Title: Passive Immunity Trial for Our Nation

National Clinical Trial (NCT) Identified Number: NCT04362176

Protocol: Version 6.0 **Date:** January 28, 2021

Title: Passive Immunity Trial for Our Nation

Acronym: PassItOn

Protocol Number: 200738

National Clinical Trial (NCT) Identified Number: NCT04362176

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Coordinating Center: The Vanderbilt Coordinating Center

Funders: Dolly Parton COVID-19 Research Fund and the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH)

Protocol: Version 6.0

Date: January 28, 2021

Summary of Changes

Protocol version 5.0 dated September 15, 2020 to Protocol version 6.0 dated January 28, 2021

Affected Section(s)	Summary of Revisions Made	Rationale
General	Revise Protocol version to 6.0 dated January 28, 2021	Administrative Change
Page 1 Title Page	Changed Protocol Version 5.0 dated September 15, 2020 to January 28, 2021.	Administrative Change
Pages 1-21 Summary of Changes		
Page 22 Protocol Signature Page	Changed Protocol Version 5.0 dated September 15, 2020 to January 28, 2021	Administrative Change
Pages 23-25 Table of Contents	Revised Table of Contents	Revised Table of Contents to reflect protocol additions and changes
Page 26 Section 1. Abbreviations	New Abbreviations " SOFA Sequential organ failure assessment" "sIRB single Institutional Review Board" "TRALI Transfusion associated acute lung injury" "TACO Transfusion associated circulatory overload" "VCC Vanderbilt Coordinating Center" "VUMC Vanderbilt University Medical Center"	To add missing abbreviations

Pages 27-28 Study Summary		
Study Design	Add "comparing outcomes of patients randomized to COVID-19 convalescent plasma versus placebo."	To further define the study design
Intervention group treatment	Remove "pathogen reduced"	To ensure accuracy of the plasma description
Inclusion Criteria	Remove "of age"	Grammar correction
Exclusion Criteria	Previous Number 5 Text "Receipt of COVID-19 convalescent plasma or pooled immunoglobulin in the past 30 days Current Number 5. Text "Receipt of any SARS-CoV-2 passive immunity therapy, such as convalescent plasma, monoclonal antibodies, or pooled immunoglobulin, in the past 30 days." New Number 9. "Previous laboratory-confirmed SARS-CoV-2 infection before the current illness" New Number 11 "Prior receipt of SARS-CoV-2 vaccine"	To ensure patient has not previously received any SARS-CoV-2 passive immunity therapy within 30 days of enrollment. To ensure patient has not previously had SARS-CoV-2 infection before the current illness. To ensure patient has not previously received the SARS-CoV-2 vaccine
Page 29 Section 3.1 Background	Sentence 5 add the word "suggested" Change "effectiveness" to "efficacy"	Grammar corrections
Page 30 Section 3.1.4 Rationale for a randomized trial among hospitalized patients	Change "effectiveness" to "efficacy"	Grammar correction
Page 30 Section 3.3 Study Design	Previous Text "Plasma will be collected and distributed to sites through Vanderbilt University Medical Center's blood donation center partner. Anti-SARS-CoV-2 antibody quantification assays will be completed on donor plasma at Vanderbilt University Medical Center (VUMC) prior to plasma distribution." Current Text "Plasma will be collected and distributed to sites through blood donation groups partnering with VUMC's blood donation center partner. Anti-SARS-CoV-2 antibody quantification assays will be completed on donor plasma at Vanderbilt University Medical Center (VUMC) prior to plasma distribution."	To allow for multiple blood donation centers
Page 31 Section 4.1 Inclusion Criteria	Remove "of age"	Grammar correction
Page 31 Section 4.2 Exclusion Criteria	Previous Number 5 Text "Receipt of COVID-19 convalescent plasma or pooled immunoglobulin in the past 30 days Current Number 5. Text "Receipt of any SARS-CoV-2 passive immunity therapy, such as convalescent plasma, monoclonal antibodies, or pooled immunoglobulin, in the past 30 days."	To ensure patient has not previously received any SARS-CoV-2 passive immunity therapy within 30 days of enrollment. To ensure patient has not previously

	New Number 9. "Previous laboratory-confirmed SARS-CoV-2 infection before the current illness" New Number 11 "Prior receipt of SARS-CoV-2 vaccine"	had SARS-CoV-2 infection before the current illness. To ensure patient has not previously received the SARS-CoV-2 vaccine
Page 31 Section 4.5 Assessment of Eligibility and Exclusion Tracking	Remove "For all excluded patients, including refusal by the treating clinician or patient/surrogate, a small number of de-identified variables will be collected including month and year the patient met screening criteria, age, sex, ethnicity, patient location, and reason(s) patient was excluded. For the safety of research personnel and conservation of personal protective equipment, these encounters may occur via telephone or videophone."	Administrative change
Page 32 Section 4.6 Process of Obtaining Informed Consent	Previous Text "Suggestions for the three approaches are outlined here." Current Text "Suggestions for the two approaches are outlined here."	Typographical correction
Page 34 Section 4.7 Randomization and Blinding	Remove "For the duration of the study, the only individuals that are knowledgeable about the treatment assignment are the VCC Data Specialist and designated Clinical Research Associate, the study statistician (unblinded), and the study personnel administering the plasma or placebo product." Previous Text "Clinical personnel who administer the study product (convalescent plasma vs placebo) will not be blinded. Current Text "Clinical personnel who administer the study product (convalescent plasma vs placebo) such as the bedside nurse, will not be blinded."	To align with the blinding SOP
Page 34 Section 4.8 Minorities and Women	Previous Text "The demographics of the patients recruited will mirror those of patients admitted to the hospital with COVID-19. Current Text "The demographics of the patients approached for enrollment will mirror those of patients admitted to the hospital with COVID-19.	To clarify recruitment
Pages 34-35 Section 5.1 Treatment of Study Participants	Previous Text "Timing of study procedures is based on the time of randomization, which is defined as "Time 0". Study Day 1 is defined as the day of randomization. Current Text "Timing of study procedures is based on the time of initiation of the study product infusion, which is defined as "Time 0". Study Day 1 is defined as the calendar day of study product infusion." New Text "For patients who are randomized but do not receive study product, time of randomization will be considered "Time 0" and Study 1 will be the calendar day of randomization. For most patients, randomization and study product infusion will occur on the same day; in the event the study product is infused on a different calendar day than randomization, Study Day 1 is defined as the day on which study product is infused. "Baseline status" represents the patient's status immediately prior to study infusion, and	To clarify Time 0 and Study 1 in relation to randomization.

	baseline variables should represent information available before and as close as possible to initiation of the study infusion." Previous Text "Participants randomized to active treatment will receive 1 unit of convalescent plasma, which has a volume of 200-399 ml. Current Text "Participants randomized to active treatment will receive 1 unit of convalescent plasma, which has a volume of 200-399 ml infused intravenously." Previous Text "The study product (convalescent plasma vs placebo) will be infused intravenously over 1-3 hours, with the specific rate of infusion determined by the site investigator based on an assessment of how quickly the participant can safely receive the intravascular volume load." Current Text "The duration of infusion is recommended to be between approximately 1 hour and 3 hours (at the discretion of the provider), with the specific rate of infusion determined by the site investigator based on an assessment of how quickly the participant can safely receive the intravascular volume load." Previous Text "Study personnel will monitor patients for adverse reactions to the transfusion while the patient is in the hospital for 72 hours following the infusion; that is transfusion adverse reaction monitoring will be continued until Study Day 3. For patients who are discharged prior to Day 3, study personnel will obtain safety outcomes from the patient or surrogate via telephone follow-up scheduled at Day 8." Current Text "Study personnel will monitor patients for adverse reactions to the transfusion while the patient is in the hospital for 72 hours following the infusion; that is transfusion adverse reaction monitoring will be continued until Study Day 4. For patients who are discharged prior to Day 4, study personnel will obtain safety outcomes from the patient or surrogate via telephone follow-up scheduled at Day 8."	To clarify that convalescent plasma will be infused intravenously To clarify that the rate of infusion is based on the investigator's assessment Typographical correction
Page 35 Section 5.1 Treatment of Study Participants under Screening	Previous Text "Screening (pre-randomization) 1. Screening (must be completed before randomization) 2. Subject informed consent (obtained before performing study related activities) 3. Baseline Evaluation (at screening) (much of the information will be obtained from the medical record) 4. Demographics (Age, sex, ethnicity, race) 5. Medical history (acute and chronic medical condition, medications, and allergies). Any medical condition arising after enrollment should be recorded as AE 6. COVID-19 symptom screen (fevers, cough, shortness of breath), onset of symptoms, source of exposure 7. Vital signs (blood pressure, pulse, respirations, and temperature)	To clarify Screening, consent, and baseline

	8. Determination of eligibility as per inclusion/exclusion criteria. 9. SARS-CoV-2 RT-PCR for eligibility (can be done up to 14 days prior to randomization) 10. ABO type and screen (to be done at a timepoint during current hospital admission) Current Text "Screening, consent, and baseline (pre-randomization) 1. Confirm inclusion and exclusion criteria, including identifying a positive SARS-CoV-2 test 2. Subject informed consent (obtained before performing study related activities) 3. Randomization of eligible subject 4. Demographics 5. Medical history 6. COVID-19 symptoms 7. Record vital signs 8. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale) 9. Record new medical conditions 10. Record concomitant medication 11. Adverse Event (AE) evaluation 12. Collection of data for later SOFA score calculation 13. Prior to study infusion, collect, process and store blood for SARS-CoV-2 antibody testing, which will be done at the central study laboratory. 14. C-reactive protein (CRP) measurement (record the results of a clinically obtained CRP performed within 24 hours prior to study product infusion; if a CRP was not obtained clinically, perform a CRP measurement by study protocol in the local clinical laboratory) 15. Complete Blood Count (CBC) and Complete Metabolic Panel (CMP) measurement (record the results of a clinically obtained CBC and CMP performed within 24 hours prior to study product infusion; if a CBC and/or CMP was not obtained clinically, perform them on study protocol in the local clinical laboratory)	
Page 35 Section 5.1 Treatment of Study Participants under Day 1	Previous Text "Day 1 1. Randomization of eligible subjects 2. Study Product Administration:1unit of convalescent plasma or Lactated Ringer's solution with multivitamins will be transfused. Study infusion will be monitored per site institutional transfusion policy. 3. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale) 4. New medical conditions, concomitant medication, Adverse Event (AE) evaluation 5. Blood for COVID-19 Titer testing, must be collect prior to study infusion 6. CBC, CMP, if not performed as part of standard of care 7. SOFA Score 8. C-reactive protein (CRP) measurement"	To clarify study Day 1

	Current Text "Day 1 (Day of Transfusion) 1. Study Product Administration: 1 unit of convalescent plasma or Lactated Ringer's solution with multivitamins will be transfused. Study infusion will be monitored per site institutional transfusion policy. 2. Adverse Event (AE) evaluation"	
Page 35 Section 5.1 Treatment of Study Participants under Day 2	New Text "Day 2 (first calendar day after transfusion) 1. Record vital signs. 2. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale) 3. Record new medical conditions 4. AE evaluation 5. Collection of data for later SOFA score calculation 6. CBC and CMP measurement (record the results of a clinically obtained CBC and CMP; if a CBC and/or CMP was not obtained clinically, perform them on study protocol in the local clinical laboratory if patient remains hospitalized) 7. If patient remains hospitalized, collect, process and store blood for SARS-CoV-2 antibody testing, which will be done at the central study laboratory."	To clarify study assessments and procedures for Day 2
Page 35 Section 5.1 Treatment of Study Participants under Days 3-8	Previous Text "Daily on Day 2 thru 8 (or until hospital discharge if discharged before Day 8) 1. Vital signs 2. COVID-19 symptom screen (fevers, cough, shortness of breath) 3. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale) 4. New medical conditions, AE evaluation (Days 2 and 3 only) 5. CBC, CMP, if not performed as part of standard of care (Days 2, 8 only) 6. SOFA score (Day 2 and 8 only) 7. Blood for COVID-19 Titer testing (Day 2 only, if still hospitalized)" Current Text "Day 3-8 (Daily assessments only while patient hospitalized) 1. Record vital signs 2. Record new medical conditions 3. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale 4. AE evaluation (through Day 4 only) 5. Record the results of a clinically obtained CBC and CMP (Day 8 only and only if clinically available)"	To clarify study assessments and procedures for Days 3-8
Page 36 Section 5.1 Treatment of Study Participants under Days 15 and 29	Previous Text "Day 15 and 29: 1. COVID-19 symptom screen (fevers, cough, shortness of breath) 2. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale 3. New medical conditions Current Text "Day 8, 15, and 29 (by phone if patient discharged before assessment day): 1. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale)	To clarify study assessments and procedures for Days 15 and 29

	2. New medical conditions 3. Vital status check"	
Page 36 Section 5.2 Convalescent Plasma Group	Previous Text "Patients randomized to the active treatment arm will receive a single dose of 1 unit (200-399 ml) of convalescent plasma infused intravenously over 1-3 hours." Current Text "Patients randomized to the active treatment arm will receive a single dose of 1 unit (200-399 ml) of convalescent plasma infused intravenously per site institutional policy governing blood product transfusions." New Text "Plasma that is believed to be neutralizing will be used in this trial and will be prioritized based on neutralizing capabilities."	To clarify that convalescent plasma is infused per institutional policy and that it is infused intravenously To clarify prioritization of plasma
Page 36 Section 5.3 Control Group	Remove of 1-3 hours	Administrative change
Page 36 Section 5.4 Co-interventions	Move Text from Last to 1st paragraph "Use of open label convalescent plasma in the first 15 days of the study is strongly discouraged and will be tracked as protocol non-compliance. Remove "("rescue therapy")	Administrative changes
Page 36 Section 5.5 On-Study Monitoring	Previous Text "At any point, if the clinical team has concern about a transfusion reaction, they will report that concern to the blood bank or as per institutional policy." Current Text "At any point, if a clinical team member has a concern about a potential transfusion reaction, he/she will report that concern to the blood bank or as per institutional policy."	Administrative changes
Page 36 Section 5.6 Criteria for Stopping Study Infusion	Previous Text "Infusion of study treatment will be halted if any of the following manifestations of transfusion reaction develop fever, rash, diffuse itching, tachycardia (increase in heart rate by greater than 20 beats per minute)." Current Text "Infusion of study treatment will be halted if any of the following manifestations of transfusion reaction develop fever, rash, diffuse itching, acute increase in heart rate by greater than 20 beats per minute." Previous Text "If there is significant concern that the symptoms, beyond rash or itching, are secondary to transfusion alone, then transfusion will not be re-started, and the patient will be evaluated for transfusion reaction." Current Text "If there is significant concern that the symptoms, beyond rash or itching, are secondary to the infusion, then infusion will not be re-started, and the patient will be evaluated for transfusion reaction." Previous Text "In addition, the infusion will be stopped and not restarted if the patient develops any of the following signs or	Administrative changes

	symptoms of anaphylaxis: hives; pruritus; flushing; swollen lips, tongue or uvula; worsening of shortness of breath wheezing; stridor; hypoxemia; a decrease in systolic blood pressure to less than 90 mmHg or greater than 30% decrease from baseline or a diastolic drop of greater than 30% from baseline; bradycardia less than 40 beats per minute that is associated with dizziness, nausea or feeling faint; any other symptom or sign which in the good clinical judgment of the study clinician or supervising physician warrants halting the infusion. 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 severe adverse event (SAE) criteria. Current Text "In addition, the infusion will be stopped and not restarted if the patient develops any of the following signs or symptoms of anaphylaxis: hives; pruritus; flushing; swollen lips, tongue or uvula; worsening of shortness of breath; wheezing; stridor; hypoxemia; a decrease in systolic blood pressure to less than 90 mmHg or greater than 30% decrease from baseline or a diastolic drop of greater than 30% from baseline; bradycardia less than 40 beats per minute that is associated with dizziness, nausea or feeling faint; any other symptom or sign which in the good clinical judgment of the study clinician or supervising provider warrants halting the infusion. For example, the rapid onset of gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and cramps, may be manifestations of anaphylaxis and may warrant an immediate halt prior to meeting full severe adverse event (SAE) criteria." Previous Text "Any suspected reactions related to study product that result in stopping of study infusion must be reported as an adverse event." Current Text "Any suspected reactions related to study product that result in stopping of study transfusion must be reported as an adverse event."	
Page 37 Section 5.7 Plan for Plasma Shortages	Previous Text "In the event of a shortage of study treatment at a participating trial site, site personnel should contact the Vanderbilt Coordinating Center (VCC) Clinical Trials Operations Manager regarding this issue. Participants will only be randomized when the local site has convalescent plasma and placebo available." Current Text "In the event of a shortage of convalescent plasma or multivitamin solution for use in the trial at a participating trial site, site personnel should contact the Vanderbilt Coordinating Center (VCC) Clinical Trials Operations Manager. Participants will only be randomized when convalescent plasma and the placebo solution are available.	Administrative changes
Page 37 Section 6. OUTCOMES	New Text "Definitions for each outcome are detailed in the trial's statistical analysis plan (SAP)."	To clarify location of outcomes definitions

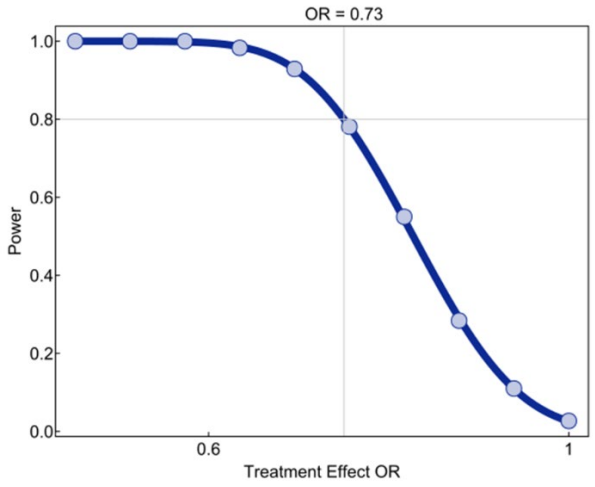
Page 38 Section 6.4 Rationale for Primary Outcome	Previous Text "Since the majority of morbidity from COVID-19 relates to hypoxemia, the fact that this outcome is tied to degree of hypoxemic respiratory failure increases its face validity and relevance. " Current Text "Since the majority of morbidity from COVID-19 relates to hypoxemia, the fact that COVID-19 Ordinal Scale is tied to degree of hypoxemic respiratory failure increases its face validity and relevance. "	Administrative change
Page 38 Section 7. DATA AND BIOLOGICAL SPECIMEN COLLECTION	Previous Text "7. DATA Current Text "7. DATA AND BIOLOGICAL SPECIMEN COLLECTION Previous Text "We will emphasize data that can be collected from the electronic health record, radiographs obtained as part of routine clinical care, and assessments that can be completed over the telephone as needed." Current Text "We will emphasize data that can be collected from the electronic health record, and assessments that can be completed over the telephone." Previous Text "Biological specimens will be collected as part of this trial in the form of plasma. Specimens will be shipped to VUMC for future analysis." Current Text "Plasma samples will be collected as part of this trial at baseline (prior to study infusion) and on study Day 2 (approximately 24 hours after the study infusion. Specimens will be shipped to VUMC for future analysis, which will include quantitative anti SARS-CoV-2 antibody measurements."	Administrative changes
Page 38 Section 7.1 Baseline Variable Collection	Remove "chest imaging results" Previous Text "Highest fraction of inspired oxygen, lowest arterial oxygen saturation, highest respiratory rate, lowest systolic blood pressure, highest heart rate in the hour prior to enrollment" Current Text "Vital signs"	Administrative changes
Pages 38-39 Section 7.2 Assessments Between Hospital Presentation and Hospital Discharge	Remove "and Day 8", "S/F ratio Day 3", "chloroquine", "and time", Change "Outcomes" to "assessments" Remove "cardiomyopathy" Previous Text "Definitions for each outcome will be provided in trial standard operating procedures." Current Text "Definitions for each variable are detailed in the trials statistical analysis plan and are described for enrolling personnel in the trial manual of operations and/or electronic data capture system."	Administrative changes

Page 39 Section 7.31 Acute Care Follow-up	Previous Text "Non-laboratory safety outcomes after hospital discharge" Current Text "Selected non-laboratory safety outcomes after hospital discharge" New Text "The follow-up period for vital status (dead versus alive) is through Study Day 29. For most patients, we will establish vital status during the Study Day 29 visit (either in person for those who remain in the hospital or by phone for those who have been discharged). For patients who are not reached for the Study Day 29 visit, we will seek to establish vital status via phone calls, emails, and searches through medical records, obituaries, social media, and other sources."	Administrative changes To clarify the follow-up period for vital status
Page 40 Section 8. STATISTICAL CONSIDERATIONS	Remove "Note: We expect that given the circumstances of this trial during a rapidly evolving pandemic, the DSMB will need maximum latitude in modifying the trial if necessary. Alterations may include adding patients, adding arms to the trial, declining to stop for futility, or stopping earlier to make the results public.	Administrative changes
Page 40 Section 8.1 Summary	Previous Text "The key features of the trial are summarized in the following table. As the number of sites is still unsettled, some values are approximate. This document is a summary of the clinical trial and analysis plan which is described in greater detail in the trial simulation report (link), which will be updated to reflect the trial of 1000 subjects." Current Text "The key features of the trial are summarized in the following table (Table 1). Add header to the table "**Table 1.** Key Statistical features of the trial" Remove "Design goals 1. Frequent evaluation of efficacy and inefficacy in order to minimize the number of subjects so that results can be disseminated quickly. 2. Simple evaluation of efficacy, inefficacy, and futility. 3. Maintain Type I (false-positive) and Type II (false-negative) error rates at prespecified levels." Add " Sample Size| 1000 subjects" Add "Inference approach The primary point of inference will be the likelihood ratio and corresponding support interval for the covariate adjusted treatment effect odds ratio. Likelihood ratios more extreme than 7 (or 1/7) will be interpreted as sufficient evidence to assert efficacy. The odds ratio will be estimated with a cumulative probability ordinal regression model with logit link."	Revised statistical plan

	Remove "Analysis method "The covariate adjusted treatment effect odds ratio will be estimated with a cumulative probability ordinal regression model with logit link." Current Planned Interim Analyses Text "There are 3 interim analyses for safety endpoints, and a final analysis of efficacy endpoints. The safety interim analyses will occur after 15 days of follow-up is completed for the first 150, 450, and 750 patients. The final analysis will occur after follow-up is complete for all enrolled subjects" Previous Planned Interim Analyses Text "The first interim analysis will occur after the follow-up is recorded for 150 subjects. Subsequent analyses will occur regularly, every 2 weeks or as directed by the DSMB." Previous Planned Reporting Triggers" 1. Efficacy 2. Inefficacy 3. Futility 4. Completion of the study at the maximum sample size Current Planned Reporting Triggers "1. There are no planned reporting triggers." New Text "Planned stopping rules | At each interim analysis, the difference in mortality risk will be calculated, and the one-sided hypothesis that mortality risk in the intervention arm exceeds the mortality risk in placebo will be compared to the null hypothesis of equal mortality risk. The trial will be stopped if the likelihood ratio exceeds the threshold listed below. " "Type I error rate The combination of a 1/7 likelihood ratio threshold and the safety stopping rule result in a simulated type I error rate of 0.02" "Power The minimal detectable effect at 80% power is 0.73"	
Pages 40-41 Sections 8.2 Analyses plan 8.2.1. Model fit 8.2.2 Missing data 8.3 Triggers for DSMB review	Sections removed or renumbered	No longer applicable to the current statistical plan
Page 40 New Section 8.2	New Text	Revised statistical plan

Planned interim analyses for mortality	"At each interim analysis, the difference in mortality risk will be calculated, and the one-sided hypothesis that mortality risk in the intervention arm exceeds the mortality risk in placebo will be compared to the null hypothesis of equal mortality risk. The trial will be stopped if the likelihood ratio exceeds the threshold listed below. Generally, the level of evidence required to stop a study for safety concerns is less than the level of evidence required to assert efficacy of the intervention. Likewise, there is not the same level of concern for type 1 error control for safety outcomes as there is for efficacy endpoints; however, the threshold values were selected so that the trial-wise risk of ending early for mortality is 0.1 if the treatment is equivalent to placebo. To provide context for the LR thresholds listed in the table below, we have also provided α_N, the p-value threshold which approximates the LR threshold if the p-value were calculated from a likelihood ratio test.	
Page 41 Section 8.3.1 Model fit	Section 8.2.1 renumbered as Section 8.3.1	Revised statistical plan
Page 41 Section 8.3.2 Missing data	Section 8.2. renumbered as Section 8.3.2 with the changes listed below: Previous Text "We anticipate rare or no missingness for data points during the patients in-hospital course." Current Text "We anticipate rare or no missingness for data points during a patients in-hospital course." Remove "Missing data for a covariate used in the primary model will be imputed using multiple imputation methods." New Text "Missing data for a covariate used in the primary model will be multiply imputed using predictive mean matching if number of observations missing covariate values exceeds 5 percent. If fewer than 5% of observations have missing covariate values, missing values will be imputed with a single conditional mean."	Revised statistical plan
Page 41 Section 8.3.3 Assertion of efficacy	New Text "Likelihood ratios more extreme than 7 (or 1/7) will be interpreted as sufficient evidence to assert efficacy."	Revised statistical plan
Page 41-42 Section 8.4 Trial characteristics	Remove all text and tables	Revised statistical plan
Page 42 New Section 8.4.1 Inference	New Text "Decision making using the likelihood approach in a clinical trial centers on three quantities: the point estimate of the treatment effect (an odds ratio, for example), a corresponding interval estimate, and a single number summary that measures the relative evidence for one hypothesis compared to another. These three quantities are not unlike the point estimate, 95% confidence	Revised statistical plan

	interval, and p-value that are generated in frequentist analyses. In fact, the point estimates are often identical, and the interval estimates are often similar. The LR and the p-value, however, are distinct measures of evidence. The LR is a ratio: the density of the trial data if the treatment works (alternative hypothesis) divided by the density of the trial data if the treatment does not work (null hypothesis). A LR of 1 indicates the data are neutral; neither hypothesis is supported over the other. Large LR are evidence in support of the treatment working while small LR are evidence in support of the null. In short, the LR level of evidence is based on comparing the likelihood of the data under two competing models – the alternative hypothesis and the null hypothesis. This is different to using a p-value as the level of evidence because the p-value essentially compares what actually happened in the trial to what might have happened in the trial if it were repeated infinitely and the null hypothesis were true. Because it is impossible to compute what might have happened if the rules for decision making are not fully predefined, using a p-value for decision making is not well suited for a trial like this one in which DSMB requests and pandemic circumstances prompt design changes. The LR approach on the other hand, is based on a relative likelihood of observed outcomes under two competing models at the same point in time making it especially appropriate for settings where pre-specification of the timing or frequency of sequential analyses is not possible. Even though the LR (instead of the p-value) is the quantity of primary interest for decision making, the analysis plan does control type 1 error. Sequential likelihood ratio tests of two prespecified hypotheses have a natural bound on type 1 error of 1/k where k is the threshold for asserting efficacy. In this study, the combination of the stopping rule for mortality and the large number of subjects accrued before the first analysis for efficacy result in a bound-on type 1 error well within traditional levels of 0.05.”	
Pages 42-43 New Section 8.4.2 Type I error rate and power	New Text “ The long-run operating characteristics were estimated by generating study data to reflect different treatment effect sizes. The simulated study dataset was evaluated according to the stopping rule and analysis plan described above. For each effect size, 1000 simulated datasets were analyzed. A Type I error occurred if the study asserted efficacy when in fact there was no treatment effect. The Type I error rate was calculated as the proportion of null-effect studies in which the error occurred. A Type II error occurred if the study failed to assert efficacy when there was a beneficial treatment effect. For each treatment effect, power was calculated as the proportion of studies that did not result in a Type II error. The study endpoint for control subjects was simulated to match the outcomes in the control arm of a recent clinical trial.[3] In each simulation setting, the distribution for the treatment arm was calculated by adjusting the control arm outcome distribution	Revised statistical plan

	according to the setting-specific treatment effect size and data generation model. The figure below is the estimated power curve for the trial design (Figure 1). **Figure 1.** Power of the trial assuming enrollment of 1000 participants.  	
Page 43 New Section 8.5 Analysis plan for additional analyses of the primary endpoint"	New Section Header	Revised statistical plan
Page 43 New Section 8.5.1 and Section 8.5.2	New Text "8.5.1 Quantification of effect of donor plasma characteristics on treatment efficacy The impact of the antibody levels and neutralization activity of the donor plasma on the primary endpoint will be estimated with ordinal regression models. The models will include the same covariates listed for the primary endpoint analysis, except the treatment assignment variable will be replaced with either (a) a measure of donor plasma antibody level or (b) a measure of donor plasma neutralization. Both variables will be included in models as a restricted cubic spline in order to capture potential non-linear associations with the outcome. 8.5.2 Effect modification analyses of the primary outcome We will examine whether pre-specified baseline variables modified the effect of treatment group on the primary outcome using tests of statistical interaction in a proportional odds regression model. Independent variables will include study group assignment, the potential effect modifier of interest, the interaction between the two, and the same pre-specified covariates used in the primary model. Presence of effect modification will be assessed by reference to the LR for the interaction term, with values greater than 6 considered to suggest a potential interaction and values greater than 7 considered to confirm an interaction.	Revised statistical plan

<table>
<tr>
<td></td>
<td>We will examine whether the following pre-specified baseline variables modify the effect of study group on the primary outcome:
• Baseline recipient (trial participant) antibody quantification
• Baseline COVID scale
• Baseline SOFA
• ICU/ward enrollment location
• Age
• Race/ethnicity
• Duration of symptoms prior to randomization
• Mechanical ventilation status at baseline</td>
<td></td>
</tr>
<tr>
<td>Pages 44-45 New Section 8.6 Analysis plan for secondary endpoints
8.6.1 Ordinal outcomes
8.6.2 Binary outcomes
8.6.3 Time to event outcomes
8.6.4 Outcomes with a competing risk of death
8.6.5 Missing data</td>
<td>New Text
“The analyses for secondary endpoints will be intent-to-treat, meaning that patients will be analyzed according to the randomization schedule regardless of the treatment administered. The following is a table of secondary endpoints and analyses (Table 2).
<table>
<tr><td colspan="3">Table 2. Trial secondary outcomes</td></tr>
<tr><td>Outcome</td><td>Type</td><td>Analysis</td></tr>
<tr><td>All-location, all-cause 14-day mortality (assessed on Study Day 15)</td><td>Binary</td><td>Logistic regression</td></tr>
<tr><td>All-location, all-cause 28-day mortality (assessed on Study Day 29)</td><td>Binary</td><td>Logistic regression</td></tr>
<tr><td>Survival through 28 days</td><td>Time-to-event</td><td>Proportional hazards regression</td></tr>
<tr><td>Time to hospital discharge through 28 days</td><td>Time-to-event</td><td>Multistate model with death as a competing risk</td></tr>
<tr><td>Time to recovery (defined as time from randomization to the earlier of final oxygen receipt in the hospital or hospital discharge)</td><td>Time-to-event</td><td>CPM with logit link</td></tr>
<tr><td>COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 3, 8 and 29</td><td>Ordinal</td><td>CPM with logit link</td></tr>
<tr><td>Oxygen-free days through Day 28</td><td>Ordinal</td><td>CPM with logit link</td></tr>
<tr><td>Ventilator-free days through Day 28</td><td>Ordinal</td><td>CPM with logit link</td></tr>
</table>
</td>
<td>Revised statistical plan</td>
</tr>
</table>

Vasopressor-free days through Day 28	Ordinal	CPM with logit link	
ICU-free days through Day 28	Ordinal	CPM with logit link	
Hospital-free days through Day 28	Ordinal	CPM with logit link	

8.6.1 Ordinal outcomes
Ordinal secondary outcomes will be analyzed using the same model described for the primary endpoint. Similar steps to evaluate model fit and overly influential observations will be performed.

8.6.2 Binary outcomes
Binary secondary outcomes will be analyzed using multivariable logistic regression models with the same pre-specified covariates as the primary endpoint. To assess model calibration and overly influential observations, graphical displays of calibration and DFBETAS will be created.

8.6.3 Time to event outcomes
Survival will be analyzed with a proportional hazards regression model. The key result of the analysis is an estimate of the treatment effect hazards ratio. The same set of covariates used for the adjusted analysis of the primary endpoint will also be included in the analysis of secondary time-to-event endpoints. Model fit will be assessed with Schoenfeld residuals and with leave-one-out diagnostics like DFBETAS. The proportional odds assumption will be evaluated with graphical displays. Deviations from proportionality will trigger sensitivity analyses.

8.6.4 Outcomes with a competing risk of death
Some secondary outcomes, like the primary outcome, incorporate death as part of the scale. Others, such as time to discharge, do not. Because death censors length of stay, it is a competing outcome. Outcomes with a competing risk of death will be analyzed with a multi-state model. Both the instantaneous risk and cumulative risk of the outcome will be reported.

8.6.5 Missing data
If missing covariate data occurs, then multiple imputation methods similar to those described for the primary endpoint will be used to estimate the point estimate and confidence interval for the secondary endpoints."

Page 45 New Section 8.7 Safety Outcomes and Adverse Events	New Text " **8.7 Safety Outcomes and Adverse Events** The frequency and description of safety outcomes and adverse events will be reported. The association between intervention group and safety outcomes will be estimated without covariate adjustment. The following table lists the safety outcomes and the planned analyses (Table 3).	Revised statistical plan

<table>
<tr><td></td><td>
<table>
<tr><td colspan="3">Table 3. Trial safety outcomes.</td></tr>
<tr><td>Outcome</td><td>Type</td><td>Analysis</td></tr>
<tr><td>Receipt of renal replacement therapy</td><td>Binary</td><td>Risk difference</td></tr>
<tr><td>Documented venous thromboembolic disease (DVT or PE)</td><td>Binary</td><td>Risk difference</td></tr>
<tr><td>Documented cardiovascular event (myocardial infarction or ischemic stroke)</td><td>Binary</td><td>Risk difference</td></tr>
<tr><td>Transfusion reaction (fever/rash)</td><td>Binary</td><td>Risk difference</td></tr>
<tr><td>Transfusion related acute lung injury (TRALI)</td><td>Binary</td><td>Risk difference</td></tr>
<tr><td>Transfusion associated circulatory overload (TACO)</td><td>Binary</td><td>Risk difference</td></tr>
<tr><td>Transfusion related infection</td><td>Binary</td><td>Risk difference</td></tr>
</table>
</td><td></td></tr>
<tr><td>Page 46 Section 10.1.1 Potential risks of receiving convalescent plasma</td><td>Remove “In order to minimize the risks of disease transmission, pathogen reduction techniques will be utilized to prepare the plasma. “</td><td>Administrative change</td></tr>
<tr><td>Page 46 Section 10.2 Minimalization of Risk</td><td>Previous Text “Convalescent serum has been approved by the Food and Drug Administration and has been used in clinical practice for decades in a number of patient populations with an established safety profile.
Current Text “Convalescent plasma has been approved by the Food and Drug Administration and has been used in clinical practice for decades in a number of patient populations with an established safety profile.”</td><td>Administrative change</td></tr>
<tr><td>Page 49 Section 12. ADVERSE EVENTS</td><td>Previous Text “This protocol addresses these considerations throughout:”

Current Text “This protocol addresses these considerations including the following:”

Previous Text “3. Proactive education of treating clinicians regarding relevant reactions to use of convalescent plasma in the inpatient setting”

Current Text “3. Proactive education of treating clinicians regarding relevant adverse reactions to convalescent plasma”</td><td>Administrative changes</td></tr>
</table>

	Previous Text "4. On-study monitoring of co-interventions (e.g., medications) and patient characteristic to intervene before adverse events occur" Current Text "4. On-study monitoring of co-interventions (e.g., medications) and patient characteristic to help prevent adverse events Previous Text "5. Systematic collection of safety outcomes relevant to use of convalescent plasma in this setting" Current Text "5. Systematic collection of safety outcomes relevant to use of convalescent plasma"	
Page 49 Section 12.1 Adverse Event Definitions	Previous Text "**Reportable Serious Adverse Event**: Adverse events that are serious and have a reasonable possibility that the event was due to a study infusion or procedure. Current Text "**Serious Adverse Event**: Adverse events that are serious as defined in section 12.2 below."	Administrative change
Page 49-50 Move Section 12.3 Serious Adverse Events to Section 12.2	Previous Text "As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes:" Current Text "As per the FDA and NIH definitions, and Section 12.1 of this protocol, a serious adverse event is any adverse event that results in one of the following outcomes:" Move up with previous bullets "•Persistent or significant disability/incapacity" Previous Text "Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event." Current Text "Report an adverse event as serious if admission to the hospital or prolongation of hospitalization was a result of the adverse event." Previous Text "Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life." Current Text "Report an adverse event serious if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life."	Administrative changes

	Previous Text “Reportable serious adverse events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Current Text “Adverse events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.” Previous Text “Serious adverse events will be collected during the first 3 study days, 72 hours after completion of the study plasma infusion, or until hospital discharge, whichever occurs first, regardless of the investigator's opinion of causation.” Current Text “Serious adverse events will be collected through study day 4, 72 hours after completion of the study infusion, or until hospital discharge, whichever occurs first, regardless of the investigator's opinion of causation.	
Page 50 Section 12.3 Safety Monitoring	**Re-number Section 12.2 to 12.3 Safety Monitoring** Previous Text “The Investigators will determine daily if any adverse events occur during the period from enrollment through study day 3, 72 hours after completion of the study plasma infusion, or hospital discharge, whichever occurs first, and will determine if such adverse events are reportable. Thereafter, adverse events are not required to be reported to the IRB unless the investigator feels the adverse event was related to study infusion or study procedures. “ Current Text “The investigators will determine daily if any adverse events occur during the period from enrollment through study day 4,(which is 72 hours after completion of the study product infusion, or hospital discharge, whichever occurs first, and will determine if adverse events are related to study procedures. Adverse events are not required to be reported to the IRB unless the investigator feels the adverse event was related to study infusion or study procedures.” Previous Text “The following adverse events will be considered reportable and thus collected in the adverse event case report forms: • Serious adverse events (as defined in protocol section 12.1 of this protocol) • Non-serious adverse events that are considered by the investigator to be related to study procedures or of uncertain relationship • Events leading to permanent discontinuation of study infusion”	Administrative changes

<table>
<tr>
<td></td>
<td>Current Text “The following adverse events will be collected in the adverse event case report forms:
• Serious adverse events (as defined in protocol section 12.2 of this protocol) that are study related (or of uncertain relationship) or occur within 72 hours of the study infusion
• Non-serious adverse events that are study procedures or of uncertain relationship
• Events leading to permanent discontinuation of study infusion (which, by definition, are study related)
The protocol for reporting adverse events in the trial’s electronic data capture system are summarized in Table 4.

New Text “
Table 4. Protocol for reporting adverse events
<table><tr><th>Type of Adverse Event</th><th>Time for Recording</th></tr><tr><td>Serious, study related</td><td>24 hours</td></tr><tr><td>Serious, not study related</td><td>72 hours</td></tr><tr><td>Serious, not study related</td><td>Recording in the EDC</td></tr><tr><td>Not serious, study related</td><td>72 hours</td></tr><tr><td>Not serious, not study</td><td>Recording in the EDC</td></tr></table>
Previous Text “After randomization, adverse events must be evaluated by the investigator. If the adverse event is judged to be reportable, as outlined above, then the investigator will report to the Lead PIs for assessment of the potential relatedness of each adverse event to the study treatment or protocol procedure via electronic data entry.”

Current Text “After randomization, adverse events must be evaluated by the investigator. If the adverse event is judged to be reportable, as outlined above, then the investigator will report to the Medical Monitor for assessment of the potential relatedness of each adverse event to the study treatment or protocol procedure via electronic data entry.”

New Text “Additional information about adverse event reporting is included in Appendix B.”</td>
<td></td>
</tr>
<tr>
<td>Page 51 New Section 12.4 Medical Monitor</td>
<td>New Text “After randomization, adverse events must be evaluated by the investigator. If the adverse event is judged to be reportable, as outlined above, then the investigator will report to the Lead PIs for assessment of the potential relatedness of each adverse event to the study treatment or protocol procedure via electronic data entry.</td>
<td>Adding Medical Monitor to the study</td>
</tr>
<tr>
<td>Page 51 Section 12.5 Data and Safety Monitoring Board (DSMB)</td>
<td>Previous Text “They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the study team:”

Current Text “They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the study team. DSMB activities include:”</td>
<td>Administrative change</td>
</tr>
</table>

Page 52 Appendix A: Schedule of Events	Updated Schedule of Events	To align the body of the protocol with the Schedule of Events
Page 53-55 Appendix B: Adverse Event Reporting and Unanticipated Events	Previous Text "Investigators will report all serious adverse events that a reasonable possibility that the event was due to a study infusion or procedure (or of uncertain relatedness), to the VCC within 24 hours." Current Text "Investigators will report all serious adverse events that occur within 72 hours of study infusion to the Vanderbilt Coordinating Center (VCC) regardless of relatedness. Serious adverse events that are determined to be related to study procedures (regardless of timing related to study infusion) will be reported to the VCC within 24 hours." Change "Lead PIs" to "Medical Monitor"	To align Appendix B with the body of the protocol
Remove Appendices C and D	How the SOFA Score is calculated is being performed by the biostatisticians	SOFA Score is calculated is being performed by the biostatisticians

PROTOCOL SIGNATURE PAGE

Passive Immunity Trial for Our Nation (PassItOn)

Version 6.0

January 28, 2021

I agree to conduct the study in accordance with the relevant, current protocol and will not make changes to the protocol without prior approval from the IRB of record, except when necessary to protect the safety, rights, or welfare of study participants.

I agree to personally conduct or supervise this study.

I will ensure that the requirements relating to obtaining informed consent and Ethics Committee (EC) or Institutional Review Board (IRB) review and approval are met.

I agree to maintain adequate and accurate study records and to make those records available for inspection by authorized representatives, and/or other applicable regulatory entities.

I will ensure that an EC or IRB that complies with the requirements of 45 CFR Part 46 will complete initial and continuing review and approval of the study. I also agree to promptly report to the EC/IRB all changes to the study and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes to the study without Sponsor-Investigator and EC/IRB approval, except where necessary to eliminate apparent immediate hazards to study participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Site Investigator: _____
(Print/Type)

Institution Title: _____
(Print/Type)

Signed: _____ Date: _____

Table of Contents

1. ABBREVIATIONS

ADE	Antibody-mediated disease enhancement
AE	Adverse event
ARDS	Acute respiratory distress syndrome
CBC	Complete blood count
CMP	Complete metabolic panel
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
DSMB	Data safety monitoring board
DSMBc	Data safety monitoring board coordination
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report forms
ELISA	Enzyme linked immunosorbent assay
FDA	Food and Drug Administration
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
ICU	Intensive care unit
LAR	Legally authorized representative
LR	Lactated Ringer's Solution
MERS	Middle East Respiratory Syndrome
PE	Pulmonary embolism
PI	Principal investigator (a clinician responsible for the trial)
PPE	Personal protective equipment
RBD	Receptor binding domain
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SARS	Severe Acute Respiratory Syndrome
SOFA	Sequential organ failure assessment
sIRB	single Institutional Review Board
TRALI	Transfusion associated acute lung injury
TACO	Transfusion associated circulatory overload
VCC	Vanderbilt Coordinating Center
VUMC	Vanderbilt University Medical Center

2. STUDY SUMMARY

Title	**Passive Immunity Trial for Our Nation**
Acronym	PassItOn
Background	Effective therapies for COVID-19 are urgently needed. Convalescent COVID-19 donor plasma is the liquid part of blood that is collected from patients who have recovered from COVID-19 infection. This plasma contains SARS-CoV-2 specific antibodies that may help patients with COVID-19 recover. Preliminary reports suggest potential efficacy in small human studies. Clinical trial data are needed to determine whether convalescent donor plasma is efficacious in treating COVID-19.
Study Design	Multicenter, blinded, placebo-controlled randomized clinical trial comparing outcomes of patients randomized to COVID-19 convalescent plasma versus placebo. Use of open label convalescent plasma in the first 15 days of the study is strongly discouraged.
Intervention group treatment	1 unit (200–399 ml) of SARS-CoV-2 convalescent plasma infused intravenously
Control group treatment	250 ml of Lactated Ringer's with multivitamins, which visually resembles plasma, infused intravenously
Sample Size	1000
Inclusion Criteria	1. Age greater than or equal to 18 years 2. Currently hospitalized or in an emergency department with anticipated hospitalization 3. Symptoms of acute respiratory infection, defined as one or more of the following: a. Cough b. Chills, or a fever (greater than 37.5° C or 99.5° F) c. Shortness of breath, operationalized as a patient having any of the following: i. Subjective shortness of breath reported by a patient or surrogate. ii. Tachypnea with respiratory rate of greater than 22 breaths per minute iii. Hypoxemia, defined as SpO2 less than 92% on room air, new receipt of supplemental oxygen to maintain SpO2 greater than or equal to 92%, or increased supplemental oxygen to maintain SpO2 greater than or equal to 92% for a patient on chronic oxygen therapy 4. Laboratory-confirmed SARS-CoV-2 infection within the past 14 days
Exclusion Criteria	1. Prisoner 2. Unable to randomize within 14 days after onset of acute respiratory infection symptoms 3. Patient, legal representative, or physician not committed to full support (Exception: a patient who will receive all supportive care except for attempts at resuscitation from cardiac arrest will not be excluded.) 4. Inability to be contacted on Day 29-36 for clinical outcome assessment 5. Receipt of any SARS-CoV-2 passive immunity therapy, such as convalescent plasma, monoclonal antibodies, or pooled immunoglobulin, in the past 30 days. 6. Contraindications to transfusion or history of prior reactions to transfused blood products 7. Plan for hospital discharge within 24 hours of enrollment

	8. Previous enrollment in this trial 9. Previous laboratory-confirmed SARS-CoV-2 infection before the current illness 10. Enrollment in another clinical trial evaluating monoclonal antibodies, convalescent plasma, or another passive immunity therapy. 11. Prior receipt of SARS-CoV-2 vaccine
Randomization	Eligible participants will be randomized 1:1 to convalescent plasma versus lactated Ringer's solution with multivitamins. Randomization will be completed in permuted blocks and stratified by site, gender, and age.
Blinding	Patients and outcome assessors will be blinded to group assignment.
Primary Outcome	COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 15: 1. Not hospitalized with resumption of normal activities. 2. Not hospitalized, but unable to resume normal activities. 3. Hospitalized, not on supplemental oxygen. 4. Hospitalized, and on supplemental oxygen. 5. Hospitalized, on nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both 6. Hospitalized, on ECMO, invasive mechanical ventilation, or both. 7. Death
Secondary Outcomes	• All-location, all-cause 14-day mortality (assessed on Study Day 15) • All-location, all-cause 28-day mortality (assessed on Study Day 29) • Survival through 28 days • Time to hospital discharge through 28 days • Time to recovery (defined as time from randomization to the earlier of final oxygen receipt in the hospital or hospital discharge). • COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 3, 8, and 29 • Oxygen-free days through Day 28 • Ventilator-free days through Day 28 • Vasopressor-free days through Day 28 • ICU-free days through Day 28 • Hospital-free days through Day 28
Safety Outcomes	• Acute kidney injury • Receipt of renal replacement therapy • Documented venous thromboembolic disease (DVT or PE) • Documented cardiovascular event (myocardial infarction or ischemic stroke) • Transfusion reaction (fever/rash) • Transfusion related acute lung injury (TRALI) • Transfusion associated circulatory overload (TACO) • Transfusion related infection
Analysis	The primary analysis will be an intent-to-treat analysis comparing scores on the COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Day 15 between patients randomized to convalescent plasma versus patients randomized to placebo. The key result of the analysis will be an estimate of the treatment effect odds ratio, which will be estimated from a cumulative probability ordinal regression model (CPM) with logit link. Covariates in the regression model will include age, sex, baseline Sequential Organ Failure Assessment (SOFA) score, baseline COVID-19 Ordinal Outcomes Scale score, time from symptom onset, and site.

3. TRIAL DESCRIPTION

3.1 Background

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infectious illness caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2).[1,2] Although the epidemiology has not been fully elucidated, most adults with COVID-19 appear to experience fever, cough, and fatigue and then recover within 1-3 weeks. However, a portion of adults with COVID-19 develop severe illness, often manifesting as pneumonia and hypoxemic respiratory failure, with continued progression to acute respiratory distress syndrome (ARDS) and death in some cases.[1–3] Effective therapies that prevent the progression of COVID-19 are urgently needed. Passive antibody therapy via convalescent donor serum has generated substantial interest due to its established safety and suggested efficacy in other viral diseases including influenza[4,5], Ebola[6], and notably, two other novel coronavirus respiratory diseases, Middle East Respiratory Syndrome (MERS)[7] and Severe Acute Respiratory Syndrome (SARS)-CoV-1.[8] As patients continue to recover from COVID-19, convalescent donor plasma becomes a readily available and viable treatment option for COVID-19. However, there are potential risks to passive antibody therapy including antibody-mediated enhancement of infection (ADE). Thus, data on the safety and efficacy of convalescent plasma for the treatment of COVID-19 are needed to inform clinical practice. In this trial, we will evaluate the safety and efficacy of convalescent serum for the treatment of adults hospitalized with COVID-19.

3.1.1 COVID-19 Infection

COVID-19 was first identified as a cluster of cases of pneumonia among a group of workers from a seafood wholesale market in Wuhan, China in December 2019.[9] This observation, along with subsequent viral genotyping showing significant genetic similarities to the bat coronaviruses[10] suggest a zoonotic origin, although the specific reservoir and intermediary species remain unclear.[11] COVID-19 represents the seventh coronavirus known to cause disease in humans.[12] Four of the coronaviruses are known to cause symptoms of the common cold in immunocompetent individuals while two others (SARS-CoV and MERS-CoV) have caused recent outbreaks of severe and sometimes fatal respiratory diseases.[13] SARS-CoV-2 appears to exploit the same cellular receptor as SARS-CoV and MERS-CoV,[14] and its severity may similarly result from a predilection for intrapulmonary epithelial cells over cells of the upper airways.[15,16]

Since the first documented human case, COVID-19 has spread exponentially with over 20 million confirmed cases and over 750,000 deaths globally as of August 14, 2020. While most patients recover after a mild, brief illness with fever and cough, the disease has a clinical spectrum ranging from asymptomatic infection[17] to ARDS and death.[18] The most common reasons for ICU care are respiratory failure and ARDS, with a minority developing shock and cardiomyopathy.[19] The case fatality rate is estimated to be 0.25% to 3.0%.[20]

3.1.2 Passive antibody therapy

Passive antibody therapy or passive immunization is the transfer of an active humoral immune response from a donor to a recipient. Passive immunity occurs naturally in maternal fetal interactions as the mother's antibodies are given to the fetus across the placenta and are transferred to the newborn in breastmilk.[21] More relevant to this proposal, artificial passive immunity takes place when antibodies from a disease-immune individual are given via plasma as a medication or therapy to a non-immune individual.[4] Passive antibody therapy has been used to treat infectious diseases since the late 1800's, and was successfully used in the 1920's and 30's to treat a wide variety of infections including pneumococcal pneumonia, meningococcal meningitis, diphtheria, scarlet fever, and measles.[22] Convalescent plasma has been used more recently in the setting of viral epidemics. One example is the 2009-2010 H1N1 influenza pandemic where convalescent plasma was used to treat individuals with severe infection requiring intensive care. Results showed that individuals who received convalescent plasma had a reduced viral load, inflammatory cytokine levels, and mortality.[23] Anecdotal evidence also exists for the success of convalescent plasma treatment in the H5N1[24,25] and H7N9[26] avian flu outbreaks. In addition, convalescent plasma was used in the 2013 West Africa Ebola epidemic where a small nonrandomized study in Sierra Leone showed significantly improved survival rates in

individuals who received plasma compared to controls.[6] Two US Ebola patients also received convalescent plasma and survived.[27]

3.1.3 Convalescent donor plasma as a therapeutic for COVID-19
There have been two other recent coronavirus epidemics associated with high risk of death: SARS-CoV-1 in 2003 and MERS in 2012. In the case of both SARS-COV-1 and MERS, high mortality and a lack of therapeutic options led to studies of convalescent plasma. The largest of these studies included 80 patients in Hong Kong and showed that patients treated before day 14 had improved prognosis, defined by discharge from hospital before day 22.[28] It is also important to note that individuals who were RT-PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis. A second study of three seriously ill SARS patients in Taiwan treated with 500 ml of convalescent plasma showed a reduction in plasma virus titer and each survived.[29] Similar to the SARS studies, three patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients had neutralizing antibody in their plasma.[7] Consistent with this point, an analysis of 99 samples of convalescent sera from patients with SARS showed that 87 had neutralizing antibodies with a geometric mean titer of 1:61 and authors concluded that this was suggestive of antibody titer declining over time and/or only few patients make high titer responses.[30] Convalescent plasma therapy has been used in the current COVID-19 pandemic for critically ill patients. In one case series, 4 critically ill patients, including one pregnant woman, received convalescent plasma and recovered from the infection.[31] A second case series of 5 critically ill patients with COVID-19 and ARDS requiring mechanical ventilation who received convalescent plasma with a SARS-CoV-2 specific antibody binding titer greater than 1:1000 by ELISA also all survived.[32] In late February 2020, it was reported that China had treated 245 COVID-19 patients with convalescent plasma and 91 cases had shown improvement in clinical indicators and symptoms.[33]

3.1.4 Rationale for a randomized trial among hospitalized patients
The initial symptoms of COVID-19 develop approximately 2-10 days after infection with the SARS-CoV-2 virus,[34] with the progression to respiratory failure and ARDS occurring approximately 7-10 days after the onset of symptoms.[35] The period between onset of symptoms and development of severe respiratory failure represents a potential window for treatment of hospitalized patients to prevent disease progression. Convalescent plasma is now commonly being administered to hospitalized patients with COVID-19. However, the effectiveness of convalescent plasma in this setting remains unknown. Therefore, rigorous clinical trial data on the efficacy and safety of convalescent plasma as a treatment for COVID-19 are urgently needed to inform clinical practice.

3.2 Study Aims
3.2.1 Study aim
To compare the effect of convalescent plasma versus placebo on clinical outcomes, measured using the COVID-19 7-point Ordinal Clinical Progression Outcomes Scale at Day 15, among adults hospitalized with COVID-19.

3.2.2 Study hypothesis
Among adults hospitalized with COVID-19, administration of convalescent plasma will improve clinical outcomes at Day 15.

3.3 Study Design
We will conduct a multi-site, investigator-initiated, blinded, placebo-controlled, randomized clinical trial evaluating convalescent donor plasma for the treatment of adults hospitalized with COVID-19. Plasma will be collected and distributed to sites through blood donation groups partnering with Vanderbilt University Medical Center (VUMC)'s blood donation center partner. Anti-SARS-CoV-2 antibody quantification assays will be completed on donor plasma at VUMC prior to plasma distribution. Only plasma with antibody quantification above the neutralizing threshold will be used in the trial.

4. STUDY POPULATION AND ENROLLMENT

4.1 Inclusion Criteria

1. Age greater than or equal to 18 years
2. Currently hospitalized or in an emergency department with anticipated hospitalization.
3. Symptoms of acute respiratory infection, defined as one or more of the following:
    a. cough
    b. Chills, or a fever (greater than 37.5° C or 99.5° F)
    c. shortness of breath, operationalized as a patient having any of the following:
        i. Subjective shortness of breath reported by a patient or surrogate.
        ii. Tachypnea with respiratory rate greater than 22 breaths per minute.
        iii. Hypoxemia, defined as SpO2 less than 92% on room air, new receipt of supplemental oxygen to maintain SpO2 greater than or equal to 92%, or increased supplemental oxygen to maintain SpO2 greater than or equal to 92% for a patient on chronic oxygen therapy
4. Laboratory-confirmed SARS-CoV-2 infection within the past 14 days.

4.2 Exclusion Criteria

1. Prisoner
2. Unable to randomize within 14 days after onset of acute respiratory infection symptoms
3. Patient, legal representative, or physician not committed to full support (Exception: a patient who will receive all supportive care except for attempts at resuscitation from cardiac arrest will not be excluded.)
4. Inability to be contacted on Day 29-36 for clinical outcome assessment
5. Receipt of any SARS-CoV-2 passive immunity therapy, such as convalescent plasma, monoclonal antibodies, or pooled immunoglobulin, in the past 30 days
6. Contraindications to transfusion or history of prior reactions to transfused blood products
7. Plan for hospital discharge within 24 hours of enrollment
8. Previous enrollment in this trial
9. Previous laboratory-confirmed SARS-CoV-2 infection before the current illness
10. Enrollment in another clinical trial evaluating monoclonal antibodies, convalescent plasma, or another passive immunity therapy.
11. Prior receipt of a SARS-CoV-2 vaccine

4.3 Justification of Exclusion Criteria

The exclusion criteria are primarily designed for patient safety. In addition to excluding specific vulnerable populations (e.g., prisoners), these criteria are designed to exclude patients for whom receipt of convalescent plasma might increase the risk of serious adverse events. Pregnant women are not excluded from the trial.

4.4 Screening

The site investigator or delegate will screen for hospitalized patients with laboratory confirmed COVID-19 (that is, a positive laboratory test for SARS-CoV-2) or a pending SARS-CoV-2 test. Treating clinicians will also be instructed to contact the site investigator or delegate for patients with a high clinical suspicion of COVID-19.

4.5 Assessment of Eligibility and Exclusion Tracking

For patients who appear to meet eligibility criteria after screening, an electronic case report form will be completed to determine eligibility and track exclusions. The electronic case report form will be accessed and stored in the electronic database. At the time of entry into the screening database, the patient will be assigned a screening number.

If a patient appears to meet all eligibility criteria, the site investigator or delegate will approach the treating clinician to ask permission to approach the patient or Legally Authorized Representative (LAR) to confirm eligibility, discuss potential study recruitment, and proceed with informed consent.

4.6 Process of Obtaining Informed Consent

Informed consent will be obtained from the patient or from a surrogate decision maker if the patient lacks decision-making capacity. Sites will follow local policies and procedures for obtaining consent.

Bringing a paper consent form and pen to the bedside of a patient with known COVID-19 and then taking these out of the room would violate infection control principles and policies. Given the infectious risk from COVID-19 and potential shortages of personal protective equipment (PPE), there is a moral and practical imperative to minimize face-to-face contact between patients and non-clinical personnel. The current epidemic also presents unique challenges to obtaining consent from participant's legally authorized representative (LAR). To minimize infectious risk, many institutions are not allowing visitors to enter the hospital. Furthermore, the LAR is likely to have been exposed to the patient and may therefore be under self-quarantine at the time of the informed consent discussion.

Therefore, we will use "no-touch" consent procedures for this trial, employing two main pathways, "paper-based" and "electronic." Suggestions for the two approaches are outlined here.

Paper-based approach

1. The informed consent document is delivered to the patient or LAR.
    a. If the patient or LAR is on-site, the informed consent document many be delivered to the patient or LAR either by research staff or by clinical staff
    b. If the LAR is off-site, the informed consent document may be emailed, faxed, or otherwise electronically transferred to the LAR (method dictated by institutional policy)
2. Research staff discuss the informed consent document with the patient or LAR either in-person or by telephone or videophone. *This step confirms subject/LAR identity*.
3. If the patient or LAR decides to consent to participate, the patient or LAR signs the paper copy of the informed consent document.
4. A photograph is taken of the signature page of the informed consent document and uploaded into the electronic database (e.g. REDCap).
    a. If using the patient's device (such as a patient's personal cellular phone), a survey link can be sent to their device to allow direct upload of the image into the electronic database (e.g. REDCap).
    b. If using a staff device, it must be approved to store PHI by the local institution. In that case, research personnel can take a photograph of the signature page of the informed consent document either directly or through the window or glass door leading into the patient's room. The photograph can then be uploaded into the electronic database. If a staff device is taken into the patient's room to take a photograph it must be able to be disinfected according to local institutional practices.
5. Research staff and witness provide signatures within the electronic database (e.g. REDCap) confirming their participation in the informed consent process.
6. The patient or LAR retains the paper consent document. The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

Electronic approach

1. The electronic informed consent document is opened on a research device or a link for the electronic informed consent document is sent to the patient's or LAR's device.
2. Research staff discuss the informed consent document with the patient or LAR either in person or by telephone or videophone. *This step confirms subject/LAR identity*.
3. If the patient or LAR decides to consent to participate the patient or LAR signs the electronic informed consent document. This signature may be either:
    a. an actual signature (often tracing a finger on the screen) OR
    b. a username and password specific to the individual signing
4. Research staff and witness provide signatures within the electronic database (e.g., REDCap) confirming their participation in the informed consent process.

5. The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

If a hospital device is provided to facilitate electronic or paper-based consent, that device will be disinfected according to institutional protocols.

Attestation of informed consent

If none of the options outlined above (traditional signature and storage of a paper consent form, electronic photographs of a signed consent page, or e-consent) are available, study personnel may attest to completion of the informed consent process using the procedures outlined below. Importantly, the process of informed consent using this attestation option should not change compared with the traditional method of obtaining informed consent for trial participation except for the method of documenting the consent process in the research record. Rather than storing a paper document with the participant's signature, a member of the research team and an impartial witness will attest to completion of the informed consent process and that the participant signed the informed consent document. This option of attestation of informed consent is not available when obtaining consent through an LAR.

Procedures for attestation of informed consent:

1. An unsigned paper consent form is provided to the patient by a heath care worker or study member.
2. The study member obtaining consent arranges an in-person meeting or three-way call or video conference with himself/herself, the patient, and an impartial witness. If desired and feasible, additional people requested by the patient (e.g., next of kin) may also join this discussion.
3. Study member reviews consent and answers questions in the presence of the impartial witness.
4. Patient signs the paper informed consent document while the witness is listening on the phone or directly observing.
5. Patient provides verbal confirmation that he/she would like to participate in the trial, and he/she has signed and dated the informed consent document. This signed informed consent document stays with the patient due to the risk of spreading the virus.
6. Study member and witness attest that other techniques for documenting informed consent were not available for this participant and that the participant provided written informed consent for trial participation by signing a paper informed consent document. This attestation page with signatures from the study member and witness will be save as evidence of the informed consent process. A signature from the participant will not be saved in the research record.

This approach to informed consent detailed above complies with relevant regulations and sub-regulator guidance at 45 CFR 46.117, 45 CFR 164.512, 21 CFR 11 Subpart C (11.100–11.300), https://www.hhs.gov/ohrp/regulations-and-policy/guidance/use-electronic-informed-consent-questions-and-answers/index.html, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent.

The information for the informed consent discussion will be provided in a formal document (or electronic equivalent) that has been approved by the IRB and in a language comprehensible to the potential participant, using an interpreter if necessary. The information presented in the consent form and by the research staff will detail the nature of the trial and what is expected of participants, including any potential risks and benefits of taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Where a patient does not speak English, a short-form consent and qualified interpreter will be employed, using similar "no-touch" principles. Use of an interpreter and the interpreter's identity will be documented on the electronic consent.

After allowing the potential participant or LAR time to read the informed consent document, research staff will answer any additional questions.

4.7 Randomization and Blinding

Participants confirmed to meet all eligibility criteria who have provided informed consent will be randomized 1:1 to convalescent plasma versus placebo. A randomized group assignment will be provided from a centralized, web-based platform to an unblinded study personnel or delegate, who will order the study product (convalescent plasma or matching placebo). Randomization will require provision of the screening number and confirmation of patient eligibility.

Randomization will be completed in permuted blocks and stratified by site, sex, and age. Randomization will be accessed through Research Electronic Data Capture (REDCap). The randomization module in REDCap allows the statistician to load a randomization table that will allow the study personnel to click a 'randomize' button. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Patients, families, and outcome assessors will be blinded to treatment arm assignment. All other study personnel will be encouraged to remain blinded to the participant's treatment assignment. Additional blinding procedure information will be in the PassItOn Blinding Procedure Document.

Plasma can vary in color, volume, and viscosity depending on donor variables. Therefore, developing a universal matching placebo is not possible. In this trial, the placebo solution is lactated Ringer's with multivitamin additives, which looks similar to plasma. The goal of the placebo solution is to maintain blinding of the participant, outcome assessors, and study personnel who are not closely involved in administering the study product. Clinical personnel who administer the study product (convalescent plasma vs placebo) such as the bedside nurse, will not be blinded. As an additional layer of blinding for the participant, plasma and placebo will be placed in matching blinding bags prior to administration.

4.8 Minorities and Women

No patients will be excluded based on race, ethnicity, or sex. The demographics of the patients approached for enrollment will mirror those of patients admitted to the hospital with COVID-19.

5. STUDY INTERVENTIONS

5.1 Treatment of Study Participants

A summary of the trial's schedule of events is included in Appendix A.

Timing of study procedures is based on the time of initiation of the study product infusion, which is defined as "Time 0". Study Day 1 is defined as the calendar day of study product infusion. For patients who are randomized but do not receive study product, time of randomization will be considered "Time 0" and Study 1 will be the calendar day of randomization. For most patients, randomization and study product infusion will occur on the same day; in the event the study product is infused on a different calendar day than randomization, Study Day 1 is defined as the day on which study product is infused. "Baseline status" represents the patient's status immediately prior to study infusion, and baseline variables should represent information available before and as close as possible to initiation of the study infusion. The primary outcome will be assessed on Study Day 15 which corresponds to 2 weeks (14 days) after the receipt of the study infusion.

Transfusion of convalescent plasma or placebo will be administered as a single dose by clinical or research personnel while the patient is hospitalized and within 24 hours of randomization. Participants randomized to active treatment will receive 1 unit of convalescent plasma, which has a volume of 200-399 ml infused intravenously. Patients randomized to placebo will receive 250 ml of lactated Ringer's with multivitamin additives infused intravenously. The duration of infusion is recommended to be between approximately 1 hour and 3 hours (at the discretion of the provider), with the specific rate of infusion determined by the site investigator based on an assessment of how quickly the participant can safely receive the intravascular volume load.

Study personnel will monitor patients for adverse reactions to the transfusion while the patient is in the hospital for 72 hours following the infusion; that is transfusion adverse reaction monitoring will be continued until Study

Day 4. For patients who are discharged prior to Day 4, study personnel will obtain safety outcomes from the patient or surrogate via telephone follow-up scheduled at Day 8. Research personnel will also assess patients at Day 15 and Day 29; these assessments will be completed by phone if the patient has been discharged from the hospital.

Screening, consent, and baseline

1. Confirm inclusion and exclusion criteria, including identifying a positive SARS-CoV-2 test
2. Subject informed consent (obtained before performing study related activities)
3. Randomization of eligible subject
4. Demographics
5. Medical history
6. COVID-19 symptoms
7. Record vital signs
8. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale)
9. Record new medical conditions
10. Record concomitant medication
11. Adverse Event (AE) evaluation
12. Collection of data for later SOFA score calculation
13. Prior to study infusion, collect, process and store blood for SARS-CoV-2 antibody testing, which will be done at the central study laboratory.
14. C-reactive protein (CRP) measurement (record the results of a clinically obtained CRP performed within 24 hours prior to study product infusion; if a CRP was not obtained clinically, perform a CRP measurement by study protocol in the local clinical laboratory)
15. Complete Blood Count (CBC) and Complete Metabolic Panel (CMP) measurement (record the results of a clinically obtained CBC and CMP performed within 24 hours prior to study product infusion; if a CBC and/or CMP was not obtained clinically, perform them on study protocol in the local clinical laboratory)

Day 1 (Day of Transfusion)

1. Study Product Administration: 1 unit of convalescent plasma or Lactated Ringer's solution with multivitamins will be transfused. Study infusion will be monitored per site institutional transfusion policy.
2. Adverse Event (AE) evaluation

Day 2 (first calendar day after transfusion)

1. Record vital signs.
2. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale)
3. Record new medical conditions
4. AE evaluation
5. Collection of data for later SOFA score calculation
6. CBC and CMP measurement (record the results of a clinically obtained CBC and CMP; if a CBC and/or CMP was not obtained clinically, perform them on study protocol in the local clinical laboratory if patient remains hospitalized)
7. If patient remains hospitalized, collect, process and store blood for SARS-CoV-2 antibody testing, which will be done at the central study laboratory.

Day 3-8 (Daily assessments only while patient hospitalized)

1. Record vital signs
2. Record new medical conditions
3. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale
4. AE evaluation (through Day 4 only)
5. Record the results of a clinically obtained CBC and CMP (Day 8 only and only if clinically available)

Day 8, 15, and 29 (by phone if patient discharged before assessment day):

1. Assessment of clinical status (COVID-19 7-point Ordinal Clinical Progression Outcomes Scale)
2. New medical conditions
3. Vital status check

5.2 Convalescent Plasma Group

Patients randomized to the active treatment arm will receive a single dose of 1 unit (200-399 ml) of convalescent plasma infused intravenously per site institutional policy governing blood product transfusions. Convalescent plasma used in this trial will be ABO compatible with the participant's blood type. The convalescent plasma will be supplied to enrolling sites for the trial. Quantitative SARS-CoV-2 antibody testing will be completed at Vanderbilt University Medical Center on convalescent plasma used in the trial. Plasma that is believed to be neutralizing will be used in this trial and will be prioritized based on neutralizing capabilities. Only plasma that contains anti-SARS-CoV-2 antibodies at a level above the threshold for neutralization will be used in the trial.

5.3 Control Group

Participants randomized to the control group will receive a single 250 ml dose of lactated Ringer's containing multivitamins intravenously. This placebo solution will be mixed by local site pharmacies. It is stable under refrigeration for up to 24 hours. This solution is similar in appearance to plasma and is used to help blind patients, families, and study personnel to treatment assignment.

5.4 Co-interventions

Use of open label convalescent plasma in the first 15 days of the study is strongly discouraged and will be tracked as protocol deviations. All other treatment decisions will be made by treating clinicians without influence from the protocol. Administration of other antiviral medications will be allowed. The decision to administer other antiviral medications will be made by treating clinicians and will be recorded in the case report form. The decision to administer immunomodulating medications, including corticosteroids, will be made by treating clinicians and will be recorded in the case report from.

5.5 On-Study Monitoring

All patients enrolled in the study will be initially hospitalized and will therefore receive monitoring as a part of routine clinical care, including monitoring by their physicians, nurses, respiratory therapists, and ancillary staff.

In addition to routine clinical monitoring, enrolled patients will be monitored per site institutional transfusion policy before, during and following the study infusion. If the patient develops abnormal vital signs during the infusion, the infusion will be held, and the patient will undergo evaluation for a transfusion reaction before the infusion can be restarted. At any point, if a clinical team member has a concern about a potential transfusion reaction, he/she will report that concern to the blood bank or as per institutional policy.

5.6 Criteria for Stopping Study Infusion

Infusion of study treatment will be halted if any of the following manifestations of transfusion reaction develop fever, rash, diffuse itching, acute increase in heart rate by greater than 20 beats per minute. If any of these symptoms develop, the patient will be evaluated by a clinician or study team member. Study treatment will be held until resolution of the symptoms. Study treatment will be restarted one time, but if symptoms recur, study treatment will be discontinued and not restarted. If the patient has recurrent symptoms on restarting study treatment, the blood bank will be notified to evaluate for potential transfusion reaction. If there is significant concern that the symptoms, beyond rash or itching, are secondary to the infusion, then infusion will not be re-started, and the patient will be evaluated for transfusion reaction.

In addition, the infusion will be stopped and not restarted if the patient develops any of the following signs or symptoms of anaphylaxis: hives; pruritus; flushing; swollen lips, tongue or uvula; worsening of shortness of breath; wheezing; stridor; hypoxemia; a decrease in systolic blood pressure to less than 90 mmHg or greater than 30% decrease from baseline or a diastolic drop of greater than 30% from baseline; bradycardia less than 40 beats per minute that is associated with dizziness, nausea or feeling faint; any other symptom or sign which

in the good clinical judgment of the study clinician or supervising provider warrants halting the infusion. For example, the rapid onset of gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and cramps, may be manifestations of anaphylaxis and may warrant an immediate halt prior to meeting full severe adverse event (SAE) criteria.

Any suspected reactions related to study product that result in stopping of study transfusion must be reported as an adverse event.

5.7 Plan for Plasma Shortages

In the event of a shortage of convalescent plasma or multivitamin solution for use in the trial at a participating trial site, site personnel should contact the Vanderbilt Coordinating Center (VCC) Clinical Trials Operations Manager. Participants will only be randomized when convalescent plasma and the placebo solution are available.

6. OUTCOMES

Definitions for each outcome are detailed in the trial's statistical analysis plan (SAP).

6.1 Primary Outcome

COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 15:

1. Not hospitalized with resumption of normal activities.
2. Not hospitalized, but unable to resume normal activities.
3. Hospitalized, not on supplemental oxygen.
4. Hospitalized, on supplemental oxygen.
5. Hospitalized, on nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both
6. Hospitalized, on ECMO, invasive mechanical ventilation, or both.
7. Death

6.2 Secondary Outcomes

- All-location, all-cause 14-day mortality (assessed on Study Day 15)
- All-location, all-cause 28-day mortality (assessed on Study Day 29)
- Survival through 28 days
- Time to hospital discharge through 28 days
- Time to recovery (defined as time from randomization to the earlier of final oxygen receipt in the hospital or hospital discharge)
- COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 3, 8 and 29
- Oxygen-free days through Day 28
- Ventilator-free days through Day 28
- Vasopressor-free days through Day 28
- ICU-free days through Day 28
- Hospital-free days through Day 28

6.3 Safety Outcomes

- Acute kidney injury
- Receipt of renal replacement therapy
- Documented venous thromboembolic disease (DVT or PE)
- Documented cardiovascular event (myocardial infarction or ischemic stroke)
- Transfusion reaction (fever/rash)
- Transfusion related acute lung injury (TRALI)
- Transfusion associated circulatory overload (TACO)
- Transfusion related infection

6.4 Rationale for Primary Outcome

COVID-19 has a broad spectrum of clinical severity. Even among hospitalized patients, most recover without experiencing critical illness.[36] Designing a trial with statistical power to detect a meaningful difference in ICU-free days or mortality might require an unfeasibly large sample size and could miss significant morbidity experienced by the majority of hospitalized patients. Since the majority of morbidity from COVID-19 relates to hypoxemia, the fact that COVID-19 Ordinal Scale is tied to degree of hypoxemic respiratory failure increases its face validity and relevance. For similar reasons, previous trials of severe influenza have employed a similar ordinal outcome.[37] This ordinal scale has been selected as an outcome in multiple ongoing COVID-19 trials and is a preferred outcome by the World Health Organization Research and Development Blueprint for COVID-19.[38] Use of this standardized outcome will increase the potential to compare the results of this trial with other trials and perform meta-analyses. Validated techniques to ask questions about the resumption of normal daily activities will be used to distinguish between category 1 and category 2 on the scale.

7. DATA AND BIOLOGICAL SPECIMEN COLLECTION

Given the infectious risk from COVID-19 and potential shortages of personal protective equipment (PPE), we will minimize face-to-face contact between patients and non-clinical staff. Additionally, minimizing research activities and conducting the trial in a pragmatic manner will increase the ability to complete the trial in the face of strained clinical and research resources during the COVID-19 pandemic. We will emphasize data that can be collected from the electronic health record, and assessments that can be completed over the telephone.

Plasma samples will be collected as part of this trial at baseline (prior to study infusion) and on study Day 2 (approximately 24 hours after the study infusion. Specimens will be shipped to VUMC for future analysis, which will include quantitative anti SARS-CoV-2 antibody measurements. The study principal investigator (PI) and collaborators have approval to use all research bio-specimens collected during the conduct of this trial to address the research questions described in the consent document.

7.1 Baseline Variable Collection

- Presence or absence of each inclusion and exclusion criterion
- Date and time of randomization
- Date of symptom onset
- Admission data: date and time of presentation, origin (home, skilled nursing facility, rehabilitation/LTACH, nursing home, outside hospital, outside ICU), location at randomization [Emergency Department (ED), hospital ward, ICU]
- Demographics (age, sex, race, ethnicity, height, weight)
- Comorbidities
- Acute signs and symptoms: altered mental status, acute hypoxemic respiratory failure, hematology laboratory tests, liver function tests, renal function, coagulation studies
- Sequential Organ Failure Assessment (SOFA)[33] at enrollment
- Chronic use of medications: corticosteroids, ACE inhibitors, angiotensin receptor blockers, non-steroids anti-inflammatory drugs, other
- Receipt of open label immunomodulators between hospital presentation and enrollment: corticosteroids, tocilizumab, sarilumab, interferon β, other
- Receipt of invasive mechanical ventilation, non-invasive ventilation, high-flow nasal cannula, vasopressors, and oxygen therapy between hospital presentation and enrollment
- Vital signs
- COVID-19 7-point Ordinal Clinical Progression Outcomes Scale at enrollment
- CRP, recorded if measured clinically, and collected for research if not measured clinically

7.2 Assessments Between Hospital Presentation and Hospital Discharge

- Specimen type, date, and result of SARS-CoV-2 testing conducted clinically
- Date and time of study infusion

- COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on every day of hospitalization (study Day 8, 15 and 29 by phone if participant is no longer hospitalized)
- SOFA on Day 2, if hospitalized
- Receipt of open label antivirals between enrollment and hospital discharge: hydroxychloroquine, remdesivir, lopinavir/ritonavir, other
- Receipt of open label immunomodulators between enrollment and hospital discharge
- Receipt of open label COVID-19 convalescent plasma
- Date of first receipt of supplemental oxygen (if applicable)
- Date of final receipt of supplemental oxygen (if applicable)
- Date of first receipt of high flow nasal cannula (if applicable)
- Date of final receipt of high flow nasal cannula (if applicable)
- Date of first receipt of non-invasive ventilation (if applicable)
- Date of final receipt of non-invasive ventilation (if applicable)
- Date of first receipt of invasive mechanical ventilation (if applicable)
- Date of final receipt of invasive mechanical ventilation (if applicable)
- Date of first receipt of extracorporeal membrane oxygenation (if applicable)
- Date of final receipt of extracorporeal membrane oxygenation (if applicable)
- Date of first receipt of vasopressors (if applicable)
- Date of final receipt of vasopressor (if applicable)
- Date of first ICU admission (if applicable)
- Date of final ICU discharge (if applicable)
- Date e of hospital discharge (if applicable)
- Date of death (if applicable)
- Clinically obtained laboratory tests, including blood counts, chemistries, and CRP
- Safety assessments: myocardial infarction, ischemic stroke, deep venous thrombosis or pulmonary embolism, aspartate aminotransferase or alanine aminotransferase levels that are greater than twice the local upper limit of normal, stage II or greater acute kidney injury according to KDIGO creatinine criteria[39], receipt of new renal replacement therapy, transfusion reaction, transfusion related acute lung injury (TRALI), Transfusion associated cardiac overload (TACO), transfusion related infection. Definitions for each variable are detailed in the trials statistical analysis plan and are described for enrolling personnel in the trial manual of operations and/or electronic data capture system.

7.3 Assessments Following Hospital Discharge

7.3.1 Acute Care Follow-up

For participants discharged to home or a post-acute care facility (e.g., long term acute care facilities, skilled nursing facilities, or acute rehabilitation facilities) prior to the Day 8, Day 15 or Day 29 assessment, we will perform these assessments via telephone follow-up. The Day 8 call window will be Day 8 through 14. The Day 15 call window will be Day 15 through 22. The Day 29 call window will be Day 29 through 36. During these telephone calls, we will interview the patient, LAR, or facility staff to assess:

- Date of death (if applicable)
- ED visits and hospital readmissions after hospital discharge
- Location at the time of the call (home, long term acute care facility, skilled nursing facility, acute rehabilitation facility, hospital)
- Selected non-laboratory safety outcomes after hospital discharge
- COVID-19 7-point Ordinal Clinical Progression Outcomes Scale

The follow-up period for vital status (dead versus alive) is through Study Day 29. For most patients, we will establish vital status during the Study Day 29 visit (either in person for those who remain in the hospital or by phone for those who have been discharged). For patients who are not reached for the Study Day 29 visit, we will seek to establish vital status via phone calls, emails, and searches through medical records, obituaries, social media, and other sources.

8. STATISTICAL CONSIDERATIONS

8.1 Summary

The key features of the trial are summarized in the following table (Table 1).

Table 1. Key Statistical features of the trial

Feature	Description
Primary endpoint	COVID-19 7-point Ordinal Clinical Progression Outcomes Scale captured on study Day 15
Primary AIM	Assess if the treatment intervention improves the day 15 endpoint compared to the control arm
Sample size	1000 subjects
Inference approach	The primary point of inference will be the likelihood ratio and corresponding support interval for the covariate adjusted treatment effect odds ratio. Likelihood ratios more extreme than 7 (or 1/7) will be interpreted as sufficient evidence to assert efficacy. The odds ratio will be estimated with a cumulative probability ordinal regression model with logit link.
Planned Interim Analyses	There are 3 interim analyses for safety endpoints, and a final analysis of efficacy endpoints. The safety interim analyses will occur after 15 days of follow-up is completed for the first 150, 450, and 750 patients. The final analysis will occur after follow-up is complete for all enrolled subjects.
Planned Reporting Triggers	There are no planned reporting triggers.
Planned stopping rules	At each interim analysis, the difference in mortality risk will be calculated, and the one-sided hypothesis that mortality risk in the intervention arm exceeds the mortality risk in placebo will be compared to the null hypothesis of equal mortality risk. The trial will be stopped if the likelihood ratio exceeds the threshold listed below.
Type I error rate	The combination of a 1/7 likelihood ratio threshold and the safety stopping rule result in a simulated type I error rate of 0.02
Power	The minimal detectable effect at 80% power is 0.73

8.2 Planned interim analyses for mortality

At each interim analysis, the difference in mortality risk will be calculated, and the one-sided hypothesis that mortality risk in the intervention arm exceeds the mortality risk in placebo will be compared to the null hypothesis of equal mortality risk. The trial will be stopped if the likelihood ratio exceeds the threshold listed below. Generally, the level of evidence required to stop a study for safety concerns is less than the level of evidence required to assert efficacy of the intervention. Likewise, there is not the same level of concern for type 1 error control for safety outcomes as there is for efficacy endpoints; however, the threshold values were selected so that the trial-wise risk of ending early for mortality is 0.1 if the treatment is equivalent to placebo. To provide context for the LR thresholds listed in the table below, we have also provided α_N, the p-value threshold which approximates the LR threshold if the p-value were calculated from a likelihood ratio test.

N	LR Threshold	α_N
150	6.3	0.0275
450	4.0	0.0479
750	3.3	0.0612

8.3 Analysis plan for primary endpoints

The statistical analysis plan (SAP) contains a more complete description of analysis methods, definitions, and sensitivity analyses. In this section, we reprint relevant portions of the SAP.

The data from the clinical trial will be analyzed after follow-up is completed for all study subjects. The analysis will be intent-to-treat, meaning that patients will be analyzed according to the randomization schedule regardless of the treatment administered. The key result of the analysis is an estimate of the treatment effect odds ratio, its likelihood ratio when compared to the null, and the corresponding 1/7 likelihood support interval, all of which will be estimated from a cumulative probability ordinal regression model (CPM) with logit link. The marginal likelihood function for the treatment effect parameter will be the asymptotic regression coefficient distribution; specifically, it will be the normal distribution density function with mean and standard deviation equal to the regression estimates. Likelihood ratios more extreme than 7 will be interpreted as sufficient evidence to assert efficacy. In order to increase study power, the following variable will also be included into the regression:

1. Treatment (1 parameter)
2. Age (2 parameters, restricted cubic spline)
3. Sex (1 parameter)
4. SOFA score (1 parameter, linear term)
5. Baseline COVID-19 7-point Ordinal Clinical Progression Outcomes Scale score (possible range:3-6) (2 parameters, quadratic)
6. Time from symptom onset in days (2 parameter, non-linear term)
7. Site indicator variables (either as a main effect or as a random effect, depending on the number of sites enrolling patients)

8.3.1 Model fit

Model fit will be assessed with probability scale residuals and with leave-one-out diagnostics like DFBETAS. If model diagnostics indicate that an alternative link function provides a superior fit, then supplementary information will be sent to the DSMB to decide if an alternative link function should be used.

8.3.2 Missing data

We anticipate rare or no missingness for data points during a patients in-hospital course. There may be missing data for the COVID-19 7-point Ordinal Clinical Progression Outcomes Scale score after hospital discharge, which relies on phone follow-up. After discharge, distinguishing between category 1 and category 2 on the scale requires speaking to the participant or surrogate about normal daily activities. If the patient is not reached for follow-up phone calls after discharge, the COVID-19 7-point Ordinal Clinical Progression Outcomes Scale score will be classified as category 2 (not hospitalized, but unable to resume normal activities). If the patient is reached for a follow-up call post-charge and reports category 1, this classification of category 1 will be carried forward to future follow-up calls if the patient cannot be reached. For example, if the patient cannot be reached for the Day 8, 15, or 29 follow-up calls, a category 2 score will be reported for all three visits. If the patient is successfully contacted on the Day 8 call and reports category 1, and then the patient cannot be reached for a Day 15 call, the category 1 score from Day 8 will be carried forward to Day 15.

Missing data for a covariate used in the primary model will be multiply imputed using predictive mean matching if number of observations missing covariate values exceeds 5 percent. If fewer than 5% of observations have missing covariate values, missing values will be imputed with a single conditional mean.

8.3.3 Assertion of efficacy

Likelihood ratios more extreme than 7 (or 1/7) will be interpreted as sufficient evidence to assert efficacy.

8.4 Trial characteristics

8.4.1 Inference

Decision making using the likelihood approach in a clinical trial centers on three quantities: the point estimate of the treatment effect (an odds ratio, for example), a corresponding interval estimate, and a single number summary that measures the relative evidence for one hypothesis compared to another. These three quantities are not unlike the point estimate, 95% confidence interval, and p-value that are generated in frequentist analyses. In fact, the point estimates are often identical, and the interval estimates are often similar. The LR and the p-value, however, are distinct measures of evidence. The LR is a ratio: the density of the trial data if the treatment works (alternative hypothesis) divided by the density of the trial data if the treatment does not work (null hypothesis). A LR of 1 indicates the data are neutral; neither hypothesis is supported over the other. Large LR are evidence in support of the treatment working while small LR are evidence in support of the null. In short, the LR level of evidence is based on comparing the likelihood of the data under two competing models – the alternative hypothesis and the null hypothesis. This is different to using a p-value as the level of evidence because the p-value essentially compares what actually happened in the trial to what might have happened in the trial if it were repeated infinitely and the null hypothesis were true. Because it is impossible to compute what might have happened if the rules for decision making are not fully predefined, using a p-value for decision making is not well suited for a trial like this one in which DSMB requests and pandemic circumstances prompt design changes. The LR approach on the other hand, is based on a relative likelihood of observed outcomes under two competing models at the same point in time making it especially appropriate for settings where pre-specification of the timing or frequency of sequential analyses is not possible.

Even though the LR (instead of the p-value) is the quantity of primary interest for decision making, the analysis plan does control type 1 error. Sequential likelihood ratio tests of two prespecified hypotheses have a natural bound on type 1 error of 1/k where k is the threshold for asserting efficacy. In this study, the combination of the stopping rule for mortality and the large number of subjects accrued before the first analysis for efficacy result in a bound-on type 1 error well within traditional levels of 0.05.

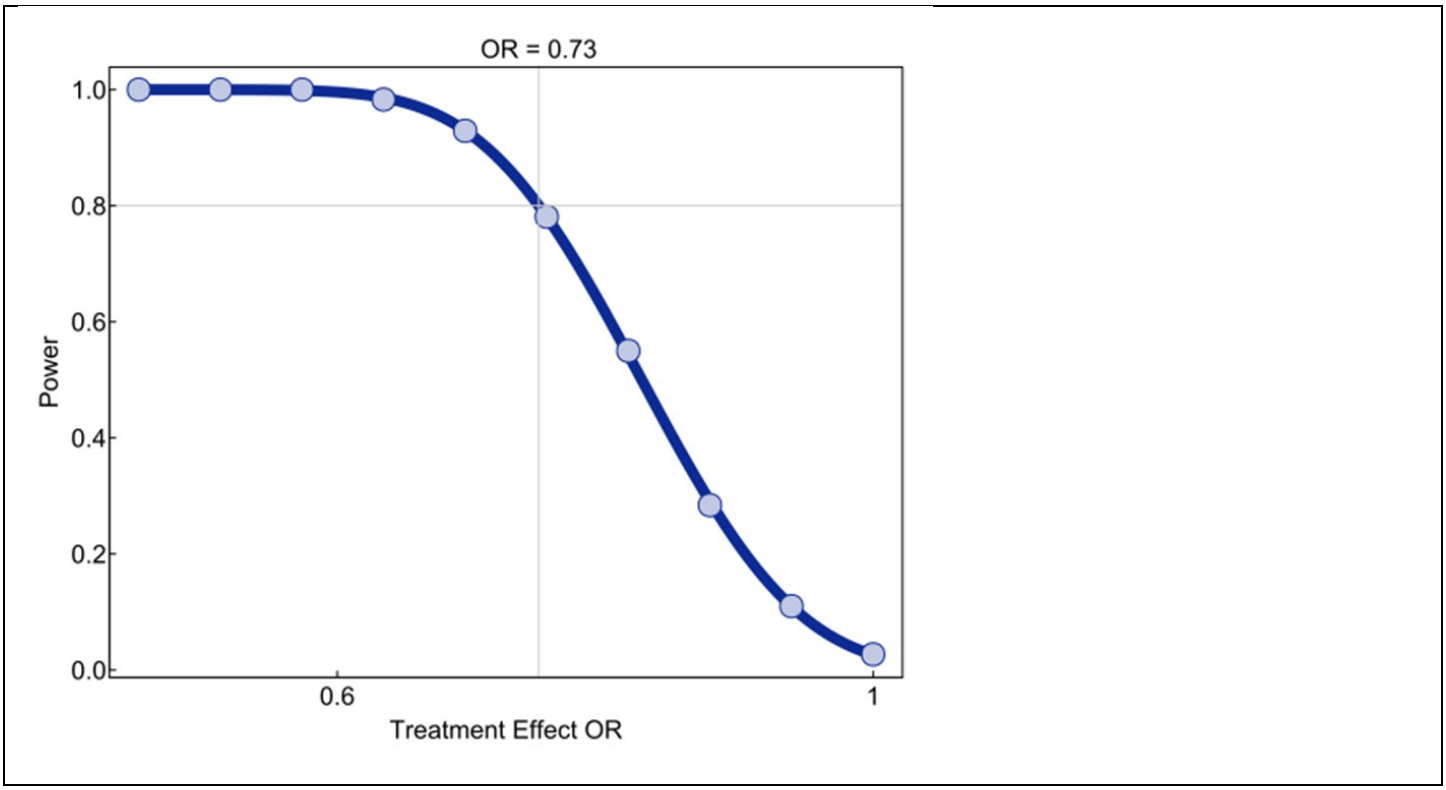
8.4.2 Type I error rate and power

The long-run operating characteristics were estimated by generating study data to reflect different treatment effect sizes. The simulated study dataset was evaluated according to the stopping rule and analysis plan described above. For each effect size, 1000 simulated datasets were analyzed. A Type I error occurred if the study asserted efficacy when in fact there was no treatment effect. The Type I error rate was calculated as the proportion of null-effect studies in which the error occurred. A Type II error occurred if the study failed to assert efficacy when there was a beneficial treatment effect. For each treatment effect, power was calculated as the proportion of studies that did not result in a Type II error.

The study endpoint for control subjects was simulated to match the outcomes in the control arm of a recent clinical trial.[3] In each simulation setting, the distribution for the treatment arm was calculated by adjusting the control arm outcome distribution according to the setting-specific treatment effect size and data generation model.

The figure below is the estimated power curve for the trial design (Figure 1).

Figure 1. Power of the trial assuming enrollment of 1000 participants.



8.5 Analysis plan for additional analyses of the primary endpoint

8.5.1 Quantification of effect of donor plasma characteristics on treatment efficacy

The impact of the antibody levels and neutralization activity of the donor plasma on the primary endpoint will be estimated with ordinal regression models. The models will include the same covariates listed for the primary endpoint analysis, except the treatment assignment variable will be replaced with either (a) a measure of donor plasma antibody level or (b) a measure of donor plasma neutralization. Both variables will be included in models as a restricted cubic spline in order to capture potential non-linear associations with the outcome.

8.5.2 Effect modification analyses of the primary outcome

We will examine whether pre-specified baseline variables modified the effect of treatment group on the primary outcome using tests of statistical interaction in a proportional odds regression model. Independent variables will include study group assignment, the potential effect modifier of interest, the interaction between the two, and the same pre-specified covariates used in the primary model. Presence of effect modification will be assessed by reference to the LR for the interaction term, with values greater than 6 considered to suggest a potential interaction and values greater than 7 considered to confirm an interaction.

We will examine whether the following pre-specified baseline variables modify the effect of study group on the primary outcome:

- Baseline recipient (trial participant) antibody quantification
- Baseline COVID scale
- Baseline SOFA
- ICU/ward enrollment location
- Age
- Race/ethnicity
- Duration of symptoms prior to randomization
- Mechanical ventilation status at baseline

8.6 Analysis plan for secondary endpoints

The analyses for secondary endpoints will be intent-to-treat, meaning that patients will be analyzed according to the randomization schedule regardless of the treatment administered. The following is a table of secondary endpoints and analyses (Table 2).

Table 2. Trial secondary outcomes

Outcome	Type	Analysis
All-location, all-cause 14-day mortality (assessed on Study Day 15)	Binary	Logistic regression
All-location, all-cause 28-day mortality (assessed on Study Day 29)	Binary	Logistic regression
Survival through 28 days	Time-to-event	Proportional hazards regression
Time to hospital discharge through 28 days	Time-to-event	Multistate model with death as a competing risk
Time to recovery (defined as time from randomization to the earlier of final oxygen receipt in the hospital or hospital discharge)	Time-to-event	CPM with logit link
COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 3, 8 and 29	Ordinal	CPM with logit link
Oxygen-free days through Day 28	Ordinal	CPM with logit link
Ventilator-free days through Day 28	Ordinal	CPM with logit link
Vasopressor-free days through Day 28	Ordinal	CPM with logit link
ICU-free days through Day 28	Ordinal	CPM with logit link
Hospital-free days through Day 28	Ordinal	CPM with logit link

8.6.1 Ordinal outcomes

Ordinal secondary outcomes will be analyzed using the same model described for the primary endpoint. Similar steps to evaluate model fit and overly influential observations will be performed.

8.6.2 Binary outcomes

Binary secondary outcomes will be analyzed using multivariable logistic regression models with the same pre-specified covariates as the primary endpoint. To assess model calibration and overly influential observations, graphical displays of calibration and DFBETAS will be created.

8.6.3 Time to event outcomes

Survival will be analyzed with a proportional hazards regression model. The key result of the analysis is an estimate of the treatment effect hazards ratio. The same set of covariates used for the adjusted analysis of the primary endpoint will also be included in the analysis of secondary time-to-event endpoints. Model fit will be assessed with Schoenfeld residuals and with leave-one-out diagnostics like DFBETAS. The proportional odds assumption will be evaluated with graphical displays. Deviations from proportionality will trigger sensitivity analyses.

8.6.4 Outcomes with a competing risk of death
Some secondary outcomes, like the primary outcome, incorporate death as part of the scale. Others, such as time to discharge, do not. Because death censors length of stay, it is a competing outcome. Outcomes with a competing risk of death will be analyzed with a multi-state model. Both the instantaneous risk and cumulative risk of the outcome will be reported.

8.6.5 Missing data
If missing covariate data occurs, then multiple imputation methods similar to those described for the primary endpoint will be used to estimate the point estimate and confidence interval for the secondary endpoints.

8.7 Safety Outcomes and Adverse Events
The frequency and description of safety outcomes and adverse events will be reported. The association between intervention group and safety outcomes will be estimated without covariate adjustment. The following table lists the safety outcomes and the planned analyses (Table 3).

Table 3. Trial safety outcomes.

Outcome	Type	Analysis
Receipt of renal replacement therapy	Binary	Risk difference
Documented venous thromboembolic disease (DVT or PE)	Binary	Risk difference
Documented cardiovascular event (myocardial infarction or ischemic stroke)	Binary	Risk difference
Transfusion reaction (fever/rash)	Binary	Risk difference
Transfusion related acute lung injury (TRALI)	Binary	Risk difference
Transfusion associated circulatory overload (TACO)	Binary	Risk difference
Transfusion related infection	Binary	Risk difference

9. DATA QUALITY MONITORING AND STORAGE
9.1 Data Quality Monitoring
Data quality will be reviewed remotely using front-end range and logic checks at the time of data entry and back-end monitoring of data using application programming interface tools connecting the online database to statistical software to generate data reports. Patient records and case report forms will also be reviewed by the Vanderbilt Coordinating Center (VCC) to evaluate the accuracy and completeness of the data entered into the database and monitor for protocol compliance per the study monitoring plan. The VCC will perform remote monitoring of each study site to examine the completeness and accuracy of informed consent documents for study participants, documentation of eligibility criteria, and the completeness of study outcome collection. Fully identifiable source documents will be requested from participating sites in order to carry out the study monitoring plan.

9.2 Data Storage
Data will be entered into a secure online database. All data will be maintained in the secure online database until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

10. RISK ASSESSMENT
10.1 Potential Risk to Participants
Although convalescent plasma is an FDA approved treatment with an established safety profile, potential risks exist to participating in this study of convalescent plasma versus placebo for the treatment of COVID-19.

10.1.1 Potential risks of receiving convalescent plasma

One potential risk to receiving convalescent plasma is the possibility of developing antibody-mediated enhancement of infection (ADE). ADE can happen in the setting of viral and bacterial diseases and occurs when antibodies increase the severity of disease. ADE has been described in other types of coronaviruses, and it is also possible that antibodies to one type of coronavirus could enhance disease with another strain.[43] However, in the setting of MERS and the closely related SARS-CoV-1, evidence suggests that the use of convalescent plasma is safe.[7,28,44] Anecdotal evidence of the use of convalescent plasma in COVID-19 also indicates that this is a safe treatment option.[32,33] Another possible risk to receiving convalescent plasma is that the patient may mount a sub-optimal humoral immune response resulting in susceptibility to reinfection as has been seen with respiratory syncytial virus.[45] However, these concerns seem minor as compared to the possibility of limiting the duration and severity of disease, and avoiding interventions like mechanical ventilation, ARDS and sepsis. There are also risks associated with any transfusion of plasma including transmission of transfusion transmitted viruses (e.g. HIV, HBV, HCV, etc.), allergic transfusion reactions, anaphylaxis to transfusion, febrile transfusion reaction, transfusion related acute lung injury (TRALI), transfusion associated cardiac overload (TACO), and hemolysis should ABO incompatible plasma be administered. Another risk of plasma is thrombotic (clotting) complications, such as deep venous thrombosis, pulmonary embolism, myocardial infarction, and stroke. All study participants will be closely monitored for adverse events by study personnel.

10.1.2 Potential risks of receiving lactated Ringer's solution with multivitamins with COVID-19

One potential risk to participating in this study is receiving LR with multivitamins rather than convalescent plasma. This risk is only relevant if convalescent plasma is ultimately found to be an effective therapy for COVID-19 and is not relevant if convalescent plasma is ultimately found to be an ineffective therapy for COVID-19. This trial protocol minimizes this risk through rigorous design to minimize the number of patients who must be enrolled to determine whether convalescent plasma is an effective therapy for COVID-19. The other risks of receiving LR are very low and include volume overload and allergic reaction to multivitamins. All study participants will be closely monitored for adverse events by study personnel.

10.2 Minimalization of Risk

Federal regulations at 45 CFR 46.111(a)(1) require that risks to participants are minimized by using procedures which are consistent with sound research design. This trial protocol incorporates numerous design elements to minimize risk to patients that meet this human subject protection requirement. Convalescent plasma has been approved by the Food and Drug Administration and has been used in clinical practice for decades in a number of patient populations with an established safety profile. The dose and route of administration of convalescent serum in this trial are comparable to the dose and route of administration approved for the treatment of other acute viral infections such as SARS and MERS. The trial protocol includes monitoring of adverse events, clinical outcomes, and interim analyses by an independent data and safety monitoring board empowered to stop or modify the trial at any time. In addition, all patients will be hospitalized or in an ED with plans to be hospitalized. They will be closely monitored by nursing staff during the infusion of the plasma.

10.3 Potential Benefit

Study participants may or may not receive any direct benefits from their participation in this study. Administration of convalescent plasma may improve clinical outcomes among adults hospitalized for COVID-19 infection.

10.4 Risk in Relation to Anticipated Benefit

Federal regulations at 45 CFR 46.111 (a)(2) require that "the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits. Convalescent plasma has been used in clinical practice for decades and previously evaluated for the treatment of patients acutely ill from infection with substantial data to support its safety and potential efficacy.

11. HUMAN SUBJECTS PROTECTIONS

Each study participant will undergo a consent process as outlined above. Approval of the central institutional review board will be required before any participant is entered into the study.

11.1 Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The emergency departments, hospital wards, and ICUs of participating sites will be screened to determine if any patient meets inclusion and exclusion criteria. Data that have been collected as part of the routine clinical care of the patient will be reviewed to determine eligibility. If any patient meets criteria for study enrollment, then the attending physician responsible for his or her care will be asked for permission to approach the patient or his or her LAR for informed consent. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals for participation in the research. Hence, the recruitment of participants conforms to the principle of distributive justice.

11.2 Justification of Including Vulnerable Subjects

The present research aims to investigate the safety and efficacy of convalescent plasma for the treatment of patients with COVID-19 who are at high risk for respiratory failure and mortality. Due to the nature of this patient population, many of these patients will have impaired decision-making capabilities. Moreover, those with intact decision-making capacities probably have milder disease than those with impaired capacity. Therefore, the validity of the study and its generalizability to severely ill patients would be compromised by enrolling only those participants with retained decision-making capacity. Hence, participants recruited for this trial are not being unfairly burdened with involvement in this research.

11.3 Informed Consent

Federal regulations 45 CFR 46.111(a)(5) require that informed consent will be sought from each patient or the patient's LAR. Study personnel obtaining informed consent are responsible for ensuring that the patient or LAR understands the risks and benefits of participating in the study, answering any questions the patient or LAR may have throughout the study and sharing any new information in a timely manner that may be relevant to the patient's or LAR's willingness to permit the patient's continued participation in the trial. The study personnel obtaining informed consent will make every effort to minimize coercion. All patients or their LARs will be informed of the objectives of the study and the potential risks. The informed consent document will be used to explain the risks and benefits of study participation to the patient or LAR in simple terms before the patient is entered into the study, and to confirm that the patient or LAR is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The investigator is responsible for ensuring that informed consent is given by each patient or LAR. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures including administration of study agent.

For additional details, see Section 4.

11.4 Continuing Consent

Patients for whom consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while in hospital will be approached for consent for continuing participation, including continuance of data acquisition. The consent form signed by the LAR should reflect that such consent should be obtained. The process for obtaining consent from these patients will be the same as that outlined in section 4.

11.5 Withdrawal of Consent

Participating patients may withdraw or be withdrawn (by the LAR, treating physician, or investigator) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use data has also been withdrawn. Withdrawal of consent prior to randomization will constitute a screen-failure and will be recorded. Withdrawal of consent after randomization will lead to discontinuation of study interventions but site staff will request access to medical records for data related to the trial.

11.6 Identification of Legally Authorized Representatives

Many of the patients approached for participation in this research protocol will have impaired decision-making capacity due to critical illness and will not be able to provide informed consent. Accordingly, informed consent will be sought from the patient's LAR.

Regarding consent from the LAR, the existing federal research regulations ('the Common Rule') states at 45 CFR 46.116 that "no investigator may involve a human being as a subject in research…unless the investigator

has obtained the legally effective informed consent of the subject or the subject's legally authorized representative"; and defines at 45 CFR 46 102 (c) a LAR as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." The Office of Human Research Protections (OHRP) defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the LAR to provide consent for participant participation in the research. Interpretation of "applicable law" may be state specific and will be addressed by the central IRB.

According to a previous President's Bioethics Committee (National Bioethics Advisory Committee (NBAC)), an investigator should accept a relative or friend of the potential participant who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place.[46] Finally, OHRP has stated in their determination letters that a surrogate could serve as a LAR for research decision making if such an individual is authorized under applicable state law to provide consent for the "procedures" involved in the research study

11.7 Justification of Surrogate Consent

According to the Belmont Report, respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. One method that serves to protect patients is restrictions on the participation of patients in research that presents greater than minimal risk. Commentators and research ethics commissions have held the view that it is permissible to include incapable participants in greater than minimal risk research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits similar to that available in the clinical setting.[47] Several U.S. task forces have deemed it permissible to include incapable participants in research. For example, the American College of Physicians' document allows surrogates to consent to research involving incapable participants only "if the net additional risks of participation are not substantially greater than the risks of standard treatment".[48] Finally, NBAC stated that an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the participant, provided that "the potential subject's LAR gives permission…".[46]

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable participant in research and the previous assessment of risks and benefits in the previous section, the present trial presents a balance of risks and potential direct benefits that is similar to that available in the clinical setting.

11.8 Additional Safeguards for Vulnerable Participants

The present research will involve participants who might be vulnerable to coercion or undue influence. As required in 45CFR46.111(b), we recommend that sites utilize additional safeguards to protect the rights and welfare of these participants. Such safeguards might include but are not limited to a) assessment of the potential participant's capacity to provide informed consent, and b) the availability of the LAR to monitor the participant's subsequent participation and withdrawal from the study. The specific nature of the additional safeguards will be left to the discretion of the central IRB, in conjunction with the sites.

11.9 Confidentiality

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data. At no time during this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. All data collected for this study will be entered directly into a secure online database. All data will be maintained in the secure online database until the time of study publication. At the time of publication, a de-identified version of the database will be generated. Further, tools within the secure online database will be used so that only the VCC and investigators from the enrolling site will have access to data from participants enrolled at that site.

12. ADVERSE EVENTS

Assuring patient safety is an essential component of this protocol. Convalescent plasma has been approved by the Food and Drug Administration and used in clinical practice for decades with an established safety profile. Use of convalescent plasma for the treatment of acute respiratory infection due to COVID-19, however, raises unique safety considerations. This protocol addresses these considerations including the following:

1. Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events with receipt of convalescent plasma
2. Inpatient monitoring of the patient by bedside nurses during and after infusion of the plasma
3. Proactive education of treating clinicians regarding relevant adverse reactions to convalescent plasma
4. On-study monitoring of co-interventions (e.g., medications) and patient characteristic to help prevent adverse events
5. Systematic collection of safety outcomes relevant to use of convalescent plasma
6. Structured reporting of adverse events

12.1 Adverse Event Definitions

Adverse Event: Any untoward medical occurrence associated with the use of an infusion or a study procedure, whether or not considered infusion related.

Serious Adverse Event: Adverse events that are serious as defined in section 12.2 below.

Adverse Reaction: An adverse reaction means any adverse event caused by a study intervention. An adverse reaction is a subset of all suspected adverse events where there is a reason to conclude that the study intervention caused the event.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the study procedures caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the study procedures and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both unexpected (not consistent with risks outlined in the study protocol or investigator brochure), serious, and meets the definition of a suspected adverse reaction.

12.2 Serious Adverse Events

Serious adverse event collection begins after randomization and study procedures have been initiated. If a patient experiences a serious adverse event after consent, but prior to randomization or starting study procedures, the event will NOT be collected. Study site personnel must alert the VCC, via data entry in the adverse event case report form, of any **serious and study procedure related** adverse event within 24 hours of investigator awareness of the event. If a serious adverse event is communicated to the VCC is via telephone, it should be immediately followed with official notification on the adverse event case report form.

As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or re-hospitalization
- Persistent or significant disability/incapacity

As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report an adverse event as serious if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency department visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report an adverse event serious if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Adverse events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events will be collected **through study day 4,** 72 hours after completion of the study infusion, or until hospital discharge, whichever occurs first, regardless of the investigator's opinion of causation.

12.3 Safety Monitoring

Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. The investigators will determine daily if any adverse events occur during the period from enrollment through **study day 4,(which is** 72 hours after completion of the study product infusion, or hospital discharge, whichever occurs first, and will determine if adverse events are related to study procedures. Adverse events are not required to be reported to the IRB unless the investigator feels the adverse event **was related** to study infusion or study procedures.

The following adverse events will be collected in the adverse event case report forms:

- Serious adverse events (as defined in protocol section 12.2 of this protocol) that are study related (or of uncertain relationship) or occur within 72 hours of the study infusion
- Non-serious adverse events that are study procedures or of uncertain relationship
- Events leading to permanent discontinuation of study infusion (which, by definition, are study related)

The protocol for reporting adverse events in the trial's electronic data capture system are summarized in Table 4.

Table 4. Protocol for reporting adverse events

Type of Adverse Event	Time for Recording in the EDC
Serious, study related	**24 hours**
Serious, not study related and within 72 hours of infusion	72 hours
Serious, not study related and after 72 hours following	Recording in the EDC is not required
Not serious, study related	72 hours
Not serious, not study related	Recording in the EDC is not required

Study-specific clinical outcomes (Primary, Secondary and Safety Outcomes and Assessments During the Study), including serious outcomes such as organ failures and death, are systematically recorded in the case report forms and are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study plasma or the conduct of study procedures (or of uncertain relationship).

After randomization, adverse events must be evaluated by the investigator. If the adverse event is judged to be reportable, as outlined above, then the investigator will report to the Medical Monitor for assessment of the potential relatedness of each adverse event to the study treatment or protocol procedure via electronic data entry. Investigators will assess if there is a reasonable possibility that the study procedure caused the event. Investigators will also consider if the event is unexpected. Unexpected adverse events are events not listed in the study protocol or investigator's brochure. Investigators will also determine if adverse events are unanticipated given the patient's clinical course, previous medical conditions, and concomitant medications.

If a patient's treatment is discontinued as a result of an adverse event, study site personnel must also report the circumstances and data leading to discontinuation of treatment in the adverse event case report forms. Additional information about adverse event reporting is included in Appendix B.

12.4 Medical Monitor

The relationship or attribution of an adverse event to the study therapy will be initially determined by the site investigator and recorded on the appropriate eCRF. Final determination of attribution for safety reporting will be determined by the independent medical monitor. The Medical Monitor may escalate reported events to the DSMB chair as appropriate per the DSMB charter.

The activities of the Medical Monitor will include:

- Being on call for investigators to report and discuss AEs and SAEs
- Reviewing safety data delivered to the DSMB and any safety reports
- Attending DSMB meetings to participate in discussions about safety and AEs
- Participation in discussions about unblinding study team members to study drug allocation to facilitate safe treatment of study participants

12.5 Data and Safety Monitoring Board (DSMB)

The principal role of the DSMB is to assure the safety of participants in the trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the study team. DSMB activities include:

- Review of adverse events
- Interim results of the study for evidence of efficacy or adverse events
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance
- Possible modifications in the clinical trial protocol
- Performance of individual centers

The DSMB is selected by the study team for their expertise in relevant fields. The DSMB reviews all protocols for safety. The DSMB will consist of members with expertise in acute lung injury, transfusion medicine, biostatistics, ethics, and clinical trials. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. An unblinded statistician and coordinating center personnel will be responsible for the preparation of all DSMB and adverse event reports and may review unblinded data. The DSMB will develop a charter and review the protocol and sample consent form during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter. When appropriate, conference calls may be held in place of face-to-face meetings. Recommendations to end, modify, or continue the trial will be prepared by the DSMB. Recommendations for major changes, such as stopping the trial, will be communicated to the executive committee/sponsor-investigator.

APPENDICES

Appendix A: Schedule of Events

	Screening & Consent	Baseline & Transfusion	Follow-up								
Day	1 or before	1	2	3	4	5	6	7	8[1]	15[1]	29[1]
Confirm eligibility, including positive SARS-CoV-2 test	x										
Informed consent	x										
Randomization		x									
Demographic and Medical history		x									
ABO type (complete on study protocol if clinical results not available; follow institutional policy)		x[4]									
Study infusion		X[2]									
Record vital signs		x	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]		
COVID-19 symptom screen		x									
Concomitant medications		x									
Assessment with COVID-19 7-point Ordinal Clinical Progression Outcomes Scale		x	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x	x	x
Collect data for later calculation of SOFA score		x	x[3]								
Record new medical conditions		x	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x	x	x
Adverse event monitoring		x	x[3]	x[3]	x[3]						
CRP (complete on study protocol if clinical results not available)		x[4]									
CBC and CMP (complete on study protocol if clinical results not available)		x[4]	x[3, 4]								
Blood for COVID-19 titer testing		x[5]	X[3]								
Record the results of a clinically obtained CBC and CMP (only if clinically available)									x		

[1] If patient is discharged before the follow-up visits on Day 8, 15, and 29, follow-up study activities on these days will be performed via phone calls. Day 8 call window will be Day 8 through 14. The Day 15 call window will be Day 15 through 22. The Day 29 call window will be Day 29 through 36

[2] Study infusion will be monitored per site institutional transfusion policy.

[3] Only performed if hospitalized.

[4] Only if not performed as part of standard of care.

[5] Must be drawn prior to study infusion.

Appendix B: Adverse Event Reporting and Unanticipated Events

Investigators will report all serious adverse events that occur within 72 hours of study infusion to the Vanderbilt Coordinating Center (VCC) regardless of relatedness. Serious adverse events that are determined to be related to study procedures (regardless of timing related to study infusion) will be reported to the VCC within 24 hours. Hence, all serious adverse events judged to be related or possibly related to study procedures will be reported within 24 hours (Figure 2). The VCC will then notify the single Institutional Review Board (sIRB).

The Medical Monitor will work collaboratively with the reporting investigator to determine if a serious adverse event has a reasonable possibility of having been caused by the study infusion or study procedure, as outlined in 21 CFR 312.32**(a)**(1), and below. The Medical Monitor will be unblinded and will also determine if the event is unexpected for convalescent plasma. An adverse event is considered "unexpected" if it is not listed in the investigator brochure or the study protocol [21 CFR 312.32(a)]. If a determination is made that a serious adverse event has a reasonable possibility of having been caused by a study procedure or the study infusion, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a serious unexpected suspected adverse reaction (SUSAR).

The VCC will report all unexpected deaths, serious and treatment related adverse events, and SUSARs to the DSMB and sIRB within 7 days after receipt of the report from a clinical site. A written report will be sent to the, DSMB, FDA, and the sIRB within 15 calendar days. The DSMB will also review all reported adverse events and clinical outcomes during scheduled interim analyses. The VCC will distribute the written summary of the DSMB's periodic review of reported adverse events to the sIRB.

B.1. Unanticipated Problems (UP)

Investigators must also report Unanticipated Problems, regardless of severity, associated with study procedures within 24 hours. An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all the following criteria:

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

B.2. Determining Relationship of Adverse Events to Study Infusion or Study Procedures

Investigators will be asked to grade the strength of the relationship of an adverse event to study infusion or study procedures as follows:

- Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) Evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
- Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.
- Probably Not Related: The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
- Definitely Not Related: The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.

- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

B.3. Clinical Outcomes that may be Exempt from Adverse Event Reporting

Study-specific outcomes of acute respiratory infection, COVID-19, and critical illness will be systematically collected for all patients in both study groups and are exempt from adverse event reporting unless the investigator considers the event to be Definitely Probably, or Possibly Related (or of an Uncertain Relationship) to the study infusion or study procedures. Examples of study-specific clinical outcomes include:

- Death not related to the study procedures
- Neurological events
  - Ischemic stroke
- Cardiovascular events
  - Receipt of vasopressors
  - Cardiomyopathy
  - Myocardial infarction
  - Cardiac arrest
  - Deep vein thrombosis
  - Pulmonary embolism
- Respiratory events
  - Hypoxemia requiring supplemental oxygen
  - Acute respiratory distress syndrome
  - Receipt of mechanical ventilation
  - Receipt of extra-corporeal membrane oxygenation
- Gastrointestinal events
  - Elevation of aspartate aminotransferase or alanine aminotransferase
- Renal events
  - Acute kidney injury
  - Receipt of renal replacement therapy
- Hematologic or coagulation events
  - Neutropenia, lymphopenia, anemia, or thrombocytopenia

Note: A study-specific clinical outcome may also qualify as a reportable adverse event. For example, a cardiac arrest that the investigator considers Definitely or Possibly Related to the study infusion would be both recorded as a study-specific clinical outcome and reported as a Serious and Definitely or Possibly Related Adverse Event.

B.4. Decision tree for determining if an adverse event is reportable

Figure 2. Decision tree for determining if an adverse event is reportable

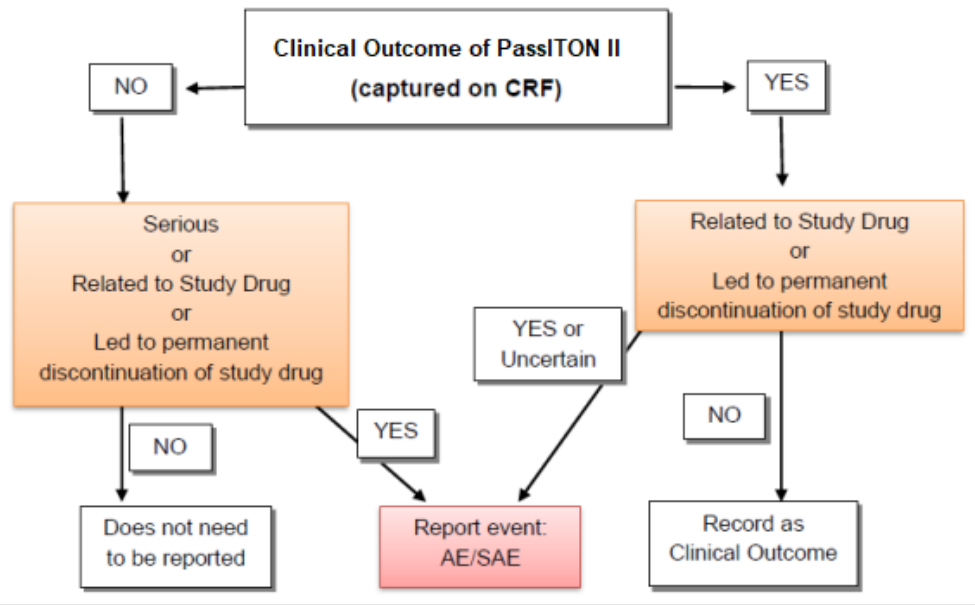


Figure adapted from Ranieri VM, Thompson BT, Barie PS et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012 May 31;366 (22):2055-64. PMID: 22616830.

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