BEST INITIATIVE

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

COVID-19 CONVALESCENT PLASMA SURVEILLANCE PROTOCOL

Convalescent coronavirus disease 2019 plasma in treatment for COVID-19

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HISTORY OF AMENDMENTS TO THE FINAL PROTOCOL

Version	Date	Amendments	Justifications

ABBREVIATIONS

Abbreviation	Definition
BSWH	Baylor Scott & White Health
CI	Confidence interval
COVID	Coronavirus disease
CP	Convalescent plasma
DHTR	Delayed hemolytic transfusion reaction
DSTR	Delayed serologic transfusion reaction
EHR	Electronic Health Records
EUA	Emergency use authorization
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICU	Intensive care unit
ISBT	International Society of Blood Transfusion
ITT	Intent-to-treat
PTP	Post transfusion purpura
RCT	Randomized controlled trial
RT-PCR	Real-Time Polymerase chain reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TACO	Transfusion associated circulatory overload
TAD	Transfusion-associated dyspnea
TRALI	Transfusion-related acute lung injury
TAGVHD	Transfusion-associated graft vs. host disease

I. INTRODUCTION

The US Food and Drug Administration (FDA) authorized compassionate use of convalescent plasma for seriously ill patients infected with SARS-CoV-2 on March 25, 2020. Under the emergency use authorization (EUA), FDA expanded the use for treatment outside the scope of a trial. Although randomized controlled trials (RCTs) provide robust data to assess the efficacy and immune response of the intervention for COVID-19, complete data may not be available during critical periods in the current pandemic. While waiting for efficacy and safety data from ongoing clinical trials, inference gleaned from observational studies using secondary data (real-world data), e.g., electronic health records (EHRs) in an observational study, may provide more timely information in real-world clinical practice.

The goal of this study is to assess safety and effectiveness of anti-SARS-CoV-2 plasma in patients with coronavirus disease 2019 (COVID-19).

II. OBJECTIVES

A. PRIMARY OBJECTIVES

(i) To estimate the relative risk of effectiveness outcomes of interest in laboratory confirmed COVID-19 patients who received convalescent plasma compared with COVID-19 patients who did not receive convalescent plasma.

(ii) To describe safety outcomes of interest in laboratory confirmed COVID-19 patients who received convalescent plasma compared with COVID-19 patients who did not receive convalescent plasma.

B. EXPLORATORY OBJECTIVES

(i) To estimate the relative risk of in-hospital mortality through 28 days among patients with HIV and laboratory confirmed COVID-19, who received convalescent plasma compared with those who did not receive convalescent plasma.

(ii) To describe demographics, clinical characteristics, and outcomes of the population of COVID-19 patients treated concurrently with remdesivir and convalescent plasma.

III. STUDY DESIGN

Study Period

July 1, 2020 to October 25, 2020 (the date of data pull)

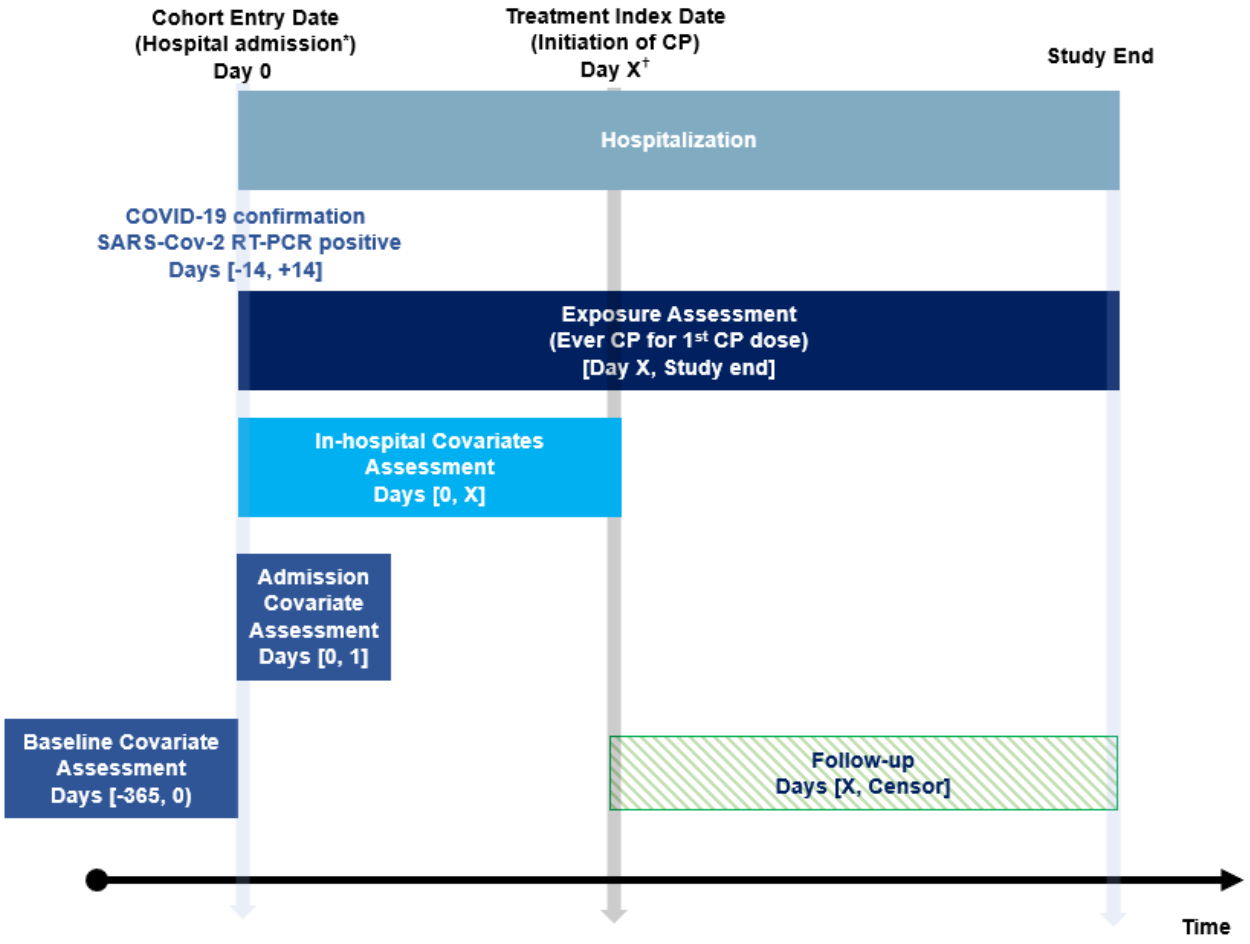
The start date is when all hospital sites started using the same ERH management system. The study period end date is October 25, 2020 with last convalescent plasma administration occurring 28 days prior on September 27, 2020.

Cohort Sampling

This is a retrospective cohort study with risk-set sampling for exposure status of convalescent plasma using EHRs in the Baylor Scott & White Health (BSWH) healthcare delivery system. In brief, patients who received convalescent plasma will be matched to a similar population who did not receive convalescent plasma around the same time (± 2 days) of transfusion across sites. The administration date of convalescent plasma for the treated population and the matched date for the untreated population are thereafter referred as the index date. The matching scheme for risk-set sampling is defined in step-by-

step points in the following paragraph. The follow-up for the matched cohort will start from the index date and continue until the end of the observation period. The observation period for this study is defined as at least 28 days from the index date. In other words, the index date must be at least 28 days prior to the date of data pull to allow for adequate follow-up and minimize selection bias from informative censoring due to death or discharge for palliative care. An unexposed patient at the index date could receive convalescent plasma during the follow-up and the follow-up will be censored at the administration date of convalescent plasma (**Figure 1**).

Figure 1. Schematic diagram for retrospective cohort study with risk-set sampling for convalescent plasma exposure



CP= convalescent plasma
* Hospital admission includes the earliest encounters at emergency or inpatient departments around COVID-19 confirmation within ±14 days.
† The earliest possible date is July 1st, 2020.

Step-by-step risk-set sampling with replacement for the retrospective cohort design to account for confounding and to strategize EHR abstraction at BSWH:

1. Identify patients hospitalized with laboratory-confirmed COVID-19 (Source population)

The study population will be patients with laboratory-confirmed COVID-19 (i.e., RT-PCR test results recorded by the BSWH laboratory informatics systems and/or the EHR system) and received or matched to a patient who received convalescent plasma from July 1st to September 28th. Patients must have at least 28 days of observation opportunity from the date of data pull to the index date (reverse order). Patients cannot have been previously admitted into hospitals due to RT-PCR laboratory confirmed COVID-19.

2. Identify patients who received convalescent plasma (Exposed group)

Blood bank records will be scanned to identify patients who had at least one order to transfuse COVID-19 convalescent plasma using the International Society of Blood Transfusion (ISBT) 128 codes (Appendix 1). The order will be linked to the administration record of the plasma to determine the date and time the product was given.

3. Risk-set sampling and matching variables (Unexposed group)

For each patient who received a first dose of convalescent plasma, we will sample from the source population who did not receive convalescent plasma (Unexposed group) at the same calendar time (±2 days) and match on the following variables. One patient could be sampled at maximum twice; first sampled into the unexposed group and later sampled into the exposed group due to initiation of convalescent plasma transfusion during follow-up.

- Calendar date around the index date within ± 2 days: Risk-set sampling to match exposed and unexposed patients will account for this factor
- Age (± 5 years)
- Sex (female, male)
- Days from hospital admission to the index date

4. Propensity score matching and baseline covariates

The propensity score is defined as the probability of a patient receiving convalescent plasma conditioned on their observed baseline covariates. Baseline is defined as the period prior to and including the index date. Baseline covariates for the propensity score modeling is listed below and further defined in Appendix 2. To account for confounding by baseline covariates described below, a logistic regression will be fitted to estimate the probability of receiving convalescent plasma. In the event of low frequency of certain covariates, that may cause model convergence problem, such covariates will be removed from the propensity score model. Covariates that are strongly related to convalescent plasma transfusion but only weakly related to the primary outcome will not be included in the propensity model to preserve precision of the estimates.[1] Exposed and unexposed patients will be matched according to propensity score with nearest neighbor caliper matching algorithm without replacement with a match ratio up to 1:4 based on the power calculation (Section V. Sample Size).[2] Propensity density plots pre- and post-matching will be evaluated for overlapping areas.

- Age (continuous)
- Race and ethnicity
- Hospital site
- Comorbidities
- Concomitant medications
- Oxygen requirements as a proxy for disease severity (Appendix 3) 4-12 hours prior to the index date

- Laboratory results: creatinine, D-dimer, troponin, absolute lymphocyte count, ferritin, C-reactive protein
- Vital signs: Respiratory rate (min^{-1}), Heart rate (min^{-1}), Systolic BP (mmHg), Temperature (°C)

Data Sources

BSWH is the largest not-for-profit integrated healthcare delivery system in Texas and one of the largest in the United States with over 1,000 access points in 46 counties, 49,000 employees, and 7,300 affiliated physicians. This study includes data from 25 hospitals across north and central Texas and 3767 inpatient beds. Data will be obtained from BSWH EHR and laboratory systems. All EHRs are managed on the Epic systems at affiliated hospitals during the study period. Laboratory data systems include SoftLab (SCC) for COVID-19 test results, and SoftBank (SCC) and SafeTrace (Haemonetics) for convalescent plasma data elements. The definition, location and time points of the data elements extracted from Epic are listed in Appendix 4. BSWH will fill this table while implementing data abstraction for transparency and data governance.

All programming scripts used to extract data from the EHRs will be programmed and then validated by a second programmer using a standardized template that requires checking for syntax errors as well as errors in logic. In addition, a random selection of records (n=10–20 records per data point) will be compared and validated against a manual chart review of the data. The programming scripts for each data element will be refined until the match rate with manual extraction is 95%.

Similarly, all programming used to assemble data into an analytic dataset will be programmed and then validated by a second programmer using a standardized template.

Exposure

COVID-19 convalescent plasma will be identified with ISBT-128 code (Appendix 1) in local Blood Bank data. First exposure to convalescent plasma is of interest for patients who received multiple doses. Patients can receive convalescent plasma any time during the hospital stay associated with the COVID-19 diagnosis.

Study Outcomes

- Safety

  Safety events related to plasma transfusion were selected from the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) Biovigilance Component Hemovigilance Module Surveillance Protocol.[a] The following safety outcomes will be identified by ICD-10-CM billing codes (Appendix 5).

  - Transfusion associated circulatory overload (TACO)
  - Transfusion-related acute lung injury (TRALI)
  - Anaphylactic reaction

[a] The following events were excluded because they are irrelevant for plasma transfusion or because there are no transfusion-specific billing codes. Transfusion-associated graft vs. host disease (TAGVHD) is associated with a cellular product. Delayed hemolytic transfusion reaction (DHTR) and delayed serologic transfusion reaction (DSTR) are associated with red cells containing products. Post transfusion purpura (PTP) is associated with platelets containing products. No transfusion specific billing codes exist for transfusion-associated dyspnea (TAD) allergic reaction and hypotensive transfusion reaction.

- Febrile non-hemolytic transfusion reaction
- Transfusion-transmitted infection
- Acute hemolytic transfusion reaction
- A composite outcome of thrombotic or thromboembolic complication including stroke, myocardial infarction, venous thromboembolism, deep vein thrombosis, and pulmonary embolism
- A composite outcome of cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, atrial arrhythmia, and cardiac arrest

- Effectiveness
  - Primary:
    - 28-day in-hospital mortality
  - Secondary:
    - Discharge alive
    - ICU transfer
    - Mechanical ventilation

Covariates

Covariates including those for risk-set sampling and propensity score matching (See Cohort Sampling) will be assessed during baseline and are listed in Appendix 2. Baseline is defined as the period prior to and including the index date. For variables (e.g., vital signs and comedications) assessed at multiple time points, the value closest to the index date will be used. However, for oxygenation, the worst measures 4-12 hours prior to the index date will be used. For variables (e.g., cardiovascular conditions) that are usually collected at hospital admission or possibly in previous healthcare encounters for other health concerns, the value will be searched in the past year from and including the hospital admission date, unless specified otherwise. The lookback period for each covariate is listed in Appendix 2.

IV. STATISTICAL ANALYSIS PLAN

All patients

Descriptive Analyses

We will describe distribution of baseline covariates (Appendix 2), including demographics, comorbidities, concomitant medications, and severity measures of COVID-19 for the exposed and unexposed groups. The number of patients, mean, standard deviation, median, interquartile range, and range will be presented for continuous variables, and counts and percentages of patients in each category will be presented for categorical variables.

Given the modest sample size and rarity of the safety outcomes,[3] we will explore the occurrence of safety outcomes, and present counts and percentages.

The crude incidence rates of death in the first 7, 14, 21, and 28 days after the index date will be estimated for the exposed and unexposed groups using the cohort before propensity score matching.

Comparative Analyses

A Kaplan-Meier curve will be plotted using the propensity score matched cohorts. To control for measured confounding, patients will be sampled in risk sets with replacement and propensity score matched. Distribution of covariates between exposure groups before and after propensity score matching will be assessed to evaluate the balance of baseline covariates and potential residual confounding. Absolute standardized differences, the differences in means or proportions divided by the pooled standard deviation, will be computed for each covariate to check its distribution balance within exposure groups. Covariates with an absolute standard difference greater than 0.1 will be further controlled in the analyses by including specific variables in the Cox model.

The adjusted incidence rates of death in the first 7, 14, 21, and 28 days after the index date will be estimated for the exposed and unexposed groups using the propensity score-matched cohort.

For the primary outcome (28-day in-hospital mortality), a Cox proportional hazards regression will estimate hazards ratios (HRs) and 95% confidence intervals (CIs) using the propensity score-matched cohort. Patients will be followed from the index date until the earliest of the following: 1) death, 2) discharge alive, 3) day 28 since the index date, or 4) the date of unexposed patients who were administrated COVID-19 convalescent plasma. Patients discharged alive will be censored at the discharge date. The proportional hazards assumption will be evaluated using Schoenfeld residuals test and visual inspection of log-log plots.

For the secondary outcome of discharge alive, we will not censor the follow-up at the date of in-hospital death but will censor at day 28 to account for this worst possible outcome and to account for the competing risk of in-hospital death. In other words, patients will be followed from the index date until the earliest of the following: 1) discharge alive, 2) day 28 since the index date, or 3) the date of unexposed patients who were administrated COVID-19 convalescent plasma.

A Cox proportional hazards regression will estimate HRs and 95%CIs using the propensity score-matched cohort for the secondary outcomes of ICU transfer and mechanical ventilation. Patients will be followed from the index date until the earliest of the following: 1) the outcome of interest, 2) death, 3) discharge alive, 4) day 28 since the index date, or 5) the date of unexposed patients who were administrated COVID-19 convalescent plasma.

<u>Secondary Analyses</u>

1) If sample size allows, stratify analyses by mechanical ventilator use prior to or at the index date
2) If sample size allows, subgroup analyses comparing patients who received convalescent plasma and remdesivir, with those who only received remdesivir.
3) If sample size allows, stratify analyses by time interval from hospital admission to the index date (<72 hours vs. ≥72 hours).
4) If sample size allows, stratify analyses by disease severity measured by oxygenation.

<u>Sensitivity Analyses</u>

1) To assess the COVID-19 cohort definition of hospital admission within ±14 days of laboratory confirmed COVID-19 diagnosis, we will further restrict the source population to those who were admitted into affiliated BSWH hospitals within ±7 days of laboratory confirmed COVID-19 diagnosis. This is because COVID-19 could progress quickly and patients could also transfer to hospitals outside of the network of BSWH with a large time window around COVID-19

confirmation resulting in potential residual confounding by severity and survivor bias by prior treatment

2) Instead of ending the observation period at 28 days since the index date, we will continue follow-up until the end of the study period, unless an outcome event occurs earlier. Patients will be followed from the index date until the earliest of the following: 1) death, 2) discharge alive, 3) the end of the study period, or 4) the date of unexposed patients who were administrated COVID-19 convalescent plasma.
3) Given that mortality data after hospital discharge is limited and that patients could be discharged for palliative care due to disease worsening, the outcome "discharge alive" will be considered a competing risk for 28-day in-hospital mortality. To account for competing risk of in-hospital death and discharge alive, sub-distribution hazard ratios will be estimated from the Fine-Gray model.[4] Cumulative incidence function will be estimated by modeling the cause-specific hazard function of all causes.[5]

HIV+ patients

Among patients with HIV+ from the source population, we will explore distributions of risk-set match factors (Section III. Study Design) according to exposure to convalescent plasma. The crude incidence rates of death and discharge alive in the first 7, 14, 21, and 28 days after the index date will be estimated for the exposed and unexposed groups.

All statistical analyses will be conducted with SAS 9.4 and R 3.5.1.

V. SAMPLE SIZE

To achieve 80% power for relative risk ratios of at least 0.7 for all-cause mortality, a sample size calculation was performed based on an assumed background survival rate of 0.75 over 28 days among hospitalized COVID-19 patients receiving usual care in the RCT for dexamethasone[6] and a convalescent plasma to comparator ratio of 1:1, 1:2, 1:3 and 1:4. Using a two-sided log-rank test,[7] estimated sample sizes are listed in **Table 1**.

The feasibility assessment found that the maximum number of patients who received convalescent plasma was 729 during April 1, 2020 to August 6, 2020, we greyed out rows in **Table 1** with required sample size surpassing the maximum and deemed those inapplicable.

Table 1. Sample size estimates given background survival rate of hospitalized COVID-19 patients and 80% of power at a two-sided 0.05 significance level

Total sample size	Sample size for convalescent plasma	Match ratio	Relative risk ratio
1,000	500	1:1	0.71
1,500	750	1:1	0.76
2,000	1,000	1:1	0.79
2,500	1,250	1:1	0.81
1,000	333	1:2	0.68
1,500	500	1:2	0.74
2,000	666	1:2	0.77
2,500	833	1:2	0.80

Total sample size	Sample size for convalescent plasma	Match ratio	Relative risk ratio
1,000	248	1:3	0.65
1,500	372	1:3	0.71
2,000	496	1:3	0.75
2,500	620	1:3	0.78
1,000	200	1:4	0.61
1,500	300	1:4	0.68
2,000	400	1:4	0.73
2,500	500	1:4	0.76

VI. LIMITATIONS

Unmeasured confounding

Given that patients were not randomly assigned to receive convalescent plasma, confounding by indication may not be fully accounted for using the available data elements in EHRs. Missing data and misclassification for covariates may result in residual confounding and biased risk estimates. For example, the convalescent plasma exposed group may appear to have a more favorable clinical outcome compared to the unexposed group, because the unexposed group had more severe disease to start with, and the two groups were not comparable at the index date. Alternatively, the exposed group may appear to have no favorable clinical outcomes or even worse outcomes, because patients in this group started with more severe disease at the index date.

Although risk-set sampling and propensity score matching are used to control measured confounding, EHRs are not able to fully capture all important prognostic factors related to outcomes of interest. To evaluate the possible impact of unmeasured confounding, we will consider exploring some of the methods listed below if feasible.

- Quantitative bias analyses
- Negative outcome controls
- E-values [8]
- Instrumental variables

Informative censoring

Treatment switches or hospital transfers during follow-up may be related to worsening of COVID-19. To evaluate this potential selection bias, we will use an intent-to-treat (ITT) analysis, whereby treatment switches will not censor the follow-up and instead fixed duration of follow-up will be used. Reasons for and where patients were transferred will be assessed according to exposure groups.

Effect modification by antibody titer

This observational study does not impose the inclusion criterion of seronegative for SARS-CoV-2 because testing antibody titers before administering convalescent plasma is not the present routine clinical practice at BSWH. Hence, individual antibody titers/humoral immunity in patients is not accounted for. The neutralizing capacity of convalescent plasma received by patients is not tested nor captured in the EHRs. In addition, the effective level of neutralizing titers inpatients who have received passive antibody therapies is also unknown. If a limited or no association between convalescent plasma and the clinical outcomes are observed, the results may not be interpreted as a true “no effect” of convalescent plasma due to the uncertainty of the titer values.

Generalizability

All studies estimate effects in a specific study population. Clinical practice and coding in EHR systems differ across healthcare systems. Therefore, results from this study may not hold true in other populations.

Other

The theoretical concern of antibody-mediated enhancement of infection, where antibodies to SARS-CoV-2 could enhance infection to another viral strain, is not assessed in this study.

VII. INSTITUTIONAL REVIEW BOARD APPROVAL AND OTHER AUTHORIZATIONS

This study has been reviewed and approved by the Institutional Review Boards (IRB) of BSWH.

VIII. REFERNECES

1. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. *Am J Epidemiol.* 2006;163(12):1149-1156.
2. Austin PC. A comparison of 12 algorithms for matching on the propensity score. *Stat Med.* 2014;33(6):1057-1069.
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4. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med.* 2017;36(27):4391-4400.
5. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation.* 2016;133(6):601-609.
6. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med.* 2020.
7. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Stat Med.* 1982;1(2):121-129.
8. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med.* 2017;167(4):268-274.

IX. APPENDICES

Appendix 1. International Society of Blood Transfusion (ISBT)-128 codes for convalescent plasma

- E9743 Apheresis CONVALESCENT PLASMA|NS/XX/<=-25C|COVID-19
- E9744 Apheresis CONVALESCENT PLASMA|NS/XX/<=-25C|Methylene blue-treated|COVID-19
- E9745 Apheresis CONVALESCENT PLASMA|NS/XX/<=-25C|Psoralen-treated|COVID-19
- E9746 Apheresis CONVALESCENT PLASMA|NS/XX/<=-25C|Riboflavin-treated|COVID-19
- E9747 Apheresis CONVALESCENT PLASMA|ACD-A/XX/<=-18C|COVID-19
- E9748 Apheresis CONVALESCENT PLASMA|NS/XX/Frozen|COVID-19
- E9749 CONVALESCENT PLASMA|NS/XX/Frozen|COVID-19
- E9750 Liquid Apheresis CONVALESCENT PLASMA|NS/XX/refg|COVID-19
- E9751 Liquid CONVALESCENT PLASMA|NS/XX/refg|COVID-19
- E9752 Thawed Apheresis CONVALESCENT PLASMA|ACD-A/XX/refg|COVID-19
- E9764 Thawed Apheresis CONVALESCENT PLASMA|ACD-A/XX/refg|3rd container|COVID-19
- E9763 Thawed Apheresis CONVALESCENT PLASMA|ACD-A/XX/refg|2nd container|COVID-19
- E9754 Apheresis CONVALESCENT PLASMA|ACD-A/XX/<=-18C|1st container|COVID-19
- E9762 Thawed Apheresis CONVALESCENT PLASMA|ACD-A/XX/refg|1st container|COVID-19
- E9765 Thawed Apheresis CONVALESCENT PLASMA|ACD-A/XX/refg|4th container|COVID-19

Appendix 2. Baseline covariates

- Age (continuous)
- Race and ethnicity
- Site
- Comorbidities in the past 12 months including the index date unless specified
    - History of cancer
        - Hematopoietic
        - Solid tumor excluding non-melanoma skin cancer
        - Non-melanoma skin cancer
    - Cardiovascular conditions
        - Stroke
        - Thrombotic or thromboembolic complications including stroke, myocardial infarction, venous thromboembolism, deep vein thrombosis, and pulmonary embolism
        - Hypertension
        - Heart failure
        - Cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, atrial arrhythmia, and cardiac arrest
    - Chronic respiratory disease
        - Chronic obstructive pulmonary disease
        - Asthma
    - Diabetes
    - Chronic kidney disease 1-4
    - Chronic kidney disease 5 or end-stage renal disease
    - Chronic liver disease
    - History of organ transplantation
    - HIV
    - Obesity at admission
    - Sickle cell disease
- Pregnancy status (yes, no) from index date to study completion
- Comedications from hospital admission to the index date
    - Antiviral drugs
        - Remdesivir
        - Lopinavir/Ritonavir
        - Other HIV protease inhibitors.
    - Hydroxychloroquine/Chloroquine
    - Azithromycin
    - Glucocorticoid/Steroids
        - Dexamethasone
        - Prednisone
        - Hydrocortisone
        - Methylprednisolone
    - Anti-platelet agents
    - IL-6 inhibitor/antagonist
        - Tocilizumab
        - Sarilumab

        - Siltuximab
    - ACE-Inhibitors (ACEi)/Angiotensin Receptor Blockers (ARBs)
    - Anti-thrombotic drugs
- Disease severity based on level of oxygenation support (Appendix 3) 4-12 hours prior to index
- Vital signs closest to the index date
    - Respiratory rate
    - Heart rate
    - Systolic blood pressure
    - Temperature
- Laboratory results closest to index date
    - Creatinine,
    - D-dimer
    - Cardiac troponin (Tnl or TnT)
    - Absolute lymphocyte count
    - Ferritin
    - C-reactive protein

Appendix 3. Oxygen requirements as a proxy for disease severity (listed from lowest to highest disease severity)

- Room air
    - No documentation of the other categories listed below
- Basic oxygenation
    - Includes: Simple face mask, nasal cannula, CPAP/Bubble CPAP, T-piece, blow by, nasal prongs, open oxygen mask, tracheostomy collar, venturi mask system (if FiO2 % is < 45%), face tent (if FiO2 % is < 45%; up to 6L), nasal cannula with reservoir (i.e. oximizer; if FiO2 % is < 45%; up to 6L)
- Advanced oxygenation
    - Includes: High flow nasal cannula (HFNC), BiPAP/NPPV/NIV, Vapotherm, blender system, high flow mask, manual resuscitator, non-rebreather mask (NRB), Oxyhood, partial rebreather mask, venturi mask system (if FiO2 % is $\geq$ 45%), face tent (if FiO2 % is $\geq$ 45%; $\geq$ 7L), nasal cannula with reservoir (i.e. oximizer; if FiO2 % is $\geq$ 45%; $\geq$ 7L)
- Invasive ventilation
    - Transtracheal catheter, Invasive mechanical ventilation vent mode
        - CPT code 94002 (mechanical ventilation for initial day), 94003 (subsequent day), 94004 (per day)
- ECMO

NOTE: In cases where clinical flow sheets do not contain sufficient information to classify the level of oxygen support, categorization will be based on clinician review of the electronic health record

Appendix 4. The location and definition of the data elements

This table will be created as part of documentation of programming and validation.

Domain	Data Elements	Definition	Time Points	Source system location

Appendix 5. Code list to identify safety outcomes

Safety outcomes	ICD-10-CM	ICD-10-CM Description
Hemovigilance surveillance outcomes		
Anaphylactic reaction	T80.51XA	Anaphylactic reaction due to administration of blood and blood products, initial encounter
Febrile non-hemolytic transfusion reaction	R50.84	Febrile nonhemolytic transfusion reaction
Transfusion-associated circulatory overload (TACO)	E87.71	TACO
Transfusion-related acute lung injury (TRALI)	J95.84	TRALI
Transfusion-transmitted infection	T80.22XA	Acute infection following transfusion, infusion, or injection of blood and blood products, initial encounter
	T80.29XA	Infection following other infusion, transfusion and therapeutic injection, initial encounter
Acute hemolytic transfusion reaction (AHTR)	T80.910A	AHTR, unspecified incompatibility, initial encounter
	T80.A10A	Non-ABO incompatibility with AHTR, initial encounter
Cardiac arrhythmias		
Ventricular tachycardia ventricular arrhythmia	I47.1	Supraventricular tachycardia
	I47.9	Ventricular tachycardia
	I47.2	Paroxysmal tachycardia unspecified
Ventricular fibrillation ventricular arrhythmia	I49.01	Ventricular fibrillation
Cardiac arrest	I46.2	Cardiac arrest due to underlying cardiac condition
	I46.8	Cardiac arrest due to other underlying condition
	I46.9	Cardiac arrest, cause unspecified
Atrial arrhythmia	I48.0	Paroxysmal atrial fibrillation
	I48.1	Persistent atrial fibrillation

Safety outcomes	ICD-10-CM	ICD-10-CM Description
	I48.2	Chronic atrial fibrillation
	I48.3	Typical atrial flutter
	I48.4	Atypical atrial flutter
	I48.9	Unspecified atrial fibrillation and atrial flutter
Thromboembolic events		
Pulmonary embolism	I26.0x	Pulmonary embolism with acute cor pulmonale
	I26.9x	Pulmonary embolism without acute cor pulmonale
Deep vein thrombosis	I82.4xx	Acute embolism and thrombosis of deep veins of lower extremity
	I82.8xx	Embolism and thrombosis of other specified veins
	I81	Portal vein thrombosis
	I82.0	Budd-Chiari syndrome
	I82.2xx	Embolism and thrombosis of vena cava and other thoracic veins
	I82.6xx	Acute embolism and thrombosis of veins of upper extremity
	I82.890	Acute embolism and thrombosis of other specified veins
	I82.90	Acute embolism and thrombosis of unspecified vein
	I82.Axx	Embolism and thrombosis of axillary vein
	I82.Bxx	Embolism and thrombosis of subclavian vein
	I82.Cxx	Embolism and thrombosis of internal jugular vein
Acute myocardial infarction	I21.xx	Acute myocardial infarction
	I22.x	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
Stroke	I63.xxx	Cerebral infarction

Safety outcomes	ICD-10-CM	ICD-10-CM Description
	I65.xx	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
	I66.xx	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
	I67.6	Nonpyogenic thrombosis of intracranial venous system
	G45.x;	Transient cerebral ischemic attacks and related syndromes
	G46.x	Vascular syndromes of brain in cerebrovascular diseases
	I61.x;	Nontraumatic intracerebral hemorrhage
	I62.0x;	Nontraumatic subdural hemorrhage
	I62.9	Nontraumatic intracranial hemorrhage, unspecified
Arterial embolism and thrombosis	I74.xx	Arterial embolism and thrombosis