certified laboratory.
- Potential donors who meet these qualification standards will be referred to an FDA-registered blood center where donors will be evaluated according to current blood donation requirements; plasma will then be collected as fresh frozen plasma (FFP) or plasma frozen within 24 hours of phlebotomy (PF24).
- Plasma will be distributed to the participating study site's hospital for blinding
- Active arm will receive a minimum of 175 ml of HCIP.

Control Arm Plasma

- Control plasma will be provided to the participating site's hospital from FDA-registered blood centers as fresh frozen plasma (frozen within 8 hours) or plasma frozen within 24 hours (PF24) collected prior to 1/1/2020 and will not be tested for SARS-CoV-2 antibodies.

- Plasma collected after December 31, 2019 will be confirmed as SARS-CoV-2 seronegative.

- Control arm will receive a minimum of 175 ml of control plasma

Dose

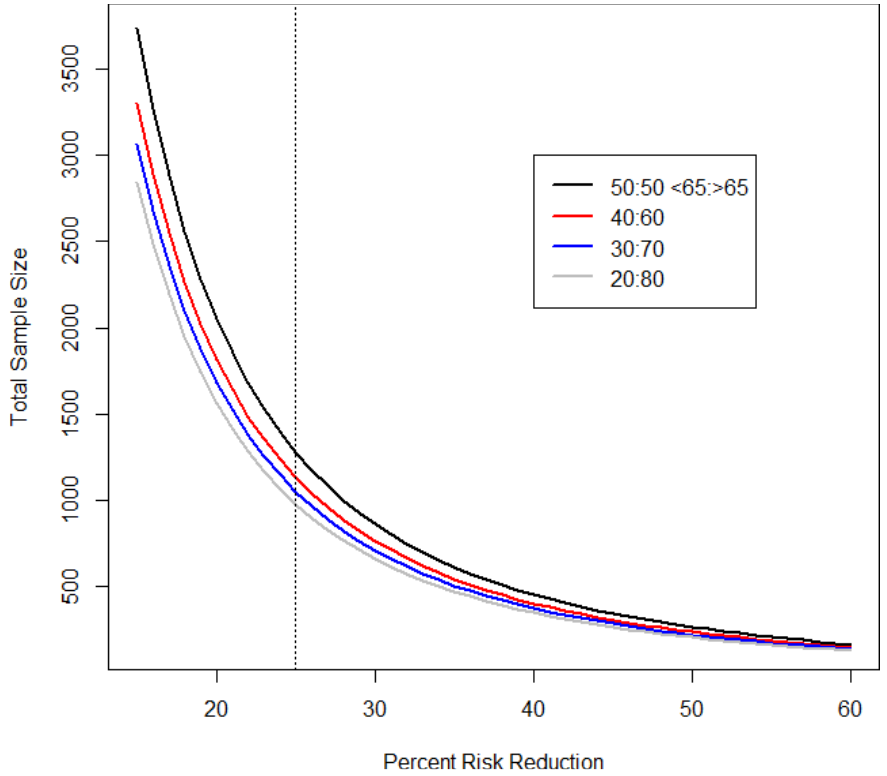
A plasma dose of 200 mLs is 7% of the total plasma volume for a 60kg individual with titer reduction to about 1:15 after dilution into the recipient.

- Also for men over age 18, the 25% to 75% range of weights is 70 to 95kg and 5% to 95% is 60 to 110 kg https://halls.md/average-weight-men/
- For women over age 18, the 25% to 75% range of weight is 60 to 80kg, and 5 to 95% is 50 to 100 kg https://halls.md/average-weight-women/
- Women will get slightly higher doses than men

Weight Kg	Blood Vol	Plasma Volume	320 Titer/ (Plasma Vol/.2L) =Final Plasma Titer
10	0.75	0.45	142.2
20	1.5	0.9	71.1
30	2.25	1.35	47.4
40	3	1.8	35.6
50	3.75	2.25	28.4
60	4.5	2.7	23.7
70	5.25	3.15	20.3
80	6	3.6	17.8
90	6.75	4.05	15.8
100	7.5	4.5	14.2
110	8.25	4.95	12.9
120	9	5.4	11.9

Sample sizes according to effect sizes, recruitment ratios of younger to older participants, and two levels of power

Power:	80% Power			90% Power		
Hospital rate Reduction	25%	30%	35%	25%	30%	35%
< 65: ≥ 65						
50:50	1280	864	615	1772	1196	852
40:60	1134	767	546	1571	1062	757
30:70	1052	712	507	1457	985	703



- Sample size by treatment effect for HCIP as a percent hospital rate reduction for four different ratios of recruitment of those <65 to ≥65 years of age
- Hospital rates are 20% in this figure

Outpatient Convalescent Plasma Site Needs

- CSSC 004 Outpatient COVID-19 positive
- Negative pressure (ideal) clinic with PPE and plasma infusion capabilities.
- Need temperature storage for plasma and area for COVID-19 informed consent and blood draws.

Screening

- Documented positive molecular test for presence of SARS-CoV-2 in fluid collected by saliva for antigen, oropharyngeal or nasopharyngeal swab within 6 days to allow for screening and transfusion by Day 8
- Experiencing any symptoms of COVID-19 including but not limited to fever (T> 100.5º F), cough, or other COVID associated symptoms like anosmia.
- Able and willing to comply with protocol requirements listed in the informed consent.
- SARS-CoV-2 vaccine status can be either no vaccine receipt or vaccine receipt from day 0 to 90 before onset of symptoms with a positive molecular test. (receipt of COVID-19 vaccine does not exclude a participant with < 8 days of symptoms and a positive test.

Meds and Prohibited Meds

Concomitant Medications

- Prescription medications
- Blood products

Prohibited Medications

- Before enrollment, any approved or investigational drug with established activity against SARS-CoV-2.

Schedule of Events

Phone days 1-10; clinic 14, 28, 90

Study period	Screen	Baseline	Trans-fusion								
Day (windows)	-1 to 0	0	0	1 (+1)	3 (-1 or +1)	5 (-1 or +1)	7 (-1 or +1)	10 (-1 or +1)	14 (-3 or +3)	28 (-3 or +3)	90 (-8 or +8)
Informed consent	x										
Demographic and Medical history	x										
COVID-19 symptom screen	x										
SARS-CoV-2 molecular test review of prior test report	x										
Pregnancy test[1]	x										
Blood typing ABO[2]	x										
Randomization		x									
Drug transfusion			x								
Study Procedures											
Vital signs	x	x	xxx[3]						x	x	x
Phone call				x	x	x	x	x			
Physical examination neuro, lung cardiac, abdominal, skin	x		x						x	x	x
Symptom screen (COVID-19 related)	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	
Adverse event monitoring		x	x	x	x	x	x	x	x	x	x
Temperature (self-administer)	x	x	x	x	x	x	x	x	x	x	
Pulse oximetry (self-administer)	x	x	x	x	x	x	x	x	x	x	
CBC, CRP and CMP	x								x	x	x
SARS-CoV-2 RNA detection test[4]	x								x	x	
SARS-CoV-2 antibody	x								x	x	x
Blood for future testing (plasma and serum)	x		X post transfusion						x	x	x

[1] Result of urine or serum pregnancy test for women of childbearing potential must be documented prior to transfusion

[2] Assessment of ABO type on file or determination of ABO type if not on file

[3] Vital sign testing: immediately prior to transfusion, 10-20 minutes after start of transfusion, at completion of transfusion and 30-60 minutes after the end of the transfusion

[4] Sites include nasopharyngeal or oropharyngeal

Study Procedures, Evaluations, and Schedules

Clinical Evaluations:

- The following clinical evaluations will be performed at the times indicated in Section 5.4 (Study Visits) and Appendix A (Schedule of Events). Any abnormalities identified during the evaluations listed below will be graded according to the EDC dictionary.

Medical history:

- Study staff will interview subjects to collect personal medical histories, including illnesses, surgeries, and medications; and demographic data, including name, sex, age, race, and ethnicity.

Physical Examination:

- Complete physical exam by study team member will include a skin examination (partially disrobed); height, weight, vital sign measurements (oral temperature, respiratory rate, heart rate, and blood pressure); examination of the head, eyes, ears, throat, lungs, heart, abdomen, extremities, joints, spine, and other sites as directed by symptoms by a study physician.

Vital Signs:

- Vital signs will be collected as indicated in Section 7. Vital sign evaluation will include measurement of temperature, pulse rate, respiratory rate, and blood pressure (systolic and diastolic).

Laboratory Evaluations

The following clinical laboratory tests will be completed at time points as specified in Section 5.4 (Study Visits) and Appendix A (Schedule of Events)

- Complete Blood Count: (approximately 5 ml blood): WBC, RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, Platelet Count, MPV and Differential (Absolute Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils)
- Serum Chemistry: (approximately 4 mL blood): Albumin, Alkaline Phosphatase, ALT, AST, Calcium, Bicarbonate, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen C-Reactive Protein
- Blood oxygen saturation: Percent oxygen saturation of blood as measured by finger pulse oximetry (where available)

Other Laboratory Evaluations to be processed centrally by JHU:

- Antibody levels: Serum SARS COV-2 antibody by ELISA, neutralization test or other FDA-approved test
- SARS-CoV-2 levels: Upper respiratory tract fluid (nasopharyngeal or oropharyngeal swab) for presence and level of SARS-CoV-2 RNA by RT-PCR

Study Visits

Day -1 or 0 Visit (in person in an appropriate location for patients with positive COVID-19 per local policy)

- Informed consent (obtained before performing study related activities preferably by remote consent)
- Screening (must be completed before randomization)
- Baseline Evaluation (at screening)

Screening

- Demographics (Age, sex, ethnicity, race)
- Medical history dates of first and last exposure to COVID-19 source patient (if known), acute and chronic medical condition, medications, allergies. Any medical condition arising after consent should be recorded as AE. Date and source institution of positive result of previous SARS-CoV-2 positive test)
- COVID-19 symptom screen (dates of onset and resolution of fever, cough, shortness of breath, diarrhea, anosmia); date and level of highest recorded temperature
- Vital signs (temperature, degrees F; pulse, beats per minutes; respirations per minute; BP, systolic and diastolic, mm Hg)
- Physical examination (neurological, respiratory, cardiac, abdomen, skin)
- Collection of nasopharyngeal or oropharyngeal swab for COVID-19 testing (RNA detection test) prior to transfusion (not for clinical testing)
- Collection of blood for:
    - o ABO typing, unless documentation of ABO type from medical record
    - o SARS-CoV-2 antibody (Stored for later research analysis)
    - o Comprehensive metabolic panel (CMP) and CRP- CLIA
    - o Complete blood count (CBC) CLIA
    - o Stored plasma and serum specimen for future studies
- Urine or serum pregnancy test for females of childbearing potential. Results from laboratory tests obtained up to 7 days before enrollment may be used for the pregnancy test. Results must be received and documented on the case report form prior to transfusion.
- Determination of eligibility as per inclusion/exclusion criteria
- Provision of daily diary form for subject to complete twice daily (preferably morning and evening) through Day 14, including cough (frequency and intensity of episodes), shortness of breath (frequency and intensity of episodes), anosmia (frequency and intensity of episodes), other symptoms (frequency, intensity, time of onset), oral temperature, and blood oxygen saturation.
- Provision of oral digital thermometer and pulse oximeter (where available) and training on use. Staff-observed and subject-acquired data should be entered on CRF as the temperature, pulse and blood oxygen saturation.

Study Visit Day 0

Treatment Visit

- Randomization of eligible subject in IWRS
- COVID-19 symptom screen (fevers, cough, shortness of breath)
- Assessment of clinical status (composite outcome of disease severity)
- Collection and review of AE, New medical conditions, concomitant medication, AE evaluation
- Physical examination
- Collection of nasopharyngeal or oropharyngeal swab for COVID-19 testing if not obtained on Day -1 (RNA detection test) prior to transfusion (not for clinical testing)
- Collection of blood if not obtained on day -1 for
  - SARS-CoV-2 antibody (Stored for later research analysis)
  - Comprehensive metabolic panel (CMP) and CRP- CLIA
  - Complete blood count (CBC) CLIA
  - Stored plasma and serum specimen for future studies
- Study Plasma Administration: A single unit of plasma will be transfused. Time at start and end of transfusion will be recorded and Vital signs will be measured immediately prior to transfusion, 10-20 minutes after start of transfusion, at completion of transfusion and 30-60 minutes after the end of the transfusion.
- Draw plasma and serum 15 to 30 minutes after transfusion for research antibody levels for peak antibody levels

Study Plasma Administration

- Plasma will be administered within 24 hours of enrollment.
- Transfusions will be performed by qualified/skilled personnel in settings equipped to handle potential complications of transfusion. We have planned to administer transfusion of convalescent plasma in a hospital or ambulatory clinic setting.
- Transfusion rate ≤500 mL/hour
- Medicines to minimize mild transfusion reactions during occurrence (e.g., acetaminophen, diphenhydramine) may be given at the discretion of the investigator.
- If an AE develops during transfusion, the transfusion may be slowed or stopped as per investigator's decision.
- Management of transfusion-associated AE will follow AABB guidelines; anything more than a simple allergic transfusion reaction, the transfusion will be discontinued and investigated appropriately (i.e., per standard practice guidelines).

Rules for Halting Plasma Transfusion

Transfusion of plasma will be halted, and will not be restarted, if any of the following manifestations of anaphylaxis develop:

- Skin or mucous membrane manifestations: hives, pruritus, flushing, swollen lips, tongue or uvula
- Respiratory compromise: dyspnea, wheezing, stridor, hypoxemia
- A decrease in systolic blood pressure to < 90 mmHg or >30% decrease from baseline or a diastolic drop of >30% from baseline.
- Tachycardia with an increase in resting heart rate to > 130bpm; or bradycardia <40 that is associated with dizziness, nausea or feeling faint.
- Syncope
- Confusion
- Any other symptom or sign which in the good clinical judgment of the study clinician or supervising physician warrants halting the transfusion. For example, the rapid onset of gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and cramps, for instance, may be manifestations of anaphylaxis and may warrant an immediate halt prior to meeting full SAE criteria

Phone Calls

Day 1 (Phone Call) window of +1 day

- Phone call to recipient for review of subject diary, symptom screen and AE assessment.

Day 3 (Phone Call) window of -1 or +1 day

- Phone call to recipient for review of subject diary, symptom screen and AE assessment.

Day 5 (Phone Call) window of -1 or +1 day

- Phone call to recipient for review of subject diary, symptom screen and AE assessment.

Day 7 (Phone Call) window of -1 or +1 day

- Phone call to recipient for review of subject diary, symptom screen and AE assessment.

Day 10 (Phone Call) window of -1 or +1 day

- Phone call to recipient for review of subject diary, symptom screen and AE assessment.

Day 14 Study Visit

Day 14 window of -3 or +3 days (in person in an appropriate location for patients with positive COVID-19 per local policy)

- Vital signs
- Blood oxygen saturation
- Review of subject diary, symptom screen and AE assessment
- Physical examination
- Blood specimens for CBC, CRP, CMP
- SARS-CoV-2 antibody, plasma and serum specimens for future studies (Stored for later research analysis)
- Nasopharyngeal or oropharyngeal swab for SARS-CoV-2 testing (RNA detection test) (not for clinical testing)

Day 28 Study Visit

Day 28 (Clinic or Home) window of -3 or +3 days

- Vital signs
- Blood oxygen saturation
- AE assessment
- Physical examination
- Blood specimens for CBC, CRP & CMP CLIA
- SARS-CoV-2 antibody, plasma and serum specimens for future studies (Stored for later research analysis)
- Nasopharyngeal or oropharyngeal swab for SARS-CoV-2 testing (RNA detection test) (not for clinical testing)

Day 90 Study Visit

Day 90 (Clinic or Home) window of -8 or +8 days

- Interim medical history and AE assessment
- Vital signs
- Physical examination (if indicated)
- Blood specimens for CBC, CRP&CMP- CLIA
- SARS-CoV-2 antibody, plasma and serum specimens for future studies (Stored for later research analysis)

Study Monitoring

As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. Monitors will verify that:

- There is documentation of the informed consent process and signed informed consent documents for each subject
- There is compliance with recording requirements for data points
- All SAEs are reported as required
- Individual subjects' study records and source documents align
- Investigators are in compliance with the protocol.
- Regulatory requirements as per Office for Human Research Protections-OHRP), FDA, and applicable guidelines (ICH-GCP) are being followed

Infection Control

- All local sites must supply sufficient personal protective equipment (PPE) for their study personnel and the study participants. Specific types of required PPE and level of protection will be determined by the local HEIC or equivalent office.
- All local sites must inform the CCC of any local restrictions or requirements related to COVID-19 research that may impact the health and safety of the participant and conduct of the study. Any limitations or requirements will be evaluated for study impact by the CCC on a case-by-case basis.

Prior to initiation, study sites will provide documentation of:

- Local HEIC approval or equivalent
- Sufficient access to personal protective equipment (PPE) and other resources to carry out the protocol to keep both the subjects and the study personnel safe
- Policies about local restrictions and requirements on COVID-19 related research

Thank you for completing this training module!